

CON--CPAP Does Not Improve CV Outcomes in OSA

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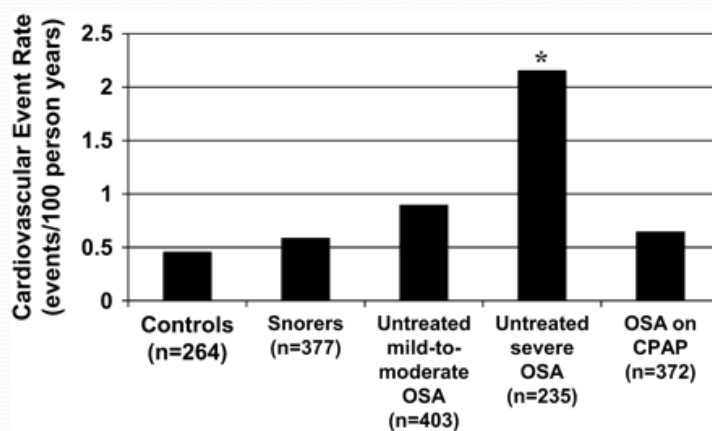
Outline of Lecture

- What do epidemiological association studies tell us?
- Randomized trials
- Meta-analyses

Is This Evidence of Causative Role of Severe Untreated OSA in Cardiovascular Events?

(10 Year Follow-Up)

(Marin et al, Lancet 365:1046, 2005)



All cohorts matched for age and BMI

From Pack, AJRCCM 173:7-15, 2006

But What Are the Problems?

- Cannot rule out that there are confounders that are not accounted for
- Can differences in those using CPAP and those not be equated with an observed effect being due to obstructive sleep apnea?

What Confounders May Be Important?

- Matching for BMI is not sufficient
- Fat distribution is important
 - Visceral fat (central adiposity) plays an independent role in risk of CV disease beyond BMI¹
 - Pericardial fat (increased coronary atherosclerosis by local mechanisms)²
 - Perivascular fat (increases atherosclerosis)³

¹Despres JP, et al, Nature 444:881, 2006

²Lim S, et al, Int J Cardiol 169:166, 2013

³Lee HY, et al, Atherosclerosis 230:177, 2013

What Confounders May Be Important?

- Physical activity levels
 - American Heart Association identified reduced physical activity as risk factor for CAD¹
 - Association shown in large cohort studies^{2,3}
 - Dose-dependent reduction in mortality with increased exercise^{4,5}

¹Kaminsky LA, et al, Circulation 127:652, 2013

²Cremer PC, et al, JAMA Cardiol 2:15, 2017

³Lauer MS, et al, JAMA 281:524, 1999

⁴Al-Mallah MH, et al, Clin Cardiol 37:456, 2014

⁵Kim J, et al, Arch Med Sci 12:303, 2016

Given that association studies do
not prove causality,
we need randomized trials

**Effect of Positive Airway Pressure on Cardiovascular Outcomes in
Coronary Artery Disease Patients with Nonsleepy Obstructive
Sleep Apnea**

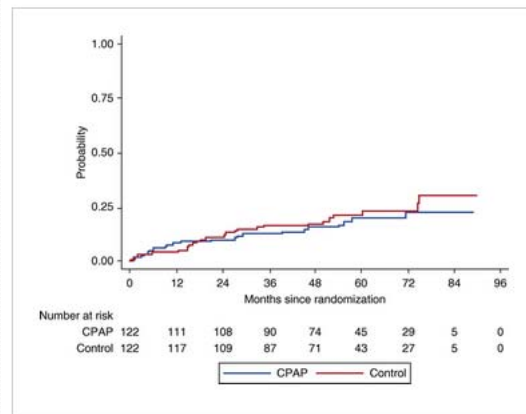
The RICCADSA Randomized Controlled Trial

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No Difference in Cardiovascular Event Rate Between Group on CPAP and Controls (Peker Y, et al, AJRCCM 194:613, 2016)



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CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea

R. Doug McEvoy, M.D., Nick A. Antic, M.D., Ph.D., Emma Heeley, Ph.D., Yuanming Luo, M.D., Qiong Ou, M.D., Xilong Zhang, M.D., Olga Mediano, M.D., Rui Chen, M.D., Luciano F. Drager, M.D., Ph.D., Zhihong Liu, M.D., Ph.D., Guofang Chen, M.D., Baoliang Du, M.D., Nigel McArdle, M.D., Sutapa Mukherjee, M.D., Ph.D., Manjari Tripathi, M.D., Laurent Billot, M.Sc., Qiang Li, M.Biostat., Geraldo Lorenzi-Filho, M.D., Ferran Barbe, M.D., Susan Redline, M.D., M.P.H., Jiguang Wang, M.D., Ph.D., Hisatomi Arima, M.D., Ph.D., Bruce Neal, M.D., Ph.D., David P. White, M.D., Ron R. Grunstein, M.D., Ph.D., Nanshan Zhong, M.D., and Craig S. Anderson, M.D., Ph.D., for the SAVE Investigators and Coordinators*

Design of SAVE Trial

- Multi-center (89 sites; n=2,717)
- Randomized, parallel group trial – CPAP vs. usual care
- Inclusion
 - Diagnosed with cerebrovascular or cardiovascular disease
 - Previous stroke (43.9, 44.4%)
 - Previous myo infarct (32.3, 34.8%)
- Had to have AHI >12 events/hour on home study (ApneaLink)
- Had to have >3 hours use of CPAP in initial run-in

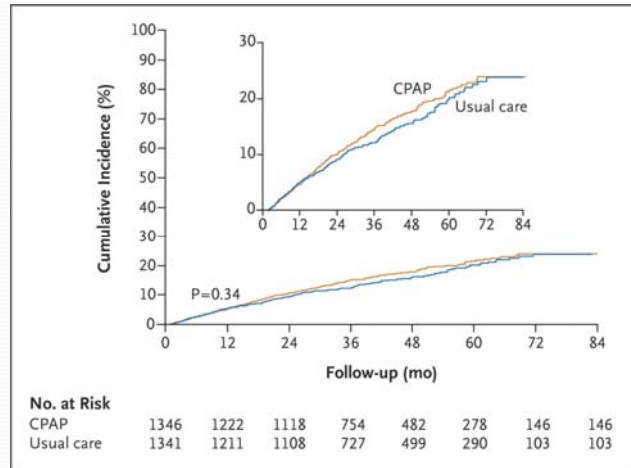
Results

- Positive outcomes (significant)
 - Greater reductions in Epworth Sleepiness Score in CPAP group
 - Greater improvements in depression scores in CPAP group
 - Greater improvements in SF36 scores in CPAP group

Hence, cannot claim that trial was negative. It was just negative for CV end-points.

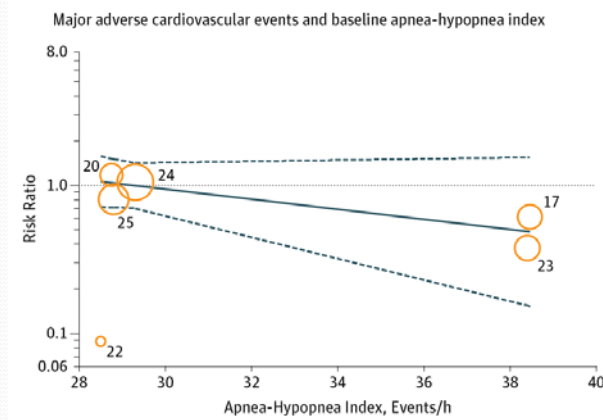
No Effect on Cardiovascular End-Points

(McEvoy RD, et al, NEJM 375:919, 2016)



Meta-Analyses of Effects of CPAP on Cardiovascular Events Are Also Negative – Not Significant

(Yu J, et al, JAMA 318:156, 2017)



Circles indicate weight given to each study

Conclusions

- Data from epidemiological association studies seem compelling

BUT

- Association studies do not prove causation
- Likely to be unrecognized confounder effects
- Lack evidence from randomized clinical trials
 - Studies are negative



Conclusions

- Where do we go from here?



Unlikely to be able to attract funding for major new type 3 randomized clinical trial for CV end-points

What are next logical steps?