

## CPAP and Hypertension in Nonsleepy Patients

Commentary on Barbe F, Duran-Cantolla J, Sanchez-de-la-Torre M, et al. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. *JAMA* 2012;307:2161-2168.

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### ARTICLE SUMMARY

**Question:** Is continuous positive airway pressure (CPAP) therapy better than no therapy in reducing the incidence of hypertension or cardiovascular (CV) events in a cohort of nonsleepy patients with obstructive sleep apnea (OSA)?

**Design:** Randomized, controlled trial; no placebo CPAP used. ClinicalTrials.gov Identifier: NCT00127348.

**Allocation:** Randomization was performed using a computer generated list of random numbers in the coordinating center and results were mailed to participating centers in numbered opaque envelopes.

**Blinding:** Primary outcome was evaluated by individuals not involved in the study and who were blinded to patient allocation. Patients, investigators, and the statistician were not blinded.

**Follow-Up Period:** median 4 (interquartile range, 2.7-4.4) years.

**Setting:** 14 academic medical centers in Spain.

**Subjects:** 725 adults (mean age 51.8 y, 14% women) who were diagnosed with OSA with apnea hypopnea index (AHI)  $\geq$  20 events per hour and Epworth sleepiness score (ESS)  $\leq$  10 were randomized. Subjects with previous CV events were excluded. However, patients with a history of hypertension were not excluded (50% of the sample were hypertensive at baseline).

**Intervention:** Patients were randomized to receive CPAP treatment or no active intervention. All participants received dietary counseling and advice about sleep hygiene.

**Outcomes:** The primary outcome was the incidence of either systemic hypertension (among participants who were normotensive at baseline) or CV events (among all participants). The secondary outcome was the association between the incidence of hypertension or CV events (nonfatal myocardial

infarction, nonfatal stroke, transient ischemic attack, hospitalization for unstable angina or arrhythmia, heart failure, and CV death) and the severity of OSA assessed by the AHI and oxygen saturation. The sample size was calculated assuming that the incidence of hypertension or new CV event in this population over a period of 3 years would be 10% annually; 345 patients per group were needed to detect a 60% reduction in incidence of new hypertension or CV events (90% power, 2-sided  $\alpha = 0.05$ , assuming 10% study dropout).

**Patient Follow-Up:** 83% complete (only patients who received the allocated intervention were included in analysis of primary outcome).

**Main Results:** A total of 147 patients with new hypertension and 59 cardiovascular events were identified (Table). In the CPAP group, there were 68 patients with incident hypertension and 28 CV events. Of the 357 participants in the CPAP group, 127 used CPAP  $<$  4 hours/night (36%). In the control group, there were 79 patients with new hypertension and 31 CV events. There was no statistically significant difference between the groups in the primary outcome.

**Conclusion:** In adults with moderate to severe OSA and no symptoms of daytime sleepiness, CPAP therapy did not reduce incident hypertension or CV event compared with no active therapy.

**Sources of Funding:** Instituto de Salud Carlos III (PI 04/0165) (Fondo de Investigaciones Sanitarias, Ministerio de Sanidad y Consumo, Spain), Spanish Respiratory Society (SEPAR) (Barcelona), Resmed (Bella Vista, Australia), Air Products-Carburos Metalicos (Barcelona), Respiroics (Murrysville, Pennsylvania), and Breas Medical (Madrid, Spain).

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### COMMENTARY

The effect of Continuous Positive Airway Pressure (CPAP) on hypertension and cardiovascular (CV) events is complex and only partly understood. The Joint National Committee on Hypertension lists Obstructive Sleep Apnea (OSA) first on the list of treatable causes of hypertension (1), and randomized-controlled trials have tended to show that CPAP improves hy-

pertension in OSA patients (2). But many questions remain, including whether or not nonsleepy hypertensive patients benefit from CPAP and whether or not there is a dose response effect. To address these issues, this productive group of Spanish investigators randomized over 700 patients to CPAP or usual care, and followed them for about 4 years. For the group as a whole, there were no significant differences in a modified intention-to-treat analysis. In a post-hoc analysis those who used

## Risk for incident hypertension or cardiovascular event

Outcome	Control (n = 366)	CPAP (n = 357)	Post hoc Analysis by Adherence	
			CPAP < 4 h/night (n = 127)	CPAP ≥ 4 h/night (n = 230)
Events	110	96	37	59
Person-years	997.84	1043.44	296.43	747.01
Events/100 person-years (95% CI)	11.02 (8.96-13.08)	9.20 (7.36-11.04)	12.48 (8.46-16.50)	7.90 (5.88-9.91)
p value		0.20	0.51	0.04
NNT		Not significant		

NNT, number needed to treat. p-value calculated when compared to control.

CPAP at least 4 hours a night had statistically (and clinically) significant reduction in blood pressure and CV events. About two-thirds of those randomized to CPAP used it at this threshold. It is unfortunate that these meticulous scientists took the “glass half empty” approach, and probably even more unfortunate that they lacked the resources to undertake a larger study or longer follow-up period, which they acknowledge “might have been able to identify a significant association between treatment and outcome.” Additionally, the inclusion of patients with pre-existing hypertension, and not including an estimate of CPAP compliance in their initial sample size calculations might have further compounded the problem of insufficient study power.

Well-done, randomized controlled trials like this one are rare in our field, and the authors were able to make a couple of other notable observations. The first has to do with correlates of CPAP adherence; in this large cohort, adherent patients were heavier, had bigger necks, were more likely to be hypertensive, and had more severe sleep apnea, and hypoxemia. In other words, they were sicker. These investigators also noted that the patients randomized to CPAP were less likely to lose weight than those in the control group, validating suggestions that CPAP certainly does not promote weight loss (3). With regards to characteristics of OSA subjects that developed CV events, the degree and duration of hypoxemia predicted adverse events better than Apnea Hypopnea Index (AHI), yet again confirming that the AHI is probably a less important metric than Oxygen Desaturation Index (ODI) or time below 90% SaO<sub>2</sub>.

My take on this paper is that CPAP works, sort of like birth control pills do. You have to use it. And it's important to remember that sleep apnea is a multi-organ disease. Cardiovascular consequences are important, but OSA is associated with many other consequences, including Metabolic Syndrome, cerebrovascular accidents, cognitive dysfunction, motor vehicle crash, mood disturbance, and death. To decide that CPAP shouldn't be used in nonsleepy patients on the basis of this study disregards the likely benefits of CPAP for many other conditions.

### CITATION

Phillips B; Shafazand S. CPAP and hypertension in nonsleepy patients. *J Clin Sleep Med* 2013;9(2):181-182.

### REFERENCES

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