A meta-analysis of positive airway pressure treatment for cardiovascular prevention: why mix apples and pears?

Yuksel Peker,1,2,3 Patrick J Strollo3,4

1Department of Pulmonary Medicine, Faculty of Medicine, Marmara University, Istanbul, Turkey, 2Department of Molecular and Clinical Medicine/Cardiology, Sahilgrena Academy, University of Gothenburg, Gothenburg, Sweden, 3Division of Pulmonary, Allergy, and Critical Care Medicine, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA, 4VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania, USA

Correspondence to: Professor Yuksel Peker, Department of Pulmonary Medicine, Faculty of Medicine, Marmara University, Pendik Education and Research Hospital, Sleep Medicine Center, Pendik, Istanbul, Turkey; yuksel.peker@marmara.edu.tr

Commentary on: Yu J, Zhou Z, McEvoy RD, et al. Association of positive airway pressure with cardiovascular events and death in adults with sleep apnea: a systematic review and meta-analysis. JAMA 2017;318:156-66.

Context
Despite an increasing body of evidence supporting an independent association between sleep apnoea and cardiovascular outcomes, there is still a lack of convincing data to suggest that treating this disorder reduces the cardiovascular risk. Sleep apnoea may be either obstructive (OSA) or central (CSA), or of a combination of both types, especially in patients with concomitant cardiovascular disease (CVD). Randomised controlled trials (RCT) have shown that continuous positive airway pressure (CPAP) treatment reduces excessive daytime sleepiness and improves quality of life in sleepy patients with CSA.1 Randomisation of patients with this phenotype to no treatment has been considered unethical. Thus, the long-term RCTs during the last decade have been focused on asymptomatic or minimally symptomatic patients with OSA. Positive airway pressure (PAP) for patients with CSA with adaptive servo-ventilation (ASV) has also been targeted.

Methods
This review and meta-analysis included data from 10 RCTs (nine CPAP; one ASV) for patients with sleep apnoea (n=7266; mean age, 61 years; 81% men), after identification of 5765 records through EMBASE, MEDLINE and Cochrane Library and after extracting data using standardised forms. Summary relative risks (RRs), risk differences (RDs) and 95% CI were obtained using random effects meta-analysis. The main outcomes were a composite of major adverse cardiovascular events (MACEs) including acute coronary syndrome (ACS) events, stroke or vascular death as well as cause-specific vascular events and all-cause death.

Findings
Among 356 MACEs and 613 deaths recorded, the authors found no significant association of PAP neither with MACEs (RR 0.77; 95% CI 0.53 to 1.13 and RD –0.01; 95% CI –0.03 to 0.01) nor with cardiovascular death (RR 1.15; 95% CI 0.88 to 1.50), all-cause death (RR 1.13; 95% CI 0.99 to 1.29), ACS (RR 1.00; 95% CI 0.65 to 1.55), stroke (RR 0.90; 95% CI 0.92 to 1.21) and heart failure (RR 1.03; 95% CI 0.92 to 1.16). Meta-regressions failed to identify any significant association of PAP with outcomes for different levels of apnoea severity, follow-up duration or adherence to PAP (all P values >0.13).

Commentary
The current meta-analysis is unfortunately compromised by a rather heterogeneous and inappropriate group of studies that included sleep clinic23 as well as cardiac4–8 and cerebrovascular cohorts.4–8 Studies that examined primarily OSA2–3,6–8 and CSA2,3 were included. This may be problematic since OSA is considered to be a risk factor for cardiac disease, and CSA can be a consequence of cardiac disease in populations with sleep-disordered breathing. Primary outcomes were quite different (for instance, the Apnea Positive Pressure Long-term Efficacy Study (APPLES) trial),3 and studies that involved primary7 and secondary prevention of CVD4–8 were included. The follow-up varied substantially (6–68 months) as well as the sample sizes (n=83 to n=2717). The analysis was hampered by poor adherence with the exception of the Parra et al report.6 Taking the above limitations into account, particularly the inappropriate combination of studies as well as the rather uniform low adherence, it is difficult to draw firm conclusions regarding the value of PAP in mitigating cardiovascular risk.

Implications for practice
What can we take away from this report? First, excluding significant sleepiness in PAP RCTs may be excluding populations that would benefit from treatment. This work highlights that adequate adherence in these cohorts is a considerable clinical challenge. Second, there appears to be a differential response to patient-centred measures of improvement (sleepiness and quality of life) versus improvement in cardiac outcomes. The later may require more complete treatment (ie, adherence throughout the entire sleep period) and particularly treatment during rapid eye movement sleep. Further, carefully designed RCTs are needed to address the limitations noted above before we abandon PAP therapy in patients with OSA at risk or with established cardiovascular disease.

Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.
References

1. Khayat R, Pleister A. Consequences of obstructive sleep apnea: cardiovascular risk of obstructive sleep apnea and whether continuous positive airway pressure reduces that risk. Sleep Med Clin 2016;11:273–86.
2. Barbe F, Durán-Cantolla J, Sánchez-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;307:2161–8.
3. Kushida CA, Nichols DA, Holmes TH, et al. Effects of continuous positive airway pressure on neurocognitive function in obstructive sleep apnea patients. Sleep 2012;35:1593–602.
4. Bradley TD, Logan AG, Kimoff RJ, et al. Continuous positive airway pressure for central sleep apnea and heart failure. N Engl J Med 2005;353:2025–33.
5. Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. N Engl J Med 2015;373:1095–105.
6. Parra O, Sánchez-Armengol Á, Capote F, et al. Efficacy of continuous positive airway pressure treatment on 5-year survival in patients with ischaemic stroke and obstructive sleep apnea: a randomized controlled trial. J Sleep Res 2015;24:47–53.
7. Peker Y, Glantz H, Eulenburg C, et al. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea. The RICADSA randomized controlled trial. Am J Respir Crit Care Med 2016;194:613–20.
8. McEvoy RD, Antic NA, Heeley E, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. N Engl J Med 2016;375:919–31.