

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

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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 OSA.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 clinic^{2,3} as well as cardiac^{4–8} and cerebrovascular cohorts.^{6,8} Studies that examined primarily OSA^{2,3,6–8} and CSA^{4,5} 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 primary² and secondary prevention of CVD^{4–8} 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.

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