Meta-Analysis of Cardiovascular Outcomes With Continuous Positive Airway Pressure Therapy in Patients With Obstructive Sleep Apnea

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Obstructive sleep apnea (OSA) is associated with increased cardiovascular morbidity and mortality. Continuous positive airway pressure (CPAP) is the main treatment of OSA. The present study explores the impact of CPAP on cardiovascular outcomes. A systematic search of electronic databases for randomized controlled trials comparing CPAP with medical therapy alone in patients with OSA who reported cardiovascular outcomes of interest was performed. The main outcome was major adverse cardiac events. Other outcomes included cardiac mortality, myocardial infarction, angina pectoris, stroke, and transient ischemic attack. Fixed effect model was used in all analyses except for subgroup analysis in which the random effect DerSimonian and Laird's model was used. Four randomized controlled trials with a total of 3,780 patients were included. Compared with medical therapy alone, CPAP use was not associated with reduced risk of major adverse cardiac events (relative risk [RR] 0.94, 95% confidence interval [CI] 0.78 to 1.15, p = 0.93, I^2 = 0%) except in the subgroup that wore CPAP >4 hours (RR 0.70, 95% CI 0.52 to 0.94, p = 0.02, I^2 = 0%). Furthermore, no reduction in the risk of cardiac mortality (RR 1.14, 95% CI 0.66 to 1.97, p <0.36, I^2 = 2%), myocardial infarction (RR 0.96, 95% CI 0.64 to 1.44, p <0.15, I^2 = 47%), angina pectoris (RR 1.16, 95% CI 0.9 to 1.50, p <0.51, I^2 = 0%), stroke (RR 1.01, 95% CI 0.73 to 1.38, p <0.0.86, I^2 = 0%), and transient ischemic attack (RR 1.36, 95% CI 00.69 to 2.68, p <0.24, I^2 = 30%) was observed. Subgroup analysis of CPAP adherence in regards to cardiac outcomes showed that CPAP use is not associated with decreased risk of heart failure (RR 0.91, 95% CI 0.50 to 1.66, p <0.55, I^2 = 0%). In conclusion, compared with medical therapy alone, utilization of CPAP in patients with OSA is not associated with improved cardiac outcomes except in patients who wore it for >4 hours. **© 2017 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2017;120:693−699)**

Obstructive sleep apnea (OSA) is associated with an increased risk of cardiovascular morbidity and mortality.[1] Its prevalence in patients with cardiovascular diseases can be as high as 47% to 83% compared with only a 5% to 10% incidence in general population.[2] Continuous positive airway pressure (CPAP) is currently the general care for moderate to severe OSA.[3] It was proved to improve hypertension, dyslipidemia, and endothelial cell dysfunction in OSA patients,[4–6] with data from observational studies reporting a protective role of CPAP usage against cardiovascular events in those patients.[1] A previous meta-analysis of observational studies showed a lower cardiovascular mortality (hazard ratio [HR] 0.37, 95% confidence interval [CI] 0.16 to 0.54) in CPAP-treated than in untreated patients.[1] Herein, we performed a meta-analysis of randomized controlled trials (RCTs) to evaluate the role of CPAP therapy in patients with OSA compared with general care alone.

Methods

We searched electronic databases according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[7] Initially, a systematic review of PubMed, MEDLINE, Embase, and Cochrane Central Register of Controlled Trials, without any language restriction, was performed from inception through December 2016. We used the following keywords: "apnea, obstructive sleep"; "CPAP ventilation"; and "assessments, outcomes" (Figure 1). After eligible trials were retrieved, we screened their bibliographies for any potential missed trials through the initial search. Furthermore, previous

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See page 698 for disclosure information.

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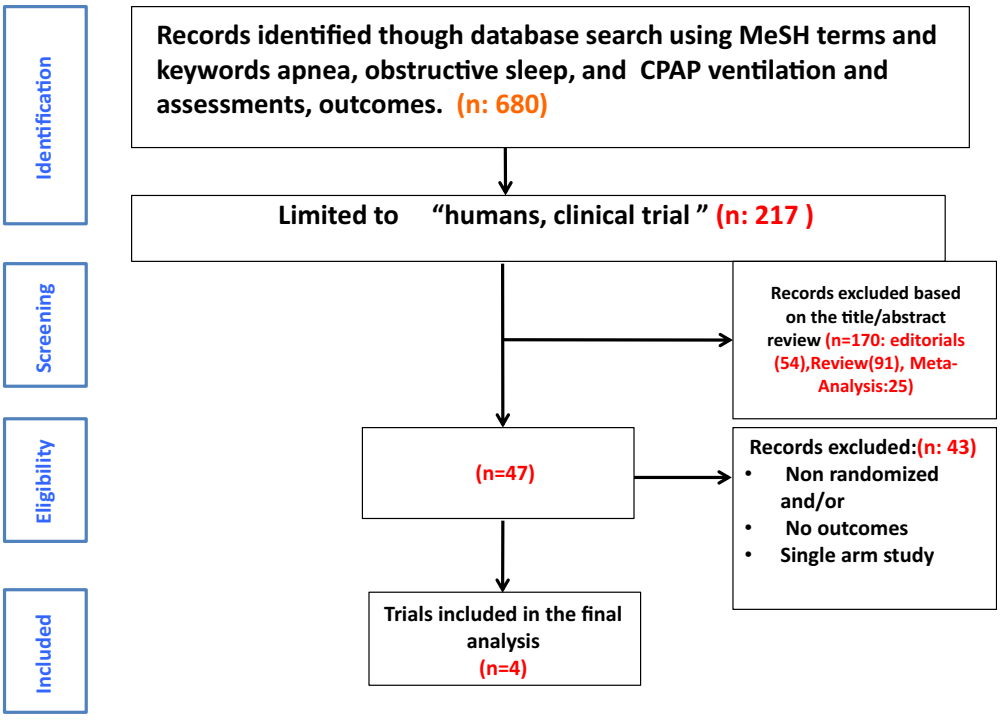

Figure 1. Flow chart for study selection.

meta-analyses were reviewed to ensure that all eligible trials are included. This meta-analysis is registered with the International Prospective Register for Systematic Reviews (CRD42016053764).[8]

To be eligible for inclusion, studies had to be RCTs; randomizing adult patients with OSA to either CPAP use or standard therapy alone (control group); and reporting outcomes of interest. We excluded trials with no outcome reports.

Two independent authors extracted comprehensive data on study characteristics, patients' demographics, and quality assessment data. The numbers of events for outcomes of interest in the 2 arms were tabulated. A third author revised the extracted data. Discrepancies were resolved by consensus among all the authors.

The quality of the included trials and the risk of bias were assessed by 2 independent reviewers using the components described by the Cochrane Collaboration.[9] This included the following: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Trials were considered as low risk of bias if meeting <2 high-risk components, and as high risk of bias if meeting >4 high-risk components. The overall quality of evidence for each outcome was further assessed using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) tool recommended by the Cochrane Handbook for Systematic Reviews of Interventions.[9]

The primary outcome assessed in this meta-analysis was major adverse cardiac events (MACE). We also assessed the following secondary outcomes: cardiac mortality angina, stroke, and transient ischemic attack. Outcomes were reported at the longest follow-up.

We pooled data using fixed effect model as minimal heterogeneity was observed in the studies. The effects of CPAP were expressed in the following terms: relative risk (RR) (95% CI) in case of dichotomous outcomes and mean difference (95% CI) in case of physical and mental competency score. Descriptive analyses were conducted using weighted frequencies for categorical variables, and weighted means with SDs for continuous variables. We used the I^2 statistics to assess heterogeneity between studies and the chi-square test with a p value <0.10 to define a significant degree of heterogeneity. Funnel plots were drawn to check for publication bias. Egger and Begg tests were conducted to assess the asymmetry of funnel plots when the number of studies was sufficient. We used Review Manager Version 5.3.5[10] and metafor R package[11] to conduct statistical analysis.

Results

As outlined in Figure 1, our initial electronic database search yielded 680 articles. On further screening, 4 RCTs met our eligibility[12–15] criteria with a total of 3,780 subjects. All trials enrolled exclusively patients with OSA. The primary outcome in all trials was MACE. The weighted mean age was 61 years and 74% were men. The weighted mean Apnea Hypopnea Index was 33.75. Details about the trials' characteristics and patients' baseline demographics are summarized in Table 1.

The risk of bias was assessed using the Cochrane Collaboration tool. All trials were deemed to have low risk of bias. Furthermore, using the GRADE assessment tool, the quality of the body of evidence for the outcomes was considered to be of high quality. The assessment of the

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