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RESEARCH ARTICLE

Continuous Positive Airway Pressure Therapy and Long-Term Outcomes in Patients with Coronary Artery Disease and Obstructive Sleep Apnea: A Meta-Analysis of Randomized Trials

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Abstract

Background: Obstructive sleep apnea (OSA) is highly common in patients with coronary artery disease (CAD) and it is a strong predictor of subsequent cardiovascular events. However, whether treatment with continuous positive airway pressure (CPAP) can decrease this risk remains controversial.

Methods: PubMed, EMBASE, the Cochrane Library, and ClinicalTrials.gov were systematically searched to identify randomized clinical trials reporting cardiovascular events from database inception to February 12, 2022.

Results: Four trials with 3043 participants were included. The median follow-up duration ranged from 3 to 4.75 years. Compared with usual care alone, CPAP was not associated with decreased MACCE risk (RR 0.96, 95% CI 0.77–1.21, P = 0.75), and the results were consistent regardless of CPAP adherence (≥4 hours/night vs. <4 hours/night, RR 0.48, 95% CI 0.20–1.16). Similarly, no significant differences were observed between groups in the risks of all-cause death (RR 0.81, 95% CI 0.52–1.26), cardiovascular death (RR 0.70, 95% CI 0.36–1.33), myocardial infarction (RR 1.08, 95% CI 0.73–1.60), revascularization (RR 1.03, 95% CI 0.77–1.38), and cerebrovascular events (RR 0.77, 95% CI 0.23–2.61).

Conclusion: Existing evidence does not support an association between CPAP treatment and decreased risk of recurrent cardiovascular events in patients with CAD and OSA, regardless of adherence to CPAP.

Keywords: continuous positive airway pressure; obstructive sleep apnea; coronary artery disease; cardiovascular outcomes; meta-analysis

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List of Abbreviations: ACS: acute coronary syndrome; AHI: apnea-hypopnea index; CABG, coronary artery bypass graft; CAD: coronary artery disease; CI: confidence interval; CPAP: continuous positive airway pressure; ESS: Epworth Sleepiness Scale; MACCEs: major adverse cardiovascular and cerebrovascular events; MI: myocardial infarction; ODI: oxygen desaturation index; OSA: obstructive

sleep apnea; PCI, percutaneous coronary intervention; RCT: randomized clinical trial; RR: relative risk; TIA: transient ischemic attack.

Background

Obstructive sleep apnea (OSA) is highly prevalent among people with cardiovascular disease, affecting approximately half of those with coronary artery disease (CAD) [1–3]. Accumulating evidence indicates an association between OSA and elevated risk of cardiovascular or cerebrovascular events in a large range of subsets of patients with CAD, despite the application of contemporary therapies [1, 4–7]. Continuous positive airway pressure (CPAP) therapy can improve sleep measures and surrogate endpoints, including blood pressure, insulin resistance, glycemic control, and left ventricular ejection fraction [8–11]. Current guidelines recommend CPAP for patients with moderate to severe OSA [12, 13]. However, several trials have unexpectedly demonstrated a neutral effect of CPAP therapy on secondary cardiovascular prevention among patients with CAD and OSA [14–16]. The most recent study addressing this issue, the Impact of Sleep Apnea syndrome in the evolution of Acute Coronary syndrome (ISAACC) study, has suggested that CPAP does not decrease cardiovascular events in patients with acute coronary syndrome (ACS) and OSA [14]. Thus, uncertainty persists regarding the associations of CPAP with hard endpoint clinical outcomes, such as cardiovascular events and death, in patients with established CAD and OSA. Therefore, we conducted a systematic review and meta-analysis including a relatively large sample to assess the association between CPAP therapy and long-term cardiovascular outcomes among patients with established CAD and OSA.

Methods

Data Sources and Search Strategies

This meta-analysis complied with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [17]. PubMed, EMBASE, the Cochrane Library, and ClinicalTrials.gov were systematically searched for randomized clinical trials (RCTs) from database inception to February 12, 2022, by two independent reviewers (R.G. and Q.G.). Both Medical Subject Heading terms and related text words "obstructive sleep apnea," "sleep apnea," "continuous positive airway pressure," "myocardial ischemia," and "coronary disease" (Supplemental Table 1) were used. The reference lists of the included studies, reviews, and reports were thoroughly screened to identify additional relevant articles.

Study Selection and Inclusion Criteria

Potentially eligible articles were identified by 2 reviewers (R.G. and Q.G.). RCTs reporting the effects of CPAP versus a control group (usual care or sham CPAP) among patients (≥18 years of age) with CAD and OSA were considered for inclusion. No language restrictions were imposed. Duplicate reports and trials lacking follow-up data on cardiovascular outcomes of interest were excluded. After removal of duplicates, animal studies, and irrelevant studies by screening of the titles and abstracts, two authors reviewed each full-text article for eligibility (R.G. and Q.G.), and a third author (X.W.) provided verification.

Data Extraction and Validity Assessment

For each included study, data were extracted independently in duplicate with a standardized electronic form. Any disagreements were resolved by consultation among authors. The following data were extracted: lead author, year of publication, time span, location, main inclusion criteria for OSA, number of participants, demographic characteristics, methods of OSA assessment, follow-up duration, and cardiovascular events.

The primary outcome was major adverse cardiovascular and cerebrovascular events (MACCEs, a composite of all-cause or cardiovascular death, myocardial infarction [MI], hospitalization for heart failure or unstable angina, repeated revascularization, stroke/transient ischemic attack [TIA], or cerebrovascular death). Secondary outcomes included all-cause death, cardiovascular death, MI, revascularization, and cerebrovascular events (stroke, TIA, and cerebrovascular death). Definitions of events across the included studies were consistent during their study

periods, ensuring uniformity in defining MACCEs. Endpoints were assessed at the longest follow-up.

Two investigators (R.G. and Q.G.) independently evaluated the quality of each included trial with the Cochrane Collaboration tool [18] for assessing risk of bias in RCTs. Random sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting, and other sources of bias were evaluated and classified as low, unclear, or high. Any disagreement was resolved by discussion and consultation with a third reviewer (X.W.).

Data Synthesis and Analysis

The pooled effects of CPAP were quantified by the relative risk (RR) with a confidence interval (CI) of 95%. A two-sided P value of <0.05 was considered significant. Because we considered the included studies to be sufficiently similar, we used a random-effects model (Mantel-Haenszel) to better estimate the effect size of different studies with small samples, and to provide more conservative estimates regardless of the presence of significant heterogeneity. The heterogeneity of results among studies was assessed with the I^2 statistic with a significance threshold of $P < 0.10$, whereas heterogeneity was considered low if $I^2 < 25\%$, moderate if I^2 was between 26% and 75%, and high if I^2 was > 75%. Sensitivity analyses were performed by exclusion of each study, one at a time, to investigate the influence of each study on the pooled estimates. Statistical analyses were performed in RevMan 5.4 and Stata 12.0.

Results

Characteristics of the Included Studies

The literature search yielded 1761 articles, from which 158 duplicates were removed, and 1439 were excluded after title/abstract review. After screening of the full-texts, four studies involving 3043 patients and reporting outcomes of interest met the inclusion criteria (Figure 1).

The study characteristics are listed in Table 1. All studies enrolled patients with CAD and OSA with long-term follow-up data. The mean follow-up duration was 3.7 years in the SAVE study and ranged from 3 to 4.75 years in the other three studies. Patients with OSA, defined by an apnea-hypopnea index [AHI] [9, 14, 15] ≥ 15 or oxygen

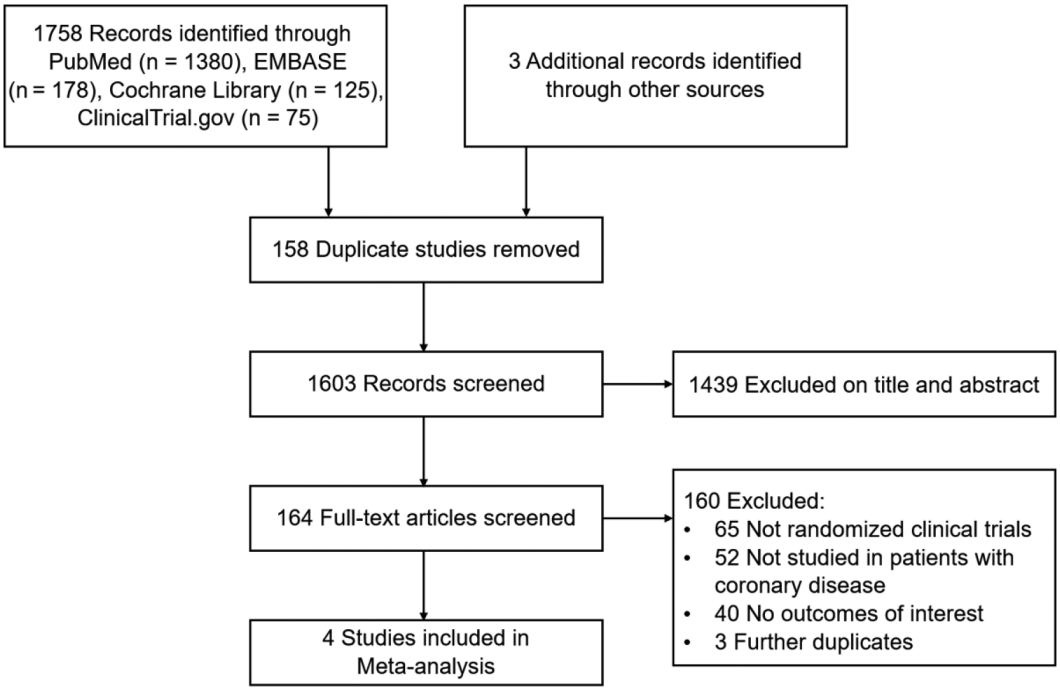

Figure 1 Flow Chart of the Study Selection Process for Meta-Analysis.

Table 1 Basic Characteristics of the Included Trials.

	Huang 2015	McEvoy 2016 (SAVE)	Peker 2016 (RICCADSA)	Manuel 2019 (ISAACC)
Study design, location, years	**Single-center in China, 2009–2012**	**International multi-center, 2008–2013**	**Single-center in Sweden, 2005–2010**	**Multi-center in Spain, 2011–2018**
Main inclusion criteria	AHI≥15, ESS<15; CAD	ODI≥12, ESS≤15; CAD	AHI≥15, ESS<10; post-PCI or CABG	AHI ≥15, ESS ≤10; ACS
Sample Size, n				
CPAP	36	732	122	629
Control	37	739	122	626
Mean age, yrs.	62.4	61.0	66.0	60.0
Male, %	82.2	81	84.1	84
Mean BMI, kg/m^2	27.7	29.0	28.5	29.5
Mean AHI, events/h	28.5	29.3	28.8	36
Mean ESS, points	8.8	7.4	5.5	5.32
Average use of CPAP, h/night	4.5±1.1 (at least 4)	3.3±2.3	5.8±1.7 (first year, n = 76)	2.78±2.6
Median follow-up, yrs.	3	3.7	4.75	3.35
OSA assessment	Polysomnography	Portable polygraph	Polysomnography	Portable polygraph
Outcomes of interest (MACCEs)	MI, hospitalization for heart failure, repeated revascularization, stroke, and cardiovascular or cerebrovascular mortality	MI, cardiovascular death, stroke/TIA, hospitalization for unstable angina, or heart failure	MI, repeat revascularization, stroke, or cardiovascular mortality	MI, cardiovascular death, non-fatal stroke, hospitalization for heart failure or unstable angina, or TIA

AHI, apnea-hypopnea index; ESS, Epworth Sleepiness Scale; CAD, coronary artery disease; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; OSA, obstructive sleep apnea; BMI, body mass index; CPAP, continuous positive airway pressure; MACCEs, major adverse cerebrovascular and cardiovascular events; MI, myocardial infarction; TIA, transient ischemic attack.

desaturation index [ODI] [16] ≥ 12, underwent primary assessment via overnight polysomnography in two studies [9, 15], and through validated portable diagnostic devices in two other studies [14, 16]. Average nightly CPAP use ranged from 2.78 to 6.6 hours. The risk of bias in the included studies is shown in Supplemental Table 2. In general, blinding of patients appeared to be difficult because of the nature of the intervention.

Primary Outcomes

A total of 532 MACCEs (264 in the CPAP group and 268 in the control group) were reported. Treatment with CPAP compared with standard care was not associated with a diminished risk of MACCE (RR 0.96, 95% CI 0.77–1.21, P = 0.75) (Figure 2). Additionally, three studies [9, 14, 15] reported results for participants with adequate use of CPAP (≥4 hours/night). However, in the stratified analysis, the results remained consistent (RR 0.48, 95% CI 0.20–1.16, P = 0.10) (Figure 3).

Secondary Outcomes

Data extracted from three trials [9, 15, 16] involving a total of 1572 patients were extracted to evaluate the effects of CPAP on the outcomes of all-cause death (RR 0.81, 95% CI 0.52–1.26, P = 0.35), cardiovascular death (RR 0.70, 95% CI 0.36–1.33, P = 0.28), MI (RR 1.08, 95% CI 0.73–1.60, P = 0.70), revascularization (RR 1.03, 95% CI 0.77–1.38, P = 0.82), and cerebrovascular events (RR 0.77, 95% CI 0.23–2.61, P = 0.68). No association was observed between CPAP and decreases in these individual clinical events (Figure 4).

Sensitivity Analysis

Evidence of moderate and high heterogeneity (I^2 = 36%) was observed for MACCEs among the included studies (Figure 2). We conducted leave-one-out sensitivity analyses, systematically excluding one study at a time to evaluate the influence of each individual study on the results. Through this analysis, we identified the SAVE trial as the source of heterogeneity. Exclusion of that study from the

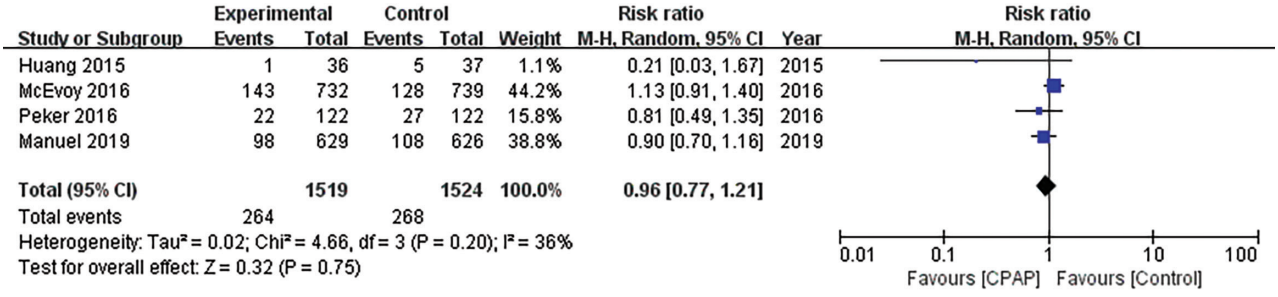

Figure 2 Meta-Analysis of the Association of CPAP with MACCEs.
Abbreviations: CPAP, continuous positive airway pressure; M-H, Mantel-Haenszel random-effects model; CI, confidence interval.

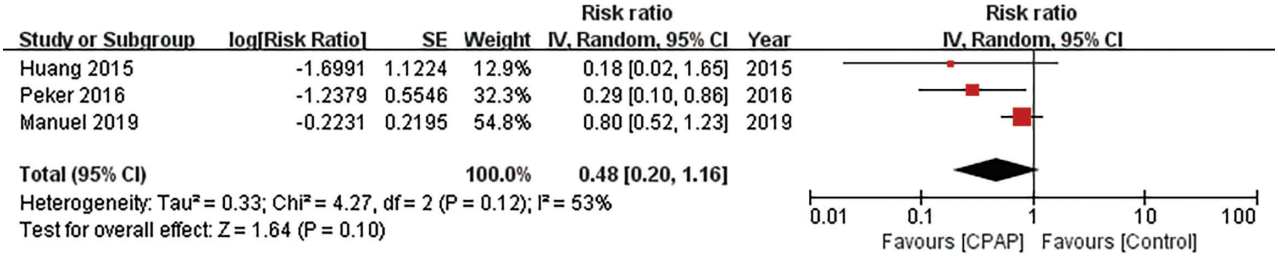

Figure 3 Meta-Analysis of Association of Adequate use of CPAP (≥4 hours/night) with MACCEs.
Abbreviations: CPAP, continuous positive airway pressure; IV, inverse variance random-effects model; CI, confidence interval.

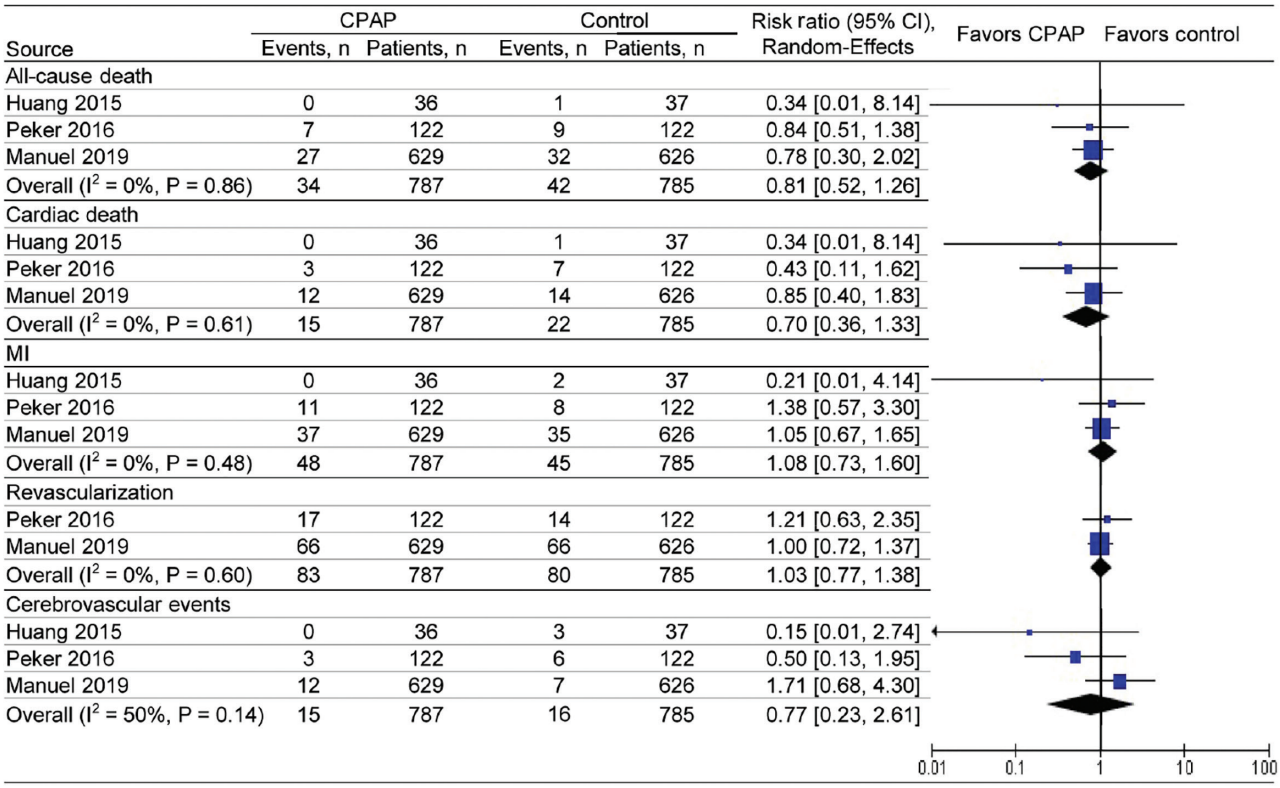

Figure 4 Meta-Analysis of Association of CPAP with Individual Cardiovascular and Cerebrovascular Events. Abbreviations: CPAP, continuous positive airway pressure; CI, confidence interval; MI, myocardial infarction.

analysis decreased the study heterogeneity (I^2 = 0%, P = 0.37), whereas the combined RR remained insignificantly protective (RR 0.87, 95% CI 0.70–1.09, P = 0.22).

Discussion

The present study, to our knowledge, is the most up-to-date meta-analysis of RCTs investigating the effectiveness of CPAP in patients with CAD and OSA, including the most recent ISAACC trial [14] designed to investigate this subset of patients. Previous meta-analyses of observational studies or highly heterogeneous RCTs have demonstrated controversial effects of CPAP in patients with OSA and any cardiovascular disease [6, 19, 20]. The current meta-analysis focused on patients with established CAD and OSA. We pooled data from four RCTs involving a total of 3043 participants with long-term follow-up. Our findings indicated that CPAP, as a measure of secondary prevention, did not prevent MACCEs in patients with CAD with OSA, regardless adherence to CPAP (use for more or less than 4 hours/night). In addition, no additional benefits of CPAP were observed in preventing subsequent all-cause death, cardiovascular death, MI, revascularization, and cerebrovascular events (stroke, TIA, and cerebrovascular death).

CPAP use for ≥4 hours/night was widely considered to be most effective and clinical meaningful for cardiovascular and cerebrovascular outcomes in patients with OSA [15, 16, 21–23]. Adjusted on-treatment analysis of the RICCADSA trial showed that, compared with CPAP use < 4 hours/night or no CPAP, CPAP use ≥4 hours/night was associated with significant cardiovascular risk reduction (HR 0.29; 95% CI 0.1–0.86; P = 0.026) [15]. Furthermore, propensity-score matched analysis of the ISAACC study indicated an HR of 0·80 (95% CI 0.52–1.23; P = 0.32) for incidence of cardiovascular events in the adherent subgroup [14, 24]. Stratified analysis (≥4 hours/night) of the meta-analysis did not show a positive effect of CPAP on MACCEs. Whether this time course or threshold of CPAP therapy is optimal

or appropriate to decrease cardiovascular risk requires further investigation.

The neutral results of recent CPAP randomized trials in demonstrating protection against vascular events and death may have several explanations. First, OSA is a potential cause of artery atherosclerosis and endothelial dysfunction [25–27], but epidemiological evidence has indicated that OSA has lower adverse effects on coronary circulation than cerebrovascular circulation [28]. Furthermore, protective collateral vessels have been suggested to develop in the presence of OSA [29], and CPAP does not decrease inflammatory biomarkers in patients with stable CAD and OSA [30]. Therefore, CPAP therapy may have more profound benefits in primary cardiovascular prevention rather than secondary prevention. Second, notably, all trials included in our analysis were completed in the past decade. Contemporary therapies such as extensive lipid-lowering and antihypertensive drugs, antiplatelet therapy, and new-generation drug-eluting stents, might hinder the detection of additional cardioprotective effects of treatment of OSA with CPAP. Third, the lack of benefits of adequate use of CPAP might be due to the use time and timing of CPAP treatment. The average CPAP use time was typically between 2 and 5 hours (only half the total sleep time). The duration of CPAP use may not be sufficient to reduce the risk of cardiovascular and cerebrovascular events. Another explanation may be the timing of CPAP use. OSA during REM sleep is associated with longer apnea length [31, 32], and patients who have OSA only during REM sleep show poorer CPAP adherence than other patients with OSA [33]. Fourth, because this study was a meta-analysis of RCTs, the results might have been affected by biases inherent to RCTs, including selection bias and ethical issues. Patients with excessive daytime sleepiness according to different thresholds (ESS > 10 or 15) in the four RCTs were all excluded, because assigning those patients to a control group would have been unethical and unreasonable. However, patients with OSA presenting excessive sleepiness have the greatest cardiovascular risk and are mostly likely to benefit from treatment with CPAP [34]. Therefore, real-world observational data and analysis techniques, such as using propensity scores to overcome selection bias, have been suggested as alternative approaches [35]. The final potential explanation may be population heterogeneity. The inclusion criteria varied from chronic to acute phase CAD, including both acute or elective PCI and CABG.

Moreover, our previous prospective cohort study [36] has demonstrated that OSA is associated with a 2.5-fold elevated risk of 1-year MACCE after ACS in patients with diabetes mellitus but not in patients without diabetes mellitus. Other studies have reported that OSA might have deleterious effects specifically in certain phenotypes of patients with CAD [37]. The negative findings are most likely to be due to the diverse patient phenotypes, only some of which can benefit from CPAP therapy [38]. Therefore, targeted selection among homogeneous patients with CAD to identify those at high risk (e.g., with ACS, MI, ST-segment-elevation MI, or complication with diabetes mellitus) and stand to benefit from CPAP is crucial.

Study Limitations

Several potential study limitations should be acknowledged. First, a considerable degree of heterogeneity existed among studies, partly because of differences in populations, co-morbidity burden, sample size, methods of CPAP application, and sleep evaluation. Second, statistically moderate heterogeneity was found in the meta-analyses. Sensitivity analysis indicated that differences in OSA definitions and assessments contributed to the variance among studies. ODI was used exclusively by the SAVE trial, whereas the other studies used AHI. Third, the risk estimates of individual cardiovascular or cerebrovascular events might have been insufficient because of relatively smaller subpopulations in the included studies and inconsistent event definitions. Fourth, because only four RCTs were included, a meta-regression analysis and funnel plot analysis could not be used to assess possible publication bias. Finally, the performance bias was considered high, because these RCTs did not blind patients, given the nature of the intervention.

Conclusions

In summary, current evidence does not support that CPAP therapy can prevent future cardiovascular and

cerebrovascular events in patients with CAD with OSA, regardless of adherence to CPAP. However, drawing a conclusion may be premature, and real-world cohort studies and innovative investigation strategies are warranted in the future.

Data Availability Statement

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

Ethics Statement

Not applicable.

Author Contributions

S.N., X.W., and R.G. contributed to the conception or design of the study. R.G., Q.G., W.H., J.F., and X.W. contributed to the acquisition, analysis, or interpretation of data for the work. R.G., Q.G., and X.W. wrote the draft of the manuscript. All authors critically revised and approved the final manuscript, and agree to be accountable for all aspects of work, ensuring integrity and accuracy.

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Competing Interests

The authors declare that they have no competing interests.

Supplementary Material

Supplementary materials are available at the following link https://cvia-journal.org/wp-content/uploads/2023/12/Supplemental_Material-20221215.pdf

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