Research paper

Impact of continuous positive airway pressure ventilation on cardiovascular outcomes among patients with obstructive sleep apnea: A meta-analysis of randomized trials

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ABSTRACT

Background: The impact of continuous positive airway pressure (CPAP) on cardiovascular outcomes among patients with obstructive sleep apnea (OSA) is controversial.
Objective: To evaluate the impact of CPAP on reducing cardiovascular outcomes in patients with OSA.
Methods: We performed a computerized search of MEDLINE, EMBASE and COCHRANE databases through April 2021 for randomized trials evaluating the impact of CPAP versus control on cardiovascular outcomes in patients with OSA. Summary estimates were reported using both fixed and random effects model. The main study outcome was major adverse cardiac events (MACE).
Results: The final analysis included 8 randomized trials with total of 5684 patients. The weighted mean follow-up was 42.6 months. There was no difference between the CPAP and control groups in the risk of MACE (14.4% versus 14.8%, risk ratio [RR]: 0.97; 95% confidence interval [CI]: 0.85 to 1.10; p = 0.60; I^2 = 21%). Subgroup analysis suggested that CPAP was associated with lower MACE (by 36%) in CPAP-adherent patients ($\geq$4 h/night) ($P_{interaction}$ = 0.08). There was no difference between the CPAP and control groups in the risk of all-cause mortality, cardiovascular mortality, acute stroke, acute myocardium infarction or hospitalizations for angina.
Conclusions and relevance: CPAP use might not be associated with lower cardiovascular events among patients with OSA. However, patients adherent to CPAP ($\geq$4 h/night) might derive a benefit on cardiovascular outcomes. Future studies are warranted to evaluate the impact of CPAP in reducing cardiovascular events among patients with severe OSA and with optimal adherence rates to CPAP therapy.

1. Introduction

Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder, which is associated with repetitive collapse of the upper airway during sleep [1]. OSA is estimated to be prevalent in 40 to 60% of patients diagnosed with cardiovascular disease [1,2]. Studies have demonstrated an independent association between OSA with multiple forms of cardiovascular disease; including hypertension, coronary artery disease (CAD), heart failure, atrial fibrillation, stroke and sudden cardiac death [1–3]. Continuous positive airway pressure

(CPAP) is an established treatment for OSA which reduces hypoxemic events and improves symptoms [1]. Although the use of CPAP treatment in OSA patients is associated with improvement of blood pressure and glycemic control; the impact of CPAP on cardiovascular events in patients with OSA remains controversial [4,5]. While some randomized studies failed to demonstrate benefit for CPAP in reducing cardiovascular outcomes, previous meta-analyses suggested the lack of beneficial outcomes is related to poor CPAP adherence [6,7]. Recently, the ISAACC study (Impact of Sleep Apnea syndrome in the evolution of Acute Coronary syndrome) did not show a significant benefit for CPAP in reducing cardiovascular events among patients with OSA and recent acute coronary syndrome [8]. In order to examine the totality of available data, we conducted this meta-analysis of randomized controlled trials to evaluate the impact of CPAP on reducing cardiovascular outcomes in patients with OSA.

2. Methods

2.1. Data sources and search strategy

We performed a computerized search of MEDLINE, EMBASE and COCHRANE databases without language restrictions through January 2021, using the terms "obstructive sleep apnea", "CPAP ventilation", and "cardiovascular outcomes" separately and in combination to identify any randomized clinical trials that evaluated the cardiovascular outcomes with CPAP use among patients with OSA. A similar search strategy was also done for abstracts of the major scientific sessions (American College of Cardiology, European Society of Cardiology and the American Heart Association) up to March 2020. We further screened the bibliographies of the retrieved studies, prior meta-analyses as well as ClinicalTrials.gov for any relevant studies not retrieved through the initial search. This meta-analysis was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplemental Table 1) [9].

2.2. Selection criteria

We included randomized clinical trials that evaluated the comparative outcomes of using CPAP versus control group (i.e. conventional medical therapy alone), in patients with OSA and reported cardiovascular endpoints. We excluded non-randomized studies and studies on central sleep apnea.

2.3. Data extraction

The study design, baseline characteristics, intervention strategies, main outcomes and other study characteristics were extracted by 2 independent investigators (A.E and M.M). Discrepancies among investigators were resolved by consensus.

2.4. Outcomes

The primary outcome of the study was major adverse cardiac events (MACE), as defined per each study. The secondary outcomes included all-cause mortality, cardiovascular mortality, acute myocardial infarction, acute stroke and hospitalizations for angina. Outcomes were reported at the longest follow-up.

2.5. Assessment of the quality of the included studies

The quality of included trials was assessed using the Cochrane bias risk assessment tool based on 7 criteria; random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias [10].

2.6. Statistical analysis

Data were pooled using fixed-effects and random-effects models by using the Mantel-Haenszel and inverse variance methods. Results using fixed-effects model were adopted as main model for our study since the degree of statistical heterogeneity for the outcomes was low. We also reported the results using random-effects models as a secondary analysis. Statistical heterogeneity across trials was assessed by I^2 statistics, with I^2 statistic values <25%, 25% to 50%, and >50% considered as low, moderate, and high degree of heterogeneity, respectively [11]. Outcome measures were described using mean differences for continuous variables and risk ratio for categorical variables. Sub-group analysis was performed for the primary outcome in studies with mean CPAP ≥4 h/night, versus those with mean CPAP <4 h/night. A sensitivity analysis were conducted after excluding studies with unclear or high risk of bias. Meta-regression analyses were pre-specified for the primary outcome according to age, body mass index, apnea/hypopnea index (AHI) score and Epworth Sleepiness Scale (ESS) score to evaluate for any modification in the outcome with baseline characteristics. Since the number of included studies was <10, we could not assess for publication bias [12]. P-values were 2-tailed and considered statistically significant if <0.1 when evaluating subgroup interaction, and ≤0.05 in all other analysis. Statistical analyses were conducted using RevMan 5.0 software (Cochrane Collaboration, Oxford, UK).

3. Results

3.1. Included studies

Study selection process is outlined in Fig. 1. The final analysis included 8 randomized studies with total of 5684 patients. The weighted follow up was 42.6 months [1,8,13–18]. The baseline characteristics of included studies are outlined in Table 1. The weighted mean age was 61.1 years, 77.7% were men and 28.4% had diabetes. The weighted mean CPAP use across the studies was 3.4 h per night. Studies with average CPAP usage ≥4 h/night included Parra et al., Barbe et al., Huang et al., and Peker et al. [13,14,16,17] All studies included patients with known cardiovascular disease, except for the study by Barbe et al. which excluded patients with prior cardiovascular events [16].

The quality of included studies is outlined in Supplemental Table 2. All studies were open label, with no blinding of participants to allocated treatment. For all other risk of bias criteria, all studies were deemed to be of low-risk of bias, except for the study by Parra et al. [13], due to lack of data on blinded outcome assessment.

3.2. Primary outcome

The main study outcome of MACE was analyzed in all 8 studies (Supplemental Table 3). There was no overall difference between the CPAP and control groups (14.4% versus 14.8%, RR 0.97; 95% CI 0.85 to 1.10; P = 0.60; I^2 = 21%) (Fig. 2; panel A). Sensitivity analysis excluding the study with lack of data on blinded outcome assessment (Parra et al) showed similar results (RR 0.99; 95% CI 0.87 to 1.12; P = 0.52; I^2 = 0%) [13]. In a subgroup analysis according to CPAP adherence (defined as ≥4 h/night), CPAP was associated with lower MACE in the CPAP-adherent subgroup (9.9% incidence of MACE), compared with CPAP non-adherent subgroup (15.5% incidence of MACE) ($P_{interaction}$ = 0.08), with estimated 36% lower risk of MACE in CPAP-adherent patients (Fig. 2; panel B). Meta-regression analysis did not reveal any evidence of effect modification based on age (P = 0.58), body mass index (P = 0.40), AHI score (P = 0.13) or ESS score (P = 0.76).

3.3. Secondary outcomes

All studies reported all-cause mortality, with no observed difference between CPAP and control groups (RR 0.93; 95% CI 0.71 to 1.23; P =
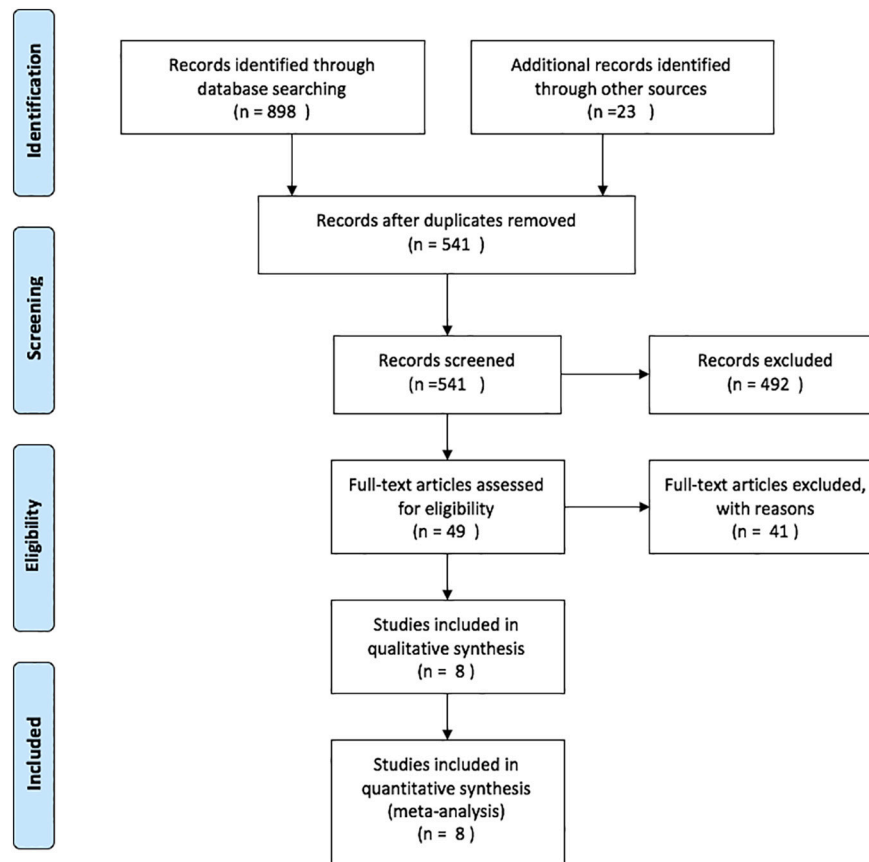
Fig. 1. Study flow sheet.

Table 1
Baseline characteristics of included randomized trials.

Study	Year	Number of patients (CPAP/Control)	Key inclusion criteria	Mean age, years (CPAP/Control)	Male% (CPAP/Control)	HTN% (CPAP/Control)	DM% (CPAP/Control)	Mean BMI (CPAP/Control)	Mean AHI (CPAP/Control)	Mean ESS score (CPAP/Control)	Average CPAP use (hours per night)
Parra et al.	2011	57/69	CVD/AHI ≥ 20	63.7/65.5	41/48	60.0/63.2	38.2/36.8	30.2/28.8	38.4/38.4	8.3/7.3	Mean 5.3 (±1.9)
Barbe et al	2012	358/367	AHI ≥ 20/h, ESS ≤ 10	52.0/51.8	87.7/83.6	53.2/50.0	NR	31.3/31.1	42/35	6.5/6.5	Median 5.00 (IQR 2.18-6.25)
Craig et al.	2012	195/196	ODI > 7.5 per hour, ESS ≥ 9	57.9/57.6	78.5/77.6	77.4/76.0	11.8/20.4	32.2/32.5	NR	7.9/8.0	Median 2 h, 39 min.
McMillan et al	2014	140/138	New OSA/ODI > 7.5 per hour, ESS ≥ 9	70.9/71.3	86/79	70.0/75.0	29.0/31.0	33.9/33.6	28.1/29.4	11.6/11.6	Median 1 h 26 min.(IQR 4 min - 4 h 45 min)
Huang et al	2014	42/41	AHI >15 + CVD/HTN	62.7/62.0	86.5/77.8	100/100	37.8/33.3	27.5/27.9	28.7/28.3	8.3/9.3	Mean 4.5 (±1.1)
McEvoy et al	2016	1346/1341	CAD or CVD/ODI ≥ 12	61.3/61.2	81.1/80.7	78.7/78.2	30.2/29.4	28.8/28.5	29.0/29.6	7.3/7.5	Mean 3.3 (±2.3)
Perker et al	2016	122/122	Revascularized CAD/AHI ≥ 15	65.5/66.5	82/86	68.9/59	27.9/20.5	28.4/28.5	28.3/29.3	5.5/5.5	Mean 6.6 (±1.3)
de-la-Torre et al	2019	633/631	Recent ACS/EES ≤ 10	59.9/60.7	84/85	56/57	27.0/25.0	29.6/29.4	36.4/35.5	5.36/5.28	Mean 2·78 (±2·73)

CPAP = Continuous positive airway pressure; CVD = Cardiovascular disease; AHI = apnea/hypopnea index; ESS = Epworth Sleepiness Scale; ODI = oxygen desaturation index; HTN = hypertension; CAD = coronary artery disease; ACS = acute coronary syndrome; DM = diabetes mellites.

0.62; $I^2 = 0\%$). Cardiovascular mortality was analyzed in 5 studies, with no observed difference between CPAP and control groups (RR 0.92; 95% CI 0.60 to 1.42; $P = 0.71$; $I^2 = 17\%$). Acute myocardial infarction was reported in 7 studies and showed no significant difference between CPAP and control groups (RR 1.01; 95% CI 0.76 to 1.36; $P = 0.93$; $I^2 = 24\%$). Acute stroke was reported in all studies, with no observed difference between the CPAP and control groups (RR 0.96; 95% CI 0.72 to 1.28; $P = 0.78$; $I^2 = 0\%$). Angina was reported in 6 studies with no observed difference between CPAP and control groups (RR 1.00; 95% CI 0.81 to 1.24; $P = 1.00$; $I^2 = 0\%$) (Fig. 3). Similar results were obtained
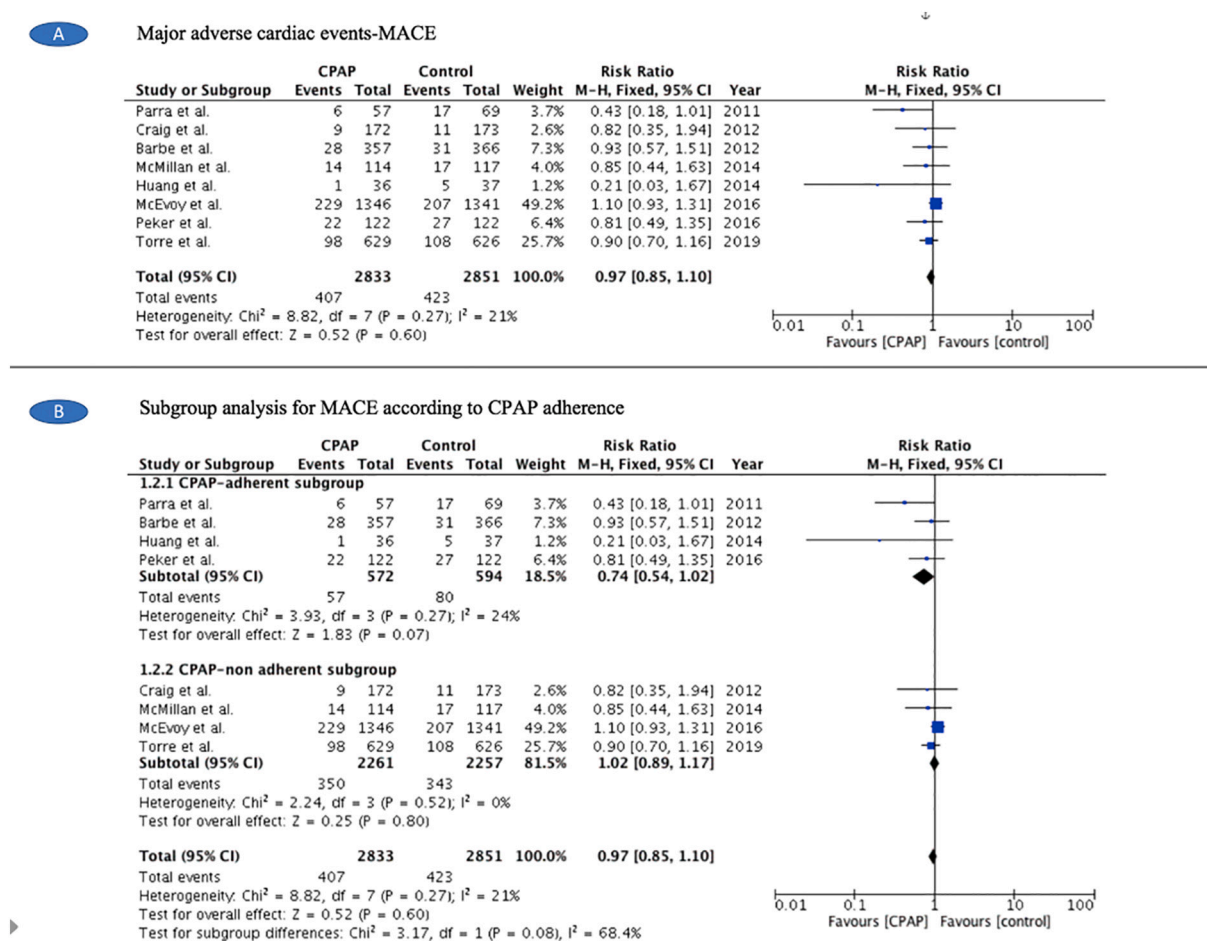
Fig. 2. Panel A: Forest plot for MACE in CPAP versus control groups; Panel B: Forest plot for MACE according to CPAP adherence.

when analyzing using random-effects model (Supplemental Table 4).

4. Discussion

In this updated meta-analysis of 8 randomized clinical trials including 5684 patients with OSA, we sought to evaluate the impact of CPAP on cardiovascular events. The principal findings of this analysis were: 1) there was no significant difference between the CPAP and control groups in occurrence of MACE at a mean follow up of 42.6 months; 2) On subgroup analysis, CPAP use was associated with lower MACE among the CPAP-adherent subgroup (≥4 h/night), compared with CPAP non-adherent subgroup (<4 h/night); 3) there was no significant difference between the CPAP and control groups in terms of all-cause mortality, cardiovascular mortality, acute myocardial infarction, acute stroke or hospitalizations for angina.

Previous meta-analyses have been conducted evaluating role of CPAP in reducing cardiovascular outcomes in patients with OSA. In their meta-analysis, Yu et al. reported no significant effect for CPAP in improving cardiovascular outcomes, regardless of adherence to CPAP [19]. However, that analysis was not exclusive for OSA, and included patients with central sleep apnea as well. Abuzaid et al. conducted a meta-analysis inclusive of 4 randomized trials, and found that the use of CPAP was not associated with improved cardiac outcomes compared to medical therapy alone, except in adherent patients to CPAP (>4 h/night) [7]. Similar results were also demonstrated in the meta-analysis by Khan et al., with beneficial impact of CPAP on cardiovascular events only in CPAP adherent patients [6]. The current meta-analysis represents the most comprehensive analysis to-date which includes the totally of available randomized data to-date evaluating outcomes of

CPAP in patients with OSA, including the recently published ISAAC study inclusive of ≈1300 patients. Moreover, the current analysis represents the largest meta-analysis to-date exclusively evaluating outcomes of CPAP among patients with OSA and not including those with central sleep apnea [8]. The pathophysiology behind cardiovascular complications among patients with OSA is unique compared with patients with central sleep apnea [20,21]. Many patients with central sleep apnea have underlying severe LV systolic dysfunction or stroke, and are at unique higher risk for further cardiovascular events irrespective of CPAP treatment [20,21]. Hence, the magnitude of benefit from CPAP therapy would differ between OSA and central sleep apnea, and combining both conditions might dilute the actual benefits from CPAP therapy.

Overall, our analysis showed that CPAP was not associated with improved cardiovascular outcomes when compared with medical therapy alone. The lack of benefit for CPAP in reducing cardiovascular events in OSA was noted in the main randomized trials in this topic as well as in previous meta-analyses [6,7]. The Sleep Apnea Cardiovascular Endpoints (SAVE) trial is the largest trial to-date, inclusive of 2717 patients with OSA. After a follow up of 44 months, the investigators found no significant difference in major adverse cardiac or cerebral events in the CPAP group compared with the usual care group [1]. The recently published ISAAC study, evaluated the impact of CPAP treatment on non-sleepy OSA patients admitted for acute coronary syndrome. After 3.3 years, the authors did not find a significant difference in cardiovascular events among patients treated with CPAP versus standard of care [8].

Our analysis suggested possible benefit for CPAP in reducing cardiovascular events among patients who are adherent to CPAP, however, it is important to note that this was based on a subgroup analysis and
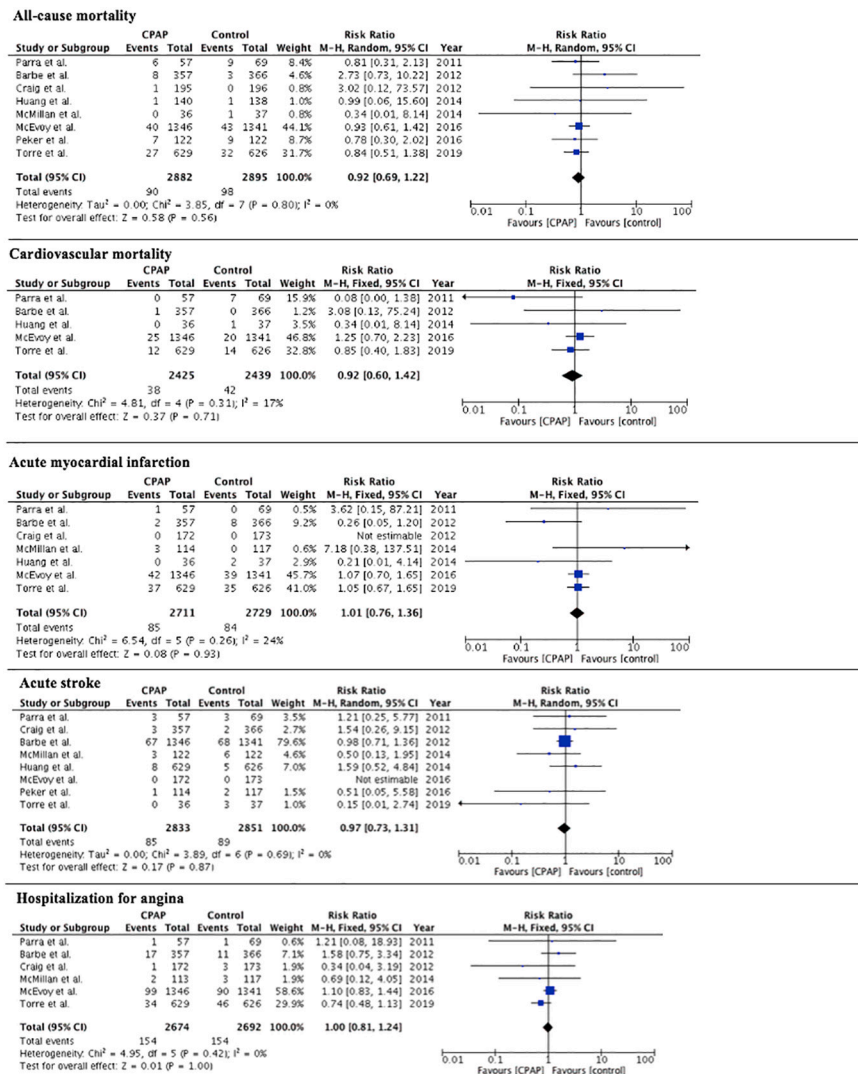
Fig. 3. Forest plot for all-cause mortality, cardiovascular mortality, acute myocardial infarction, acute stroke and hospitalizations for angina in CPAP versus control groups.

should be interpreted as a hypothesis generating finding. The RICCADSA (Randomized Intervention with Continuous Positive Airway Pressure in CAD and OSA) was a multicentered trial including 244 patients with recently revascularized CAD and OSA who were randomized to CPAP versus standard of care. Similar to other trials, the RICCADSA showed no significant difference in long term cardiovascular events between CPAP and standard of care. However, when analyzed by CPAP adherence, the authors found significant a reduction in cardiovascular events at 57 months among the group of patients who used CPAP ≥4 h/night compared to non-CPAP adherent or usual care group of patients (2.3% versus 5.3%, respectively). The disparity in outcomes according to adherence to CPAP in patients with OSA was also suggested in post-hoc analysis of the studies by Barbe et al. and Sorriano et al. [16,22] In a post-hoc analysis of the HIPARCO-2 trial, Sorriano et al. evaluated the cardiovascular events in 163 patients with OSA according to CPAP adherence [22], and found that among patients who used CPAP ≥4 h/night, there was a 3-fold reduction in risk of cerebrovascular events after a follow up period of 58 months [22]. Similarly, subgroup analyses from some of the previous meta-analyses suggested similar benefit for CPAP adherence in reducing major cardiac events in patients with OSA [6,7].

The associated increased cardiovascular events with OSA has been attributed to several pathophysiological mechanisms. The intermittent airway obstruction with ensuing hypoxemia and intra-thoracic pressure

swings are probably the main inciting pathological mechanisms [23,24]. This results in secondary enhanced systemic inflammatory response, oxidative stress, sympathetic activation, endothelial dysfunction and hypercoagulable state [23]. Other suggested mechanisms include disturbances in cerebral autoregulation and pro-atherogenic state [23,24]. By reducing hypoxemic burden and obstructive episodes, CPAP treatment was proven to improve symptoms as well as other surrogate outcomes such as blood pressure and glycemic control [4,22]. Hypothetically, counteracting the aforementioned mechanisms, CPAP treatment is also expected to reduce risk of cardiovascular events among patients with OSA.

The lack of an overall benefit for CPAP therapy in our analysis should be interpreted while considering certain limitations in the included randomized trials. First, the majority of studies have mostly included non-severe OSA. The largest of the included trials, the SAVR trial, excluded patients with severe daytime sleepiness or severe hypoxemia. Prior observational studies suggested that patients with severe OSA carry the highest risk of cardiovascular events; hence, the magnitude of benefit of CPAP could be underestimated by eliminating those patients [1,25]. Second, the magnitude of benefit from CPAP might differ in primary prevention versus secondary prevention in patients with OSA. Most of the randomized trials included patients with established cardiovascular events, and high cardiac risk factors, in whom OSA might

not play a substantial risk factor compared to other lower risk population. Therefore, the role of CPAP in primary prevention of cardiovascular events cannot be determined from the current randomized data. Finally, many of the included studies suffered poor adherence to CPAP therapy among the included patients [1,8,15,18,22]. Our subgroup analysis is hypothesis generating and suggests that adherence to CPAP may play an important role in determining the impact of CPAP on cardiovascular outcomes. We hypothesize that achieving a clinically meaningful reduction in cardiovascular events mandates application of CPAP 4 h or more daily, in order to reverse airway obstruction, hypoxemia and ensuing detrimental mechanisms.

Overall, better designed randomized trials are warranted in order to appreciate the true role of CPAP therapy on cardiovascular events among patients with OSA. Proposedly future trials should pursue alternate designs in order to maximize CPAP adherence rates among participants, and importantly enroll sleepy patients with OSA who would hypothetically have more benefit from CPAP therapy [26].

The current analysis has several limitations. The inclusion criteria and definition of primary endpoints had some variations across the included studies. Certain outcomes were applicable for evaluation in only a portion of included studies. The lack of patient-level data precluded the identification of patient related characteristics which might drive a potential benefit. It would have been of great value to examine the outcomes with CPAP therapy among specific subgroup of patients such as those with diabetes, hypertension, heart failure or according to BMI. However, data regarding these specific subgroups were not available in the included trials. Despite those limitations, there was low degree of heterogeneity in the assessment of all study outcomes ($I^2 < 25\%$). Also, we adopted random and fixed effects model, as well as multiple meta-regression, sensitivity and subgroup analyses to reduce the impact of potential bias.

5. Conclusion

In this meta-analysis of randomized clinical trials, the utilization of CPAP in patients with OSA was not associated with reduced cardiovascular events. On subgroup analysis, CPAP was associated with a reduction in cardiovascular events among patients using CPAP $\geq$4 h/night. Future studies are warranted to better evaluate the beneficial impact of CPAP in reducing cardiovascular events among patients with severe OSA and with optimal adherence rates to CPAP therapy.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2021.100056.

Declaration of competing interest

Ayman Elbadawi,[a] MD, Islam Y. Elgendy,[b] MD, Mina Shnoda,[c] MD, Ahmed S. Abuzaid,[d] MD, Kirolos Barssoum,[e] MD, Hend I. Shahien,[a] MD, Michael Megaly,[f] MD, Wissam I. Khalife,[a] MD, Martha Gulati,[g] MD, Hani Jneid,[j] MD, have no conflict of interest to declare.

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