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Association of Positive Airway Pressure With Cardiovascular Events and Death in Adults With Sleep Apnea
A Systematic Review and Meta-analysis

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Supplemental content

IMPORTANCE Sleep apnea (obstructive and central) is associated with adverse cardiovascular risk factors and increased risks of cardiovascular disease. Positive airway pressure (PAP) provides symptomatic relief, whether delivered continuously (CPAP) or as adaptive servo-ventilation (ASV), but the associations with cardiovascular outcomes and death are unclear.

OBJECTIVE To assess the association of PAP vs control with cardiovascular events and death in patients with sleep apnea.

DATA SOURCES AND STUDY SELECTION MEDLINE, EMBASE, and the Cochrane Library were systematically searched from inception date to March 2017 for randomized clinical trials that included reporting of major adverse cardiovascular events or deaths.

DATA EXTRACTION AND SYNTHESIS Two authors independently extracted data using standardized forms. Summary relative risks (RRs), risk differences (RDs) and 95% CIs were obtained using random-effects meta-analysis.

MAIN OUTCOMES AND MEASURES The main outcomes were a composite of acute coronary syndrome (ACS) events, stroke, or vascular death (major adverse cardiovascular events); cause-specific vascular events; and death.

RESULTS The analyses included data from 10 trials (9 CPAP; 1 ASV) of patients with sleep apnea (N = 7266; mean age, 60.9 [range, 51.5 to 71.1] years; 5847 [80.5%] men; mean [SD] body mass index, 30.0 [5.2]. Among 356 major adverse cardiovascular events and 613 deaths recorded, there was no significant association of PAP with major adverse cardiovascular events (RR, 0.77 [95% CI, 0.53 to 1.13]; $P = .19$ and RD, −0.01 [95% CI, −0.03 to 0.01]; $P = .23$), cardiovascular death (RR, 1.15 [95% CI, 0.88 to 1.50]; $P = .30$ and RD −0.00 [95% CI, −0.02 to 0.02]; $P = .87$), or all-cause death (RR, 1.13 [95% CI, 0.99 to 1.29]; $P = .08$ and RD, 0.00 [95% CI, −0.01 to 0.01]; $P = .51$). The same was true for ACS, stroke, and heart failure. There was no evidence of different associations for CPAP vs ASV (all P value homogeneity >.24), and meta-regressions identified no associations of PAP with outcomes for different levels of apnea severity, follow-up duration, or adherence to PAP (all P values > .13).

CONCLUSIONS AND RELEVANCE The use of PAP, compared with no treatment or sham, was not associated with reduced risks of cardiovascular outcomes or death for patients with sleep apnea. Although there are other benefits of treatment with PAP for sleep apnea, these findings do not support treatment with PAP with a goal of prevention of these outcomes.

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Sleep apnea is characterized by repetitive episodes of shallow breathing or apnea during sleep. Sleep apnea can result in episodic hypoxemia and is associated with elevated blood pressure, oxidative stress, inflammation, and hypercoagulation.[1-3] Observational studies indicate sleep apnea is associated with elevated risk of serious cardiovascular events, including coronary artery disease, heart failure, stroke, and sudden death.[4]

Positive airway pressure (PAP) is an established treatment for the symptoms of sleep apnea[5] and has been reported to lead to modest decreases in blood pressure among affected patients.[6,7] The 2014 American Heart Association/American Stroke Association (AHA/ASA) guidelines[8] for the use of PAP advise that treatment should be considered for patients with acute ischemic stroke or transient ischemic attack. Several trials[9-11] have reported the associations of PAP with cardiovascular outcomes, but individual trial results have been imprecise, and there remains uncertainty about the associations of PAP with vascular disease and death. Although prior meta-analyses[6,7] exist, none included the large Sleep Apnea Cardiovascular Endpoints (SAVE) trial, which adds substantive new data and insights into the likely effects of PAP on major clinical outcomes. The purpose of this systematic review and meta-analysis is to evaluate the association of PAP with cardiovascular events and death in adults with sleep apnea.

ACS *acute coronary syndrome*
ASV *adaptive servo-ventilation*
CPAP *continuous positive airway pressure*
CSA *central sleep apnea*
OSA *obstructive sleep apnea*
PAP *positive airway pressure*

Key Points

Question Does the use of positive airway pressure (PAP) to treat sleep apnea reduce risk of cardiovascular events and death?

Findings In this meta-analysis of 10 randomized clinical trials including 7266 patients, there was no significant association of PAP compared with no treatment (or sham PAP) on a composite outcome of acute coronary syndrome events, stroke, or vascular death (relative risk, 0.77 [95% CI, 0.53-1.13]). There was also no significant association with individual outcomes or all-cause death.

Meaning Although there are other benefits of PAP use for treating sleep apnea, these findings do not support treatment with a goal of preventing cardiovascular outcomes or improving survival.

Methods

Search Strategy and Selection Criteria

A systematic search of the scientific literature was done according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement for the conduct of meta-analyses of intervention studies.[12] The searches included MEDLINE via Ovid (from January 1, 1946, to March 2017), EMBASE (from January 1, 1974, to March 2017), and the Cochrane Library database (Cochrane Central Register of Controlled Trials, no date restriction) using relevant text words and Medical Subject Headings that consisted of terms relating to *randomized trial* and *sleep apnea* (see the eAppendix in the Supplement for detailed search strategy). The search was limited to randomized clinical trials (RCTs) but without language restriction. Additionally, reference lists from trials, review articles, and reports were manually scanned to identify any other relevant data (including conference abstracts). The clinicaltrials.gov website was searched for RCTs that were registered as completed but not yet published.

Trial Inclusion Criteria

All RCTs assessing the association of PAP compared with standard care (or sham PAP) among adults (aged ≥18 years) with obstructive sleep apnea (OSA) or central sleep apnea (CSA) were potentially eligible for inclusion. Duplicate reports, trials that lasted 12 weeks or less, trials with less than 100 patient-years of follow-up per randomized group, and trials that did not report on outcomes of interest (cardiovascular events or death) were excluded. We also excluded scientific reports that presented pooled trial data for which the individual trials could not be identified to prevent double counting.

Study Selection and Data Extraction

The review of potentially eligible scientific reports identified by the searches was completed by 2 authors (J.Y. and Z.Z.) to identify reports for review in full text. Each full-text article was then reviewed for eligibility by these authors and, for each included study, data were extracted independently and in duplicate using a standardized electronic form. Any disagreement in extracted data was settled by consultation. Data sought were the first author, year of publication, country where the study was conducted, number of participants, percent of male participants, mean age of participants, inclusion criteria for OSA or CSA, intervention type, participant adherence, follow-up duration, cardiovascular events, and deaths (including cardiovascular death, noncardiovascular death, and all-cause death).

Two investigators (J.Y. and Z.Z.) also judged the quality of each included trial according to the Cochrane Collaboration's tool for assessing risk of bias. There were 7 quality items assessed: (1) random sequence generation, (2) allocation sequence concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) completeness of outcome data, (6) selective reporting, and (7) other sources of bias, which were each classified as low, unclear, or high.[13]

Outcomes

The composite outcomes of interest were major adverse cardiovascular events (cardiovascular death, nonfatal acute coronary syndrome [ACS], and nonfatal stroke) and major adverse cardiovascular events with hospitalization for unstable angina.

The cause-specific outcomes were fatal or nonfatal ACS, fatal or nonfatal stroke, hospitalization for unstable angina, and fatal or hospitalized heart failure. All-cause death, cardiovascular death, and noncardiovascular death were also studied.

Some studies reported intermediate outcomes: systolic and diastolic blood pressure, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), blood lipids (high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, and triglycerides), fasting glucose, glycated hemoglobin A_{1c}, and scores from the Epworth Sleepiness Scale (ESS), Sleep Apnea Quality of Life Index (SAQLI), European Quality of Life-5 Dimensions (EQ-5D), the 36-item Short-Form (SF-36), and the Hospital Anxiety and Depression Scale (HADS).

Analysis

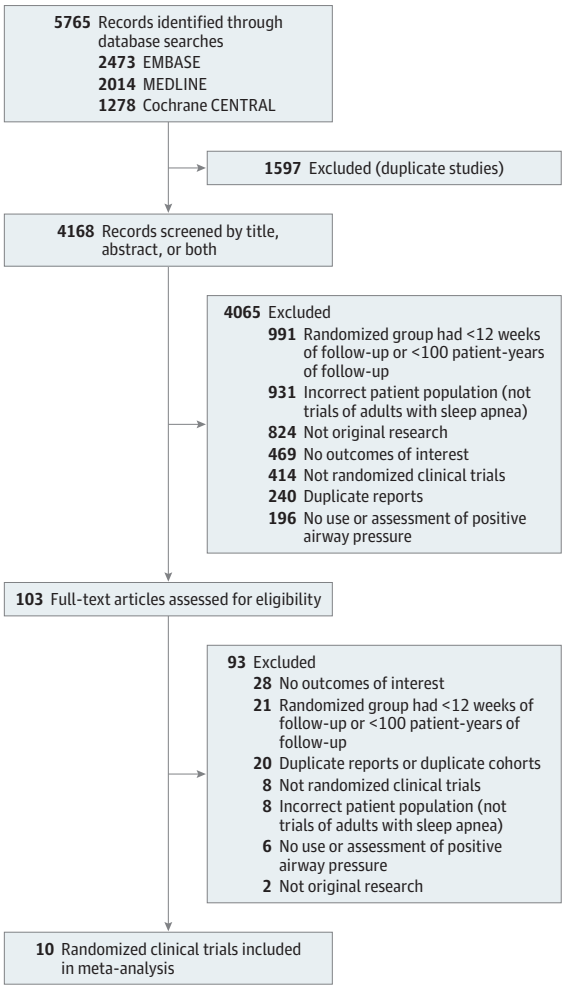
The numbers of dichotomous outcomes were summarized and mean values with standard deviations were collated for continuous outcomes. Summary relative risks (RRs) and risk differences (RDs) with 95% CIs were estimated for primary and secondary outcomes using the DerSimonian and Laird random-effects model.[14] For continuous parameters, weighted mean differences were calculated using end-of-trial mean (SD) values and treatment group size. A 2-sided *P* value of less than or equal to .05 was deemed significant. The percentage of variability across the pooled estimates attributable to heterogeneity beyond chance was estimated using the I^2 statistic[13] and by calculating the *P* value for heterogeneity. An I^2 statistic[13] was considered to reflect low likelihood (0%-25%), moderate likelihood (26%-75%), and high likelihood (76%-100%) of differences beyond chance, as was a *P* value of less than or equal to .05 for heterogeneity.[15] Where there was a moderate or high likelihood of differences beyond chance, sensitivity analyses were done excluding individual studies to try and obtain an understanding of the reasons for the differences. Random-effects meta-regression analyses were used to investigate the associations of length of follow-up, adherence to randomized treatment, and apnea-hypopnea index with the observed RR for each trial. Subgroup analyses were done by grouping trials according to adherence to PAP (<4 vs ≥4 h/d), type of sleep apnea (OSA vs CSA), type of intervention (CPAP vs ASV), and whether vascular outcomes or death were prespecified outcomes. Evidence of publication bias was sought using the Egger regression test for funnel asymmetry in addition to visual inspection of the funnel plots. Statistical analyses were performed with Stata, version 12.0.

Results

Search Results and Characteristics of Included Studies

The literature search yielded 5765 articles of which 103 were reviewed in full text (**Figure 1**). Of these, 10 RCTs (7266 patients [5683 OSA; 1583 CSA]) met inclusion criteria.[16-25] Among these patients, 356 major adverse cardiovascular events, 635 major adverse cardiovascular events with hospitalization for unstable angina, and 613 deaths were reported. The majority of other studies identified by our search had less than 12 weeks of follow-up[26] or less than 100 patient-years of follow-up per randomized group[27,28] or did not report on the clinical outcomes of interest.[29,30]

Figure 1. Flow Diagram of Literature Search



All trial results[17-25] were published during or after 2010 except 1 trial[16] in 2005 (**Table 1**). All studies[16-21,23,24] except 2 were multicenter trials.[22,25] Studies assessed the association of PAP (9 CPAP[16-20,22-25] and 1 ASV[21]) with standard care (9 studies[16-18,20-25]) or sham PAP (1 study[19]). Sample size ranged from 83 participants[22] to 2717 participants[24] (median follow-up range, 6 months[18,19] to 68 months[23]). Diagnosis of sleep apnea was based on conventional polysomnographic or polygraphic monitoring in all but 1 trial that used a home sleep study.[24] Mean or median adherence to the intervention ranged between 1.4 hours per day[20] and 6.6 hours per day.[25]

The assessments of risk of bias (eFigure 1 in the Supplement) showed that only 1 trial[19] included blinding of participants and personnel to the intervention, but all except 1 did blinded assessment of cardiovascular outcomes.[23] Funnel plots

Table 1. Characteristics of Included Randomized Clinical Trials

Source	Baseline Characteristics						Key Inclusion Criteria	Intervention[c] Type and Duration, h/d	Follow-up, Median (Range), mo
	Men, No./Total No. (%)	Age, Mean (SD), y	BMI, Mean (SD)[a]	Current Smoker, No. (%)	AHI Events/h, Mean (SD)[b]	Sleep Apnea Diagnosis			
Bradley et al,[16] 2005 (Canada)	249/258 (97)	63.4 (9.5)	29.1 (6.0)	NR	40.0 (16.0)	PSG	HF, CSA (AHI≥15/h[b], central apnea and hypopnea ≥50%)	CPAP, median, 3.6	24 (0-64)
Barbé et al,[17] 2012 (Spain)	619/725 (85)	51.9 (11.0)	31.2 (4.9)	207 (29)	38.5, median	PSG or PG	AHI≥20/h[b], ESS≤10[d]	CPAP, median, 5.0	48 (0-64.6)
Craig et al,[18] 2012 (United Kingdom and Canada)	305/391 (78)	57.7 (7.4)	32.4 (5.6)	45 (12)	NR	PG	ODI≥7.5/h[e]	CPAP, median, 2.4	6
Kushida et al,[19] 2012 (United States)[c]	719/1105 (65)	51.5 (12.2)	32.3 (7.2)	NR	40.1 (25.3)	PSG	AHI≥10/h[b]	CPAP, mean, 3.8	6
McMillan et al,[20] 2014 (United Kingdom)	229/278 (82)	71.1 (4.7)	33.8 (6.1)	14 (5)	28.7	PG	New obstructive sleep apnea	CPAP, median, 1.4	12
Cowie et al,[21] 2015 (Europe and Australia)	1198/1325 (90)	69.5 (10.0)	28.5 (5.0)	NR	31.4 (3.0)	PSG or PG	HF, predominantly CSA (AHI≥15/h with ≥50% apnea or hypopnea and a central AHI≥10/h)[b]	ASV, mean, 3.7	31 (0-80)
Huang et al,[22] 2015 (China)	60/83 (72)	62.4 (6.8)	27.7 (3.1)	42 (51)	28.5 (12.7)	PSG	CVD, AHI≥15/h[b]	CPAP, mean (SD), 4.5 (1.1)	36 (24-54)[f]
Parra et al,[23] 2015 (Spain)	89/140 (64)	64.7 (9.1)	29.4 (4.3)	47 (34)	38.4 (13.7)	PG	CVD	CPAP, mean (SD), 5.3 (1.9)	68
McEvoy et al,[24] 2016 (Asia, Australia, Europe, North and South America)	2174/2717 (80)	61.3 (7.8)	28.7 (4.5)	407 (15)	29.3 (16.2)[g]	PG[h]	CVD, 4% ODI≥12/h[e]	CPAP, mean (SD), 3.3 (2.3)	44
Peker et al,[25] 2016 (Sweden)	205/244 (84)	66.0 (8.4)	28.5 (3.7)	39 (16)	28.8 (13.4)	PG	CVD, AHI≥15/h[b]	CPAP, mean, (SD), 6.6 (1.3)	57

Abbreviations: AHI, apnea-hypopnea index; ASV, adaptive servo-ventilation; BMI, body mass index; CPAP, continuous positive airway pressure; CSA, central sleep apnea; CVD, cardiovascular disease; ESS, Epworth Sleepiness Scale score; HBP, high blood pressure; HF, heart failure; NR, not reported; ODI, oxygen desaturation index; PG, cardiorespiratory or respiratory polygraphy; PSG, polysomnography (includes electroencephalogram assessment of sleep).

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] AHI score range (0 [minimal] to ≥30 [severe]) is based on the number of apneas or hypopneas per hour.

[c] All trials used standard of care for control except Kushida[19] (sham CPAP).

[d] ESS score range (0 [less severity] to 24 [greater severity] with a score higher than 10 indicating pathologic sleepiness[24]) is based on a self-administered questionnaire of 8 questions to assess daytime sleepiness.

[e] Indicates the number of times per hour during oximetry recording that the blood oxygen saturation level declines by at least 4%.

[f] Reported values indicate interquartile range.

[g] Calculated from a screening sleep apnea device (ApneaLink, ResMed) that resulted in systematic underestimation of AHI.

[h] PG was restricted to nasal pressure and oximetry.

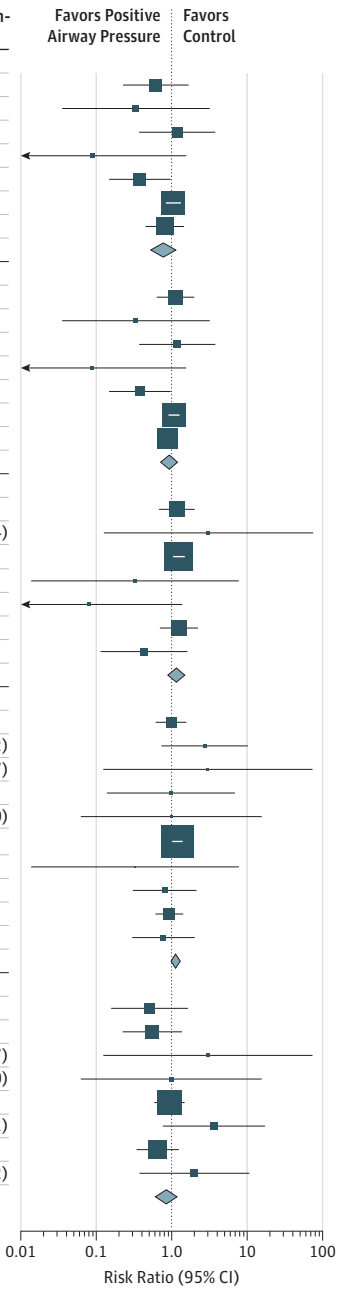
and Egger regression tests identified no strong evidence of publication bias with just 1 significant result for major adverse cardiovascular events (P = .03) (eFigure 5 in the Supplement).

Association of PAP With Cardiovascular Outcomes and Death

There were no associations of PAP with major adverse cardiovascular events (RR, 0.77 [95% CI, 0.53 to 1.13; P = .19] and RD, −0.01 [95% CI, −0.03 to 0.01; P = .23]), major adverse cardiovascular events plus hospitalization for unstable angina (RR, 0.92 [95% CI, 0.71 to 1.20; P = .54] and RD, −0.01 [95% CI, −0.03 to 0.01; P = .42]), cardiovascular death (RR, 1.15 [95% CI, 0.88 to 1.50; P = .30] and RD, −0.00 [95% CI, −0.02 to 0.02; P = .87]), all-cause death (RR, 1.13 [95% CI, 0.99 to 1.29; P = .08] and RD, 0.00 [95% CI, −0.01 to 0.01; P = .51]), or noncardiovascular death (RR, 0.85 [95% CI, 0.60 to 1.19; P = .33] and RD, −0.00 [95% CI, −0.01 to 0.01; P = .51]) (**Figure 2** and eTable 1 in the Supplement). Additionally, there were no associations of PAP with cause-specific outcomes of ACS (RR, 1.00 [95% CI, 0.65 to 1.55; P = .99] and RD, −0.00 [95% CI, −0.02 to 0.01; P = .45]), stroke (RR, 0.90 [95% CI, 0.66 to 1.21; P = .47] and RD, −0.00 [95% CI, −0.02 to 0.01; P = .52]), hospitalization for unstable angina (RR, 1.15 [95% CI, 0.89 to 1.49; P = .29] and RD, 0.01 [95% CI, −0.01 to 0.03; P = .21]) or heart failure (RR, 1.03 [95% CI, 0.92 to 1.16; P = .60] and RD, −0.00 [95% CI, −0.01 to 0.01; P = .87]) (**Figure 3** and eTable 1 in the Supplement). The meta-regression analyses identified no association between the length of follow-up, adherence to PAP, baseline apnea-hypopnea index, and the relative risks of events reported for the individual trials (**Figure 4**; eFigure 2 and eFigure 3 in the

Figure 2. Meta-analysis of the Association of Positive Airway Pressure With Cardiovascular Events and Death

Source	Positive Airway Pressure Events or Deaths, No.	Positive Airway Pressure Participants, No.	Control Events or Deaths, No.	Control Participants, No.	Risk Ratio (95% CI), Random-Effects Model
Major adverse cardiovascular events[a]					
Barbé et al,[17] 2012	6	357	10	366	0.62 (0.23-1.67)
Craig et al,[18] 2012	1	195	3	196	0.34 (0.04-3.19)
McMillan et al,[20] 2014	6	140	5	138	1.18 (0.37-3.79)
Huang et al,[22] 2015	0	42	5	41	0.09 (0.01-1.56)
Parra et al,[23] 2015	5	57	16	69	0.38 (0.15-0.97)
McEvoy et al,[24] 2016	134	1359	127	1358	1.05 (0.84-1.33)
Peker et al,[25] 2016	17	122	21	122	0.81 (0.45-1.46)
Overall (I^2 = 34.10%, P = .17)	169	2272	187	2290	0.77 (0.53-1.13)
Major adverse cardiovascular events plus[a,b]					
Barbé et al,[17] 2012	23	357	21	366	1.12 (0.63-1.99)
Craig et al,[18] 2012	1	195	3	196	0.34 (0.04-3.19)
McMillan et al,[20] 2014	6	140	5	138	1.18 (0.37-3.79)
Huang et al,[22] 2015	0	42	5	41	0.09 (0.01-1.56)
Parra et al,[23] 2015	5	57	16	69	0.38 (0.15-0.97)
McEvoy et al,[24] 2016	233	1359	217	1358	1.07 (0.91-1.27)
Peker et al,[25] 2016	47	122	53	122	0.89 (0.66-1.20)
Overall (I^2 = 35.30%, P = .16)	315	2272	320	2290	0.92 (0.71-1.20)
Cardiovascular death					
Bradley et al,[16] 2005	23	128	20	130	1.17 (0.68-2.02)
Barbé et al,[17] 2012	1	357	0	366	3.08 (0.13-75.24)
Cowie et al,[21] 2015	199	666	158	659	1.25 (1.04-1.49)
Huang et al,[22] 2015	0	42	1	41	0.33 (0.01-7.77)
Parra et al,[23] 2015	0	57	7	69	0.08 (0.00-1.38)
McEvoy et al,[24] 2016	25	1359	20	1358	1.25 (0.70-2.24)
Peker et al,[25] 2016	3	122	7	122	0.43 (0.11-1.62)
Overall (I^2 = 15.30%, P = .31)	251	2731	213	2745	1.15 (0.88-1.50)
All-cause death					
Bradley et al,[16] 2005	27	128	28	130	0.98 (0.61-1.57)
Barbé et al,[17] 2012	8	357	3	366	2.73 (0.73-10.22)
Craig et al,[18] 2012	1	195	0	196	3.02 (0.12-73.57)
Kushida et al,[19] 2012	2	556	2	542	0.97 (0.14-6.90)
McMillan et al,[20] 2014	1	140	1	138	0.99 (0.06-15.60)
Cowie et al,[21] 2015	232	666	193	659	1.19 (1.02-1.39)
Huang et al,[22] 2015	0	42	1	41	0.33 (0.01-7.77)
Parra et al,[23] 2015	6	57	9	69	0.81 (0.31-2.13)
McEvoy et al,[24] 2016	40	1359	43	1358	0.93 (0.61-1.42)
Peker et al,[25] 2016	7	122	9	122	0.78 (0.30-2.02)
Overall (I^2 = 0.00%, P = .80)	324	3622	289	3621	1.13 (0.99-1.29)
Noncardiovascular death					
Bradley et al,[16] 2005	4	128	8	130	0.51 (0.16-1.64)
Barbé et al,[17] 2012	7	357	13	366	0.55 (0.22-1.37)
Craig et al,[18] 2012	1	195	0	196	3.02 (0.12-73.57)
McMillan et al,[20] 2014	1	140	1	138	0.99 (0.06-15.60)
Cowie et al,[21] 2015	33	666	35	659	0.93 (0.59-1.48)
Parra et al,[23] 2015	6	57	2	69	3.63 (0.76-17.31)
McEvoy et al,[24] 2016	15	1359	23	1358	0.65 (0.34-1.24)
Peker et al,[25] 2016	4	122	2	122	2.00 (0.37-10.72)
Overall (I^2 = 4.80%, P = .39)	71	3024	84	3038	0.85 (0.60-1.19)



Box sizes are proportional to study weight (box center positioned at point estimate of effect). Horizontal lines indicate 95% CIs. The I^2 value indicates the percentage of variability across the pooled estimates attributable to heterogeneity beyond chance (0%-25%, low likelihood; 26%-75%. moderate likelihood; 76%-100%, high likelihood), and the P value is for a test of heterogeneity across all studies (P value <.05 indicates likely variation across pooled estimates beyond chance). If 0 events were reported for 1 cell in a comparison, a value of 0.5 was added to both cells automatically before calculating the risk ratio (95% CI). Risk ratio data are rounded to 2 decimal places but plotted to exact values.

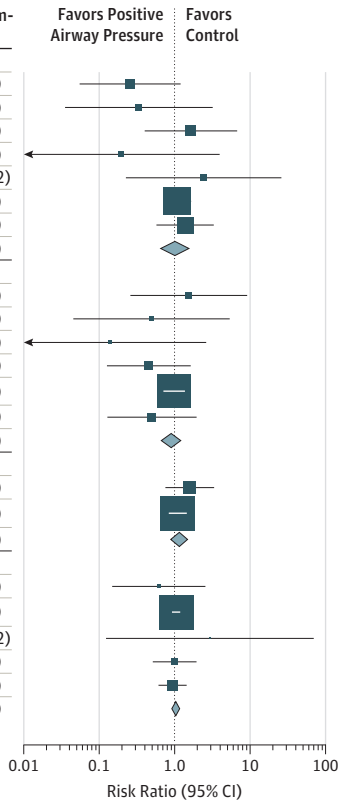
[a] Major adverse cardiovascular events consist of cardiovascular death, nonfatal acute coronary syndrome, and nonfatal stroke.

[b] Plus indicates major adverse cardiovascular events in addition to hospitalization for unstable angina.

Supplement). There was some evidence of heterogeneity in trial results observed for the outcomes of major adverse cardiovascular events (I^2 = 34%) and major adverse cardiovascular events with hospitalization for unstable angina (I^2 = 35%), which was in part attributable to the extreme result of 1 small study[22] (eFigure 4 in the Supplement). Tests of heterogeneity between subgroups of studies that included participants with OSA vs CSA showed no differences of associations

Figure 3. Meta-analysis of the Association of Positive Airway Pressure With Cardiovascular Outcomes

Source	Positive Airway Pressure Events, No.	Positive Airway Pressure Participants, No.	Control Events, No.	Control Participants, No.	Risk Ratio (95% CI), Random-Effects Model
Acute coronary syndromes					
Barbé et al,[17] 2012	2	357	8	366	0.26 (0.05-1.20)
Craig et al,[18] 2012	1	195	3	196	0.34 (0.04-3.19)
McMillan et al,[20] 2014	5	140	3	138	1.64 (0.40-6.74)
Huang et al,[22] 2015	0	42	2	41	0.20 (0.01-3.95)
Parra et al,[23] 2015	2	57	1	69	2.42 (0.23-26.02)
McEvoy et al,[24] 2016	42	1359	39	1358	1.08 (0.70-1.65)
Peker et al,[25] 2016	11	122	8	122	1.38 (0.57-3.30)
Overall (I^2 = 10.20%, P = .35)	63	2272	64	2290	1.00 (0.65-1.55)
Stroke					
Barbé et al,[17] 2012	3	357	2	366	1.54 (0.26-9.15)
McMillan et al,[20] 2014	1	140	2	138	0.49 (0.05-5.37)
Huang et al,[22] 2015	0	42	3	41	0.14 (0.01-2.62)
Parra et al,[23] 2015	3	57	8	69	0.45 (0.13-1.63)
McEvoy et al,[24] 2016	67	1359	68	1358	0.98 (0.71-1.37)
Peker et al,[25] 2016	3	122	6	122	0.50 (0.13-1.95)
Overall (I^2 = 0.00%, P = .51)	77	2077	89	2094	0.90 (0.66-1.21)
Hospitalization for unstable angina					
Barbé et al,[17] 2012	17	357	11	366	1.58 (0.75-3.34)
McEvoy et al,[24] 2016	99	1359	90	1358	1.10 (0.83-1.45)
Overall (I^2 = 0.00%, P = .37)	116	1716	101	1724	1.15 (0.89-1.49)
Heart failure					
Barbé et al,[17] 2012	3	357	5	366	0.62 (0.15-2.55)
Cowie et al,[21] 2015	287	666	272	659	1.04 (0.92-1.18)
Huang et al,[22] 2015	1	42	0	41	2.93 (0.12-69.92)
McEvoy et al,[24] 2016	17	1359	17	1358	1.00 (0.51-1.95)
Peker et al,[25] 2016	30	122	32	122	0.94 (0.61-1.44)
Overall (I^2 = 0.00%, P = .88)	338	2546	326	2546	1.03 (0.92-1.16)



Box sizes are proportional to study weight (box center positioned at point estimate of effect). Horizontal lines indicate 95% CIs. The I^2 value indicates the percentage of variability across the pooled estimates attributable to heterogeneity beyond chance (0%-25%, low likelihood; 26%-75%. moderate likelihood; 76%-100%, high likelihood), and the P value is for a test of heterogeneity across all studies (P value <.05 indicates likely variation across pooled estimates beyond chance). If 0 events were reported for 1 cell in a comparison, a value of 0.5 was added to both cells automatically before calculating the risk ratio (95% CI). Risk ratio data are rounded to 2 decimal places but plotted to exact values.

for cardiovascular death (P = .45), all-cause death (P = .33), or noncardiovascular death (P = .73) (**Figure 5**). There were no subgroup analyses that showed clear evidence of heterogeneity between subgroups of studies (all P values for homogeneity were >.09), but the summary RR for the 4 trials that achieved at least 4 hours of adherence did have a 95% CI that just excluded unity (RR, 0.58 [95% CI, 0.34 to 0.99]).

Association of PAP With Intermediate Outcomes

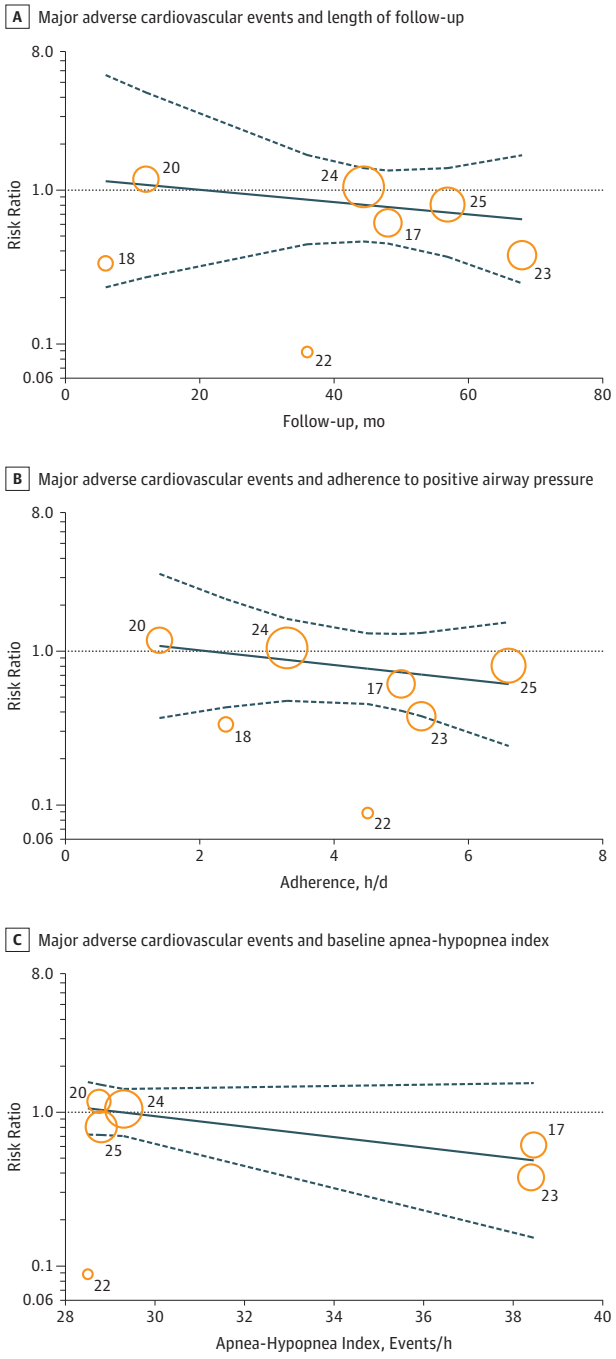
Data describing the associations of PAP with intermediate outcomes were diverse and inconsistently described. Comparable data reported by more than 1 study ranged in quantity from sleepiness reported by 5 studies[17,19,20,22,24] (n = 4285 participants) to total cholesterol reported by just 2 studies[18,20] (n = 527 participants) (**Table 2**). For the included studies, there was no association of treatment with PAP detected for blood pressure, BMI, any lipid parameter, glycemia, or EQ-5D, but associations were observed for sleepiness and a range of measures of physical and mental well-being. For several of these intermediate measures, there was evidence of differences in the association with PAP across the contributing trials (Table 2).

Discussion

In this meta-analysis of RCTs, there were no significant associations between PAP treatment and a range of cardiovascular events or death, although anticipated associations with some other outcomes related to sleep apnea were observed.[7,32-35] Based on the available evidence, it is reasonable to recommend PAP therapy for the improvement of symptoms in patients with OSA but not for protection against vascular disease or death. It is possible that an enhanced evidence base able to better explore effects in patient subgroups might identify protective effects of PAP treatment for some patient subsets. In the meantime, these data emphasize the importance of proven therapies, such as blood pressure lowering, lipid lowering, and antiplatelet therapy in patients with sleep apnea, who should be treated according to established guidelines for patients at elevated cardiovascular risk.[36-38]

Sleep apnea is highly prevalent[39-43] and is associated with an elevated risk of serious vascular outcomes[4] and multiple risk factors including hypertension,[1,44,45] obesity,[46,47] insulin

Figure 4. Meta-Regressions of Selected Trial Characteristics and Individual Trial Risk Ratios for Major Adverse Cardiovascular Events



A, Meta-regression of risk ratio (RR) for major adverse cardiovascular events[17,18,20,22-25] according to length of follow-up with regression coefficient of −0.01 [95% CI, −0.04 to 0.02]; $P = .52$. B, Meta-regression on RR of major adverse cardiovascular events according to adherence to intervention or control[17,18,20,22-25] with regression coefficient of −0.11 [−0.41 to 0.19]; $P = .40$. C, Meta-regression on RR of major adverse cardiovascular events according to apnea-hypopnea index at baseline[17,20,22-25] with regression coefficient of −0.08 [−0.19 to 0.04]; $P = .13$.

Major adverse cardiovascular events comprise cardiovascular death, nonfatal acute coronary syndrome, and nonfatal stroke. Circle sizes indicate the weight given to each study (centered on the intersection of the RR for major adverse cardiovascular events on the y-axis and the mean trial value of the metric of interest on the x-axis).

resistance, and dyslipidemia. PAP has been reported to lower blood pressure,[6,7,32,33,48] improve insulin resistance,[49] enhance endothelial function,[50] and increase insulin sensitivity,[51,52] although improvements in glycemic control[49] and BMI have not been demonstrated.[50,52] Jointly, the observed associations of sleep apnea with vascular risk and the apparent beneficial effects of PAP on intermediate biomarkers provided a rationale for expecting that adequately powered trials of PAP would show beneficial effects on hard vascular outcomes.

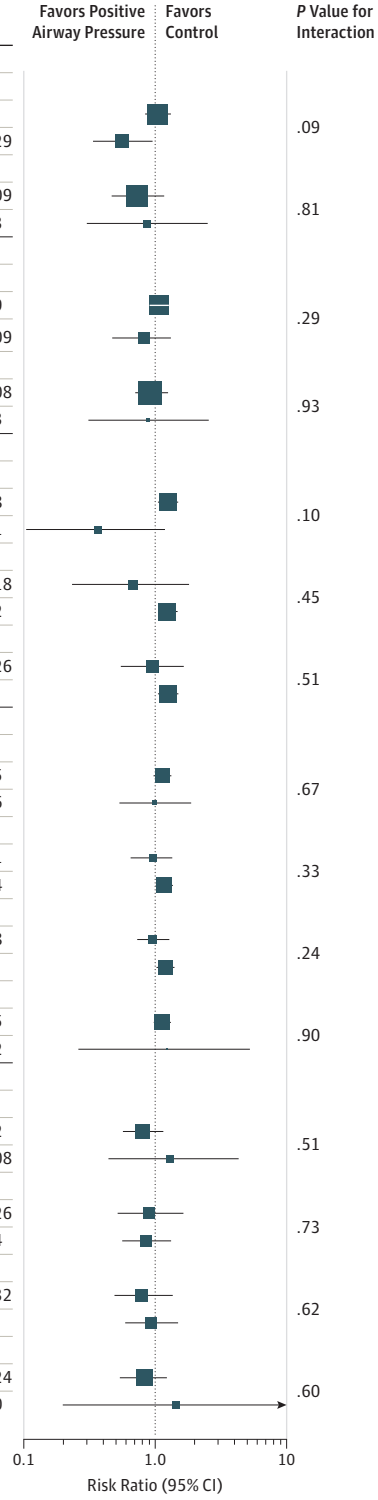
There have been several reasons postulated for the failure of PAP trials to demonstrate protection against vascular outcomes. It is possible that the limited adherence to therapy in many trials was insufficient to drive protection, and there have been several reports of differential benefits of PAP in more vs less adherent patients derived from post hoc analyses.[17,25] A weakness of these reports is that analyses based on nonrandomized comparisons may reflect confounding due to differences between adherent and nonadherent individuals rather than their use of PAP. The methodologically more robust meta-regression approach reported herein identified no association of adherence with the effectiveness of PAP for prevention of vascular disease, although statistical power to detect modest effects was low. Likewise, there was no heterogeneity detected between the associations observed in subgroups of trials that achieve adherence less than 4 vs 4 or more hours per night. The statistically significant benefit (RR, 0.58 [95% CI, 0.34 to 0.99]) observed for the major adverse cardiovascular events outcome in trials with at least 4 hours per night may be interpreted as indicating the importance of good adherence to achieving benefits with PAP. However, the absence of any comparable association for other outcomes, the post hoc nature of the subgroup analyses, and the multiple comparisons made also make chance a plausible explanation. The short follow-up duration of most trials may have given insufficient time for PAP to have affected vascular outcomes,[23] although the meta-regression identified no association between follow-up time and the hazard ratio for PAP vs control in the contributing trials. It has been suggested that PAP may be ineffective in patients with advanced disease, but this has not been observed for other interventions targeting vascular conditions in which treatments have typically proven effective in primary and secondary prevention settings.[53-57]

The absence of any significant association of PAP with intermediate markers of vascular risk in the trials included in this overview may explain the null associations of PAP with hard vascular outcomes. The disparity with earlier reports of protection for several intermediate markers of vascular risk[6,7,49,52,58] might reflect the small and inconsistently reported benefits in the prior studies and interpretation influenced by publication bias. It is also possible that differences in the characteristics of participants included in the present systematic review and meta-analysis, compared with prior studies, may account for the discrepancies, and this warrants further investigation.

The positive association of PAP observed with the Epworth Sleepiness Scale (reported previously)[28] provides reassurance that PAP was delivered with sufficient integrity, in these

Figure 5. Association of Positive Airway Pressure With Vascular Outcomes and Deaths in Trial Subgroups

Subgroup	Studies, No.	Positive Airway Pressure: Events or Deaths, No.	Positive Airway Pressure: Participants, No.	Control: Events or Deaths, No.	Control: Participants, No.	Risk Ratio (95% CI)	Heterogeneity	P Value for Interaction
Major adverse cardiovascular events[a]								
Adherence								
<4 h/d	3	141	1694	135	1692	1.05 (0.84-1.31)	I^2 = 0%, P = .60	.09
≥4 h/d	4	28	578	52	598	0.58 (0.34-0.99)	I^2 = 19.70%, P = .29	
Outcome								
Specified	5	162	1937	179	1956	0.73 (0.46-1.16)	I^2 = 50.90%, P = .09	.81
Not specified	2	7	335	8	334	0.91 (0.32-2.55)	I^2 = 0.00%, P = .33	
Major adverse cardiovascular events plus[b]								
Adherence								
<4 h/d	3	240	1694	225	1692	1.07 (0.90-1.26)	I^2 = 0.00%, P = .59	.29
≥4 h/d	4	75	578	95	598	0.76 (0.45-1.27)	I^2 = 52.90%, P = .09	
Outcome								
Specified	5	308	1937	312	1956	0.91 (0.68-1.22)	I^2 = 51.70%, P = .08	.93
Not specified	2	7	335	8	334	0.91 (0.32-2.55)	I^2 = 0.00%, P = .33	
Cardiovascular death								
Adherence								
<4 h/d	3	247	2153	198	2147	1.24 (1.05-1.46)	I^2 = 0.00%, P = .98	.10
≥4 h/d	4	4	578	15	598	0.41 (0.14-1.18)	I^2 = 0.00%, P = .41	
Sleep apnea								
OSA	5	29	1937	35	1956	0.70 (0.27-1.80)	I^2 = 36.50%, P = .18	.45
CSA	2	222	794	178	789	1.24 (1.04-1.47)	I^2 = 0.00%, P = .82	
PAP								
CPAP	6	52	2065	55	2086	0.96 (0.57-1.61)	I^2 = 23.60%, P = .26	.51
ASV	1	199	666	158	659	1.25 (1.04-1.49)		
All-cause death								
Adherence								
<4 h/d	6	303	3044	267	3023	1.14 (0.99-1.31)	I^2 = 0.00%, P = .85	.67
≥4 h/d	4	21	578	22	598	0.99 (0.53-1.85)	I^2 = 5.70%, P = .36	
Sleep apnea								
OSA	8	65	2828	68	2832	0.96 (0.69-1.35)	I^2 = 0.00%, P = .81	.33
CSA	2	259	794	221	789	1.17 (1.00-1.35)	I^2 = 0.00%, P = .44	
PAP								
CPAP	9	92	2956	96	2962	0.97 (0.74-1.27)	I^2 = 0.00%, P = .88	.24
ASV	1	232	666	193	659	1.19 (1.02-1.39)		
Outcome								
Specified	7	320	2731	286	2745	1.13 (0.98-1.29)	I^2 = 0.00%, P = .55	.90
Not specified	3	4	891	3	876	1.23 (0.29-5.11)	I^2 = 0.00%, P = .82	
Noncardiovascular death								
Adherence								
<4 h/d	5	54	2488	67	2481	0.81 (0.57-1.15)	I^2 = 0.00%, P = .72	.51
≥4 h/d	3	17	536	17	557	1.37 (0.40-4.69)	I^2 = 59.40%, P = .08	
Sleep apnea								
OSA	6	34	2230	41	2249	0.94 (0.51-1.72)	I^2 = 22.60%, P = .26	.73
CSA	2	37	794	43	789	0.86 (0.56-1.32)	I^2 = 0.00%, P = .34	
PAP								
CPAP	7	38	2358	49	2379	0.82 (0.49-1.36)	I^2 = 14.70%, P = .32	.62
ASV	1	33	666	35	659	0.93 (0.59-1.48)		
Outcome								
Specified	6	69	2689	83	2704	0.84 (0.55-1.27)	I^2 = 25.60%, P = .24	.60
Not specified	2	2	335	1	334	1.59 (0.20-12.85)	I^2 = 0.00%, P = .60	



Box sizes are proportional to study weight (box center positioned at point estimate of effect). The I^2 value indicates the percentage of variability across the pooled estimates attributable to heterogeneity beyond chance (0%-25%, low likelihood; 26%-75%, moderate likelihood; 76%-100%, high likelihood), and the *P* value is for a test of heterogeneity across all studies. Abbreviations: ASV, adaptive servo-ventilation; CPAP, continuous positive airway pressure; CSA, central sleep apnea; OSA: obstructive sleep apnea; PAP, positive airway pressure.

[a] Major adverse cardiovascular events comprise cardiovascular death, nonfatal acute coronary syndrome, and nonfatal stroke.

[b] Plus indicates major adverse cardiovascular events in addition to hospitalization for unstable angina.

Table 2. Association of Positive Airway Pressure With Intermediate Outcomes

Outcome	Reference No. for Included Studies	No. of Participants		Pooled Mean Difference, Random-Effects Model (95% CI)[a]	Heterogeneity I^2, %	*P* Value
		PAP Group	Control Group			
Systolic blood pressure, mm Hg	18, 20, 22, 24	1510	1507	−0.20 (−2.29 to 1.89)	61.50	.05
Diastolic blood pressure, mm Hg	18, 20, 22, 24	1481	1477	−0.21 (−1.06 to 0.65)	0.00	.80
Body mass index[b]	17, 18, 20, 22	677	692	0.36 (−0.17 to 0.88)	0.00	.91
HDL cholesterol, mmol/L	18, 20	276	275	−0.02 (−0.11 to 0.07)	56.70	.13
LDL cholesterol, mmol/L	18, 20	266	267	0.02 (−0.14 to 0.19)	0.00	.46
Total cholesterol, mmol/L	18, 20	263	264	−0.05 (−0.23 to 0.14)	0.00	.60
Triglycerides, mmol/L	18, 20	274	276	0.04 (−0.14 to 0.23)	33.60	.22
Glucose, mmol/L[c]	18, 20	275	276	−0.09 (−0.40 to 0.23)	0.00	.95
Hemoglobin A_{1c}, %	18, 20	268	267	−0.04 (−0.27 to 0.18)	0.00	.90
ESS score[d]	17, 19, 20, 22, 24	2169	2116	−1.92 (−2.79 to −1.06)	91.50	.00
SAQLI score[e]	18, 20	288	282	0.51 (0.31 to 0.70)	8.70	.29
EQ-5D score[f]	18, 24	1362	1336	0.00 (−0.02 to 0.03)	0.00	.32
Component scores						
SF-36 score, physical[g]	18, 23, 24	1446	1426	1.91 (−1.01 to 4.83)	68.00	.04
SF-36 score, mental[g]	18, 23, 24	1440	1416	1.73 (0.01 to 3.46)	50.70	.13
HADS score, anxiety[h]	20, 24	1334	1307	−0.40 (−0.67 to −0.13)	0.00	1.00
HADS score, depression[h]	20, 24	1334	1306	−0.70 (−1.09 to −0.31)	21.90	.26

Conventional unit conversion factors: to convert HDL cholesterol, LDL cholesterol, and total cholesterol to mg/dL, divide by 0.0259; for triglycerides to mg/dL, divide by 0.0113; for glucose to mg/dL, divide by 0.0555.

Abbreviations: EQ-5D, European Quality of Life-5 Dimensions questionnaire; ESS, Epworth Sleepiness Scale score; HADS, Hospital Anxiety and Depression Scale; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SAQLI, Sleep Apnea Quality of Life Index; SF-36, 36-Item Short-Form Health.

[a] Outcomes were pooled using random-effects models.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Indicates fasting glucose.

[d] ESS (range, 0 [less severity] to 24 [greater severity] with a score >10 indicating pathologic sleepiness[24]) is a self-administered questionnaire to assess daytime sleepiness.

[e] SAQLI (range, 1 [worse] to 7 [better quality of life]) is a disease-specific instrument to evaluate health-related quality of life (daily functioning, social interactions, emotional functioning, and symptoms) in OSA patients in clinical trials of CPAP.[31]

[f] EQ-5D (range, 1 [fewer] to 3 [more problems across 5 categories]) assesses quality of life.

[g] SF-36 (range, 0 [lower] to 100 [higher health-related quality of life]) assesses 8 health concepts (physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy vs fatigue, and general health perceptions.[24]

[h] HADS (range, 0 [less] to 21 [more symptoms]) assesses anxiety and depression.

included trials, to deliver anticipated benefits. This overview also shows beneficial effects on anxiety, depression, and physical function (previously reported in the individual studies). These benefits are of importance to patients and support the use of PAP for treating sleep apnea even in the absence of evidence of vascular protection. Further investigation of the effects of PAP on these outcomes is warranted.

The inclusion of 2 trials of patients with predominantly central sleep apnea helped to increase statistical power to address questions about the associations of PAP treatment with outcomes, while concurrently enabling formal investigation for evidence of different associations of PAP treatment in patients with different types of sleep apnea. The absence of evidence of heterogeneity of the associations between PAP treatment and outcomes across the obstructive sleep apnea and central sleep apnea subgroups, along with the absence of a significant association within either subgroup, strengthens the primary conclusion of no effect.

This study has several limitations. First, the summary data represent the available evidence from moderate-to-large-sized RCTs able to describe the association of PAP with vascular outcomes and death, but there are still relatively few events recorded. Most outcome events derived from a small number of studies, and many were from high-risk patient subsets. It is possible that more data might reveal moderate benefits of PAP that were beyond the power of this overview to detect, although the absence of improvement in intermediate risk markers makes this a low likelihood.

The second limitation, conversely, is that it is possible that additional data might reveal adverse effects since point estimates of the associations of PAP with vascular death and all-cause death were suggestive of harm rather than benefit.

Third, the participants in the contributing trials were mostly those without excessive sleepiness, and it may be that effects of PAP on vascular outcomes are restricted to patients with more severe symptomatology. However, it is difficult to envisage how this hypothesis could be tested in a trial because PAP treatment is indicated for most individuals with more severe symptomatology, and randomization to a control group would not be feasible.

An ongoing trial of CPAP following ACS (NCT01335087) and one of ASV in patients with heart failure (NCT01128816) will provide additional insight, but the practical complexity and cost associated with conducting PAP trials make it unlikely that substantial additional data will be forthcoming in the near future. If a new and very well-tolerated method of

delivering PAP becomes available, this may be worth evaluating in another large trial since it remains possible that strong adherence may produce benefits. In the meantime, the evidence from these RCTs suggests that the association of sleep apnea with vascular outcomes and death, seen in observational studies, may represent disease processes that cannot be ameliorated by PAP delivered at the average intensity achieved in these clinical trials or by currently feasible methods in clinical practice.

Conclusions

The use of PAP compared with no treatment or sham was not associated with reduced risks of cardiovascular outcomes or death for patients with sleep apnea. Although there are other benefits of treatment with PAP for sleep apnea, these findings do not support treatment with PAP with a goal of prevention of these outcomes.

ARTICLE INFORMATION

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