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CLINICAL REVIEW

Cardiovascular effects of oral appliance therapy in obstructive sleep apnea: A systematic review and meta-analysis

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SUMMARY

Obstructive sleep apnea (OSA) is associated with increased cardiovascular morbidity and mortality. This study systematically reviews the effects of oral appliance therapy (OAT) on a broad spectrum of cardiovascular outcomes.

A literature search was performed up to December 31st 2016. Twenty-five relevant full-text articles were retrieved. Sixteen articles were considered methodologically sufficient, including 11 randomized controlled trials.

Pooled data of the RCTs showed significant reductions in daytime systolic and diastolic blood pressure compared to baseline, but no significant reductions in heart rate, except for daytime heart rate when compared to inactive/placebo OAT. OAT and continuous positive airway pressure (CPAP) were equally effective in reducing blood pressure. Studies assessing the effect of OAT on heart rate variability, circulating cardiovascular biomarkers, and endothelial function and arterial stiffness, generally involved small numbers of patients, and were heterogeneous and inconclusive. Studies assessing the effect of OAT on cardiac function showed no effects on echocardiographic outcomes. One observational study showed that OAT was as effective as CPAP in reducing cardiovascular death.

It could be speculated that OAT may lead to a reduction in long-term cardiovascular morbidity and mortality in OSA patients. However, further methodologically high quality, longitudinal studies are warranted to address this key question.

Introduction

Obstructive sleep apnea (OSA) is a common (34% of men, 17% of women) sleep-related breathing disorder in the general adult population [1]. OSA is the result of repetitive collapse of the upper airway, leading to flow limitation or complete cessation (apnea) in airflow, causing intermittent hypoxia. This intermittent hypoxia is believed to set off a chain of events, including activation of the sympathetic nervous system, systemic inflammation [2], oxidative stress [3], endothelial dysfunction [4], and eventually atherosclerosis [5]. Ultimately, cardiovascular consequences of OSA may include an increased risk of developing alterations in heart rate (variability) [6], systemic hypertension [7–9], and cardiovascular disease, such as myocardial infarction, cardiac arrhythmias, and stroke [10–18].

Continuous positive airway pressure (CPAP) is an effective treatment modality for moderate to severe OSA. Extensive literature on the effects of CPAP on cardiovascular outcomes shows that

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Abbreviations

ABPM	ambulatory blood pressure monitoring
CPAP	continuous positive airway pressure
CVC	cutaneous vascular conductance
DBP	diastolic blood pressure
ECG	electrocardiography
HRV	heart rate variability
NT-pro-BNP	N-terminal pro-brain-type natriuretic peptide
OAT	oral appliance therapy
ODI	oxygen desaturation index
OSA	obstructive sleep apnea
PSG	polysomnography
PWV	pulse wave velocity
RCT	randomized controlled trial
RDI	respiratory disturbance index
SBP	systolic blood pressure

CPAP reduces systolic (SBP) and diastolic (DBP) blood pressure [19], and has a positive effect on inflammation (e.g., reduction of C-reactive protein and interleukin-6) [20], arterial stiffness [21,22], and cardiovascular morbidity and mortality [23,24]. However, patients using CPAP occasionally report discomfort or intolerance, potentially resulting in reduced therapeutic compliance and, eventually, reduced effectiveness.

Oral appliance therapy (OAT), which improves upper airway patency, is an effective alternative for CPAP in mild to moderate OSA [25,26]. In some cases, OAT may be an effective treatment in severe OSA as well [27,28]. Depending on the type of OAT used, oral appliances are well accepted and rated as more comfortable than CPAP, as reflected by higher therapeutic compliance [29]. Despite a generally favorable outcome of OAT in the treatment of OSA, comparative studies focusing on cardiovascular outcomes, including studies comparing OAT to CPAP, are relatively scarce [30].

To date, two systematic reviews on the effect of oral appliances on blood pressure have been published [31,32]. Modest reductions in blood pressure by OAT compared to baseline [31] and inactive control therapies [32] were reported. However, systematic reviews assessing a more complete spectrum of cardiovascular outcomes are lacking. Therefore, this study aims to systematically review current literature on the effects of OAT on a broader spectrum of cardiovascular outcomes; these also include heart rate, heart rate variability, endothelial function, arterial stiffness, circulating cardiovascular biomarkers, cardiac function, and cardiovascular death.

In clinical practice, oral appliances that advance the mandible in a forward position, i.e., mandibular advancement devices, are used most often. Therefore, the present study will exclusively focus on this type of oral appliances.

Methods

Search strategy

A literature search using the databases of PubMed, Embase and CINAHL, was performed up to December 31st 2016. The following keywords were used in the search: (obstructive) sleep apnea (or apnoea), sleep disordered breathing, SAHS, OSA, OSAS, OSAHS, mandibular advancement, removable orthodontic appliances, orthodontic device(s), orthodontic appliance(s), mandibular advancement, mandibular reposition(er/ing), dental device(s), dental appliance(s), oral device(s), oral appliance(s), stroke, cardiovascular disease(s), cardiovascular risk, hypertension, blood pressure, vascular disease, heart disease, atrial fibrillation, coronary artery disease, arterial stiffness, cerebrovascular accident, CVA, transient ischaemic attack, and TIA. Only articles written in English were selected. Papers evaluating a pediatric population (i.e., age <18 y) were excluded from the search. A full overview of the specific searches per database is provided in Appendix 1. Reference list search of relevant review articles and eligible studies was performed to look for possible missing articles.

Inclusion criteria

Articles to be read in full were selected based on title and abstract. Two independent reviewers (GEV and AH) assessed the relevance and methodological quality of each full text article. Abstracts were excluded. Full text articles had to meet all following criteria: 1) studies concerning obstructive sleep apnea patients with an apnea–hypopnea index (AHI) or respiratory disturbance index (RDI) ≥5/h, 2) adult patients (≥18 y of age), 3) intervention with oral appliance alone, or oral appliance compared to another treatment (placebo, CPAP, lifestyle intervention, surgery), 4) report on at least one of the following cardiovascular outcomes in the study: blood pressure, cardiovascular risk, cardiovascular death, cerebrovascular accident, transient ischaemic attack, myocardial infarction, cardiovascular disease(s), vascular disease, heart disease, atrial fibrillation, coronary artery disease, arterial stiffness, endothelial function, ventricular ejection fraction, echocardiography, and cardiovascular related biochemical outcomes.

Methodological appraisal/quality assessment

After selecting the relevant full text articles, studies were individually assessed for methodological quality by two independent reviewers (GEV and AH) using the 'quality of study tool' developed by Sindhu et al. [33]. The articles were rated on 53 weighted items in 15 dimensions (i.e., control group, randomization, measurement of outcomes, design, conclusions, intention-to-treat analysis, statistical analysis, adherence to protocol, blinding, research question, follow-up, outcomes, reporting of findings, compliance, other variables) [33]. A maximum sum score of 100 points could be achieved. To decide whether a study was of sufficient methodological quality, a preset threshold value of 47 points was set based on the methodology of a previous systematic review on oral appliance therapy [34]. In a consensus meeting, all articles and their scores were discussed. In case of a disagreement (based on the sum score), on whether a study was of sufficient methodological quality, the specific item-scores were reassessed in a second meeting until agreement was reached.

Meta-analysis for randomized controlled trials (RCTs)

Statistical analysis

For RCTs that were considered methodologically sufficient, it was assessed whether the available data could be pooled for a meta-analysis.

Data were obtained from the tables and text in the original manuscripts. Standard error (of the mean) was converted into standard deviation based on the number of participants in the study. The mean difference with 95% confidence intervals was calculated for each study.

Review Manager (RevMan version 5.3. Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to produce forest plots. Due to variance in method of assessment and

sample size, random effects models were used. Data were pooled for RCTs addressing the same treatment groups (oral appliances vs. inactive/placebo oral appliances and conservative measures (inactive controls), and oral appliances vs. CPAP).

Heterogeneity among studies was assessed with the Chi^2- and I^2-test. A value of $I^2 > 50\%$ was considered to indicate a substantial level of heterogeneity. Sensitivity analyses in meta-analysis consisted of adding the studies with sufficient methodological quality to the results of RCTs, and of deleting one study at a time to assess the influence of a study on the overall result. Funnel plots were created to check for the existence of publication bias. A p-value of 0.05 was considered statistically significant for the overall effect size.

In summary, three categories were compiled based on methodological quality and study design: 1) insufficient methodological quality, 2) sufficient methodological quality non-RCT, 3) sufficient methodological quality RCT. Only studies of sufficient methodological quality (second and third category) are outlined in the results.

Results

The PubMed, Embase and CINAHL searches yielded 138, 217, and 22 publications, respectively. After deleting duplicates, the search resulted in a total of 271 unique publications. Twenty-seven articles were considered relevant and selected for reading in full. Reference list analysis rendered one additional article for consideration. Of the 28 relevant articles, 27 full text articles were available. There was agreement on 26 of the 27 articles concerning whether or not the study fulfilled the inclusion criteria mentioned in the Methods section. Consensus was reached on the remaining article after critically reassessing the inclusion criteria. A total of three publications was excluded [25,35,36] and 25 relevant full text articles were assessed (Fig. 1).

Initial agreement was reached on the methodological quality of 21 out of 25 articles. After consensus meetings, the reviewers agreed on the methodological quality of all articles. Nine articles were considered of low [37–45] and 16 articles of sufficient [46–50] methodological quality, including 11 RCTs (n = 719 patients) [51–61] (Table 1 shows the study characteristics of articles with sufficient methodological quality).

In the following sections, results are presented per outcome measure; first for RCT studies, and second for non-RCT studies of sufficient methodological quality. Forest plots are displayed for the available data derived from RCTs.

Cardiovascular outcomes

Blood pressure

Sufficient methodological quality, RCT. Gotsopoulos et al. [51] compared OAT with an inactive oral appliance (upper arch only) and found significant reductions in mean 24-h and awake DBP, measured with 24-h ABPM, with the active oral appliance compared to the inactive oral appliance after 4 wk of usage (AHI ≥ 10 events/h, mean AHI 27 events/h, n = 67, 39% on anti-hypertensive medication). Both mean SBP and mean DBP were reduced during wakefulness, but not during sleep (wakefulness and sleep recorded with a diary).

Barnes et al. [52] evaluated 24-h ambulatory blood pressure as a secondary parameter in 110 patients with mild to moderate OSA (5 ≤ AHI ≤ 30 events/h, mean AHI 21.3 events/h, 14.5% with hypertension), of which 80 patients (mean AHI 21.5 events/h) completed all three study arms (oral appliance, CPAP, placebo tablet). Only OAT significantly reduced nighttime DBP after 3 mo compared to baseline, CPAP, and the placebo tablet. A significant proportion of patients, defined as non-dippers, developed a normal nocturnal dipping pattern with oral appliance therapy.

Lam et al. [53] randomized 101 patients (5 ≤ AHI ≤ 40 events/h, mean AHI 21.4 events/h, 18.8% with hypertension) to one of three treatment arms (oral appliance, n = 34, mean AHI 20.9 events/h; CPAP, n = 34, mean AHI 23.8 events/h; conservative measures, n = 33, mean AHI 19.3 events/h). Office blood pressure was measured in the morning and evening (mean of three measurements). After 10 wk, a significant reduction in morning DBP was seen in the oral appliance and CPAP group compared to baseline. There was no difference in effect between both treatment groups.

Gauthier et al. [55] analyzed two types of oral appliances (Silencer and Klearway) in 19 mild to moderate OSA patients (5 ≤ RDI ≤ 30 events/h, mean RDI 10.7 events/h, 37.5% with hypertension). Only for the Silencer (after a treatment period of 3 mo, n = 16, mean baseline RDI 10.0 events/h, range 5–21) a significant reduction in office DBP was observed. However, differences between the Silencer and Klearway oral appliance were not significant.

Trzepizur et al. [56] (AHI ≥ 15 events/h, median AHI 40.0 events/h, n = 12, 42% on anti-hypertensive medication) did not find any changes in blood pressure (measured with a finger monitor) after 2 mo with either oral appliance or CPAP therapy.

Andrén et al. [57] (AHI ≥ 10 events/h, mean AHI 24) found a significant reduction in 24-h mean SBP, measured with 24-h ambulatory blood pressure monitoring (ABPM), exclusively in a subgroup of hypertensive patients with AHI > 15 events/h at baseline (n = 46) after 3 mo of active oral appliance treatment compared to a control group using a sham oral appliance that did not bring the mandible in a forward position (<0.5 mm).

Phillips et al. [58] (randomized group n = 126: AHI > 10 events/h, mean AHI 25.6 events/h, range 10.2–68.8, 42% with hypertension) assessed 24-h ambulatory blood pressure change in 108 OSA patients, who were subjected to 1 mo each of optimal oral appliance and CPAP therapy. Only in the hypertensive subgroup (n = 45) significant reductions in mean SBP and DBP (24-h SBP and DBP, daytime DBP, nighttime SBP) were found with both oral appliance and CPAP compared to baseline. No significant differences were observed between both treatments.

Dal-Fabbro et al. [59] analyzed 24-h ambulatory blood pressure change in 29 patients (AHI ≥ 20 events/h, mean AHI 42.3 events/h, 31% with hypertension) with 1 mo each of OAT, placebo oral appliance, and CPAP therapy. None of the blood pressure parameters changed significantly with OAT. In the oral appliance group, significantly more patients developed a DBP dipping pattern compared to the CPAP group.

Sharples et al. [60] (n = 90, 5 ≤ AHI ≤ 30 events/h, mean AHI 13.8 events/h, range 2.9–27.7, 26% of patients being treated for hypertension but no severe and/or unstable cardiovascular disease at baseline) did not find a reduction in office blood pressure (mean of three measurements) with any of the oral appliances (SleepPro 1™ (n = 77), SleepPro 2™ (n = 78), bespoke MAD (n = 74)) in mild to moderate OSA after a 6 wk period, consisting of 2 wk acclimatization and 4 wk of treatment.

Glos et al. [61] (AHI ≥ 5 events/h, mean AHI 28.5 events/h, range 10.8–83.6, n = 40) found no significant changes in office SBP after 12 wk with either oral appliance or CPAP therapy. Conversely, office DBP did change significantly with both oral appliance and CPAP therapy compared to baseline under spontaneous breathing and breathing at a fixed rate of 6/min. There were no differences between the two treatment modalities.

Sufficient methodological quality, non-RCT. Saletu et al. [46] assessed both the evening and morning blood pressure (type of measure unknown) during an adaptation night, a night using a placebo device, and a night using OAT (after 2–3 wk of use), in a group consisting of seven snorers and 43 OSA patients (AHI ≥ 5 events/h, mean AHI 16.8 events/h). Morning DBP was

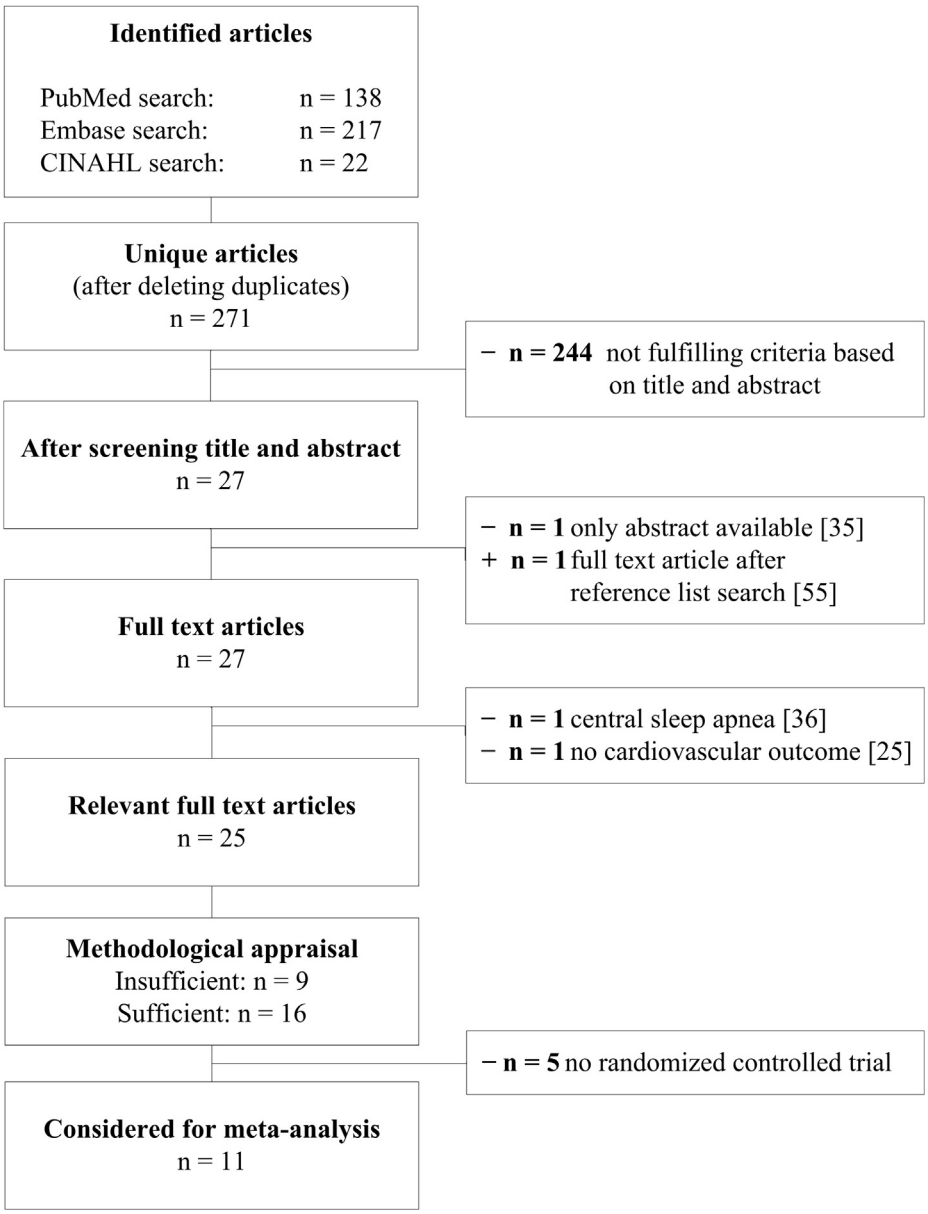

Fig. 1. Study selection procedure.

significantly lower following the oral appliance night compared to the placebo night.

Gauthier et al. [47] compared the effect of two types of oral appliances (Silencer and Klearway) in 14 mild to moderate OSA patients (5 ≤ RDI ≤ 30 events/h, mean RDI 10.4 events/h) after a long-term follow-up period of 40.9 mo. Thirteen patients were normotensive and one patient was hypertensive at baseline. Both SBP and DBP, measured with a sphygmomanometer, showed a significant reduction compared to baseline.

Similarly, Lin et al. [49] did not find a significant reduction in office blood pressure (mean of three measurements) in normotensive, moderately severe to severe OSA patients (AHI ≥ 20 events/h, mean AHI 31.6 events/h) after a two month follow-up period.

Reduction in office SBP and DBP (mean of two measurements) in mild to moderate OSA patients (5 ≤ AHI ≤ 30 events/h, mean AHI 22.9 events/h) without preexisting cardiovascular disease after 3 mo and 1 y of oral appliance treatment did not reach significance [50].

Pooled RCT data showed a significant reduction with oral appliance treatment compared to baseline in both daytime SBP (Fig. 2A, mean change −1.81 mmHg [95% CI −3.58 to −0.03], p = 0.05) and daytime DBP (Fig. 3A, mean change −2.21 mmHg [95% CI −3.86 to −0.56], p = 0.009). The larger reduction in blood pressure with OAT compared to inactive controls (inactive/placebo oral appliance, conservative measures) did not reach significance (mean change −1.55 mmHg [95% CI −3.92 to 0.82], p = 0.20, and mean change −1.14 mmHg [95% CI −2.87 to 0.59], p = 0.20 for systolic and diastolic blood pressure respectively, Figs. 2B and 3B). Compared to CPAP therapy, OAT is equally effective in reducing blood pressure (mean difference in change 0.05 mmHg [95% CI −3.06 to 3.16], p = 0.98, and mean difference in change 0.23 mmHg [95% CI −1.60 to 2.06], p = 0.81 for systolic and diastolic blood pressure, respectively, Figs. 2C and 3C).

However, meta-analysis based on 24-h ABPM and nighttime data did not show any significant reductions between baseline and follow-up values (Appendix 2).

Inclusion of the studies with sufficient methodological quality [46,47,49,50] in the meta-analyses of daytime SBP and DBP had no influence on the overall effect (mean difference from baseline

Table 1
Overview of the study characteristics of articles with sufficient methodological quality.

Study	Study quality score	Study type	Sample size (complete with OA)	Follow-up period	Mean age (y)	Male sex (%)	Mean BMI (kg/m^2)	Baseline AHI/RDI (mean events/h)	Hypertension (medication) (%)	OA type	Type of control	Endpoints
Randomized controlled trials												
Gotsopoulos et al., 2004 [51]	84	RCT Cross-over	67 (61)	2 × 4 wk	48	79	29.2	AHI ≥ 10 (27)	39%	Custom-made adjustable bibloc	Control OA (upper appliance alone) n = 61	24 h ABPM Heart rate
Barnes et al., 2004 [52]	73	RCT Cross-over	110 (85) (80 completed all three arms)	3 × 3 mo	46.4	79	31.0	AHI 5–30 (21.5)	15%	Custom-made Medical Dental Sleep Appliance, R.J. and V.K. Bird, Australia	- CPAP n = 89 - Placebo tablet n = 90	24 h ABPM Pulmonary artery pressure and left ventricular mass (echocardiography)
Lam et al., 2007 [53]	69	RCT Parallel	101 (34)	10 wk	45.7	78	27.4	AHI 5–40 (21.4)	19%	Custom-made non-adjustable Harvold type	- CPAP n = 34 - Conservative measures n = 33	Clinical BP (morning and evening, average of three readings)
Hoekema et al., 2008 [54]	61	RCT Parallel	28 (12)	2–3 mo	49.7	89	33.3	AHI > 20 (52.2)	93%	Custom-made adjustable bibloc Thornton adjustable positioner (Airway Management, Inc., Dallas, TX, USA)	CPAP n = 13	Left ventricular structure and function (echocardiography) NT-pro-BNP (venous blood samples)
Gauthier et al., 2009 [55]	76	RCT Cross-over	19 (16)	2 × 3 mo	47.9	69	28.7	RDI 5–30 (10.0)	38%	Silencer (Burnaby, British Columbia) Klearway (Ottawa, Ontario)	Klearway n = 16	Clinical BP (secondary)
Trzepizur et al., 2009 [56]	66	1: Prospective follow-up study 2: RCT cross-over	15 (12)	2 × 2 mo	56*	92	29.4*	AHI ≥ 30 (40*)	42%	Custom-made adjustable bibloc (AMC™, Artech Medical, Pantin, France)	Protocol 1: control group (AHI < 15) n = 9 Protocol 2: CPAP n = 12	Endothelial function (laser Doppler flowmetry) Clinical BP (secondary)
Andrén et al., 2013 [57]	78	RCT Parallel	72 (36)	3 mo	58	79	30	AHI ≥ 10 (24)	89%	Custom-made monobloc	Control OA (<0.5 mm) n = 36	24 h ABPM
Phillips et al., 2013 [58]	76	RCT Cross-over	126 (108)	2 × 1 mo	49.5	81	29.5	AHI > 10 (25.6)	42%	Somnodent (SomnoMed Ltd., Sydney, Australia)	CPAP n = 108	24 h ABPM Arterial stiffness (secondary)
Dal-Fabbro et al., 2014 [59]	66	RCT Cross-over	39 (29)	3 × 1 mo	47.0	83	28.4	AHI ≥ 20 (42.3)	31%	Custom-made adjustable bibloc Brazilian dental appliance	- CPAP n = 29 - Placebo OA n = 29	24 h ABPM Oxidative stress Heart rate variability (ECG of PSG)
Sharples et al., 2014 [60]	73	RCT Cross-over	90 (74)	6 wk	50.9	80	30.6*	AHI 5–30 (13.8)	26%	1. self-moulded [SleepPro 1™] 2 .semibespoke [SleepPro 2™] 3. fully bespoke [bMAD]	No treatment n = 76	Clinical BP (average of three readings)
Glos et al., 2016 [61]	58	RCT Cross-over	48 (40)	2 × 12 wk	49.5	83	28.3	AHI ≥ 5 (28.5)	unknown	Custom-made adjustable bibloc Somnodent (SomnoMed Europe AG, Zurich, Switzerland)	CPAP n = 40	Heart rate variability Continuous blood pressure Baroreceptor sensitivity
Non randomized controlled trials												
Saletu et al., 2007 [46]	51	Single blind placebo controlled case series	50 (50)	2–3 wk	59.7	74	NR	AHI ≥ 5 (16.8)	unknown	Adjustable bibloc (Intraoral Snoring Therapy)	none	Clinical BP (secondary)
Gauthier et al., 2011 [47]	58	Longitudinal design	14 (14)	40.9 mo	51.9	71	NR	RDI 5–30 (10.4)	7%	Custom-made adjustable - Silencer (Burnaby, British Columbia) - Klearway (Ottawa, Ontario)	none	Cardiac rhythm (secondary) Clinical BP with sphygmomanometer (secondary)

(*continued on next page*)

Table 1 (*continued*)

Study	Study quality score	Study type	Sample size (complete with OA)	Follow-up period	Mean age (y)	Male sex (%)	Mean BMI (kg/m^2)	Baseline AHI/RDI (mean events/h)	Hypertension (medication) (%)	OA type	Type of control	Endpoints
Anandam et al., 2013 [48]	55	Observational cohort study	562 (72)	Median 79 mo (IQR 76–88 mo)	50.8#	57#	37.1#	AHI ≥ 30 (44.5#)	51%	Custom-made	- Control group (AHI < 5) n = 208 - CPAP group n = 177 - Untreated group n = 212	Fatal cardiovascular events
Lin et al., 2015 [49]	51	Observational	30 (19)	2 mo	50	80	28.3	AHI ≥ 20 (31.6)	0%	Custom-made bibloc	- Controls without OSA n = 15 - OA failure n = 11	Endothelial function (FMD) Nitric oxide levels (blood serum) Clinical BP (average of three recordings) (secondary)
Galic et al., 2016 [50]	52	Prospective study	18 (15)	3 mo 1 y	51.2	93	28.1	AHI 5–30 (22.9)	unknown	Custom made adjustable Silensor-sl Erkodent Germany	none	Arterial stiffness (PWV) Glucose metabolism Inflammation (secondary) Clinical BP (average of two recordings) (secondary)

ABPM = ambulatory blood pressure measurement; AHI = apnea–hypopnea index; BP = blood pressure; CPAP = continuous positive airway pressure; ECG = electrocardiography; FMD = flow-mediated dilatation; IQR = interquartile range; NT-pro-BNP = N-terminal pro-brain-type natriuretic peptide; OA = oral appliance; OSA = obstructive sleep apnea syndrome; PSG = polysomnography; PWV = pulse wave velocity; RCT = randomized controlled trial; RDI = respiratory disturbance index; RH-PAT = reactive hyperemia-peripheral arterial tonometry; TBARS = thiobarbituric acid reactive substances.
* = median, # = data displayed for oral appliance group, NR = not reported.
Baseline age, gender, BMI, AHI/RDI and percentage hypertension are displayed (for the studies by Lam et al. [53], Andrén et al. [57] and Lin et al. [49], means were calculated based on the data from the randomized groups).

−1.92 mmHg [95% CI −3.47 to −0.38], p = 0.01 and −2.45 mmHg [95% CI −3.93 to −0.97], p = 0.001 for SBP and DBP, respectively). Sensitivity analyses showed a strong influence of the study by Gotsopoulos [51] on daytime SBP. A small amount of asymmetry exists in the funnel plot for DBP, but not for SBP (Appendix 2).

Heart rate

Heart rate

Sufficient methodological quality, RCT. Gotsopoulos et al. [51] assessed the heart rate derived from the 24-h ABPM. Heart rate during wakefulness was significantly lower after treatment with the oral appliance compared to the inactive oral appliance (upper arch only). However, there was no difference between the oral appliance and the control therapy when asleep.

Dal-Fabbro et al. [59] found no changes in heart rate (24-h ABPM) after 1 mo of oral appliance treatment compared to baseline, placebo oral appliance, and CPAP.

Sufficient methodological quality, non-RCT. Saletu et al. [46] assessed both evening and morning pulse rates during an adaptation night (without any device), a night using a placebo device, and a night using OAT. The morning pulse rate was significantly lower after the oral appliance night than after the placebo night.

Gauthier et al. [47] found that pulse rate significantly decreased at follow-up (mean 40.9 mo) compared to baseline.

Galic et al. [50] assessed heart rate data before, and after 3 mo, and 1 y of follow-up. There was no significant treatment effect compared to baseline.

Pooled RCT data showed no significant reductions in heart rate compared to baseline, inactive controls, and CPAP, except for mean daytime heart rate when comparing OAT to inactive controls (Fig. 4B, mean change −2.58 beats/min [95% CI −5.06 to −0.10], p = 0.04). Sensitivity analyses showed a strong influence of the study by Gotsopoulos [51] on daytime heart rate when comparing OAT to an inactive oral appliance. Results based on 24-h ABPM and nighttime data are shown in Appendix 2.

Including the studies with sufficient methodological quality [46,47,50] in the meta-analysis of daytime heart rate (comparing OAT with baseline) had no influence on the overall effect (mean difference from baseline −1.66 mmHg [95% CI −3.68 to −0.36], p = 0.11).

Heart rate variability (HRV)

Sufficient methodological quality, RCT. Dal-Fabbro et al. [59] analyzed HRV in 29 patients using the electrocardiography (ECG) signal derived from polysomnography (PSG). After 1 mo of optimal therapy with each of the treatment modalities, total power at night significantly decreased with oral appliance and CPAP compared to the placebo oral appliance. The 'high frequency' (in power ms^2/frequency Hz) at night was significantly reduced for the CPAP group only. Furthermore, a reduction in the index of sleep autonomic variation was found exclusively for OAT compared to baseline.

Glos et al. [61] studied the effect of both 12 wk of oral appliance and CPAP therapy on cardiac autonomic function during daytime under four conditions of controlled breathing (spontaneous breathing, 6, 12, and 15/min) using the ECG signal of PSG. R–R interval, low frequency, and low/high frequency ratio values did not change compared to baseline. The only significant improvement was found for the high frequency component (power in ms^2) under the 12/min breathing protocol. There were no differences between the two treatment modalities.

Meta-analysis on HRV was not possible due to a difference in the units used for the outcome parameter (power ms^2/frequency Hz vs. power ms^2).

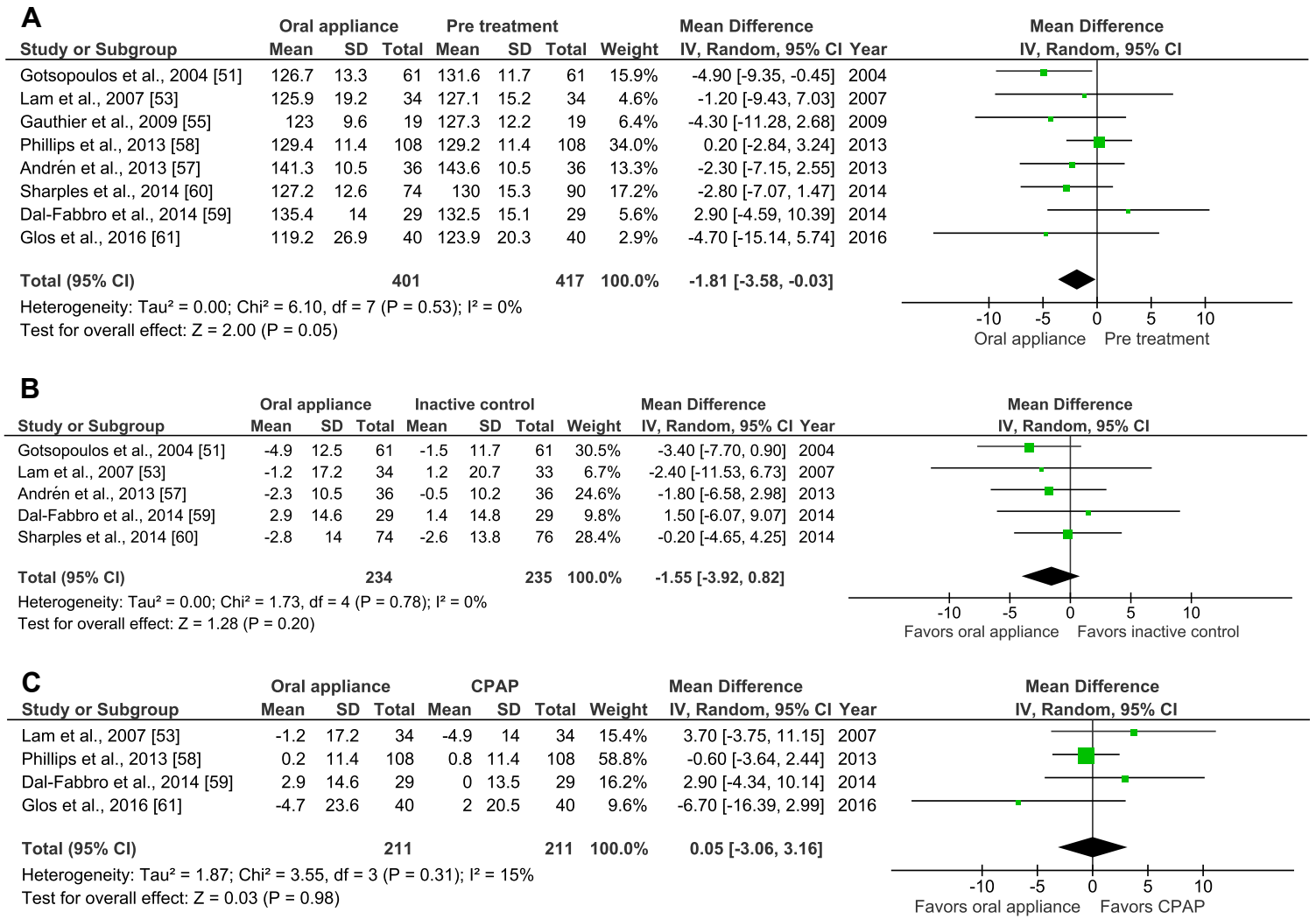

Fig. 2. Mean change in daytime systolic blood pressure (mmHg). A. Oral appliance vs. baseline. B. Oral appliance vs. inactive controls. C. Oral appliance vs. CPAP. Note: CI = confidence interval; IV = inverse variance; SD = standard deviation; Lam et al.: morning blood pressure was used, inactive control = conservative measures; Glos et al.: data for the spontaneous breathing protocol was used; Gotsopoulos et al.: per protocol analysis (efficacy) n = 61 was used; Sharples et al.: the bespoke mandibular advancement device (bMAD) was used as primary oral appliance treatment, inactive control = no treatment; Gauthier et al.: the Silencer was used as primary oral appliance treatment.

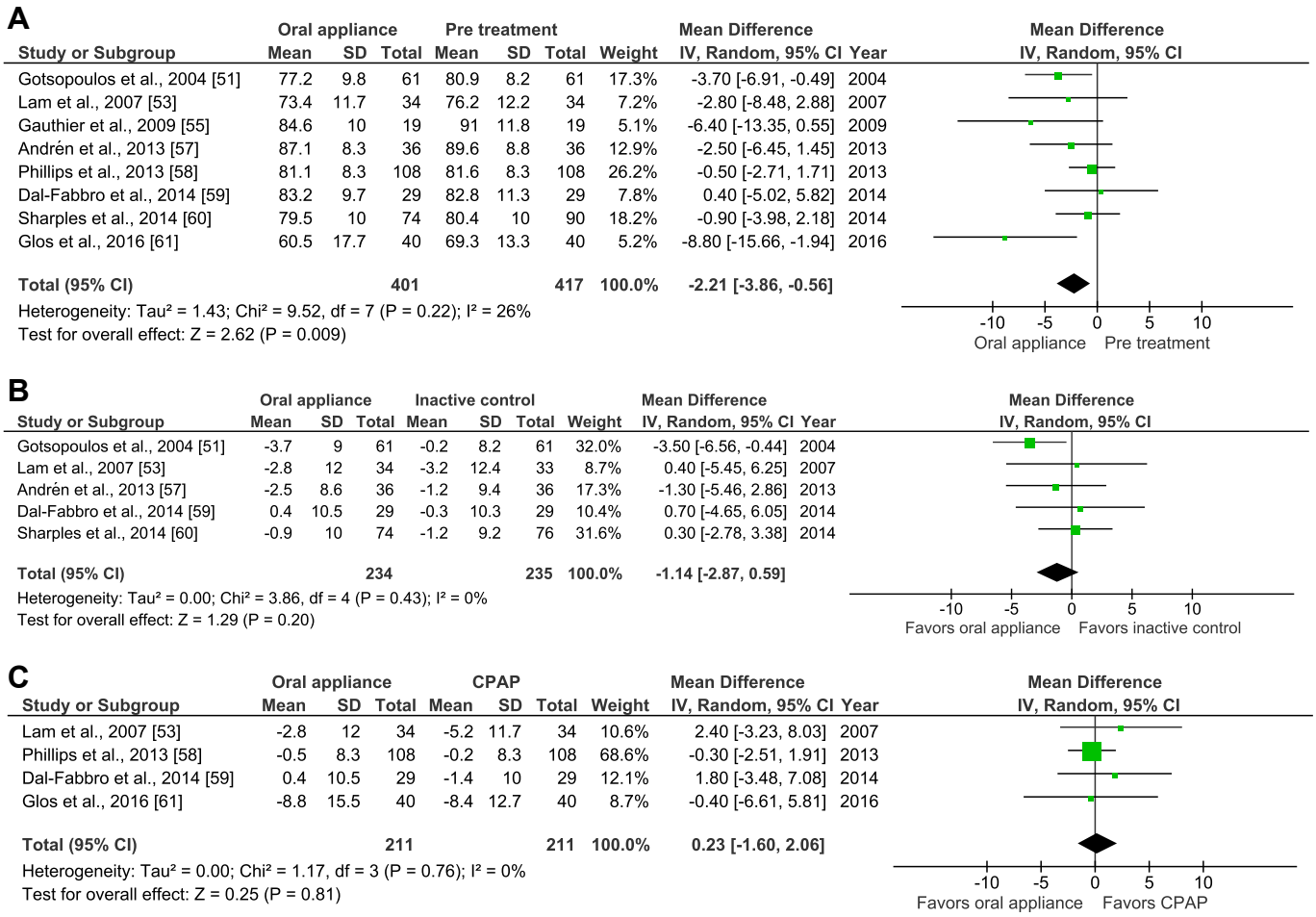

Fig. 3. Mean change in daytime diastolic blood pressure (mmHg). A. Oral appliance vs. baseline. B. Oral appliance vs. inactive controls. C. Oral appliance vs. CPAP. Note: CI = confidence interval; IV = inverse variance; SD = standard deviation; Lam et al.: morning blood pressure was used, inactive control = conservative measures; Glos et al.: data for the spontaneous breathing protocol was used; Gotsopoulos et al.: per protocol analysis (efficacy) n = 61 was used; Sharples et al.: the bespoke mandibular advancement device (bMAD) was used as primary oral appliance treatment, inactive control = no treatment; Gauthier et al.: the Silencer was used as primary oral appliance treatment.

Cardiac function

Sufficient methodological quality, RCT. Barnes et al. [52] used transthoracic echocardiography to assess the effect of an oral appliance, CPAP, and a placebo tablet on pulmonary artery pressure (n = 35) and left ventricular mass (n = 89). None of the treatments had a significant effect after 3 mo.

Hoekema et al. [54] also used echocardiography to image left ventricular structures and function in 28 patients with moderate to severe OSA (AHI > 20 events/h, mean AHI 52.2 events/h) without cardiovascular disease. Neither OAT nor CPAP therapy had significant effects on echocardiographic outcomes, including left ventricular mass after 2–3 mo of follow-up.

Barnes et al. [52] did not provide follow-up data (actual numbers) for left ventricular mass. Therefore, pooling data for OAT and CPAP therapy with data from Hoekema et al. [54] was not possible.

Circulating cardiovascular biomarkers

NT-pro-BNP

Sufficient methodological quality, RCT. Hoekema et al. [54] assessed N-terminal pro-brain-type natriuretic peptide (NT-pro-BNP) levels (pg/ml) after 2–3 mo of OAT. Median NT-pro-BNP levels with OAT decreased significantly compared to CPAP therapy. The authors stated that their results should be interpreted with caution due to baseline differences between the oral appliance and CPAP groups.

Oxidative stress

Sufficient methodological quality, RCT. Dal-Fabbro et al. [59] found no significant changes in most oxidative stress parameters (thiobarbituric acid reactive substances, erythrocyte superoxide dismutase activity, uric acid, homocysteine, folate, vitamins B_{12} and E) after 1 mo of OAT (or CPAP treatment and placebo) in 29 patients with an AHI ≥ 20 events/h. Only erythrocyte catalase activity was significantly lower, and vitamin B_6 concentrations were significantly higher after OAT compared to baseline. CPAP and placebo oral appliance resulted in significantly increased levels of vitamins C and B_6, compared to baseline. The more relevant comparisons between the groups for erythrocyte catalase activity, vitamins C and vitamin B_6 were not provided.

Sufficient methodological quality, non-RCT. Lin et al. [49] found that reduced serum levels of nitric oxide derivatives (NO_x) restored to normal after two months of successful OAT.

Inflammatory markers

Sufficient methodological quality, non-RCT. Galic et al. [50] found that inflammatory markers (high sensitivity C-reactive protein, and

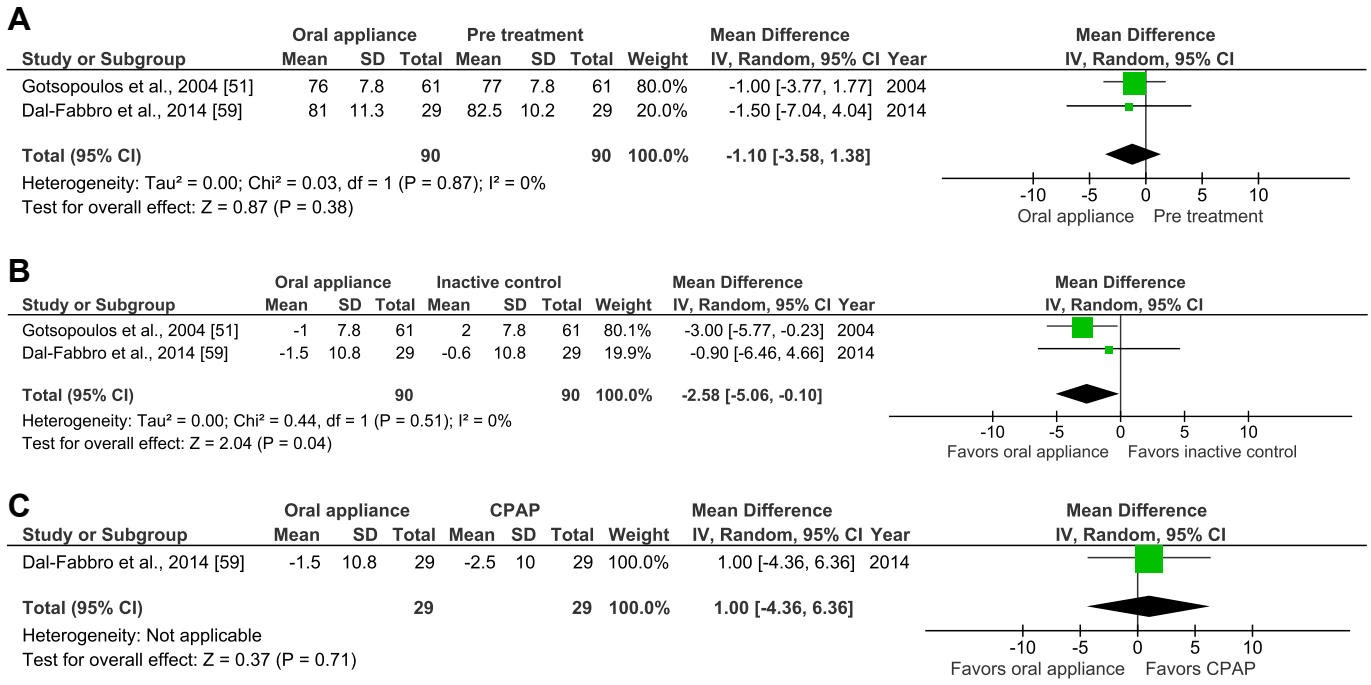

Fig. 4. Mean change in daytime heart rate (beats/min). A. Oral appliance vs. baseline. B. Oral appliance vs. inactive controls. C. Oral appliance vs. CPAP. Note: CI = confidence interval; IV = inverse variance; SD = standard deviation.

fibrinogen) were reduced after 3 mo, and 1 y of treatment with OAT in mild to moderate OSA patients, with levels of fibrinogen showing significant reductions.

Due to the heterogeneity of the outcome parameters in circulating cardiovascular biomarkers, a meta-analysis was not possible.

Endothelial function and arterial stiffness

Endothelial function

Sufficient methodological quality, RCT. Trzepizur et al. [56] measured microvascular endothelial function (cutaneous vascular conductance (CVC)) using laser doppler flowmetry combined with acetylcholine and sodium nitroprusside iontophoresis in two different protocols (protocol 1: 12 patients with OSA versus nine controls, protocol 2: 12 OSA patients receiving oral appliance and CPAP). A significantly higher peak CVC was found in the control group (AHI < 15 events/h) than in the OSA group after acetylcholine induced vasodilatation (protocol 1). Both oral appliance and CPAP treatment resulted in a significant increase in acetylcholine induced peak CVC, indicating improved endothelial function (protocol 2) after a treatment period of 2 mo.

Sufficient methodological quality, non-RCT. Lin et al. [49] compared 30 OSA patients with 15 healthy controls. Before treatment, endothelial function, measured by endothelium-dependent flow-mediated dilatation, was lower in OSA patients compared to healthy controls. After two months of OAT, successful therapy (n = 19) resulted in a significant improvement of endothelial function, whereas this positive outcome was not seen in patients categorized as treatment failures (n = 11). A comparison between groups was not provided.

Arterial stiffness

Sufficient methodological quality, RCT. Phillips et al. [58] found significant reductions in arterial stiffness (aortic augmentation index measured with sphygmocor) after 1 mo of oral appliance and CPAP therapy.

Sufficient methodological quality, non-RCT. Galic et al. [50] assessed arterial stiffness using pulse wave velocity (PWV) in 15 mild to moderate OSA patients. PWV did not change after 3 mo, but decreased significantly after 1 y of oral appliance treatment compared to baseline, indicating a reduction in arterial stiffness.

Due to the heterogeneity of the outcome parameters and paucity of studies assessing endothelial function and arterial stiffness, a meta-analysis was not possible.

Cardiovascular events

Sufficient methodological quality, non-RCT. Just one study reported on morbidity and cardiovascular mortality in OSA. Anandam et al. [48] investigated 562 subjects with severe OSA (AHI ≥ 30 events/h), who were offered CPAP initially and an oral appliance, if non-compliant, after 3 mo (n = 461 were available for analysis; CPAP group n = 177, mean AHI 44.8 events/h; OAT group n = 72, mean AHI 44.5 events/h; untreated group n = 212, mean AHI 43.4 events/h), and compared this with a control group of 208 subjects (AHI < 5 events/h) for a median follow-up of 79 mo. They concluded that an oral appliance is as effective as CPAP in reducing cardiovascular death (hazard ratio 1.08 (95% CI: 0.55–1.74), p = 0.71). Furthermore, cumulative cardiovascular death was significantly higher in untreated patients than in patients using an oral appliance (p = 0.047) or CPAP (p < 0.001).

Discussion

OSA is associated with increased cardiovascular morbidity and mortality, with worse prognosis for patients with higher OSA severity. Since systematic reviews that assess a complete spectrum of cardiovascular outcomes, and not only blood pressure, are

currently lacking, this study was performed to systematically review the available literature on the effects of OAT on blood pressure, heart rate, heart rate variability, endothelial function, arterial stiffness, circulating cardiovascular biomarkers, cardiac function, and cardiovascular death.

Blood pressure

Pooled data based on the RCTs included in our meta-analysis showed a significant reduction in both daytime SBP (−1.8 mmHg, p = 0.05) and daytime DBP (−2.2 mmHg, p = 0.009) compared to baseline values. Oral appliances and CPAP resulted in equal reductions in blood pressure. Inactive control therapy, including inactive oral appliances, conservative measures (advice to attend a weight control program when overweight), and placebo tablets also had a small effect on blood pressure [51,53,57,59,60]. This could explain why the slightly larger reduction in blood pressure with OAT was not significantly different from that seen in the inactive control group.

Nighttime SBP and DBP reductions during OAT were not statistically significant nor clinically relevant (mean differences compared to baseline were −0.07 and −0.77 mmHg for SBP and DBP, respectively; Appendix 2). The study by Hermida et al. [62], performed in subjects who were normotensive, untreated essential hypertensive, or resistant to treatment, but otherwise healthy, showed a 17% reduction in cardiovascular disease risk for every 5 mmHg reduction in mean SBP during sleep (median follow-up of 5.6 y). In addition, mean blood pressure during sleep was found to be the most significant prognostic marker of cardiovascular disease morbidity and mortality [62,63]. Although small reductions in blood pressure might therefore be clinically relevant, the reductions found in our meta-analysis seem too small, and completely lack any clinical relevance. Major differences between the study by Hermida et al. [62] and the studies included in the current meta-analysis are the follow-up period (5.6 y versus 1–3 mo), and the population studied, which might explain the smaller reduction in blood pressure in our meta-analysis. Furthermore, all studies, except for Gotsopoulos et al. [51], in the present meta-analysis using 24-h ABPM, defined the nighttime and daytime period of the 24-h ABPM based on fixed clock hours, without knowledge about actual sleep.

Compared to an earlier meta-analysis, the beneficial effect of OAT on blood pressure outcomes was less evident. In the systematic review by Iftikhar et al. [31], the application of oral appliances resulted in a lowering of −2.7 mmHg, −2.8 mmHg, and −1.7 mmHg for SBP, DBP, and nocturnal DBP, respectively, compared to baseline. This effect was primarily due to the results of the included observational studies in the meta-analysis. On average, these observational studies showed larger blood pressure lowering effects than RCTs, thereby influencing the total effect. Next to the possibility of a placebo effect, this might partly be explained by the method of blood pressure measurement used. Most observational studies used office blood pressure measurements, whereas RCTs more frequently used 24-h (or 20-h) ABPM. This explains the larger reductions found by Iftikhar et al. [31] compared to the results observed in the present meta-analysis.

Our analyses differed from those by Bratton et al. [32] in that we based our blood pressure analyses on 24-h, daytime, and nighttime measurements. Therefore, the study by Barnes et al. [52] was not included in our daytime meta-analysis, as their manuscript only provides 24-h mean SBP and DBP, and nighttime DBP. However, the overall result did not change when including this study in the meta-analysis of daytime SBP compared to inactive controls. The small difference in overall outcome is probably the result of different methods used for meta-analysis.

Although there is evidence that especially OSA patients with a non-dipping pattern at night are at higher risk for cardiovascular events [64], only a few studies assessed the relative reduction in blood pressure during sleep (dipping versus non-dipping pattern) resulting from OAT and CPAP therapy. This parameter of 24-h blood pressure measurement could be of potential value in future research.

Heart rate (variability)

Increased resting heart rates and reduced HRV may lead to increased cardiovascular morbidity and mortality [65]. Reducing heart rate and increasing HRV could therefore be beneficial for patients. In the present systematic review, pooled data on the RCTs showed that reductions in heart rate after OAT were larger during daytime than during nighttime. However, this result was based on only two RCTs, and only a significant reduction was found for daytime heart rate when comparing OAT to inactive controls; a result that was largely driven by the study of Gotsopoulos et al. [51] (mean change −2.58 beats/min, p = 0.04). Furthermore, in most subjects, despite having OSA, daytime heart rates are higher than nocturnal heart rates. As heart rate reduction usually is displayed in absolute values (beats/min), and not in percentage reduction, daytime heart rate can show larger reductions. The heart rate reductions with OAT were comparable to those found with CPAP [66].

In addition, there are studies showing a reduced HRV in OSA patients compared to controls without OSA [6,67,68]. Research on the effect of OAT on HRV is limited. Only four studies [37,40], of which two RCTs [59,61] analyzed the effect of OAT on HRV. Those two RCTs showed some beneficial effects on different outcome parameters. A closer look at the available literature suggests that frequency domain parameters (such as low frequency divided by high frequency, representing the ratio of sympathetic to parasympathetic activity) are more valuable to measure than time domain parameters, as time domain parameters only provide limited data on the function of the autonomic nervous system [6]. Thus, there appears to be some favorable effects, but data are too limited and results are too heterogeneous to draw definitive conclusions.

Cardiac function

Only two studies investigated the effect of OAT on cardiac function. Both Hoekema et al. [54] and Barnes et al. [52] assessed left ventricular mass and did not find any effect of oral appliance on this heart function parameter after 3 mo of treatment. Literature on the effect of CPAP therapy on right and left ventricular remodeling and performance is also limited and inconclusive. Positive effects found with CPAP were observed in studies with a follow-up of at least 6 mo [69,70].

To date, there is a lack of good quality (RCT) data assessing the effect of OAT on cardiac arrhythmias. This is a prominent finding, as there is accumulating evidence recognizing the association between OSA and cardiac arrhythmias, in particular atrial fibrillation [18]. Given the low incidence of atrial fibrillation in OSA, long-term studies are needed to demonstrate relevant risk reduction.

Circulating cardiovascular biomarkers

A few studies addressed the effect of OAT on circulating cardiovascular biomarkers. Our search profile for this systematic review did not include specific keywords for those markers, such as ‘inflammation’ or ‘metabolic’. Due to this limitation one study on

inflammatory and hemostatic markers [71] was not included in this systematic review. Regardless, even when taking this study into account, there are only a few studies considering the effect of OAT on circulating cardiovascular biomarkers; these studies are generally small and very heterogeneous with respect to their outcomes [49,50,54,59]. Therefore, further research is needed to elucidate the effects of OAT on circulating cardiovascular biomarkers and their clinical relevance.

Endothelial function and arterial stiffness

More consistent results have been observed with regard to the effects of oral appliances on arterial stiffness. Although meta-analysis on endothelial function and arterial stiffness was not possible, it appears that OAT improves these vascular measures. Interestingly, a recent study [72], published after our literature search (December 2016), showed that OAT reduced OSA severity and related symptoms, but had no effect on endothelial function and blood pressure, despite high treatment compliance, in moderately sleepy patients with severe OSA. The evidence for CPAP is more extensive as two meta-analyses have demonstrated decreased arterial stiffness using this strategy [21,22].

Cardiovascular events

To date, only one study [48] assessed the effect of OAT on cardiovascular events. Anandam et al. [48] concluded that an oral appliance is as effective as CPAP in reducing cardiovascular death. However, this was not an RCT and selection bias may have occurred. A study directly comparing cardiovascular event rates is important, but will probably require many patients and certainly long-term follow-up.

The effect of CPAP on cardiovascular events and mortality has been studied more extensively; two meta-analyses showed positive effects of CPAP therapy [23,24]. Conversely, a recent RCT by McEvoy et al. (SAVE study [73]) showed contradictory results in that CPAP therapy did not prevent cardiovascular events. Relative low compliance (mean usage of 3.3 h) could have prevented beneficial effects. As suggested by a post hoc analysis by Barbé et al. [74], patients with sufficient CPAP use, i.e., at least 4 h, may have lower incidence of cardiovascular events than patients with low compliance.

General issues

ODI vs. AHI

There are some general issues to consider when evaluating the effects of OAT on cardiovascular outcomes. There is debate about whether the best respiratory parameter to be used is the AHI or the oxygen desaturation index (ODI). Due to the formula of AHI, every apnea and/or hypopnea contributes to the 'weight' of this outcome measure to the same extent. Therefore, when considering cardiovascular outcomes, total duration of apneas and/or hypopneas per minute, hour, or the amount of time spent under a certain saturation threshold, might be a better measure of outcome than AHI. ODI could potentially provide more predictive information on cardiovascular effects in OSA patients, as the ODI scores the events of reductions in blood oxygen levels irrespective whether cessation in airflow is taking place. Intermittent hypoxia is thought to evoke a chain of cardiovascular responses. For example, data from the European sleep apnoea database (ESADA) cohort showed that ODI, and not AHI, was an independent predictor of prevalent hypertension [75]. ODI can be further classified based upon a $\geq$3% or $\geq$4% desaturation. A large retrospective study [76] assessed the relation between different ODI cutoff values, BMI, and AHI and found that $\geq$3% ODI performed best at predicting moderate and severe (AHI $\geq$ 15 events/h) OSA and was better than $\geq$4% ODI when examining non-obese subjects. However, Punjabi et al. [77] demonstrated that hypopneas and ODI defined based on a threshold of oxyhemoglobin desaturation of at least 4% were associated with cardiovascular disease, and that no association was found between cardiovascular disease and hypopneas and ODI based on milder (i.e., 2 or 3%) desaturations. In addition, the study by Tkacova et al. [75] showed that using the $\geq$4% oxyhemoglobin desaturation cutoff value was more predictive of arterial hypertension than the $\geq$3% desaturation cutoff value. Therefore, when measuring cardiovascular endpoints, the $\geq$4% oxyhemoglobin desaturation cutoff value might be better to use than the $\geq$3% desaturation cutoff value.

Compliance

Another issue is the compliance factor in OSA intervention trials. Oral appliances are considered less effective than CPAP, but are usually thought to be better tolerated, resulting in higher compliance rates. Grote et al. [78] introduced the concept of 'mean disease alleviation', which combines compliance and efficacy. We did not perform a meta-regression analysis for possible confounding factors, such as compliance rates. It might be interesting to assess the 'mean disease alleviation' in future research to incorporate the effect of compliance in therapeutic efficacy. Unfortunately, OAT often lacks the technology to assess objective daily compliance. Response effects can only be interpreted if compliance data can be shown. Due to the lack of objective compliance data in the OAT studies included, any interpretation of being effective or not is preliminary and inconclusive. However recently, compliance monitors have become available for OAT, allowing direct comparison between objective OAT and CPAP compliance in future studies.

Generalization of results

Furthermore, duration of the treatment period, the effect of medication and e.g., blood pressure levels at baseline could have influenced results as well. The follow-up periods used in the RTCs discussed in this systematic review, were between 1 and 3 mo, which may be too short to result in clinically relevant effects. Required follow-up periods in order to measure any effect(s) on specific cardiovascular outcomes are unknown. Studies assessing effects at different time points during a long-term follow-up period, for example 5–10 y, may shed some light on this topic. Furthermore, some cardiovascular damage may be irreversible and therefore, the time period between OSA onset and OSA diagnosis may have a large effect on study outcomes. An important finding is that most studies (observational and RCT) included patients with hypertension or patients on anti-hypertensive medication. Several studies found a significant reduction in blood pressure with OAT exclusively in the hypertensive subgroup [43,57,58]. Ideally, 24-h ABPM should be used for the diagnosis of and treatment effects on hypertension instead of office blood pressure [79]. However, as mentioned above, most studies that found a significant reduction in blood pressure assessed the office blood pressure, which may lead to an overestimation of the percentage of patients with hypertension at baseline, due to the white coat effect. As OAT is expected to reduce the activation of the sympathetic nervous system, thereby reducing the white coat effect, a larger reduction of blood

pressure could be expected at follow-up when office blood pressure rather than 24-h ABPM is used.

A strength of this meta-analysis is the fact that only methodologically sound RCTs were included, thereby excluding a substantial amount of studies. When taking a close look at the results of the insufficient methodological quality studies compared to the RCTs, it can be concluded that on average the observational studies of insufficient methodological quality demonstrate larger effects. When including those studies in the meta-analysis it could result in an overestimation of the effect of OAT.

However, the field of oral appliance therapy (and this systematic review) faces the problem of generalizing conclusions from small studies in a limited range of mild to moderately severe OSA, to the complete spectrum of sleep-disordered breathing. Studies assessing the effects of OAT are characterized by selection bias. In many studies OAT is provided after CPAP failure. Furthermore, OAT often is not a (primary) treatment option due to dental criteria, patient preference, intolerance for intraoral objects, temporomandibular disorders, or local reimbursement circumstances. This results in a sample mixture including mild OSA, but also more severe to very severe OSA. On the other hand, there is a close association between OSA severity and cardiovascular effects. Therefore, the way of sampling complicates in depth conclusions and precludes to make final conclusions. Moreover, as mentioned above, most studies included patients with arterial hypertension and/or using anti-hypertensive medication. Again, depending on the mixture of these types of patients in the study, findings will be in favor of blood pressure lowering effects of OAT or not.

Due to the heterogeneity of the outcome measures, the different methods used to analyze those outcomes, and on top of that the small number of studies on certain topics, meta-analyses could not be performed for heart rate variability, cardiac function, circulating cardiovascular biomarkers, and vascular outcomes. This may have resulted in an incomplete overview of the data. Importantly, this underscores the need for more well designed RCTs to evaluate the effect of OAT on cardiovascular outcomes.

Practice points

1) There is a scarcity of good data on cardiovascular outcomes in more severe OSA, which is remarkable given the relatively abundant data on the clinical efficacy of oral appliance therapy on many clinical domains in the treatment of obstructive sleep apnea;
2) Oral appliance therapy has beneficial, but minor, effects on daytime systolic and diastolic blood pressure compared to baseline, and on daytime heart rate compared to inactive therapies;
3) Studies assessing the effect of oral appliance therapy on endothelial function and arterial stiffness, circulating cardiovascular biomarkers, cardiac function, and heart rate variability, generally involve small numbers of patients, and are heterogeneous and inconclusive;
4) To date, only a limited number of studies have been conducted (both RCT and non-RCT) that assess more burdensome and expensive measurements, such as endothelial function and arterial stiffness, circulating cardiovascular biomarkers, and cardiac function.

Research agenda

1) Future research should focus on the long-term effects (e.g., 10 y) of oral appliance therapy on cardiovascular outcomes, including morbidity and mortality;
2) More research directly comparing the effect(s) of continuous positive airway pressure and oral appliance therapy on these outcomes is needed.

Conclusion

OAT has positive but minor effects on mean daytime SBP and DBP. In some patients, OAT and CPAP can be equally effective in reducing blood pressure. In addition, mean daytime heart rate improves with OAT compared to inactive/placebo oral appliances. Of note, this result was based on only two RCTs. Studies assessing the effect of OAT on heart rate variability, circulating cardiovascular biomarkers, and endothelial function and arterial stiffness, generally involved small numbers of patients, and were heterogeneous and inconclusive. Merely two studies assessed the effect of OAT on cardiac function, neither showed effects on echocardiographic outcomes. Only one observational study assessed the effect of OAT on cardiovascular events and showed that OAT was as effective as CPAP in reducing cardiovascular death.

It could be speculated that OAT may lead to a reduction in (long-term) cardiovascular morbidity and mortality in OSA patients. However, scientific research in the field of OAT struggles with generalizing conclusions due to selection bias, and small studies in a limited range of OSA severity, combined with a close association between OSA severity and cardiovascular effects.

The results of this review underscore the need for more well designed RCTs to evaluate the effect of OAT on cardiovascular outcomes in a larger range of OSA severity. Large databases are warranted to be able to pool individual data and show effects in different subgroups of OSA patients.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.smrv.2017.10.004.

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