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Diagnostics and therapeutic options in obstructive and central sleep apnea syndrome

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Diagnostics and therapeutic options in obstructive and central sleep apnea syndrome

Grietje Knol-de Vries

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Chapter 1

General introduction

Introduction

Sleep apnea is characterized by repetitive breathing cessations during sleep and can be divided into two prominent types: obstructive sleep apnea (OSA) and central sleep apnea (CSA).

OSA is a common sleep-related breathing disorder affecting 14% of men and 5% of women of the middle-aged working population¹. It is the result of repetitive collapse of the upper airway, resulting in airflow reduction (hypopnea) or a complete cessation in airflow (apnea), causing intermittent hypoxia and hypercapnia, and often disruptive snoring. The increased respiratory efforts to restore oxygen levels result in activation of the sympathetic nervous system, brief awakenings from sleep (arousals), sleep fragmentation, and ultimately excessive daytime sleepiness (EDS), an impaired quality of life², and increased levels of sick leave and work disability³⁻⁶. There is accumulating evidence for a causal link between OSA and the development of sustained periods of hypertension and cardiovascular diseases, such as myocardial infarction, cardiac arrhythmias and stroke⁷⁻¹⁰. Known risk factors for OSA include obesity, a large neck circumference and central body fat distribution¹¹. Male sex, increased age, alcohol use in the evening, smoking, and the use of respiratory depressant- or sedative medication also increase the risk of having apneas and/or hypopneas¹². Of these, obesity is the most important risk factor and as the number of people with obesity is increasing, the prevalence as well as the incidence of OSA will probably increase as well in the near future¹².

The major difference between OSA and CSA is the presence or absence of respiratory effort during periods of breathing cessation. In patients with OSA respiratory effort is still present, while in CSA a cessation in airflow occurs without respiratory effort. Cheyne-Stokes respiration (CSR) is the most common type of CSA and is largely driven by changes in $p\text{CO}_2$. CSR is a common crescendo-decrescendo pattern of respiratory effort and airflow and is often a consequence of heart failure (HF)¹³⁻¹⁶. Patients with HF have high filling pressures, frequently resulting in pulmonary edema, especially during the night when lying in a supine position. Consequently, pulmonary J(uxtacapillary) receptors are stretched, resulting in hyperventilation¹⁷ and a drop in PaCO_2 below the so-called apnea threshold, causing cessation in respiratory drive and breathing temporarily stops^{13,18}. Consequences of CSA include rises in blood pressure, arousals from sleep, and dyspnea. As mentioned above, OSA affects 5%–14% of the middle-aged working population¹. However, sleep apnea prevalence is much higher (50%–70%) in an HF-population¹⁹⁻²⁸, where CSA represents the most prevalent type of sleep apnea. Despite known risk factors for CSA, such as male sex, older age (>60 years), presence of atrial fibrillation, hypocapnia ($\text{PaCO}_2 < 5.0 \text{ kPa}$ ($< 38 \text{ mmHg}$) during wakefulness)²⁹, and diuretic medication use²⁸, sleep apnea remains under-recognized. The latter is possibly due to the absence of EDS in most HF-patients with CSA²², and because HF and sleep apnea share some similar symptoms. After adjustment for confounders, patients with both HF and sleep apnea have a mortality rate twice as high as patients with HF alone^{30,31}. Therefore, it is important to identify patients with sleep apnea in this population, since it might influence the progression and prognosis of HF in those patients.

Screening and diagnostic tools

Patients with sleep apnea present with a wide range of (co-)morbidities prior to their diagnosis.³² These neurobehavioral and cardiovascular morbidities may support the consideration of having sleep apnea. Yet, establishing the diagnosis still frequently takes several years, leaving many subjects undiagnosed^{33,34}. Considering the abovementioned consequences of untreated sleep apnea and the impact on societal costs³³, early diagnosis of sleep apnea is imperative. To date, sleep apnea remains underdiagnosed as it is difficult to recognize, despite the known risk factors.

Polysomnography (PSG) is considered the gold standard for diagnosing sleep apnea and is typically performed in a sleep laboratory or ambulatory in a home setting. It entails recordings of (oro)nasal airflow, oxygen saturation, respiratory effort, sleep stages, snoring, eye- and leg movements, heart rate, and body position. Based on PSG, the severity of sleep apnea is classified by the number of apneas and/or hypopneas per hour of sleep (i.e. apnea-hypopnea index; AHI). Accordingly, sleep apnea can be classified as mild (AHI 5-15 events/h), moderate (AHI 15-30 events/h), or severe (AHI>30 events/h).

As PSG is a time-consuming, costly, and specialized procedure, valid and simple alternatives are required. Polygraphy represents an alternative, but lacks the ability to identify sleep and sleep stages. Other diagnostic- and screening tools exist, for example: exclusively monitoring nasal flow and oxygen saturation, sometimes complemented with measurements of respiratory effort and pulse rate. Such devices have shown satisfactory results in terms of identifying patients with sleep apnea. Furthermore, several questionnaires, such as the Berlin questionnaire^{34,35}, Epworth sleepiness scale³⁶, STOP(-Bang)³⁷⁻³⁹, and several prediction models⁴⁰⁻⁴⁹ have been used as a screening tool to identify patients at risk for sleep apnea. While the Berlin and STOP-Bang questionnaires have acceptable sensitivity and specificity in the sleep clinic population^{39,50,51}, the questionnaires and prediction models are limited in their ability to discriminate between patients with and without sleep apnea due to low specificity⁴⁶ in the general population.

Treatment options

As sleep apnea is an important risk factor for sick leave, work disability, and cardiovascular co-morbidities, it is crucial that patients with sleep apnea receive appropriate diagnosis and effective therapy. In light of the large impact on patient health and social economics, this treatment should also be cost-effective. Cost-effective treatment will also result in future medical cost savings by preventing the consequences of sleep apnea. Treatment options depend mostly on severity and type (obstructive or central) of the disease.

OSA

Continuous positive airway pressure (CPAP) is the most frequently prescribed treatment for OSA⁵². CPAP consists of a flow generator connected to an (oro)nasal or full face mask and prevents upper airway collapse by blowing pressurized air into the upper airway⁵³ during sleep. CPAP is the gold standard in treating moderate to severe OSA⁵² and substantially reduces the number of apneas, hypopneas, and the occurrence of EDS⁵². Furthermore, CPAP is known to improve health-related quality of life and may reduce cardiovascular risk^{8,52}.

Unfortunately, low compliance rates have been reported in a substantial proportion of patients, which were accompanied by reports of discomfort.

Mandibular advancement devices (MAD) are oral appliances that advance the mandible in a forward position, thereby relieving upper airway collapse by modifying the position of the mandible, tongue, and pharyngeal structures, and increasing upper airway lumen/dimensions. MADs have emerged as an attractive alternative for the treatment of OSA, and are now recommended as primary treatment in mildly affected patients and moderate patients that prefer MADs, or for patients not responding to or failing (CPAP) therapy^{54,55}.

In patients with moderate OSA there is an area of overlap, as both CPAP and MAD therapy can be considered as primary interventions^{56,57} and are proven to be effective in reducing the AHI. Based on current literature, no consensus is evident, neither from a clinical or health economic perspective, on which treatment modality should be regarded first line in moderate OSA. While MAD therapy is considered less efficacious than CPAP therapy in more severe OSA⁵⁸⁻⁶², many patients with mild to moderate OSA report greater satisfaction with an oral appliance and generally prefer this treatment modality over CPAP.

In case of severe OSA, CPAP therapy remains the primary treatment and MAD therapy should be considered a secondary intervention. However, patients using CPAP may report pressure-related discomfort. Both a lower pressure and increased comfort may improve patients' compliance with CPAP-therapy, thereby improving therapeutic effectiveness. Combining CPAP with an oral appliance (hybrid therapy) may be an adequate alternative therapy in these cases.

Regardless of disease severity, all patients with OSA are recommended to employ conservative measures (i.e. weight reduction, avoidance of stimulants in the evening, and avoidance of sedative medication). To date, alteration of sleeping position, which simply means preventing patients from lying on their back by using positional therapy (PT), is primarily supplied to selected patients with proven positional OSA (AHI at least twice as high in supine position as in other positions). A recent cohort study showed that positional OSA was present in 75% of OSA subjects. In 36% of the OSA subjects, apneas and/or hypopneas were even exclusively present in the supine position, suggesting that a large proportion of patients with OSA could be treated with PT⁶³. Examples of PT include an alarm system⁶⁴, a backpack with ball⁶⁵ or the so-called tennis ball technique^{66,67}, behavioural therapy⁶⁸, a pillow with straps⁶⁹, and the more recently introduced neck- or chest worn vibrating devices^{70,71}.

When CPAP, MAD (or hybrid therapy), and other conservative treatments have failed, surgical interventions can be considered. The aim of surgical interventions is to improve airway patency by addressing the specific levels of the obstruction⁷². Therefore, a diversity of surgical interventions has evolved due to the different areas involved in airway narrowing⁷². Examples of applied surgical interventions in the treatment of OSA are: correction of a deviated nasal septum (septal correction), uvulopalatopharyngoplasty (UPPP), which involves removal of the tonsils, adenoids, and tissue of the uvula, soft palate and pharynx. Another type of surgical intervention is upper airway stimulation, which involves the use of an implant that stimulates the hypoglossal nerve, thereby activating the genioglossus muscle. As a result, the tongue protrudes which prevents upper airway occlusion⁷³. In case of a substantial reduction in AHI with MAD therapy, patients might consider surgical maxillo-mandibular advancement, which advances the maxilla and mandible forward, thereby improving airway patency. In patients with obesity, bariatric surgery might also result in positive effects in terms of AHI reduction⁷⁴.

CSA

In CSA, different treatment options, including continuous positive airway pressure (CPAP), bi-level PAP (BiPAP; CPAP with reduced expiratory pressure), and adaptive servoventilation (ASV), are available. All treatments are potentially effective in improving heart function and reducing AHI. The current treatment recommendations are to prescribe CPAP as standard therapy, while ASV is an option only in patients with a left ventricular ejection fraction >45%. Alternatively, BiPAP is an option when there is no effective response to CPAP therapy⁷⁵.

Aims and outline of this thesis

The general aim of this thesis is to evaluate diagnostic and therapeutic options in mild, moderate, and severe CSA and OSA, with the main focus on oral appliance and CPAP therapy in OSA.

There is a need for valid diagnostic screening tools in order to identify patients with sleep apnea. In **Chapter 2**, the validity and predictive value of a portable two-channel sleep-screening tool in the identification of sleep apnea in patients with stable HF is described. The ability to effectively determine the need for formal downstream testing, such as PSG, is evaluated, together with the predictive value of the screening tool compared with known risk factors that can be easily scored in daily clinical practice.

Chapter 3 focuses on the cardiovascular effects of oral appliance therapy in obstructive sleep apnea and systematically reviews the current literature on the effects of oral appliance therapy on a broad spectrum of cardiovascular outcomes; these include heart rate, heart rate variability, endothelial function, arterial stiffness, circulating cardiovascular biomarkers, cardiac function, and cardiovascular death.

Substantial evidence to advise clinicians in prescribing MAD or CPAP therapy in moderate OSA remains limited as to date no direct comparisons between MAD and CPAP therapy have been made in a randomized trial setting. In **Chapter 4**, the main study of this thesis, the clinical- and cost-effectiveness of MAD and CPAP are compared in patients with moderate OSA. The treatment modalities are evaluated in patients with moderate OSA from a societal perspective in terms of the incremental cost per additional point of AHI reduction and the incremental cost per utility.

MAD and CPAP therapy rendered comparable results on behavioral and other health related outcomes. This comparable effectiveness has been attributed to a suggested higher compliance with MAD than with CPAP therapy. However, a direct comparison between the objective compliance profiles of MAD and CPAP has not yet been performed. In **Chapter 5** long-term objective compliance with MAD versus CPAP therapy is compared in patients with moderate OSA.

Chapter 6 describes a pilot study of a combination of CPAP and an oral appliance (hybrid therapy) in patients with moderate to severe OSA. The aim of the study was to determine whether hybrid therapy is an adequate alternative to conventional CPAP, and it evaluates patient comfort, compliance, and preference.

Chapter 7 describes a study on the usage of PT in adults with mild, moderate, and severe OSA. Both effectiveness and long-term compliance of positional therapy as a primary treatment option in patients with different severities of positional OSA is assessed.

Chapter 8 provides an English summary and general discussion, including future perspectives. In Chapter 9, the summary and general discussion are provided in Dutch.

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Chapter 2

Validity and predictive value of a portable two-channel sleep-screening tool in the identification of sleep apnea in patients with heart failure

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Abstract

BACKGROUND

Sleep apnea is an important comorbidity in heart failure (HF) and is associated with an adverse outcome. Diagnosing sleep apnea is difficult, and polysomnography, considered to be the criterion standard, is not widely available. We assessed the validity of a portable 2-channel sleep-screening tool for the identification of sleep apnea in patients with HF.

METHODS AND RESULTS

One hundred patients with stable HF had simultaneous recordings of home-based polysomnography and the screening tool (Apnealink). To compare the apnea-hypopnea index of the screening tool with polysomnography, intraclass correlation (ICC), sensitivity, and specificity were calculated, and a Bland-Altman plot and receiver operating characteristic (ROC) curves were constructed. Ninety valid measurements with the screening tool were obtained (mean age 65.5 ± 11.0 y, 72% male, mean left ventricular ejection fraction $34.6 \pm 11.0\%$). Agreement between the screening tool and polysomnography was high (ICC 0.85). The optimal cutoff value was apnea-hypopnea index $\geq 15/h$ (area under the ROC curve 0.94). Sensitivity and specificity were 92.9% and 91.9%, respectively.

CONCLUSIONS

The screening tool is useful in excluding the presence of sleep apnea in HF patients to refer only high-risk patients for more extensive polysomnography. This method may potentially reduce the need for the more expensive polysomnography.

Key words: sleep disordered breathing; heart failure; screening; predictive value of tests

Introduction

Heart failure (HF) is a clinical syndrome with a 5-year survival rate of only 50%, despite optimal therapy¹. Moreover, HF has a large impact on quality of life and leads to high medical costs due to repeated hospitalizations. HF is frequently accompanied by comorbidities, including sleep apnea syndrome². Sleep apnea is characterized by repetitive breathing cessations during sleep and can be divided into 2 main subcategories: obstructive sleep apnea (OSA) and central sleep apnea (CSA, mainly with Cheyne-Stokes respiration (CSR)). Both OSA and CSA can be present in HF³⁻¹².

OSA can contribute to the progression of HF by means of intermittent hypoxia (repetitive oxygen desaturation and reoxygenation), activation of neurohumoral systems, afterload increase, lower stroke volume due to repetitive negative deflections in intrathoracic pressure, and inflammatory activation¹³⁻¹⁹. CSA, in contrast, has been seen as a consequence of HF and is largely driven by changes in PaCO₂¹⁹⁻²². Patients with HF have high filling pressures, which frequently lead to pulmonary edema, especially during the night when lying flat. Consequently, pulmonary J receptors are stretched, leading to hyperventilation²³. Then the PaCO₂ drops below the apnea threshold and the patient stops breathing^{20,24}.

Sleep apnea affects 5%–14% of the middle-aged working population²⁵. In an HF population, however, the prevalence is much higher (50%–70%)³⁻¹², with CSA being the most predominant type of sleep apnea in most studies. Known risk factors for sleep apnea include male sex, presence of atrial fibrillation, older age (>60 years), hypocapnia (PCO₂ <38 mm Hg during wakefulness)²⁶, and diuretic use¹¹. However, sleep apnea remains underrecognized in HF, possibly because excessive daytime sleepiness is absent in most HF patients with CSA⁴, physical examination does not suggest sleep apnea^{4,7,26}, and HF symptoms resemble sleep apnea symptoms.

After adjustment for confounders, patients with both HF and sleep apnea have a mortality rate twice as high as patients with HF only^{27,28}. Therefore, it is important to be able to identify patients at risk for sleep apnea in this population, because sleep apnea influences the progression of HF and can worsen the prognosis. Furthermore, identification is important because effective treatment might improve survival. Continuous positive airway pressure (CPAP) improved both left ventricular ejection fraction (LVEF) and heart transplant-free survival when sleep apnea was effectively suppressed²⁹.

To diagnose sleep apnea, polysomnography (PSG) is considered to be the criterion standard. However, application of PSG equipment is a time-consuming and specialized procedure, and sleeping with the equipment may be experienced as burdensome by the patient. Therefore, a valid and simple screening tool is needed to identify the HF patients with sleep apnea needing further examination and those without sleep apnea. The Apnealink, a 2-channel sleep-screening tool, has been successfully used as a screening tool for obstructive sleep apnea in suspected obstructive sleep apnea populations³⁰⁻³⁵, in a type 2 diabetes mellitus population³⁶, and in a Chinese population with high cardiovascular risk³⁷.

The aim of the present study was to assess the validity of the Apnealink sleep-screening tool for the identification of sleep apnea in patients with stable HF and to evaluate whether this tool has sufficient positive and negative predictive values to efficiently determine the need for formal downstream testing, such as PSG.

Secondary, the predictive value of this sleep-screening tool compared with known risk factors that can be easily scored in daily clinical practice was assessed.

Methods

Subjects

Patients were eligible for the study when they had stable HF for ≥ 3 months according to the clinical judgment of a cardiologist, were treated according to the European Society of Cardiology (ESC) guidelines,¹ and had optimal medication for HF. Patients had to be able to understand the procedures of the study and to sign informed consent. Patients were recruited at the outpatient clinic of the department of Cardiology, University Medical Center Groningen, Groningen, The Netherlands.

Patients were excluded from participation in this study if they 1) were <18 years old, 2) had known OSA or CSA or had undergone PSG in the previous 12 months, 3) had a history of myocardial infarction in the previous 6 months, 4) had a history of (minor) stroke in the previous 6 months, 5) had severe mitral valve dysfunction (III/III), 6) had a severe lung disease (i.e., documented chronic obstructive pulmonary disease of Global Initiative for Chronic Obstructive Lung Disease class 3 or 4), 7) were treated for a malignancy in the previous year, 8) had cardiac resynchronization therapy (CRT) implantation in the previous 6 months or were scheduled for CRT implantation, or 9) were pregnant or actively breast feeding.

The investigation conformed with the principles outlined in the Declaration of Helsinki. The study was approved by the local Ethical Committee (University Medical Center Groningen: METc2011/076). All patients provided written informed consent.

Study Design

This was a cross-sectional study. When patients fulfilled the inclusion and exclusion criteria and were willing to participate in the study, an intake was scheduled with the pulmonologist or nurse practitioner of the University Sleep Apnea Center, and a home-based PSG was scheduled at the department of Clinical Neurophysiology, University Medical Center Groningen. Measurement with the sleep-screening tool (Apnealink, Resmed, Germany) was performed at home simultaneously with PSG. Fasting blood and urine samples were collected in the morning after patients had returned the PSG equipment.

Measurements

Echocardiography. The following parameters were assessed: dimensions of atria and ventricles, LVEF (assessed with the use of the Simpson biplane method), and valvular function (i.e., regurgitation and stenosis). Echocardiographic measurements were performed in accordance with the ESC guidelines¹.

Polysomnography. Sleep apnea was diagnosed with the use of PSG (Vitaport-4 PSG; Temec Instruments, Kerkrade, the Netherlands) during overnight home-based monitoring. Sleep stages were measured with the use of surface electroencephalography, left and right electrooculography, and submental electromyography. Oxygen saturation was recorded with pulse oximetry. Cardiac function was monitored with the use of electrocardiography.

Oronasal airflow was recorded with the use of a pressure cannula. Respiratory effort was monitored with the use of thoracic and abdominal strain bands. Electromyography of the tibialis anterior muscle was measured to screen for periodic limb movements. Body position was measured with a position meter. Standardized criteria were used to score apneas and hypopneas, arousals, sleep stages, and periodic limb movements³⁸. Obstructive apnea was defined as cessation in airflow (i.e., reduction of airflow of $\geq 90\%$) for ≥ 10 seconds with measured respiratory effort. Central apnea was defined as cessation in airflow (i.e., reduction of airflow of $\geq 90\%$) for ≥ 10 seconds without measured thoracic and abdominal effort. Hypopnea was defined as a substantial (i.e., $\geq 30\%$) reduction in airflow for ≥ 10 seconds when associated with oxygen desaturation ($\geq 4\%$). When $\geq 50\%$ of the apneas and/or hypopneas were of the obstructive type, it was classified as OSA, when $\geq 50\%$ of the apneas and/or hypopneas were of the central type, it was classified as CSA.

The severity of sleep apnea was defined by the number of apneas and hypopneas per hour of sleep (apnea-hypopnea index (AHI)). Accordingly, patients were classified as having either mild (5–15 events/h), moderate (15–30 events/h), or severe (AHI >30 events/h) sleep apnea.

AHI was manually scored by a neurophysiologist and was based on total sleep time recorded over the night. The neurophysiologist scoring the PSG was blinded for the sleep-screening tool results.

Two-Channel Sleep-Screening Tool. Apnealink is a 2-channel device (Figure 1). Nasal airflow was recorded with a pressure cannula. The pressure cannula was split with a T-connector allowing for simultaneous recordings of flow by PSG equipment and the sleep-screening tool. Oxygen saturation was assessed with the use of pulse oximetry (worn on the same hand but a different finger from that for PSG). Patients were instructed to activate the sleep-screening tool when going to bed and to switch the device off when waking up in the morning.

Figure 1. A. The 2-channel sleep-screening tool. B. Example of output from sleep-screening tool. X-axis: time; Y-axis: flow signal, pulse, and saturation. The figure shows a Cheyne-Stokes breathing pattern (crescendo-decrescendo pattern of flow followed by a period of breathing cessation). CSR=Cheyne-Stokes respiration; Ds=desaturation; FL=flow limitation; UA=unclassified apnea.

The results for the sleep-screening tool were analyzed automatically. The manufacturer's default settings of the sleep-screening tool were used. Apnea was defined as a decrease in airflow by 80% of baseline airflow level for ≥ 10 seconds. The maximum apnea duration was set at 80 seconds. Hypopnea was defined as a decrease in airflow by 30% of baseline airflow level for ≥ 10 seconds. The maximum hypopnea duration was set at 100 seconds. The threshold for oxygen desaturation was set at 4%. AHI was automatically calculated based on the total flow evaluation time. When flow evaluation time was < 60 minutes, AHI data was declared to be invalid, and these patients were excluded from further analysis.

Blood and Urine Sample Assessment. Urine and fasting blood samples were collected in the morning after the sleep study night. The following parameters were assessed from fresh venous blood with the use of standard methods: hemoglobin, creatinine, liver parameters, lipid parameters, glucose. Serum levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) were assessed with the use of an immunoassay based on electrochemiluminescence. Renal function was determined using the estimated glomerular filtration rate (eGFR), calculated from the simplified Modification of Diet in Renal Disease equation. An eGFR $< 60 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ was considered to indicate renal dysfunction³⁹.

Epworth Sleepiness Scale. Excessive daytime sleepiness was measured by means of the Epworth Sleepiness Scale (ESS), a questionnaire filled in by the patient, that assesses the propensity to fall asleep in 8 different situations⁴⁰. The total score can range from 0 to 24. A score ≥ 10 is considered to be increased and indicates sleepiness.

Statistical Analysis

To compare AHI of the sleep-screening tool ($\text{AHI}_{\text{screening}}$) with the criterion standard PSG (AHI_{PSG}), the intraclass correlation coefficient (ICC; model: 2-way mixed; type: absolute agreement) was calculated. An ICC of ≥ 0.75 was interpreted to indicate good agreement. Furthermore, agreement between the 2 instruments on AHI was assessed with the use of Cohen kappa (AHI in categories) and by calculating the limits of agreement (AHI as continuous variable) as described by Bland and Altman⁴¹. A percentage agreement of 80% and Cohen kappa value ≥ 0.40 were considered to indicate acceptable agreement.

Sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and the area under the receiver operating characteristic (ROC) curve (AUC) were calculated for different cutoff points based on AHI_{PSG} (i.e., $\text{AHI} \geq 5$, $\text{AHI} \geq 10$, $\text{AHI} \geq 15$, $\text{AHI} \geq 20$).

To define the optimal value for each separate ROC curve, the square of distance between the point on the upper left hand corner of ROC space and all coordination points on the ROC curve was calculated: $d^2 = (1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$. An AUC ≥ 0.70 was considered to indicate validity of the sleep-screening tool.

To assess the predictive value of the sleep-screening tool compared with known risk factors, multiple logistic regression analyses were performed. Variables were entered into the model using the "enter" method of regression (i.e., all variables are forced into the model simultaneously, without making a decision about the order in which the variables are entered). Based on risk factors found in literature^{11,26}, the following variables were entered into the model as predictors: age ≥ 60 y, male sex, body mass index $\geq 30 \text{ kg/m}^2$, presence of atrium fibrillation, LVEF $< 45\%$, and diuretic use. In a 2nd model, excessive daytime

sleepiness measured by means of the ESS (ESS ≥ 10) was added. In a 3rd model, sleep apnea or not (cutoff AHI ≥ 15 /h) according to the sleep-screening tool was entered into the model to assess the predictive value of the sleep-screening tool alone. In all 3 models, sleep apnea or not according to the criterion standard PSG (cutoff AHI ≥ 15 /h) was used as dependent variable.

Data were analyzed with the use of SPSS 22.0 statistical software (IBM, Armonk, New York). A 2-sided *P* value of <0.05 was considered to be statistically significant.

Results

From September 2011 to May 2014, 100 patients underwent a sleep study (PSG) with simultaneous measurement with the use of the sleep-screening tool. Ninety valid measurements with the sleep-screening tool were obtained. In 7 cases the flow evaluation period time was too short (0–41 minutes), and in 3 cases, the patients did not activate the sleep-screening tool. These 10 patients were excluded from the analyses.

Patient characteristics are presented in Table 1. The mean age of the patients was 65.5 ± 11.0 years, 72% were male, and 21% of the HF patients had preserved ejection fraction. The prevalence of sleep apnea, detected with the use of PSG, was 61% and 31% for AHI cutoffs of ≥ 5 and ≥ 15 , respectively (Table 1). Twenty-seven patients (30%) had mild, 15 (17%) moderate, and 13 (14%) severe sleep apnea. Twenty-six patients (29%) had CSA, 17 (19%) OSA, and 12 (13%) a mixed form of sleep apnea (AHI_{PSG} ≥ 5). According to the sleep-screening tool, the prevalence of sleep apnea with AHI cutoffs of 5 and 15 was 76% and 34%, respectively. Median AHI on PSG was 6.9 (interquartile range (IQR) 3.3–18.6), whereas median AHI on the sleep-screening tool was 9.0 (IQR 4.8–19.3). Prevalence of sleep apnea detected with the use of PSG, was 65% and 32% for AHI cutoffs of ≥ 5 and ≥ 15 , respectively, for patients with impaired LVEF ($<45\%$), and 47% and 26%, respectively, for patients with preserved LVEF ($\geq 45\%$). Differences between patients with reduced and preserved LVEF were not significant ($\chi^2(1) = 1.91$; $p=0.17$ for AHI ≥ 5 ; and $\chi^2(1) = 0.26$; $p=0.61$ for AHI ≥ 15).

The agreement between AHI_{screening} and AHI_{PSG} was ICC 0.85 (95% confidence interval (CI) 0.78–0.90; $p<0.001$). Percentage agreement on AHI by category (no, mild, moderate, and severe sleep apnea) was 70%, and Cohen kappa was 0.59 (95% CI 0.46–0.72). The sleep-screening tool labeled 1 patient as having no sleep apnea, whereas PSG labeled that patient as having mild sleep apnea (AHI difference 9.9). This patient would be missed for further evaluation when using a cutoff of AHI ≥ 5 . The sleep-screening tool labeled 2 patients as having mild sleep apnea, whereas PSG labeled those patients as having moderate (AHI difference 13.1) and severe (AHI difference 32.1) sleep apnea. These patients would be missed for further evaluation when using a cutoff of AHI ≥ 15 (Table 2).

The Bland-Altman plot is displayed in Figure 2. In most cases (66%) the sleep-screening tool scored a higher AHI than PSG (displayed in the figure by the dots below the mean difference). The largest differences, however, were seen when PSG scored a higher AHI than the sleep-screening tool. In general, the plot shows good agreement between AHI_{screening} and AHI_{PSG}, with a broader distribution when AHI gets higher.

Table 1. Demographic Characteristics and Comorbidities (n=90)

Characteristic	Total cohort (n=90)
Age (y)	65.5 ± 11.0
Sex, n (%)	
Male	65 (72)
Female	25 (28)
BMI (kg/m ²)	28.4 ± 4.6
LVEF (%)	34.6 ± 11.0
HFpEF, n (%)	19 (21)
NT-proBNP (pg/mL)	497 (214 – 1228)
Cause of HF, n (%)	
Ischaemic	53 (59)
Nonischaemic	37 (41)
Device (PM, ICD, CRT[-D]), n (%)	47 (52)
NYHA functional class, n (%)	
I	5 (6)
II	66 (73)
III	19 (21)
IV	0 (0)
AHI on PSG (events/h)	6.9 (3.3-18.6)
Prevalence of sleep apnea, n (%)	
AHI≥5 with PSG	55 (61)
AHI≥10 with PSG	40 (44)
AHI≥15 with PSG	28 (31)
AHI≥20 with PSG	20 (22)
PLMI on PSG (events/h)	2.0 (0.0-28.0)
Minimum saturation on PSG (%)	84.7 ± 7.0
Epworth Sleepiness Scale (0-24)	7.6 ± 4.7
Epworth Sleepiness Scale ≥ 10, n (%)	32 (36)
Comorbidities, n (%)	
Diabetes	20 (22)
Peripheral artery disease	9 (10)
Chronic kidney disease	1 (1)
eGFR (mL min ⁻¹ 1.73 m ⁻²)	62.4 ± 21.8
eGFR<60 mL min ⁻¹ 1.73 m ⁻²	43 (48)
COPD (GOLD I / II)	13 (14)
Cerebral disease (CVA/TIA)	8 (9)
Hypertension	25 (28)
Medication use, n (%)	
ACEi/ARBs	88 (98)
Beta-blockers	88 (98)
Loop diuretics	73 (81)
Aldosterone antagonist	45 (50)
Antiplatelet and/or anticoagulant	59 (66)
Statins	56 (62)

Data are presented as mean ± SD, median (interquartile range), or n (%).

BMI=body mass index; LVEF=left ventricular ejection fraction; HFpEF=HF with preserved ejection fraction; NT-proBNP=N-terminal pro-B-type natriuretic peptide; HF=heart failure; PM=pacemaker; ICD=implantable cardioverter-defibrillator; CRT[-D]=cardiac resynchronization therapy [with defibrillator]; NYHA=New York Heart Association; AHI=apnea-hypopnea index; PSG=polysomnography; PLMI=periodic limb movement index; eGFR=estimated glomerular filtration rate; COPD=chronic obstructive pulmonary disease; GOLD=Global Initiative for Chronic Obstructive Lung Disease; CVA=cerebrovascular accident; TIA=transient ischemic attack; ACEi=angiotensin-converting enzyme inhibitor; ARBs=angiotensin receptor blockers.

Table 2. Agreement Based on Classic Differentiation Into No (AHI 0-5), Mild (AHI 5-15), Moderate (AHI 15-30), and Severe (AHI >30) Sleep Apnea (n=90)

Screening tool	PSG			
	No	Mild	Moderate	Severe
No	21	1	0	0
Mild	14	21	1	1
Moderate	0	4	12	3
Severe	0	1	2	9

AHI=apnea-hypopnea index; PSG=polysomnography

Table 3 presents the sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, AUC, and d^2 for the different AHI_{PSG} values. ROC curves are displayed in Figure 3. The best cutoff value (i.e., with smallest d^2) was for AHI_{PSG} ≥ 15 . Sensitivity of the sleep-screening tool for an AHI cutoff value of ≥ 15 was 92.9%, and specificity was 91.9%. The AUC for an AHI cutoff value of ≥ 15 was 0.94.

The results of the (multiple) logistic regression analyses are presented in Table 4. A combination of clinical known risk factors correctly classified 72% of the patients and explained 17% (Hosmer-Lemeshow) of the variance in having sleep apnea. Adding ESS to the model had no effect ($\Delta\chi^2 = 0.22$; $p=0.64$; Table 4). The model including only the sleep-screening tool ($\chi^2 = 66.74$; $p<0.001$) correctly classified 92% of the patients and explained 60% (Hosmer-Lemeshow) of the variance in having sleep apnea. The odds of a patient with AHI_{screening} ≥ 15 having sleep apnea were 148 times higher than those of a patient with AHI_{screening} <15 .

Figure 2. Bland-Altman plot.

Mean score per patient of apnea-hypopnea index (AHI) on polysomnography (PSG) and AHI on the sleep-screening tool plotted against the difference between the same scores. The reference line is set at the mean difference -0.061 (95% confidence interval (CI) -1.66 to 1.54) and the dashed lines at the limits of agreement between -15.3 (95% CI -18.1 to -12.6) and 15.2 (95% CI 12.4 to 18.0).

Table 3. Validity Measures of the Sleep-Screening Tool Compared with Simultaneous Polysomnography (Criterion Standard)

AHI	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR +	LR -	AUC (95% CI)	p-value	d ²
≥5	98.2	60.0	79.4	95.5	2.46	0.03	0.94 (0.89-0.99)	<0.001	0.029
≥10	92.5	86.0	84.1	93.5	6.61	0.09	0.94 (0.88-0.99)	<0.001	0.025
≥15	92.9	91.9	83.9	96.6	11.47	0.08	0.94 (0.89-1.00)	<0.001	0.012
≥20	85.0	92.9	77.3	95.6	11.97	0.16	0.95 (0.91-1.00)	<0.001	0.023

AHI=apnea-hypopnea index; PPV=positive predictive value; NPV=negative predictive value; LR=likelihood ratio; AUC=area under the receiver operating characteristic curve; CI=confidence interval; $d^2=(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$.

Figure 3. Receiver operating characteristic curves with cutoff values based on polysomnography.

Test variable: apnea-hypopnea index (AHI) on the sleep-screening tool; state variable: sleep apnea on polysomnography (yes/no); value of state variable: 1.

Discussion

The aim of this study was to assess the validity of a sleep-screening tool for the identification of sleep apnea in patients with stable HF and to evaluate whether this tool has sufficient positive and negative predictive value to implement formal downstream testing, such as PSG, more efficiently.

Secondarily, the predictive value of this sleep-screening tool compared with known risk factors that can be easily scored in daily clinical practice was assessed.

Table 4. Logistic Regression Model

Included factor	Model 1					Model 2				
	β (SE)	p-value	Exp B	95% CI		β (SE)	p-value	Exp B	95% CI	
				Lower	Upper				Lower	Upper
Age	1.1 (0.6)	0.08	3.0	0.9	10.1	1.1 (0.6)	0.08	3.0	0.9	9.9
Gender	1.8 (0.7)	0.01	6.3	1.5	26.7	1.9 (0.7)	0.01	6.6	1.5	28.4
BMI	1.2 (0.6)	0.04	3.2	1.1	9.5	1.2 (0.6)	0.04	3.3	1.1	9.9
LVEF	-0.2 (0.7)	0.73	0.8	0.2	3.0	-0.2 (0.7)	0.75	0.8	0.2	3.1
AF	0.2 (0.6)	0.67	1.3	0.4	3.8	0.2 (0.6)	0.69	1.3	0.4	3.8
Diuretic use	0.9 (0.7)	0.21	2.5	0.6	10.9	0.9 (0.7)	0.25	2.4	0.5	10.2
ESS	-	-	-	-	-	-0.3 (0.5)	0.64	0.8	0.3	2.2

CI=confidence interval; BMI=body mass index; LVEF=left ventricular ejection fraction; AF=atrial fibrillation; ESS=Epworth Sleepiness Scale.
Model 1 = Known risk factors: $R^2=0.17$ (Hosmer & Lemeshow); $R^2=0.19$ (Cox & Snell); $R^2=0.26$ (Nagelkerke). Model $\chi^2 = 18.31$, $p<0.01$.
Model 2 = Adding ESS: $R^2=0.17$ (Hosmer&Lemeshow); $R^2=0.19$ (Cox & Snell); $R^2=0.26$ (Nagelkerke). Model $\chi^2 = 18.53$, $p=0.01$ ($\Delta\chi^2=0.22$; $p=0.64$).

Sleep-Screening Tool Versus Polysomnography

This study showed good agreement between the sleep-screening tool and the criterion standard PSG (ICC 0.85, 95% CI 0.78–0.90; $p < 0.001$). The best agreement with PSG was at a cutoff value of $AHI \geq 15$. This cutoff value was found retrospectively by assessing the ROC curves for different AHI_{PSG} cutoff points and is therefore hypothesis generating in nature.

It is debatable which cutoff value should be used (e.g., $AHI_{\text{screening}} \geq 5$, ≥ 10 , or ≥ 15) for referral to further evaluation. The best validity in this study was found with the use of a cutoff of $AHI \geq 15$. However, with the use of this cutoff, 2 patients were labeled as not having sleep apnea, although PSG showed the presence of sleep apnea. Changing the cutoff value to $AHI \geq 10$ resulted in 1 more case of missed sleep apnea and therefore added nothing to the identification of patients with or without sleep apnea. Using the higher cutoff value of $AHI \geq 15$ would have the consequence that patients with mild OSA are not referred for further evaluation and that they would not receive appropriate treatment. The most frequently used cutoff point for starting treatment for CSA is $AHI \geq 15$. Patients with CSA are expected to represent the largest group in a HF population and therefore a cutoff value of $AHI \geq 15$ is defensible.

For the cutoff value of $AHI \geq 15$, sensitivity and specificity were high: 92.9% and 91.9%, respectively. The AUC also showed very high agreement between the sleep-screening tool and PSG (0.94). Our results are in accordance with other studies assessing the reliability and validity of Apnealink^{30-34,36,37,42} in patients without HF.

Although the sleep-screening tool scored a higher AHI than PSG in 66% of the cases, the largest differences between both devices were seen when PSG scored a higher AHI than the sleep-screening tool. The fact that in most cases the sleep-screening tool scored higher can be explained by the discrepancy in the definitions of apnea (sleep-screening tool reduction of airflow $\geq 80\%$ versus PSG reduction of airflow $\geq 90\%$). Except for measurement errors occurring with any device, we have no additional explanation why in some cases PSG scored a higher AHI than the sleep-screening tool. It is possible that in these cases the part of the flow cannula leading to the PSG was pinched off, leading to the recording of apnea or hypopnea. There was, unfortunately, no possibility to explore this afterwards.

When classifying sleep apnea into mild, moderate, and severe disease, agreement between the sleep-screening tool and PSG was 70%, which was below our a priori definition of acceptable agreement. Cohen kappa was 0.59 (95% CI 0.46–0.72; acceptable agreement). The relatively low absolute agreement was mainly due to the 14 patients classified as mild sleep apnea by the sleep-screening tool when in fact there was no sleep apnea (false positives). In summary, the sleep-screening tool is very good in selecting those patients with and without sleep apnea, especially at $AHI_{PSG} \geq 15$, but has difficulty classifying sleep apnea into the accurate category (mild, moderate, or severe). It can be questioned whether a screening device should be able to classify into the right severity category, because the aim of screening is to identify those patients without sleep apnea (true negatives) and those patients needing further evaluation (true positives), combining high specificity and high sensitivity. Furthermore, the diagnosis of patients identified by the sleep-screening tool always should be confirmed with PSG before treatment is started. By identifying those HF patients without sleep apnea, costs may be saved because these patients do not need to undergo a full PSG.

Predicting Sleep Apnea Syndrome

It is difficult to recognize sleep apnea based on clinical factors. This was confirmed by the results of our regression model including known clinical risk factors (age, sex, body mass index, LVEF, atrial fibrillation, diuretic use), which explained only 17% of the variance in having sleep apnea. The sleep-screening tool did much better, explaining 60% of the variance in having sleep apnea. The odds of a patient with $AHI_{\text{screening}} \geq 15$ having sleep apnea was 148 times higher than with $AHI_{\text{screening}} < 15$. A cutoff value of $AHI \geq 15$ was chosen because this was shown to represent the best cutoff in the validity analysis. Furthermore, $AHI \geq 15$ is the most frequently used cutoff point in studies assessing prevalence of sleep apnea in HF^{4-8,10,11}. The results of the regression models illustrate the fact that clinical risk factors are not helpful in deciding whether or not to refer the patient for a more extensive PSG.

Prevalence

In this study, a prevalence of 44% and 31% on PSG with $AHI \geq 10$ and $AHI \geq 15$, respectively, was found, which was slightly lower than in other studies³⁻¹². In the present study, patients with optimal medical therapy, both with preserved LVEF ($\geq 45\%$) and impaired LVEF ($< 45\%$) were included. Studies with impaired LVEF revealed a prevalence of $\sim 50\%$ with the use of a cutoff of $AHI \geq 15$ ^{5,6,8}. Changes in treatment regimens are not likely to have influenced the prevalence found in the present study, because use of beta-blockers and spironolactone¹¹ were not associated with sleep apnea prevalence.

Study Limitations

There are some limitations for this study. In 10% of the patients, no evaluable recordings could be obtained. Patients were instructed to activate the sleep-screening tool when going to bed and turn the device off when waking up. Furthermore, written instructions were provided to every patient. Despite these efforts, 3 patients did not activate the sleep-screening tool (3%). In 7 cases, the flow evaluation period time was too short (0–41 minutes). Unfortunately, it cannot be reconstructed whether this was due to technical problems of the device or to human error. In some cases the sleep-screening tool was still measuring while the patient was already awake, resulting in overestimated flow evaluation times. We corrected for this by dividing the amount of apneas and hypopneas by the time in bed period according to the PSG ($\text{corrected } AHI_{\text{screening}} = (\text{sleep-screening tool total apneas} + \text{hypopneas}) / (\text{PSG time in bed} / 60)$). These results resembled the automatically generated results.

Subjects for this study were recruited in the outpatient clinics of the department of cardiology (most in the HF outpatient clinic). Although every patient fulfilling the criteria was asked to participate in this study, a possible bias could be present because patients with sleep apnea symptoms could be more willing to participate. The lower prevalence found in our study is, however, not suggestive of such bias.

Conclusion

The sleep-screening tool is able to detect those patients with and without sleep apnea with great accuracy and is a valid and very predictive screening tool besides the known risk factors from the literature that can help specialists in identifying those patients at risk of having sleep apnea. The optimal cutoff value would be $AHI_{\text{screening}} \geq 15$ because this results in the highest combined sensitivity and specificity. Before treatment is started, PSG should be performed to confirm the presence and predominant type of sleep apnea.

The sleep-screening tool (Apnealink) is useful in excluding the presence of sleep apnea for referral of only high-risk HF patients for a more extensive PSG.

Acknowledgements

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Letter to the Editor

Response: A portable device as sleep-screening tool in the identification of obstructive sleep apnea in chronic heart failure: which value should we consider as cutoff?

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Response: A Portable Device as Sleep-Screening Tool in the Identification of Obstructive Sleep Apnea in Chronic Heart Failure: Which Value Should We Consider as Cutoff?

To the Editor:

We thank Dr Carratù and colleagues for their interest in our study and their insightful comments. In our study, the prevalence of ischemic HF in subjects with obstructive sleep apnea (OSA) was 76%, compared with 58% in subjects with central sleep apnea (CSA) and 57% when no sleep-disordered breathing (SDB) was present ($p=0.30$). Excessive daytime sleepiness (as measured with the use of the Epworth Sleepiness Scale, cutoff score ≥ 10) was similar between OSA and CSA (31% and 42%, respectively; $p=0.74$). No association between OSA with chronic heart failure (CHF) and a medical history of myocardial infarction, valve disease, or peripheral arterial disease was found. Unfortunately, we did not record specific electrocardiographic data, such as Q waves and ST-T-segment abnormalities.

We acknowledge that the Apnealink technology used in the study was not able to discriminate between OSA and CSA owing to a lack of respiratory effort data. This could be a limitation. A novel version of the Apnealink (Apnealink Plus; Resmed, San Diego, California) might solve this issue. This device also records respiratory effort using a pneumatic sensor belt, which allows discriminating obstructive from central apneic events. The Apnealink Plus has been evaluated as a screening tool for OSA in a small obese cohort. There was a moderate correlation between the number of polysomnography (PSG)-recorded central apneic events and the device-recorded events (Spearman $r=0.527$; $p=0.007$)¹. We performed a sensitivity analysis for the lower apnea-hypopnea index (AHI) levels in the OSA group, which showed a very strong agreement between PSG and Apnealink (Spearman $r=0.823$; $p<0.0001$). The Apnealink device is, however, less specific at the lowest AHI levels. Furthermore, Apnealink overestimated the AHI in most subjects (66%). Unfortunately, it is not possible to fully rule out false negatives. In our study, 1 subject (1.1%) was classified as having no SDB according to Apnealink, whereas the subject had mild SDB according to PSG. It is, however, questionable what the consequences are for the few patients who are missed with the use of Apnealink as a screening tool and consequently do not receive treatment. There is still no conclusive evidence that subjects with mild SDB should be treated to significantly reduce cardiovascular events².

In conclusion, we think that the ApneaLink technology is helpful in the diagnostic pathway of SDB in CHF patients. Apnealink should not replace PSG evaluation; patients at higher risk should undergo PSG before initiation of treatment. PSG should preferably be performed in a home-based setting, because there is a good agreement with clinical PSG and patients prefer home-based PSG³. When the screening tool outcome is equivocal or technically limited, we agree that it might be more appropriate to perform PSG instead of repeating an overnight home-based Apnealink measurement.

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Chapter 3

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.

Keywords: oral appliances; obstructive sleep apnea; cardiovascular outcomes; meta-analysis

Introduction

Obstructive sleep apnea (OSA) is a common (34% of men, 17% of women) sleep-related breathing disorder in the general adult population¹. 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 inflammation², oxidative stress³, endothelial dysfunction⁴, and eventually atherosclerosis⁵. Ultimately, cardiovascular consequences of OSA may include an increased risk of developing alterations in heart rate (variability)⁶, systemic hypertension⁷⁻⁹, and cardiovascular disease, such as myocardial infarction, cardiac arrhythmias, and stroke¹⁰⁻¹⁸.

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 CPAP reduces systolic (SBP) and diastolic (DBP) blood pressure¹⁹, 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 compliance²⁹. 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 scarce³⁰.

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 baseline³¹ and inactive control therapies³² 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) $\geq 5/h$, 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 therapy³⁴. 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 χ^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 (Figure 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 low³⁷⁻⁴⁵ and 16 articles of sufficient⁴⁶⁻⁵⁰ 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 ($5 \leq \text{AHI} \leq 30$ 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 ($5 \leq \text{AHI} \leq 40$ 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 ($5 \leq \text{RDI} \leq 30$ 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.

Andrn et al.⁵⁷ (AHI ≥ 10 events/h, mean AHI 24 events/h) 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 ($n=90$, $5 \leq \text{AHI} \leq 30$ 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 1TM ($n=77$), SleepPro 2TM ($n=78$), 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.

Figure 1. Study selection procedure.

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 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 ($5 \leq \text{RDI} \leq 30$ 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 ($5 \leq \text{AHI} \leq 30$ 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 significance⁵⁰.

Pooled RCT data showed a significant reduction with oral appliance treatment compared to baseline in both daytime SBP (Figure 2A, mean change -1.81 mmHg (95% CI -3.58 to -0.03), $p=0.05$) and daytime DBP (Figure 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, Figures 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, Figures 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 -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 Gotsopoulos⁵¹ on daytime SBP. A small amount of asymmetry exists in the funnel plot for DBP, but not for SBP (Appendix 2).

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	67 (61)	2x4 weeks	48	79	29.2	AHI≥10 (27)	39%	Custom-made adjustable bibloc	Control OA (upper appliance alone) n=61	24h ABPM Heart rate
Barnes et al. 2004 ⁵²	73	RCT	110 (85)	3x3 months	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	24h ABPM Pulmonary artery pressure and Left ventricular mass (echocardiography)
Lam et al. 2007 ⁵³	69	RCT	101 (34)	10 weeks	45.7	78	27.4	AHI 5-40 (21.4)	19%	Custom-made non-adjustable Harvold type Custom-made adjustable bibloc Thornton	- CPAP n=34 - Conservative measures n=33 CPAP n=13	Clinical BP (morning and evening, average of 3 readings) Left ventricular structure and function (echocardiography) NT-pro-BNP (venous blood samples)
Hoekema et al. 2008 ⁵⁴	61	RCT	28 (12)	2-3 months	49.7	89	33.3	AHI>20 (52.2)	93%	Custom-made adjustable positioner (Airway Management, Inc., Dallas, TX, USA)		
Gauthier et al. 2009 ⁵⁵	76	RCT	19 (16)	2x3 months	47.9	69	28.7	RDI 5-30 (10.0)	38%	Slencer (Burnaby, British Columbia)	Klearway n=16	Clinical BP (secondary)
Trzepizur et al. 2009 ⁵⁶	66	1: Prospective follow-up study 2: RCT	15 (12)	2x2 months	56 *	92	29.4 *	AHI≥30 (40 *)	42%	Custom-made adjustable bibloc (AMC TM , 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	72 (36)	3 months	58	79	30	AHI≥10 (24)	89%	Custom-made monobloc	Control OA (<0.5mm) n=36	24h ABPM
Phillips et al. 2013 ⁵⁸	76	RCT	126 (108)	2x1 month	49.5	81	29.5	AHI>10 (25.6)	42%	Somnodent (SomnoMed Ltd., Sydney, Australia)	CPAP n=108	24h ABPM Arterial stiffness (secondary)

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
Dal-Fabbro et al. 2014 ⁵⁹	66	RCT Cross-over	39 (29)	3x1 month	47.0	83	28.4	AHI≥20 (42.3)	31%	Custom-made adjustable bibloc Brazilian dental appliance	- CPAP n=29 - Placebo OA n=29	24h ABPM Oxidative stress Heart rate variability (ECG of PSG) Clinical BP (average of 3 readings)
Sharples et al. 2014 ⁶⁰	73	RCT Cross-over	90 (74)	6 weeks	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	
Glos et al. 2016 ⁶¹	58	RCT Cross-over	48 (40)	2x12 week	49.5	83	28.3	AHI≥5 (28.5)	un known	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												
Salatu et al. 2007 ⁴⁶	51	Single blind placebo controlled case series	50 (50)	2-3 weeks	59.7	74	NR	AHI≥5 (16.8)	un known	Adjustable bibloc (Intraoral Snoring Therapy)	none	Clinical BP (secondary)
Gauthier et al. 2011 ⁴⁷	58	Longitudinal design	14 (14)	40.9 months	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)
Anandam et al. 2013 ⁴⁸	55	Observational cohort study	562 (72)	Median 79 months (IQR 76-88 months)	50.8 #	57 #	37.1 #	AHI≥20 (44.5 #)	51%	Custom-made (Ontario)	- Control group (AHI<5) n=208 - CPAP group n=177 - Untreated group n=212	Fatal cardiovascular events

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
Lin et al. 2015 ⁴⁹	51	Observational	30 (19)	2 months	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 3 recordings) (secondary) Arterial stiffness (PWV) Glucose metabolism Inflammation (secondary) Clinical BP (average of 2 recordings) (secondary)
Galic et al. 2016 ⁵⁰	52	Prospective study	18 (15)	3 months 1 year	51.2	93	28.1	AHI 5-30 (22.9)	un known	Custom made adjustable Silensor-sl Erkodent Germany	none	

ABPM=ambulatory blood pressure measurement; AHI=apnea-hypopnea index; BP=blood pressure; CPAP=continuous positive airway pressure;

ECG=electrocardiography; FMD=flow-mediated dilatation, 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)

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 (Figure 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 Gotsopoulos⁵¹ 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 ms^2/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 $\text{ms}^2/\text{frequency Hz}$ vs. power ms^2).

Figure 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.

Figure 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 ¼ no treatment; Gauthier et al.: the Silencer was used as primary oral appliance treatment.

Figure 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.

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 B₁₂ 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 B₆ concentrations were significantly higher after OAT compared to baseline. CPAP and placebo oral appliance resulted in significantly increased levels of vitamins C and B₆, compared to baseline. The more relevant comparisons between the groups for erythrocyte catalase activity, vitamins C and vitamin B₆ 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 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 events⁶⁴, 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 mortality⁶⁵. 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 CPAP⁶⁶.

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 system⁶. 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 fibrillation¹⁸. 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 hemotatic markers⁷¹ 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 study⁷², 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 study⁴⁸ 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 study⁷³) showed contradictory results in that CPAP therapy did not prevent cardiovascular events. Relative low compliance (mean usage of 3.3 hours) 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 hypertension⁷⁵. ODI can be further classified based upon a $\geq 3\%$ or $\geq 4\%$ desaturation. A large retrospective study⁷⁶ assessed the relation between different ODI cutoff values, BMI, and AHI and found that $\geq 3\%$ ODI performed best at predicting moderate and severe ($\text{AHI} \geq 15$ 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 pressure⁷⁹. 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.

Conclusions

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.

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.

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

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Supplement

APPENDIX 1 Literature search up to December 31st 2016

1. PUBMED

(Sleep Apnea, Obstructive[Mesh] OR (obstruct*[tw] AND sleep[tw] AND (apnea[tw] OR apnoea[tw])) OR sleep disordered breathing[tw] OR sleep apnea[tw] OR SAHS[tw] OR OSA[tw] OR OSAS[tw] OR OSAHS[tw]) AND (Mandibular Advancement[Mesh] OR Orthodontic Appliances, Removable[Mesh] OR orthodontic device*[tw] OR orthodontic appliance*[tw] OR mandibular advancement[tw] OR mandibular reposition*[tw] OR dental device*[tw] OR dental appliance*[tw] OR oral device*[tw] OR oral appliance*[tw]) AND (stroke[MeSH Terms] OR cardiovascular diseases[MeSH Terms] OR stroke*[tw] OR atrial fibrillation[tw] OR coronary artery disease [tw] OR cardiovascular disease[tw] OR cardiovascular diseases[tw] OR cardiovascular risk[tw] OR hypertension[tw] OR "blood pressure"[tw] OR vascular disease[tw] OR heart disease[tw] OR arterial stiffness[tw] OR cerebrovascular accident[tw] OR cva[tw] OR transient ischaemic attack[tw] OR tia[tw]) AND (english[LA]) NOT (pediatr*[TI] OR child*[TI])

2. EMBASE

'sleep disordered breathing' OR (obstructive:ab,ti AND sleep:ab,ti AND (apnea:ab,ti OR apnoea:ab,ti)) OR 'obstructive sleep apnea' OR 'sleep apnea':ab,ti OR sahs:ab,ti OR osa:ab,ti OR osas:ab,ti OR osahs:ab,ti AND ('mandibular advancement' OR 'orthodontic appliances removable' OR 'orthodontic device':ab,ti OR 'orthodontic devices':ab,ti OR 'orthodontic appliance':ab,ti OR 'orthodontic appliances':ab,ti OR 'mandibular advancement':ab,ti OR (mandibular AND reposition*:ab,ti) OR 'dental device':ab,ti OR 'dental devices':ab,ti OR 'dental appliance':ab,ti OR 'dental appliances':ab,ti OR 'oral appliance':ab,ti OR 'oral appliances':ab,ti OR 'oral device':ab,ti OR 'oral devices':ab,ti) AND ('cerebrovascular accident':ab,ti OR 'transient ischemic attack':ab,ti OR 'arterial stiffness':ab,ti OR 'heart disease':ab,ti OR 'vascular disease':ab,ti OR 'hypertension':ab,ti OR 'blood pressure':ab,ti OR 'cardiovascular risk'/exp OR 'cardiovascular risk':ab,ti OR 'cardiovascular disease'/exp OR 'cardiovascular disease':ab,ti OR 'stroke'/exp OR 'stroke':ab,ti OR 'atrial fibrillation':ab,ti OR 'coronary artery disease':ab,ti) AND [english]/lim NOT (child*:ti OR pediatr*:ti)

3. CINAHL

(obstructive sleep apnea OR AB (obstruct* AND sleep AND (apnea OR apnoea)) OR AB sleep disordered breathing OR AB sleep apnea OR AB sleep apnoea OR AB osa OR AB osas OR AB osahs) AND (TX mandibular advancement device OR TX orthodontic appliances OR AB ('orthodontic device'* OR 'orthodontic appliance'*) OR AB 'mandibular advancement' OR AB 'mandibular reposition'* OR AB ('dental device'* OR 'dental appliance'*) OR AB ('oral device'* OR 'oral appliance'*)) AND (TX (stroke or cerebrovascular accident or cva) OR TX atrial fibrillation OR TX coronary artery disease OR TX cardiovascular disease OR TX cardiovascular risk OR TX hypertension OR TX blood pressure OR TX vascular disease OR TX heart disease OR TX arterial stiffness OR TX transient ischemic attack) NOT (TI child* OR TI pediatr*)

Limit: English language

<u>#1</u>	Sleep Apnea, Obstructive[Mesh]
<u>#2</u>	obstruct*[tw] AND sleep[tw] AND (apnea[tw] OR apnoea[tw])
<u>#3</u>	sleep disordered breathing[tw]
<u>#4</u>	sleep apnea[tw]
<u>#5</u>	SAHS[tw] OR OSA[tw] OR OSAS[tw] OR OSAHS[tw]
<u>#6</u>	#1 OR #2 OR #3 OR #4 OR #5
<u>#7</u>	Mandibular Advancement[Mesh]
<u>#8</u>	Orthodontic Appliances, Removable[Mesh]
<u>#9</u>	orthodontic device*[tw] OR orthodontic appliance*[tw]
<u>#10</u>	mandibular advancement[tw]
<u>#11</u>	mandibular reposition*[tw]
<u>#12</u>	dental device*[tw] OR dental appliance*[tw]
<u>#13</u>	oral device*[tw] OR oral appliance*[tw])
<u>#14</u>	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
<u>#15</u>	Stroke[Mesh]
<u>#16</u>	Cardiovascular diseases[Mesh]
<u>#17</u>	stroke*[tw]
<u>#18</u>	atrial fibrillation[tw]
<u>#19</u>	coronary artery disease[tw]
<u>#20</u>	cardiovascular disease[tw] OR cardiovascular diseases[tw]
<u>#21</u>	cardiovascular risk[tw]
<u>#22</u>	hypertension[tw] OR "blood pressure"[tw]
<u>#23</u>	vascular disease[tw]
<u>#24</u>	heart disease[tw]
<u>#25</u>	arterial stiffness[tw]
<u>#26</u>	cerebrovascular accident[tw] OR cva[tw]
<u>#27</u>	transient ischaemic attack[tw] OR tia[tw])
<u>#28</u>	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
<u>#29</u>	#6 AND #14 AND #28 AND (english[LA]) NOT (pediatr*[TI] OR

APPENDIX 2

BLOOD PRESSURE

A

B

C

Figure 1. Mean change in 24-hour 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; Gotsopoulos et al.: per protocol analysis (efficacy) n=61 was used

A

B

C

Figure 2. Mean change in 24-hour 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; Gotsopoulos et al.: per protocol analysis (efficacy) n=61 was used

A

B

C

Figure 3. Mean change in nighttime 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; Gotsopoulos et al.: per protocol analysis (efficacy) n=61 was used

A

B

C

Figure 4. Mean change in nighttime 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; Gotsopoulos et al.: per protocol analysis (efficacy) n=61 was used

HEART RATE

A

B

C

Figure 5. Mean change in 24-hour 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; Gotsopoulos et al.: per protocol analysis (efficacy) n=61 was used

A

B

C

Figure 6. Mean change in nighttime 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; Gotsopoulos et al.: per protocol analysis (efficacy) n=61 was used

FUNNEL PLOTS

Figure 7. Funnel plot for daytime systolic blood pressure (OAT compared to baseline).

Figure 8. Funnel plot for daytime diastolic blood pressure (OAT compared to baseline).

Chapter 4

Clinical- and cost-effectiveness of a mandibular advancement device versus continuous positive airway pressure in moderate obstructive sleep apnea

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Abstract

STUDY OBJECTIVES

Limited evidence exists on the cost-effectiveness of mandibular advancement device (MAD) compared to continuous positive airway pressure (CPAP) therapy in moderate obstructive sleep apnea (OSA). Therefore, this study compares the clinical- and cost-effectiveness of MAD therapy with CPAP therapy in moderate OSA.

METHODS

In a multicentre randomized controlled trial patients with an apnea-hypopnea index (AHI) of 15-30 events/h were randomized to either MAD or CPAP. Incremental cost-effectiveness and -utility ratios (ICER/ICUR, in terms of AHI reduction and quality adjusted life years (QALYs, based on the EuroQol-5D-questionnaire)) were calculated after 12 months, all from a societal perspective.

RESULTS

In the 85 randomized patients (n=42 CPAP, n=43 MAD), AHI reduction was significantly greater with CPAP (median reduction AHI 18.3 (14.8–22.6) events/h) than with MAD therapy (median reduction AHI 13.5 (8.5–18.4) events/h) after 12 months. Societal costs after 12 months were higher for MAD than for CPAP (mean difference €2,156). MAD was less cost-effective than CPAP after 12 months (ICER -€305 (-€3,003 to €1,572) per AHI point improvement). However, in terms of QALY, MAD performed better than CPAP after 12 months (€33,701 (-€191,106 to €562,271) per QALY gained).

CONCLUSIONS

CPAP was more clinically effective (in terms of AHI reduction) and cost-effective than MAD. However, costs per QALY was better with MAD as compared to CPAP. Therefore, CPAP is the first-choice treatment option in moderate OSA and MAD may be a good alternative.

Keywords: sleep apnea; costs and cost analysis; randomized controlled trial

Brief Summary

This randomized controlled trial compares the clinical- and cost-effectiveness of a mandibular advancement device (MAD) versus continuous positive airway pressure (CPAP) in moderate obstructive sleep apnea (OSA) as there is little evidence to aid in choosing between both therapies in this specific subgroup of OSA severity.

CPAP therapy is the first-choice treatment option in moderate OSA and MAD therapy may be a good alternative, particularly when patients refuse CPAP or prefer MAD therapy because of the less invasive nature of the device. Future research should focus on long-term quality of life and cardiovascular outcomes in order to provide justified treatment advice, also taking into account the initial preference of the patient to offer personalised medical care in patients with moderate OSA.

Introduction

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder characterized by recurrent upper airway obstructions during sleep, resulting in limited airflow and intermittent hypoxia¹. The resulting poor quality of sleep can lead to excessive daytime sleepiness (EDS), impaired quality of life, sick leave and work disability^{2,3}. Ultimately, cardiovascular consequences may include an increased risk of developing systemic hypertension⁴⁻⁶ and cardiovascular diseases, such as myocardial infarction, cardiac arrhythmias, and stroke⁷⁻¹⁵.

As OSA largely impacts individual health and societal costs, it is important that patients receive appropriate treatment in order to reduce symptoms, co-morbidities and economic burden. Continuous positive airway pressure (CPAP) is the gold standard in treating moderate to severe OSA¹⁶. CPAP substantially reduces the number of apneas and hypopneas, and the occurrence of EDS¹⁶. Furthermore, it improves health-related quality of life, and may reduce the risk of cardiovascular diseases and implications^{9,16}. Some patients, however, do report discomfort with CPAP, which might result in low compliance rates.

Oral appliance therapy has emerged as an attractive alternative to CPAP, especially for the treatment of mild and moderate OSA¹⁷. Benefits of MAD therapy include substantial improvements in quality of life, daytime sleepiness, and sleep quality of both patient and bed partner. Side-effects in the early phase are usually related to the forced ventral position of the mandible and are mild and of transient nature. Long-term side-effects might involve small changes in dental occlusion¹⁸.

Although MAD is generally considered less effective than CPAP¹⁹⁻²³, in a previous study it was shown not to be inferior in non-severe OSA and some patients reported greater satisfaction with MAD¹⁷. Therefore, in moderate OSA (apnea-hypopnea index (AHI) 15-30 events/h) both MAD and CPAP therapy can be considered as primary interventions^{24,25}. To date, cost-effectiveness studies assessed different types of oral appliances, also including less efficacious tongue retaining and rigid advancement devices, and included not solely patients with moderate OSA^{19,26,27}. Therefore, limited evidence exists on the cost-effectiveness of MAD when directly compared to CPAP in moderate OSA. Overall, the rationale to advise decision-makers in prescribing MAD or CPAP therapy in moderate OSA is limited and unconvincing given the lack of RCT data when considering costs in combination with health-related quality of life. Therefore, the objective of this study was to evaluate the cost-effectiveness of one commonly used adjustable type of MAD compared to CPAP therapy alongside a clinical RCT. Interventions were evaluated from a societal perspective in terms of the incremental cost per additional point of AHI reduction and per utility in patients with moderate OSA.

Methods

Study procedures and subjects

Baseline polysomnographic outcomes were those obtained at the time of diagnosis. When the diagnostic sleep study was a polygraphy, polysomnography (PSG) was performed before inclusion. All consecutive patients aged ≥ 18 years with an AHI of 15-30 events/h based on PSG (type I in-laboratory in one center, and type II home-based in two centers), and fulfilling

the in- and exclusion criteria were scheduled for a baseline visit, which included questionnaire evaluation (Epworth Sleepiness Scale (ESS)²⁸, short-form 36-item health survey (SF-36)²⁹, the functional outcomes of sleep questionnaire (FOSQ)³⁰, and the hospital anxiety and depression scale (HADS)³¹).

Subsequently, patients were randomized to either MAD or CPAP therapy using a computer program, thereby concealing the allocation sequence from the investigators. Patients could not be blinded to the intervention they received.

Patients returned 3, 6 and 12 months after the start of therapy for follow-up measurements. A PSG was performed after 3 months. In case of unsuccessful treatment (i.e. <50% AHI reduction), adjustments to the therapy were made and a second PSG was scheduled (approximately 6 months after the start of therapy). After 12 months, a final PSG was performed. For each patient individually the same type of PSG (in-laboratory/home-based) was performed during follow-up as on baseline.

Patients switching to the other therapy (randomized therapy not being effective or patient unable to comply with randomized therapy) remained part of the study and were analyzed according to their initial therapy (intention-to-treat analysis).

The study was approved by the ethical committee of the University Medical Center Groningen (number NL34138.042.10, NCT01588275 clinicaltrials.gov). All patients provided informed consent.

Interventions

MAD: Patients randomized to the MAD group were treated with a custom-made titratable bibloc MAD (SomnoDent® MAS, SomnoMed Australia/Europe AG). To start, the mandible was set at approximately 60-70% of the patient's maximum advancement.

CPAP: Patients randomized to the CPAP group were subjected to autoCPAP (Philips Respironics REMstar Auto A-Flex, provided by VitalAire BV The Netherlands) for three weeks, after which the appropriate fixed CPAP-pressure for each individual patient was set by a skilled, specialized nurse (i.e., highest pressure derived from the Hoffstein formula³² or the 90%-criterion (mean pressure $\leq$ 90% of the time) of the autoCPAP). During the study, patients were allowed to change their mask and to use chinstraps or a humidifier if desired.

Outcomes

Cost-effectiveness and cost-utility analysis

The incremental cost-effectiveness and -utility ratios (ICER/ICUR) were calculated after 12 months. ICER was based on the incremental costs and the effects on AHI reduction of MAD versus CPAP (MAD considered the alternative and CPAP the control/reference intervention). ICUR was based on the incremental costs and the effects on utility scores (EQ-5D-3L). The answers on the five domains of the EQ-5D-3L, can be converted into a single index value (also called utility value) between 0 and 1 (with 1 being the optimal health status). Different algorithms to calculate the utility values have been obtained using representative samples of the general population, thereby representing the societal perspective. For this study the Dolan algorithm was used as it is frequently used in international literature and studies, thereby facilitating international comparisons³³. Quality adjusted life year (QALY) was calculated using the utility values multiplied with the survival time (in this analysis 1 year). Bootstrap resampling (5000 replications) was performed on the cost and effect pairs to calculate confidence intervals and to depict cost-effectiveness planes. Furthermore, cost-

effectiveness acceptability curves were plotted to illustrate the probability of interventions studied being more cost-effective than the other therapy over a range of thresholds. In the Netherlands, no formal threshold for cost-effectiveness exists.

Costs

Assuming that both MAD and CPAP have a lifespan of five years, device costs were uniformly depreciated over a five year period. Costs were studied from a societal perspective, which means that all costs are included regardless of who pays them. Therefore, the following cost components were taken into account in the economic evaluation: direct medical costs, such as costs of treatment (including PSG), outpatient hospital visits, visits to general practitioner and other health care providers, and hospital stay. Direct costs outside the health care sector (direct non-medical costs) included travel expenses and parking costs. Indirect costs included income missed from being absent from paid work. In case patients switched to the other therapy, costs were calculated for both therapies together. The time horizon of this study encompassed one year, using 2015 as the reference year, therefore no discounting was applied on costs and effects. Cost components were scored according to the Dutch standard guidelines for economic evaluations³⁴.

Additional detail on the in- and exclusion criteria, study procedures, questionnaires, interventions, and cost components taken into account in the economic evaluation, is provided in the data supplement.

Statistical analysis

Descriptive statistics for continuous variables are presented as means and standard deviations (normal distribution) or medians and interquartile ranges (skewed distribution). Categorical variables are presented in terms of proportions.

Differences between baseline and follow-up variables within the groups were compared using the paired Student's t-test or Wilcoxon's signed rank test for variables with skewed distributions. Differences between treatment groups were compared using the independent Student's t-test or Mann-Whitney U test for variables with skewed distributions.

'Intention-to-treat' and 'per protocol' analyses were performed on the primary endpoints. The power analysis was based on a test on the difference between two independent means. Based on an estimated AHI reduction of 12.4 ± 8.5 points with MAD treatment and 17.4 ± 6.1 points with CPAP treatment (based on literature^{17,35-37} and own data of regular care), an alpha of 0.05 and power of 0.8, 36 patients were required per treatment group. It was expected that 10-15% of patients from each group would drop out¹⁷. Therefore, the estimated number for this randomized controlled trial was 43 patients per group, resulting in a total of 86 patients.

Differences were considered to be statistically significant when $p < 0.05$. Statistical analyses were performed using IBM SPSS Statistics 23 (IBM, New York, USA).

Results

Between June 2012 and September 2016, 118 patients were screened. Thirty-two patients were excluded after the screening visit (Figure 1). Eighty-six patients were randomized (44 MAD, 42 CPAP), of which one patient (randomized to MAD) was excluded after unjustified randomization due to having mild OSA at baseline (AHI 8.6/h based on PSG).

Figure 1. Flowchart showing allocation, switching and dropout of patients. AHI=apnea-hypopnea index; CPAP=continuous positive airway pressure; MAD=mandibular advancement device; OSA=obstructive sleep apnea; PSG=polysomnography; SAS=sleep apnea syndrome

Of the 85 patients (50.7±9.7 years, BMI 30.2±4.9 kg/m², men/women 70/15) with AHI 15-30 events/h (mean AHI 20.9±4.5 events/h), 18 switched to the other therapy (10 from MAD to CPAP, 8 from CPAP to MAD) and 19 patients dropped out during the study (14 MAD, 5 CPAP), of which six dropped out after switching to the other therapy (5 MAD, 1 CPAP). In total, 54 patients (24 MAD; 30 CPAP) completed the study period receiving the therapy to which they were initially randomized (per protocol group).

There were no significant baseline differences in age, AHI, BMI and ESS scores between dropouts and 'per protocol patients'. Furthermore, no significant baseline differences in age, AHI at baseline (20.9±4.4 for MAD and 21.0±4.7 for CPAP), BMI and ESS scores were observed between patients randomized to MAD versus CPAP therapy. Of note, minimal

oxygen saturation (SpO₂) at baseline was significantly lower in patients randomized to CPAP therapy.

During the follow-up period, in total 71 PSGs were performed in the group randomized to MAD and 72 PSGs in the group randomized to CPAP therapy. Both devices significantly reduced AHI after 12 months (MAD from median (IQR) 19.3 (17.8–23.8) to 5.2 (3.2–12.3) and CPAP from 20.6 (17.2–25.3) to 1.4 (0.5–3.5)) based on the intention-to-treat analysis. The reduction in AHI was significantly greater ($p<.01$) with CPAP (median reduction AHI 18.3 (14.8–22.6) events/h after 12 months) as compared to MAD therapy (median reduction AHI 13.5 (8.5–18.4) events/h (Table 1)). Results from the per protocol analysis were not substantially different for AHI (Table 2).

After 12 months, in total 14 patients (50%) randomized to MAD therapy (of the 28 with PSG after 12 months) could be classified as having no OSA (AHI<5 events/h), 8 patients (29%) as having mild OSA (AHI 5–15), and 6 patients (21%) had an AHI>15 events/h. In total 30 patients (86%) randomized to CPAP therapy (of the 35 with PSG after 12 months) had no OSA, 4 patients (11%) had mild OSA and 1 patient (3%) had an AHI>15 events/h.

Table 1. Polysomnographic outcomes (intention-to-treat analysis n=85)

	Baseline		After 1 year	
	MAD n=43	CPAP n=42	MAD n=28	CPAP n=35
AHI (events/hour)	19.3 (17.8 – 23.8)	20.6 (17.2 – 25.3)	5.2 (3.2 – 12.3)†	1.4 (0.5 – 3.5)†§
Snoring (%)	40.8 (26.8 – 51.8)	45.5 (21.2 – 60.7)	12.3 (5.0 – 45.2)†	4.6 (0.4 – 13.4)†§
TST night (min)	390.2 ± 56.1	408.0 ± 48.0	422.4 ± 41.4‡	401.8 ± 65.1
Minimum SpO ₂ (%)	85.0 (81.0 – 87.0)	81.0 (78.0 – 86.0)*	86.5 (84.3 – 90.0)†	91.0 (88.0 – 92.0)†§
REM sleep (%)	16.9 ± 6.3	19.7 ± 7.2	19.6 ± 7.0	22.9 ± 7.4‡

Data are displayed as mean ± SD or median (interquartile range)

AHI=apnea-hypopnea index; TST=total sleep time; REM=rapid eye movement;

MAD=mandibular advancement device; CPAP=continuous positive airway pressure

* significant difference between MAD and CPAP (Mann-Whitney U test)

† significant difference between baseline and follow-up moment (Wilcoxon signed rank test)

‡ significant difference between baseline and follow-up moment (paired-t test)

§ significant difference in Δ change from baseline between MAD and CPAP (Mann-Whitney U test)

§ significant difference in Δ change from baseline between MAD and CPAP (independent t test)

Both devices significantly reduced the percentage of snoring (MAD from median (IQR) 40.8 (26.8–51.8) to 12.3 (5.0–45.2), ($p<.01$) and CPAP from 45.5 (21.2–60.7) to 4.6 (0.4–13.4), ($p<.001$)). The reduction in percentage of snoring was significantly greater with CPAP than with MAD therapy ($p<.01$). Minimal oxygen saturation (SpO₂) increased with both MAD (median [IQR] 85.0 [81.0–87.0] to 86.5 [84.3–90.0]) and CPAP therapy (median [IQR] 81.0 [78.0–86.0] to 91.0 [88.0–92.0]). The difference between MAD and CPAP therapy in minimal oxygen saturation change from baseline was significant ($p<.001$) after 12 months, possibly due to the fact that at baseline minimal oxygen saturation was significantly lower in patients randomized to CPAP therapy.

BMI, waist circumference and fat percentage increased during 12 months in the CPAP group; no changes were observed with MAD therapy (Table 3). Daytime sleepiness, measured with the ESS, was significantly reduced with both MAD and CPAP therapy (MAD

10.3±5.3 to 7.1±5.2, $p<0.001$) and CPAP (9.8±4.1 to 5.3±3.9, $p<0.001$). Also, sleep-related functioning and quality of life measures (FOSQ and SF-36) improved with both MAD and CPAP therapy (see Table 4 for details).

After 12 months, subjective compliance with treatment did not differ significantly between patients randomized to MAD and patients randomized to CPAP. Daily objective compliance of both MAD and CPAP was monitored in two of the three participating centers ($n=59$). Of those, 40 patients (68%; MAD $n=17$, CPAP $n=23$) completed the study with the therapy to which they were randomly assigned. The median (IQR) objective compliance (h/night) in the third month was 7.4 (5.2–8.2) for MAD and 6.8 (5.7–7.6) for CPAP ($p=0.41$). In the 12th month, MAD was used for 6.9 (3.5–7.9) h/night and CPAP was used for 6.8 (5.2–7.6) h/night ($p=0.85$). When applying a worst-case scenario (i.e., compliance after dropout and crossover was scored as '0'), the intention-to-treat analysis showed no significant differences between MAD and CPAP in median h/night.

Table 2. Polysomnographic outcomes (per protocol analysis $n=54$)

	Baseline		After 1 year	
	MAD $n=24$	CPAP $n=30$	MAD $n=24$	CPAP $n=30$
AHI (events/hour)	19.9 (18.0 – 23.8)	19.6 (16.8 – 24.7)	5.9 (3.5 – 14.8)†	0.8 (0.4 – 2.7)†§
Snoring (%)	40.5 (21.7 – 62.1)	47.5 (27.1 – 61.2)	22.2 (6.2 – 51.6)†	3.2 (0.3 – 9.9)†§
TST night (min)	386.7 ± 43.5	409.3 ± 44.4	426.8 ± 40.8‡	406.4 ± 63.7
Minimum SpO ₂ (%)	84.0 (82.0 – 87.0)	82.5 (79.8 – 86.0)	86.0 (84.3 – 89.8)†	92.0 (90.2 – 93.0)†§
REM sleep (%)	17.5 ± 6.7	19.8 ± 8.0	20.4 ± 6.3‡	22.1 ± 7.5

Data are displayed as mean ± SD or median (interquartile range)

AHI=apnea-hypopnea index; TST=total sleep time; REM=rapid eye movement;

MAD=mandibular advancement device; CPAP=continuous positive airway pressure

† significant difference between baseline and follow-up moment (Wilcoxon signed rank test)

‡ significant difference between baseline and follow-up moment (paired-t test)

§ significant difference in Δ change from baseline between MAD and CPAP (Mann-Whitney U test)

§ significant difference in Δ change from baseline between MAD and CPAP (independent t test)

Table 3. Physical measures (intention-to-treat analysis $n=85$)

	Baseline		After 1 year	
	MAD $n=43$	CPAP $n=42$	MAD $n=29$	CPAP $n=37$
BMI (kg/m^2)	29.8 ± 4.9	30.7 ± 5.0	29.3 ± 4.6	31.5 ± 4.9*†
Waist circumference (cm)	106.6 ± 11.4	106.8 ± 12.7	106.0 ± 8.9	108.6 ± 12.4*
Neck circumference (cm)	41.4 ± 3.8	41.7 ± 3.5	40.6 ± 3.3	41.6 ± 3.3
Fat percentage (%)	30.7 ± 7.8	30.9 ± 9.0	29.3 ± 7.9	32.3 ± 8.2*
Distance 6MWT (m)	584.6 ± 86.0	594.8 ± 109.8	607.1 ± 86.0	615.8 ± 93.8

Data are displayed as mean ± SD.

BMI=body mass index; 6MWT=six minute walking test;

MAD=mandibular advancement device; CPAP=continuous positive airway pressure

* significant difference between baseline and follow-up moment (paired-t test)

† significant difference in Δ change from baseline between MAD and CPAP (independent t test)

After 12 months, societal costs, including direct medical and non-medical costs and indirect costs, were higher for MAD than for CPAP therapy (mean difference €2,156). Thus, in addition to MAD therapy being less effective than CPAP therapy after 12 months, it was less cost-effective as well (ICER of -€305 (-€3,003 to €1,572) per AHI point improvement) (Figure 2). Additional data on the direct medical, direct non-medical, and indirect costs, based on the trial data before bootstrapping, is provided in the data supplement (Table S2 in the supplemental material).

Figure 2. ICER after 12 months.

Incremental cost-effectiveness plane. Scatterplot displaying the cost and effect (i.e. AHI reduction) pairs for MAD versus CPAP therapy resulting from bootstrapping, with MAD considered the alternative and CPAP therapy the control intervention.

In terms of QALY, MAD performed better than CPAP (ICUR €33,701 (-€191,106 to €562,271)) (Figure 3A). The cost and effect pairs are now predominantly located in the Northeast and Southeast-quadrants of the Figure (3A), showing additional effects in terms of QALY. The acceptability curve (Figure 3B) shows the probability that MAD therapy is cost effective compared to CPAP therapy over a range of thresholds, up to €50,000 per QALY gained. At a value of around €30,000 the probability exceeds 50%, however it will not even exceed 65% at the €50,000 threshold.

A

B

Figure 3. Incremental cost-utility ratio after 12 months.

A. Incremental cost-utility plane. Scatterplot displaying the cost and effect (i.e. QALY, based on EQ-5D-3L index values 0-1) pairs for MAD versus CPAP therapy resulting from bootstrapping, with MAD considered the alternative and CPAP therapy the control intervention.

B. Cost-utility acceptability curve. The x-axis displays the “cost effectiveness threshold” and the y-axis the “probability of MAD being cost-effective compared to CPAP therapy”.

Results are expressed as a function of societal willingness to pay for additional units of health (quality-adjusted life-years gained).

Table 4. Neurobehavioral outcomes (intention-to-treat analysis n=85)

	Baseline		After 1 year	
	MAD n=40	CPAP n=39	MAD n=29	CPAP n=37
EQ5D (VAS 0-100)	69.6 ± 15.0	67.1 ± 15.6	74.4 ± 14.4	71.1 ± 12.9
ESS (0-24)	10.3 ± 5.3	9.8 ± 4.1	7.1 ± 5.2*	5.3 ± 3.9*
FOSQ (1-4)				
general productivity	3.2 (2.5 – 3.8)	3.6 (2.9 – 3.8)	3.8 (2.9 – 4.0)†	3.9 (3.6 – 4.0)†
social outcome	3.5 (2.5 – 4.0)	3.0 (3.0 – 4.0)	4.0 (3.0 – 4.0)†	4.0 (4.0 – 4.0)†
activity level	2.8 (2.0 – 3.5)	2.9 (2.3 – 3.4)	3.5 (2.7 – 3.8)†	3.7 (3.3 – 3.9)†
vigilance	2.9 (2.2 – 3.6)	3.0 (2.9 – 3.3)	3.6 (2.8 – 3.9)†	3.4 (3.2 – 4.0)†
intimate relationships & sexual activity	2.6 (1.5 – 4.0)	3.0 (2.3 – 4.0)	3.4 (2.8 – 4.0)†	4.0 (3.0 – 4.0)†
total score (5-20)	15.0 (10.5 – 17.5)	16.0 (13.1 – 17.2)	17.5 (14.3 – 19.3)†	18.4 (17.1 – 19.5)†
SF-36 (0-100)				
physical functioning	75.9 ± 18.4	72.0 ± 20.0	81.9 ± 21.7*	81.8 ± 19.7*
social functioning	67.8 ± 25.8	72.1 ± 23.0	76.7 ± 24.0	77.7 ± 26.0
role physical	50.0 (0.0 – 100.0)	25.0 (0.0 – 75.0)	100.0 (25.0 – 100.0)	100.0 (37.5 – 100.0)†
role emotional	100.0 (33.3 – 100.0)	100.0 (33.3 – 100.0)	100.0 (50.0 – 100.0)	100.0 (83.3 – 100.0)
mental health	72.7 ± 16.6	72.8 ± 17.8	72.6 ± 21.7	76.0 ± 18.7
vitality	49.8 ± 19.4	47.2 ± 17.2	59.3 ± 24.2	60.7 ± 22.5*
bodily pain	74.4 ± 26.8	68.5 ± 25.3	76.0 ± 22.5	71.1 ± 24.0
general health perception	53.3 ± 20.4	55.4 ± 21.6	63.6 ± 24.5	61.4 ± 21.5
HADS (0-21)				
anxiety	6.0 (3.0 – 10.0)	4.0 (2.0 – 8.0)	5.0 (2.0 – 7.5)	3.0 (2.0 – 7.5)
depression	5.0 (1.0 – 8.0)	5.0 (3.0 – 8.0)	3.0 (0.5 – 8.0)	4.0 (1.5 – 7.5)
total score (0-42)	9.5 (5.0 – 18.8)	10.0 (5.0 – 17.0)	8.0 (3.0 – 15.0)	6.0 (4.0 – 15.0)

Data are displayed as mean ± SD or median (interquartile range)

EQ5D=EuroQol-5D; VAS=visual analogue scale; ESS=Epworth sleepiness scale; FOSQ=functional outcomes of sleep questionnaire; SF-36=short-form 36-item health survey;

HADS=hospital anxiety and depression scale; MAD=mandibular advancement device; CPAP=continuous positive airway pressure

* significant difference between baseline and follow-up moment (paired-t test)

† significant difference between baseline and follow-up moment (Wilcoxon signed rank test)

Discussion

The strength of this study is the direct comparison of MAD versus CPAP therapy in a randomized trial, specifically following up with patients with moderate OSA over a period of 12 months. In this RCT one commonly and globally used MAD, proven to be effective, was used. A broad range of clinical measures as well as direct medical, direct non-medical and indirect costs (societal perspective) were assessed.

The main results from our RCT demonstrate that although both MAD and CPAP therapy significantly reduced AHI after 12 months, CPAP therapy was clinically more effective. These findings are in accordance with the results of other studies comparing the effectiveness of MAD and CPAP therapy³⁵⁻³⁷.

In line with our data, previously performed economic studies in patient populations with OSA^{19,26,27} suggested that both CPAP and MAD therapy are cost-effective compared to no treatment, with CPAP therapy being the most cost-effective.

The main difference between abovementioned studies and our current study is that we exclusively assessed patients with moderate OSA and that we chose AHI instead of ESS as the primary clinical outcome measure. We believe that ESS is less appropriate because of the limited correlation with the severity and consequences of OSA. Furthermore, Sadatsafavi et al.²⁶ and McDaid et al.²⁷ assessed the cost-effectiveness of different types of oral appliances simultaneously and all studies assessed a broader range than only patients with moderate OSA^{19,26,27}. From a societal perspective, MAD therapy was less cost-effective, driven by the difference in AHI reduction. Conversely, in terms of improvement in QALY, MAD therapy was the better treatment option. This difference in conclusion can be attributed to the choice of outcome measure. To date, QALY has become an important component in cost-effectiveness studies as it allows comparison across different interventions and settings by using a common unit of measure (costs per QALYs gained). A downside of using QALY is that it is difficult to generate a value for health status as it is perceived by different individuals and societies. Furthermore, thresholds do vary largely between countries, and most are informal. Therefore, it is difficult to directly compare thresholds. In the United Kingdom the National Institute for Health and Care Excellence (NICE) uses a threshold range of £20,000 to £30,000 per QALY gained for a cost-effective intervention³⁸. In North America, a similar amount of US\$50,000 per QALY gained is often used.

However, the fact that MAD therapy outperformed CPAP therapy when considering costs per QALY gained implies that patients receiving MAD therapy experience a better health status which could have important health (care) consequences in the long run. We believe that patients with moderate OSA should be advised to start CPAP. When CPAP fails MAD therapy is the second best at this moment. Besides, for patients who refuse CPAP therapy an MAD can be a primary option as it reduces AHI and excessive daytime sleepiness, and improves health-related quality of life.

The discontinuation and dropout rates in our study were higher than expected. Eighteen (21%) patients switched to the other therapy (10 from MAD to CPAP, 8 from CPAP to MAD). In total 5 patients randomized to MAD needed extra PSG measurements versus 2 patients randomized to CPAP. There was a major difference in the rationale for crossing over between therapies; all patients switching from CPAP to MAD therapy could not comply with CPAP therapy (seven patients failed CPAP therapy within 3 months; patient driven cross-over), whereas patients switching from MAD to CPAP therapy were in general treatment

failures, meaning MAD therapy was not adequately effective in reducing AHI (study/physician driven cross-over). A total of 19 patients (22%) dropped out during the study: dropout rates were higher in the MAD (n=14) than in the CPAP group (n=5). Although more patients than anticipated dropped out, resulting in a lower number of patients than estimated necessary based on the a priori power analysis (36 per group), the differential effect was more pronounced and the main results were statistically significant (actual power of 0.89).

The current study has several limitations. First, cardiovascular measures were not included in our cost-effectiveness analysis. All aforementioned previous cost-effectiveness studies^{19,26,27} used economic models having the additional value of merging cardiovascular data associated with OSA. However, a paucity in the data on (long-term) cardiovascular effects of CPAP and especially MAD therapy still exists³⁹ and the long-term clinical implications of OSA remain unclear. Therefore, cardiovascular effects were not included in our cost-effectiveness analyses.

Second, our study had a follow-up period of 12 months. Even though surpassing follow-up periods of most RCTs, an even longer follow-up would have been more desirable in assessing cost-effectiveness. For example, most costs for MAD therapy are made in the first months, as the device is custom-made. Maintenance costs for MAD are low and relatively high for CPAP therapy after the first year, which could influence cost-effectiveness when considering long-term therapy.

Third, results from this study only apply to moderate OSA-patients willing to be randomized to either MAD or CPAP therapy. This may be conducive to selection bias, thereby reducing the generalizability of this study to regular care settings (all-comers) where patients have free treatment choice and can express their a priori preference. In fact, several patients were not willing to participate as they had a clear preference for either MAD or CPAP therapy and therefore received the preferred therapy outside the study setting. Unfortunately, patient therapy preference (excluding them from participation) was not systematically assessed. Nevertheless, retrospectively, the percentage of patients with a priori preference was similar for both therapies (50-50%). Treatment preference has been assessed in some short-term cross-over studies^{35,36,40,41}, mostly indicating that the majority of patients preferred MAD over CPAP therapy^{35,36,41}. Long-term studies on treatment preference are currently lacking.

One type of MAD device was used in the present study, thereby limiting the variation in the costs and potentially limiting the generalizability to other devices. However, as prices of other devices are not substantially different, large effects on the current results are not to be expected. However, in other countries prices of different devices might differ. Furthermore, it is important to state that the costs of health care consumption used in this study apply to the Dutch health system and that those costs need to be put into perspective in countries with different health systems.

The larger positive effects of CPAP therapy on AHI and oxygen saturation suggest better long-term outcomes for CPAP therapy. In accordance, Doff and colleagues¹⁸ described significantly better improvements on AHI and the lowest oxyhemoglobin saturation with CPAP compared to MAD therapy in patients with mild, moderate, and severe OSA (AHI ≥ 5 events/h).

Currently, there is debate on which parameter to use for effect measurement of OSA treatment. The oxygen desaturation index (ODI) could potentially provide more predictive

information on cardiovascular effects in OSA patients, as ODI scores the number of events of reduction in blood oxygen levels irrespective of whether reduction in airflow is taking place. In summary, results of this RCT suggest that CPAP therapy is the first-choice treatment option in moderate OSA and that MAD therapy may be a good alternative, particularly when patients refuse CPAP therapy or prefer MAD therapy because of the less invasive nature of the device. Future research should focus on long-term quality of life and cardiovascular outcomes in order to provide justified treatment advice, also taking into account the initial preference of the patient to offer personalised medical care in patients with moderate OSA.

Abbreviations

AHI	apnea-hypopnea index
BMI	body mass index
CPAP	continuous positive airway pressure
EDS	excessive daytime sleepiness
EQ5D	EuroQol-5D
ESS	Epworth sleepiness scale
FOSQ	functional outcomes of sleep questionnaire
HADS	hospital anxiety and depression scale
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
MAD	mandibular advancement device
OSA	obstructive sleep apnea
PSG	polysomnography
QALY	quality adjusted life years
SAS	sleep apnea syndrome
SF-36	short-form 36-item health survey
VAS	visual analogue scale

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Contribution of the authors

Figures: GEDV, KMV, PJW; study design: GEDV, AH, BS, HAMK, PJW; data collection: GEDV, JQPJC, WJ, JVDM, JHVDH, PJW; data analysis: GEDV, AH, KMV, BS, HAMK, PJW; data interpretation: GEDV, AH, KMV, HAMK, PJW; writing: GEDV, AH, KMV, JQPJC, WJ, JVDM, JHVDH, BS, HAMK, PJW

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Supplement

Inclusion criteria

- 1) Individuals who have been subjected to polysomnography and are diagnosed as having moderate (AHI 15 - 30) obstructive sleep apnea;
- 2) Aged ≥ 18 years;

Exclusion criteria

Medical and psychological exclusion criteria:

- 1) Patients previously treated for OSA (e.g. CPAP, MAD);
- 2) Morphologic abnormalities of the upper airway (e.g., a compromised nasal passage, enlarged tonsils or adenoids, or upper airway soft-tissue or craniofacial abnormality);
- 3) Reported or documented unstable endocrine dysfunction (hypothyroidism, acromegaly, or pituitary adenoma);
- 4) Reported or documented severe cardiovascular- or pulmonary co-morbidity (clinically concurrent cardiovascular disease (coronary artery disease, heart failure, cardiac arrhythmias, CVA within 6 months prior to randomization, daytime respiratory insufficiency, Severe Chronic Obstructive Pulmonary Disease (COPD) (GOLD 3 or 4; FEV1 / FVC < 70% and FEV1 < 50%));
- 5) Reported or documented psychological condition precluding informed consent (e.g., mental retardation, depression or schizophrenia);
- 6) Other diseases that may impact the evaluation of the results of the study according to the investigator's judgment.

Whether the patient has unstable endocrine dysfunction, severe cardiovascular- or pulmonary co-morbidity or a psychological condition precluding informed consent, was assessed based on patient's medical records.

Dental exclusion criteria:

- 1) Extensive periodontal disease or tooth decay;
- 2) Active temporomandibular joint disease (including severe bruxism);
- 3) Restrictions in mouth opening (<25mm) or advancement of the mandible <5mm);
- 4) Partial or complete edentulism (less than eight teeth in upper or lower jaw).

Study procedures and subjects

All consecutive patients aged ≥ 18 years with an AHI of 15-30 events/h based on polysomnography (PSG), and fulfilling the selection criteria based on medical records, were asked to participate in a multicenter parallel randomized controlled trial and subsequently invited for a screening visit. When indicated, spirometry and/or electrocardiogram (ECG) were performed during the screening visit in order to exclude severe cardiovascular- and/or pulmonary disease. During the screening visit a dental examination was performed to establish that patients were suitable candidates for MAD therapy. Patients meeting all in- and exclusion criteria were scheduled for a baseline visit, which included physical examination, 24-hour ambulatory blood pressure measurement (ABPM), blood- and urine

sampling, and questionnaire evaluation. Subsequently, patients were randomized to either MAD or CPAP therapy.

Patients returned 3, 6 and 12 months after the start of therapy for follow-up measurements. A PSG was performed after 3 months to assess the effectiveness of the therapy. In case of unsuccessful treatment (i.e. <50% AHI reduction), adjustments to the therapy were made and a second PSG was scheduled (approximately 6 months after the start of therapy). After 12 months, a final PSG was performed.

Patients switching to the other therapy (randomized therapy not being effective or patient unable to comply with randomized therapy) remained part of the study and were analyzed according to their initial therapy (intention-to-treat analysis).

Randomization and masking

Randomization to either MAD or CPAP therapy was performed using a computer program, thereby concealing the allocation sequence from the investigators. Minimization was used to minimize the imbalance between the number of patients in each group over hypercholesterolemia, diabetes and hypertension status, thereby minimizing the possible effects of *a priori* cardiovascular differences between patients receiving MAD and CPAP therapy. Patients could not be blinded to the intervention they received.

Interventions

MAD: Patients randomized to the MAD group were treated with a custom-made titratable bibloc MAD (SomnoDent® MAS, SomnoMed Australia/Europe AG). To start, the mandible was set at approximately 60 to 70% of the patient's maximum advancement. The maximum advancement of the mandible was determined with a George-Gauge (H-Orthodontics, Michigan City, IN, USA) before MAD therapy was initiated. The forward position of the mandible with the appliance was adjusted to the convenience of the patient until symptoms abated or until further advancement caused discomfort.

CPAP: Patients randomized to the CPAP group were subjected to autoCPAP (Philips Respironics REMstar Auto A-Flex, provided by VitalAire BV The Netherlands) for three weeks, after which the appropriate fixed CPAP-pressure for each individual patient (device provided by the healthcare provider of the patient) was set by a skilled, specialized nurse (i.e., highest pressure derived from the Hoffstein formula ¹ or the 90%-criterion (mean pressure $\leq$ 90% of the time) of the autoCPAP). Patients were fitted with a comfortable mask prior to titration of the CPAP-pressure. During the study, patients were allowed to change their mask and to use chinstraps or a humidifier if desired.

Outcomes

Cost-effectiveness and cost-utility analysis

The incremental cost-effectiveness and -utility ratios (ICER/ICUR) were calculated after 12 months. ICER was based on the incremental costs and the effects on AHI reduction of MAD versus CPAP (MAD considered the alternative and CPAP the control/reference intervention). ICUR was based on the incremental costs and the effects on utility scores (EQ-5D-3L). The answers on the five domains of the EQ-5D-3L, can be converted into a single index value (also called utility value) between 0 and 1 (with 1 being the optimal health status). Different algorithms to calculate the utility values have been obtained using representative samples of the general population, thereby representing the societal perspective. For this study the

Dolan algorithm was used as it is frequently used in international literature and studies, thereby facilitating international comparisons². Quality adjusted life year (QALY) was calculated using the utility values multiplied with the survival time (in this analysis 1 year). Bootstrap resampling (5000 replications) was performed on the cost and effect pairs to calculate confidence intervals and to depict cost-effectiveness planes. Furthermore, cost-effectiveness acceptability curves were plotted to illustrate the probability of interventions studied being more cost-effective than the other therapy over a range of thresholds. In the Netherlands, no formal threshold for cost-effectiveness exists.

Costs

Assuming that both MAD and CPAP have a lifespan of five years, device costs were uniformly depreciated over a five year period. Costs were studied from a societal perspective, including direct costs in- and outside the health care sector as well as indirect costs. The time horizon of this study encompassed one year, using 2015 as the reference year, therefore no discounting was applied on costs and effects. The following cost components were taken into account in the economic evaluation: direct medical costs, such as costs of treatment (including PSG), outpatient hospital visits, visits to general practitioner and other health care providers, and hospital stay. Direct costs outside the health care sector (direct non-medical costs) included travel expenses and parking costs. Indirect costs included income missed from being absent from paid work. Cost components were scored according to the Dutch standard guidelines for economic evaluations³. Additional detail on the cost components taken into account in the economic evaluation is provided in Table S1.

A case record form was used to register hospital related medical resource use. Indirect costs and medical resource use outside the hospital were measured using a questionnaire (adapted version from the iPCQ and iMCQ), which was filled out by patients at baseline and after 3, 6 and 12 months.

Costs of absenteeism (productivity loss) were calculated according to the human capital method based on the multiplication of working days per week, working hours per day, and mean Dutch salary costs (differentiated for men and women)³.

All units of health care consumption, such as visits to the outpatient clinic and to the hospital (academic or periphery), were measured at patient level. Costs of health care consumption were calculated based on standard prices according to CVZ (Care insurance board) guidelines³.

Polysomnography

The mean number of apneas and/or hypopneas was assessed during (ambulatory) PSG. Baseline polysomnographic outcomes were those obtained at the time of diagnosis. When the diagnostic sleep study was a polygraphy, PSG was performed before inclusion. Apneas and hypopneas were defined according to the American Academy of Sleep Medicine (AASM) criteria.

Questionnaires

Patients filled out questionnaires at baseline, and 3, 6 and 12 months after the start of therapy. The level of subjective EDS was measured with the Epworth Sleepiness Scale (ESS)⁴. This questionnaire assesses the propensity to fall asleep in eight separate situations. Quality of life was estimated using the 36-item health survey (SF-36)⁵ and the functional outcomes

of sleep questionnaire (FOSQ)⁶, with higher scores implying better quality of life. Generic health status was assessed with the EQ-5D-3L. Current depression and anxiety was measured with the hospital anxiety and depression scale (HADS)⁷; a higher score representing higher states of anxiety and depression. Furthermore, subjective compliance, satisfaction with the current therapy and side-effects were monitored using self-reported questionnaires.

Table S1. Outline of costs first year

	Costs	Source
MAD therapy		
MAD device	€579.- including depreciation over 5-yr period = €83.95	Correspondence
Technical costs Somnodent		
Fee for starting up MAD therapy	€348.-	Correspondence Websites health insurance companies
Check-up visit	€34.89 (NZa 234191 tariff per 1-1-2015)	Dutch Healthcare Authority (NZa)
Check-up visit including reparation	€70.16 (NZa 234192 tariff per 1-1-2015)	Dutch Healthcare Authority (NZa)
CPAP therapy		
CPAP device	€900.- including depreciation over 5-yr period = €135.95	Correspondence (VitalAire and SomnoMed Goedegebuure)
CPAP mask	Depends on type of mask	Website Vivisol
Chin straps	€21.26	Website Vivisol
Setting-up visit	€74.- (weighted mean reference price 2014, medical specialist replaced by nurse practitioner (hourly rate €35.07))	Reference ³
Check-up by telephone	€18.50 (1/4 * €74.-)	Reference ³
Check-up visit	€37.- (1/2 * €74.-)	Reference ³
Polysomnography	€236.80	Dutch Healthcare Authority (NZa)
Travel expenses	€0.19 per kilometer (car and public transport)	Reference ³
Parking	€3.- per consult	Reference ³
Health care costs		
General practitioner standard consult	€33.-	Reference ³
Psychologist private practice	€94.-	Reference ³
Psychologist hospital	€64.-	Reference ³
Company doctor	€33.-	Reference ³
Medical specialist	€91.-	Reference ³
Paramedic	€33.-	Reference ³
Social worker	€65.-	Reference ³
Hospitalization day	€476.-	Reference ³
Inpatient day psychiatric institution	€302.-	Reference ³
Rehabilitation	€153.-	Reference ³
Domestic home care	€20.-	Reference ³
Salary		
men	€37.90	Reference ³
women	€31.60	Reference ³

Table S2. Direct medical, direct non-medical and indirect costs (intention-to-treat analysis n=85)

	After 3 months		After 1 year	
	MAD n=43	CPAP n=42	MAD n=43	CPAP n=42
Direct medical costs	806.2 ± 267.8	1,091.1 ± 577.1	4,573.3 ± 20,912.5	2,056.8 ± 2,534.0
Direct non-medical costs	42.1 ± 32.8	38.5 ± 26.8	54.7 ± 41.0	53.7 ± 40.2
Indirect costs	1,074.2 ± 3,396.5	689.8 ± 2,786.7	3,548.9 ± 11,434.7	5,132.3 ± 16,014.4

Data are displayed as mean±SD.

Direct medical costs: costs of treatment, visits to general practitioner and other health care providers, outpatient hospital visits, and hospital stay.

Direct non-medical costs: travel expenses and parking costs.

Indirect costs: absenteeism from paid work.

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Chapter 5

Long-term objective compliance of a mandibular advancement device versus continuous positive airway pressure in patients with moderate obstructive sleep apnea

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Abstract

STUDY OBJECTIVES

Comparable health effects of mandibular advancement device (MAD) and continuous positive airway pressure (CPAP) therapy have been attributed to higher compliance with MAD compared with CPAP therapy. The objective of this study was to make a direct comparison of the objective compliance between MAD and CPAP in patients with moderate obstructive sleep apnea (OSA).

METHODS

Compliance was monitored for 12 months in 59 patients with moderate OSA (apnea-hypopnea index (AHI) 15-30) as part of a randomized controlled trial. Objective compliance with MAD was assessed using the TheraMon[®] microsensor. Objective compliance with CPAP was assessed using the built-in registration software with read-out on SD-card. Subjective compliance with both therapies was assessed using a questionnaire.

RESULTS

Forty patients (68%) completed the study with the therapy to which they were randomly assigned. Median (IQR) objective compliance (h/night) in the third month was 7.4 (5.2–8.2) for MAD and 6.8 (5.7–7.6) for CPAP ($p=0.41$), compared to 6.9 (3.5–7.9) with MAD and 6.8 (5.2–7.6) with CPAP ($p=0.85$) in the 12th month. There were no significant changes between the third and twelfth month for both MAD ($p=0.21$) and CPAP ($p=0.46$). Changes in compliance were not significantly different between MAD and CPAP ($p=0.51$). Subjective compliance was significantly higher with MAD than CPAP at all follow-up moments. Subjective compliance with CPAP was lower than objective CPAP compliance at the sixth and twelfth month ($p=0.02$).

CONCLUSIONS

Objective compliance with MAD and CPAP is comparable and consistent over time. Subjective compliance is higher with MAD than with CPAP giving rise to interesting discrepancy between objective and subjective measured compliance with CPAP.

Keywords: sleep apnea; patient compliance; randomized controlled trial

Brief Summary

Although current evidence suggests higher compliance with a mandibular advancement device (MAD) than with continuous positive airway pressure (CPAP) therapy, a direct comparison between the objective compliance profiles of both treatment modalities has not yet been performed in patients with moderate obstructive sleep apnea (OSA).

This study shows that objective compliance with MAD and CPAP therapy is comparable and consistent over time. Subjective compliance is higher with MAD than with CPAP therapy, and objective compliance with CPAP is higher than subjective compliance with CPAP. This study enhances the knowledge about compliance rates of two regularly used treatment modalities in moderate OSA. The results do not support the general idea that compliance with MAD is higher compared with CPAP therapy.

Introduction

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder¹ characterized by repeated upper airway collapse during sleep resulting in a complete cessation or a substantial reduction in airflow. The repetitive airflow limitation causes intermittent hypoxia, which in turn sets off a chain of events, including activation of the sympathetic nervous system, brief awakenings from sleep (arousals) and sleep fragmentation. Other consequences may include excessive daytime sleepiness, impaired quality of life, an increased risk to become involved in occupational^{2,3} and traffic accidents^{4,5}, sick leave and work disability⁶. Ultimately, cardiovascular consequences of OSA may include an increased risk of developing systemic hypertension⁷⁻⁹ and cardiovascular disease, such as myocardial infarction, cardiac arrhythmias, and stroke¹⁰⁻¹⁸.

As OSA has a large impact on individual health and societal costs, it is important that patients receive appropriate treatment in order to reduce symptoms, co-morbidities and its economic burden. Treatment with continuous positive airway pressure (CPAP) prevents upper airway collapse by pneumatically “splinting” the upper airway¹⁹ and is the most frequently prescribed treatment for OSA²⁰. Oral appliance therapy has become an attractive alternative, especially in mild and moderate OSA²¹. Mandibular advancement devices (MAD) are oral appliances that advance the mandible in a forward position, thereby aiming at relieving upper airway collapse by modifying the position of the mandible, tongue, and pharyngeal structures. MADs are now recommended in mild and moderate patients who prefer MADs or for patients who do not respond to or fail CPAP therapy^{22,23}.

In moderate OSA (apnea-hypopnea index (AHI) 15-30 events/hour) MAD^{24,25} and CPAP can be considered as primary interventions as both have been proven effective in reducing the AHI. In terms of AHI reduction, MAD is considered less efficacious than CPAP²⁶⁻³⁰. However, MAD and CPAP show comparable results on behavioral and other health related outcomes³¹. This comparable effectiveness is attributed to a suggested higher compliance with MAD than with CPAP. The latest systematic review by Schwartz et al.²⁷ showed that compliance with MAD was significantly higher than with CPAP, where compliance with MAD was completely based on self-reported usage. Unfortunately, MAD often lacks the technology to objectively assess daily compliance. Recently, objective compliance monitors have become available for MAD therapy. Although evidence suggests a higher (objective) compliance with MAD than with CPAP therapy^{30,32,33}, a direct comparison between the objective compliance profiles of MAD and CPAP has not yet been performed³⁴. Therefore, the aim of this study is to assess the long-term objective and subjective compliance of MAD versus CPAP in patients with moderate OSA.

Methods

Study design

Patients (aged ≥ 18 years) with an AHI of 15-30 events/h (primarily of the obstructive type) were invited to take part in a parallel multicenter RCT, assessing the clinical and cost-effectiveness of MAD versus CPAP. Details about this study, including the complete in- and exclusion criteria and data on the total participating group can be found in a separate article. This current article describes the compliance monitored in patients of two of the three

participating centers. The RCT study was approved by the local Ethical Committee (University Medical Center Groningen: METc2010/355, NL34138.042.10) and is registered at ClinicalTrials.gov No.: NCT01588275. All patients provided written informed consent.

Randomization and masking

The randomization procedure was performed using a computer program, thereby concealing the allocation sequence from the investigators. Minimization was applied to minimize the imbalance between the number of patients in each group (MAD versus CPAP) regarding cardiovascular parameters (i.e. hypercholesterolemia, diabetes and hypertension status at baseline). It was not possible to blind patients to the intervention they received.

MAD and CPAP

MAD: Patients randomized to the MAD group were treated with a custom-made titratable bibloc MAD (SomnoDent MAS, SomnoMed Australia/Europe AG). To start, the mandible was set at 70 % of the patient's maximum advancement. The forward position of the mandible with the appliance was adjusted to the convenience of the patient until symptoms abated or until further advancement caused discomfort.

CPAP: Patients randomized to the CPAP group were subjected to autoCPAP (Philips Respironics REMstar Auto A-Flex, provided by VitalAire BV The Netherlands) for three weeks, after which the appropriate fixed CPAP-pressure for each individual patient (device provided by the healthcare provider of the patient) was set by a skilled specialized nurse (i.e., highest pressure derived from the Hoffstein formula³⁵ or the 90%-criterion (mean pressure $\leq$ 90% of the time) of the autoCPAP). Patients were fitted with a comfortable mask before titration of the CPAP-pressure. Patients were allowed to change their mask during the study and to use chinstraps or a humidifier if required.

Compliance measurements

Objective compliance with MAD was assessed using a microsensor. The TheraMon[®] Orthosmart BV microsensor is a safe method to use³². It is 9.0 x 13.0 x 4.5 mm in size, fully covered by acrylic and embedded in the lower part of the MAD. The microsensor measures the existing temperature (setting: min 33.5°C en max 39.5°C measured every 15 minutes) and stores these values in an inbuilt memory. The memory can store the measurement data of approximately 100 days. Objective compliance with CPAP was recorded via the software read out of a built-in SD-card. Subjective compliance was assessed using a questionnaire after 3, 6 and 12 months after the start of therapy and asked patients who many days per week and hours per night they generally use their therapy.

Calculation of compliance

Read-outs were performed and questionnaires filled in 3, 6 and 12 months after the start of the therapy. Night to night usage was retrieved for 365 days. The following variables were calculated for the 3rd, 6th and 12th month: 1) objective compliance (h/night) calculated over all registered nights, 2) objective compliance (h/night) calculated over the nights the device was used (i.e., >0 h), 3) subjective compliance (h/night), 4) percentage of nights the device was used (i.e., >0 h) over all registered nights, 5) percentage of nights the device was used $\geq$ 4h calculated over all registered nights, 6) percentage of nights the device was used $\geq$ 4h calculated over those nights the device was used (i.e., >0 h).

Polysomnography

Patient underwent (ambulatory) polysomnography (PSG) to assess the effectiveness of the therapy at 3 months, and 1 year after the start of therapy. When adjustments were made to the therapy based on the PSG results after 3 months, an extra PSG was performed with the adjusted therapy.

Statistical analysis

Descriptive statistics are presented as medians and interquartile ranges (IQR) or means $\pm$ standard deviations for continuous variables dependent on normality. Categorical variables are presented in terms of proportions. Mann-Whitney U tests were performed to assess the difference in compliance between MAD and CPAP at each follow-up moment (3rd, 6th and 12th month), and to assess the difference between MAD and CPAP in compliance measures over time. Wilcoxon signed rank tests were performed to assess the change in compliance over time for each therapy separately.

In the primary per protocol analysis only patients, who completed the entire study period of 1 year using their randomized therapy, were included. A second analysis, i.e. an intention-to-treat analysis was performed, also including the patients who dropped out of the study and patients who switched to the alternative therapy during the study. Compliance for dropouts and patients who switched was scored according to a worst-case scenario (i.e., compliance after dropping out and switching was scored as '0'). Patients who did not start therapy were coded as having missing data.

Data were analysed with SPSS 23.0 statistical software (IBM, Armonk, New York). A 2-sided p-value of <0.05 was considered to be statistically significant.

Results

From June 2012 – September 2016, 86 patients were randomized. Daily compliance of both MAD and CPAP was monitored in two of the three participating centers (n=59). For those 59 participants (51.1 $\pm$ 9.7 years, AHI 21.3 $\pm$ 4.4 events/h, BMI 30.4 $\pm$ 4.9 kg/m², men/women: 50/9) objective and subjective compliance data were collected (MAD n=26, CPAP n=33). There were no significant differences in age, AHI, BMI and Epworth sleepiness scale (ESS) at baseline between both intervention groups and between the 59 patients from the two centers where objective compliance was assessed compared with the patients from the third center.

Three patients did not start with therapy due to different reasons (n=2 MAD, n=1 CPAP). In total 56 patients started with the therapy they were randomly assigned to (Figure 1). Three patients stopped during the study (n=1 MAD, n=2 CPAP), and two patients were lost to follow-up (n=2 MAD). Four of the 24 (17%) patients who started MAD switched to CPAP therapy (all treatment failures, n=1 after 3 months of therapy, n=3 after 6 months of therapy). In the CPAP group seven of the 32 (22%) patients switched to MAD therapy (all compliance failures, n=6 after baseline, n=1 after 6 months of therapy). All patients who switched to the other therapy completed the study.

Of the 59 randomized patients, 40 patients (68%; MAD n=17, CPAP n=23) completed the study with the therapy to which they were randomly assigned. There were no significant differences at baseline in age, AHI, BMI and ESS between both groups. There were no

differences at baseline between patients who switched or dropped out versus patients who completed the entire study with their randomized therapy. Figure 1 shows the flowchart for the availability of objective data for the MAD and CPAP group.

Figure 1. Flowchart available objective data MAD and CPAP therapy.

MAD=mandibular advancement device; CPAP=continuous positive airway pressure

The median (IQR) objective compliance (h/night) in the third month was 7.4 (5.2–8.2) for MAD and 6.8 (5.7–7.6) for CPAP ($p=0.41$). In the 12th month, MAD was used for 6.9 (3.5–7.9) h/night and CPAP was used for 6.8 (5.2–7.6) h/night ($p=0.85$) (Figure 2). There were no significant differences in objective compliance between MAD and CPAP at each specific time period, except for the percentage of nights the device was used during the 12th month, which was higher for CPAP when compared with MAD ($p<0.05$). The percentage of nights the

device was used for at least 4h did not differ between MAD and CPAP therapy (see Table 1 for all data).

The objective usage (h/night) was stable over time and there were no significant changes (all nights) between the third and twelfth month for both MAD ($p=0.21$) and CPAP therapy ($p=0.46$). Changes in compliance were not significantly different between MAD and CPAP therapy ($p=0.51$). Subjective compliance was significantly higher with MAD when compared with CPAP at all follow-up moments ($p=0.02$, $p=0.03$, $p<0.05$ respectively). There was a significant underestimation of CPAP compliance at the sixth and twelfth month, i.e. subjective compliance with CPAP was lower when compared with objective CPAP compliance ($p=0.02$ for both follow-up moments).

Table 1. Objective and subjective compliance for the 3rd, 6th and 12th month with MAD and CPAP therapy (per protocol analysis)

	MAD	CPAP	p-value
3 rd month (days 60-90)	n=12	n=22	
Objective hours/night (all nights)	7.4 (5.2 – 8.2)	6.8 (5.7 – 7.6)	0.41
Objective hours/night (when worn)	8.0 (6.2 – 8.2)	6.9 (6.2 – 7.8)	0.06
Subjective hours/night (when worn)	7.3 (7.0 – 8.0)	7.0 (6.0 – 7.0)	0.02
Nights used (%)	95.2 (83.9 – 100.0)	100.0 (96.0 – 100.0)	0.08
≥4h per night all nights (%)	91.9 (75.0 – 100.0)	96.8 (85.5 – 100.0)	0.36
≥4h per night when worn (%)	96.7 (89.8 – 100.0)	98.4 (87.1 – 100.0)	0.80
6 th month (days 150-180)	n=12	n=23	
Objective hours/night (all nights)	6.8 (4.9 – 7.9)	6.9 (5.9 – 7.2)	0.73
Objective hours/night (when worn)	7.2 (6.1 – 7.9)	7.1 (6.4 – 7.7)	0.51
Subjective hours/night (when worn)	7.3 (6.8 – 8.0)	7.0 (6.1 – 7.0)	0.03
Nights used (%)	96.8 (84.1 – 100.0)	100.0 (93.5 – 100.0)	0.32
≥4h per night all nights (%)	88.2 (69.4 – 100.0)	96.8 (83.9 – 100.0)	0.46
≥4h per night when worn (%)	93.9 (88.7 – 100.0)	100.0 (93.5 – 100.0)	0.17
12 th month (days 330-360)	n=14	n=21	
Objective hours/night (all nights)	6.9 (3.5 – 7.9)	6.8 (5.2 – 7.6)	0.85
Objective hours/night (when worn)	7.5 (6.3 – 8.1)	7.1 (6.2 – 7.6)	0.34
Subjective hours/night (when worn)	7.1 (6.6 – 8.0)	6.8 (6.0 – 7.0)	<0.05
Nights used (%)	88.7 (55.6 – 100.0)	100.0 (91.9 – 100.0)	<0.05
≥4h per night all nights (%)	88.7 (52.2 – 100.0)	96.8 (68.4 – 100.0)	0.25
≥4h per night when worn (%)	100.0 (89.5 – 100.0)	96.8 (87.7 – 100.0)	0.37

Subjective hours/night MAD n=16,14,16 for 3rd, 6th, 12th month respectively; subjective hours/night CPAP n=22,20,22 for 3rd, 6th, 12th month respectively

MAD=mandibular advancement device; CPAP=continuous positive airway pressure

The intention-to-treat analysis (worst-case scenario) showed no significant differences between MAD and CPAP in median objective hours/night, percentage nights/used and the percentage of nights used ≥ 4 hours (Table 2).

Table 2. Objective and subjective compliance for the 3rd, 6th and 12th month with MAD and CPAP therapy (intention-to-treat analysis)

	MAD	CPAP	p-value
3 rd month (days 60-90)	n=16	n=31	
Objective hours/night (all nights)	6.1 (4.1 – 8.1)	6.3 (0.0 – 7.4)	0.23
Objective hours/night (when worn)	7.9 (6.2 – 8.2)	6.9 (6.2 – 7.8)	0.11
Subjective hours/night (when worn)	7.0 (6.3 – 8.0)	7.0 (6.0 – 7.0)	<0.05
Nights used (%)	90.3 (54.8 – 100.0)	96.8 (0.0 – 100.0)	0.66
≥ 4 h per night all nights (%)	79.0 (49.2 – 99.2)	87.1 (0.0 – 100.0)	0.95
≥ 4 h per night when worn (%)	96.7 (82.8 – 100.0)	98.4 (87.1 – 100.0)	0.54
6 th month (days 150-180)	n=16	n=32	
Objective hours/night (all nights)	6.3 (1.5 – 7.9)	6.4 (0.0 – 7.1)	0.40
Objective hours/night (when worn)	7.4 (6.2 – 7.9)	7.1 (6.4 – 7.7)	0.46
Subjective hours/night (when worn)	7.0 (5.5 – 8.0)	7.0 (6.1 – 7.0)	0.09
Nights used (%)	91.9 (28.2 – 100.0)	96.8 (0.0 – 100.0)	0.86
≥ 4 h per night all nights (%)	82.0 (21.8 – 99.2)	90.3 (0.0 – 99.2)	0.96
≥ 4 h per night when worn (%)	92.6 (88.9 – 100.0)	100.0 (93.5 – 100.0)	0.12
12 th month (days 330-360)	n=21	n=30	
Objective hours/night (all nights)	3.8 (0.0 – 7.7)	5.3 (0.0 – 7.4)	0.92
Objective hours/night (when worn)	7.5 (6.3 – 8.1)	7.1 (6.2 – 7.6)	0.34
Subjective hours/night (when worn)	7.1 (6.6 – 8.0)	6.8 (6.0 – 7.0)	<0.05
Nights used (%)	59.1 (0.0 – 98.4)	95.2 (0.0 – 100.0)	0.20
≥ 4 h per night all nights (%)	54.5 (0.0 – 96.8)	69.7 (0.0 – 100.0)	0.34
≥ 4 h per night when worn (%)	100.0 (89.5 – 100.0)	96.8 (87.7 – 100.0)	0.37

Subjective hours/night MAD n=21,17,16 for 3rd, 6th, 12th month respectively; subjective hours/night CPAP n=25,20,22 for 3rd, 6th, 12th month respectively

MAD=mandibular advancement device; CPAP=continuous positive airway pressure

Figure 3 shows the mean objective compliance (h/night) with MAD and CPAP therapy, over a time period of 1 year. Days 181 – 264 of MAD could not be displayed as the memory card can only store from the preceding 100 days and therefore data is missing for this specific time period.

AHI significantly reduced with both MAD and CPAP. However, the AHI reduction with CPAP was significantly larger than with MAD (Table 3).

Figure 2. Objective and subjective compliance (h/night) for the 3rd, 6th and 12th month with mandibular advancement device (MAD) and continuous positive airway pressure (CPAP). Boxplots represent the median and interquartile ranges, whiskers represent the minimum and maximum. A = median hours/night measured over all nights; B = median hours/night measured over the nights when device was used; C = subjective median hours/night

Figure 3. Mean usage (hours/night) for MAD and CPAP therapy over 365 days. MAD=mandibular advancement device; CPAP=continuous positive airway pressure

Table 3. Polysomnographic outcomes, body mass index and ESS scores for baseline, and 3 and 12 months with therapy (n=40)

	Baseline		After 3 months		After 1 year	
	MAD n=17	CPAP n=23	MAD n=17	CPAP n=23	MAD n=17	CPAP n=23
AHI (events/hour)	20.4 (19.0 – 23.5)	20.8 (17.6 – 25.5)	4.7 (2.0 – 9.2)#	0.8 (0.1 – 2.4)#¶	5.6 (2.5 – 10.5)#	0.6 (0.2 – 1.6)#¶
TST night (min)	379.0 (345.5 – 412.5)	424.0 (378.0 – 445.0)	405.0 (368.5 – 459.0)	404.0 (373.0 – 431.0)	445.0 (406.0 – 455.5)#	399.0 (349.0 – 446.0)¶
Minimum SpO2 (%)	83.0 (80.5 – 87.0)	80.0 (79.0 – 85.0)	86.0 (80.5 – 89.0)	91.0 (88.8 – 92.3)#¶	85.0 (83.5 – 90.0)	92.0 (90.1 – 93.0)#¶
BMI (kg/m ²)	29.3 ± 5.1	30.3 ± 5.1	29.8 ± 5.3*	30.7 ± 4.8*	29.7 ± 4.9	31.3 ± 4.7*
ESS (0-24)	8.7 ± 4.9	9.2 ± 4.4	5.3 ± 3.1*	5.4 ± 3.8*	5.8 ± 3.7*	4.6 ± 4.1*

Data are displayed as mean ± SD or median (interquartile range)

AHI=apnea-hypopnea index; BMI=body mass index; ESS=Epworth sleepiness scale; TST=total sleep time

MAD=mandibular advancement device; CPAP=continuous positive airway pressure

significant difference between baseline and follow-up moment (Wilcoxon signed rank test)

* significant difference between baseline and follow-up moment (paired-t test)

¶ significant difference between MAD and CPAP therapy (Mann-Whitney U test)

Discussion

This is the first study showing that objective compliance with MAD and CPAP is comparable and consistent over time. Subjective compliance is higher with MAD than with CPAP and objective compliance with CPAP is higher than subjective compliance with CPAP.

Objective and subjective compliance

In general, non-compliance with therapy is an important and well-known problem. In our study eight patients dropped out of the study, and in total 11 patients switched to the other therapy (n=4, MAD to CPAP; n=7 CPAP to MAD). After 1 year, 17 (65%) patients could be considered continuing users of MAD and 23 (70%) patients as continuing users of CPAP.

In the group of continuing users we did not find significant differences in compliance between MAD and CPAP therapy in both the 3rd and 12th month. The percentage of nights the device was used for at least 4h was high for both MAD and CPAP and did not significantly differ between both treatment modalities.

The objective MAD compliance at the 3-month follow-up is comparable with the results found by Vanderveken et al.³² and Dieltjens et al.³³ (median (IQR) of 7.0 (5.9–7.6)). Furthermore, compliance (h/night) was stable over time as there were no significant changes between the third and twelfth month for both MAD (p=0.21) and CPAP therapy (p=0.46). This result is comparable with the results found by Dieltjens et al.³³, who also showed a stable median use rate over 1 year in continuing MAD users.

When comparing the compliance rate of CPAP found in our study, we observed a higher therapeutic compliance when compared with most other studies. In our study, CPAP was used for a median (IQR) of 6.8 (5.7–7.6) h/night in the third month (mean±SD 6.6±1.2 h/night), while the mean CPAP use, based on 66 studies, reported by Rotenberg et al.³⁶ was 4.6 h/night. When taking the dropouts and patients who switched to MAD into account (intention-to-treat analysis – worst-case scenario) CPAP was used for a median (IQR) of 6.3 (0.0–7.4) h/night (mean±SD 4.7±3.2 h/night). The higher CPAP compliance rate in our group of continuing users might be explained by the fact that patients were not blinded to the aims of the study and were present when read outs were performed. The continued and close follow-up of patients could have led to higher compliance rates. Furthermore, all participants were willing to be randomized to either MAD or CPAP. This entails that patients did not have an a priori aversion against CPAP, which might have led to the higher compliance rates compared with other studies, where in some cases patients only had CPAP therapy as a treatment option. Although more patients randomized to CPAP experienced comfort (and thereby compliance) problems, the intention-to-treat analysis, including those patients who dropped out and switched to the other therapy, showed the same results as the per protocol analysis. It can be concluded that when the patient accepts CPAP, compliance is comparable with MAD.

Subjective compliance was significantly higher with MAD than with CPAP at all follow-up moments ($p=0.02$, $p=0.03$, $p<0.05$ respectively). This difference could largely be explained by the significant underestimation of CPAP usage at the sixth and twelfth month. This finding contrasts to what is generally observed in literature, namely a higher subjective compliance when compared with objective compliance. The subjective mismatch in CPAP users in our study might be the result of a decrease in total sleep time (TST) with CPAP (while TST in the MAD group increased), giving the patient using CPAP a feeling of shorter usage time.

Strengths and limitations

The strength of this study is that objective compliance was obtained in a randomized controlled trial, giving us the opportunity to directly compare compliance rates of MAD versus CPAP. Furthermore, data were collected over a period of 1 year. Therefore, we are in the opinion that this is a unique study providing important new knowledge that is very useful for future decision-making.

On the other hand, we know that every study has its limitations. In our study patients were not blinded and were aware of the fact that compliance was monitored. The patients were physically present when read outs were performed as it was part of the outpatient control visits and patients were instantly informed about their compliance rates. The consequence of this procedure could be that patients use their device more frequently and during longer periods. However, the results of this study show comparable compliance rates found in other studies assessing objective MAD compliance. For CPAP however, this could have led to a higher compliance rate compared with other studies.

Future perspectives

There is still debate whether the commonly used cutoff value of 4h/night³⁷ is clinically relevant. The evidence for the use of dichotomizing patients in two groups based on this cutoff value and assessing long-term outcomes in those two groups is limited. Although this study is an important step forward in the knowledge of objective compliance of MAD compared to CPAP therapy, more studies are needed to assess the effects of MAD (and CPAP) compliance on long-term (i.e., 10 y) quality of life and cardiovascular outcomes³⁸.

Conclusions

This study is the first to directly compare (long-term) objective night-to-night compliance with MAD versus CPAP in patients with moderate OSA. Objective compliance with MAD and CPAP was comparable and consistent over time. Subjective compliance was higher with MAD than with CPAP and objective compliance with CPAP was higher than subjective compliance with CPAP.

Abbreviations

AHI	apnea-hypopnea index
BMI	body mass index
CPAP	continuous positive airway pressure
ESS	Epworth sleepiness scale
MAD	mandibular advancement device
OSA	obstructive sleep apnea
PSG	polysomnography

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Contribution of the authors

Figures: GEDV, PJW; study design: GEDV, AH, BS, HAMK, PJW; data collection: GEDV, JQPJC, CS, PJW; data analysis: GEDV, AH, BS, HAMK, PJW; data interpretation: GEDV, AH, HAMK, PJW; writing: GEDV, AH, JQPJC, CS, BS, HAMK, PJW

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Chapter 6

Continuous positive airway pressure and oral appliance hybrid therapy in obstructive sleep apnea: patient comfort, compliance, and preference: A pilot study

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Abstract

STUDY OBJECTIVES

Patients with obstructive sleep apnea syndrome (OSAS) using continuous positive airway pressure (CPAP) often report pressure-related discomfort. Both lower pressure and increased comfort may improve patients' compliance with CPAP-therapy, thereby improving therapeutic effectiveness. Combining CPAP with an oral appliance (hybrid therapy) could be an adequate alternative therapy.

METHODS

Seven patients with moderate to severe OSAS who tolerated their CPAP despite high pressures (≥ 10 cm H₂O) were fitted with hybrid therapy. The mandible was set at 70% of patient's maximum protrusion, and CPAP pressure was set at 6 cm H₂O. When OSAS complaints persisted, pressure was increased. After 3 months, a polysomnographic study was performed. At baseline (conventional CPAP) and after 3 months (hybrid therapy) patients filled in questionnaires assessing comfort, compliance, and satisfaction with treatment, excessive daytime sleepiness, and quality of life.

RESULTS

Four of seven patients reported hybrid therapy to be more comfortable and effective and preferred it over conventional CPAP. There were no differences between baseline (conventional CPAP) and follow-up (hybrid therapy) scores in compliance, satisfaction, daytime sleepiness, and quality of life. Effectiveness of hybrid therapy was good as apnea-hypopnea index (AHI) significantly decreased from median AHI 64.6/h (interquartile range (IQR) 31.0–81.0) at diagnosis to median AHI 1.5/h (IQR 1.0–33.4) with hybrid therapy. There was no statistical difference in effectiveness between conventional CPAP and hybrid therapy (median AHI with conventional CPAP was 2.4/h (IQR 0.0–5.0)).

CONCLUSIONS

Although pressure could be lowered and hybrid therapy seems a comfortable alternative to conventional CPAP, there were no differences between both therapies regarding compliance, satisfaction, and both objective and experienced effectiveness. Combined therapy is feasible in OSAS and should now be investigated in a RCT including assessment of comfort and long-term compliance.

Keywords: obstructive sleep apnea syndrome; continuous positive airway pressure; oral appliance; treatment

Introduction

Treatment with continuous positive airway pressure (CPAP) prevents upper airway collapse by pneumatically “splinting” the upper airway during sleep¹ and is the most frequently prescribed treatment for OSAS². In severe OSAS (apnea hypopnea index (AHI) >30/h), it is the current standard of treatment and improves symptoms and quality of life as well as cardiovascular outcomes^{2–4}. Oral appliance therapy, however, has become an attractive alternative, especially in mild and moderate OSAS⁵. Oral appliance therapy aims at relieving upper airway collapse during sleep by modifying the position of the mandible, tongue, and pharyngeal structures. Side effects have been reported to be mild, improve with time, and are mostly reversible^{6–9}.

Patients with moderate to severe OSAS using CPAP often report pressure-related discomfort or intolerance. Other frequently mentioned complaints with the device are claustrophobia, comfort problems due to the mask or straps on the head, leakage, and dry eyes and nose. Discomfort can ultimately result in reduced therapeutic compliance.

Optimal compliance is essential for a therapy such as CPAP to be successful and effective. It is important to search for alternative treatment options that are equally effective to CPAP in the treatment of moderate to severe OSAS. Combining CPAP with an oral appliance could be such an alternative therapy (hybrid therapy). By combining both therapies, CPAP pressure may be lowered substantially as an oral appliance increases upper airway patency. Second, the CPAP nose mask can be fixed onto the oral appliance, which could improve the comfort of the treatment (no headstrap required, no shifting of the hose/tube). Both lower pressure and increased comfort may improve patients' compliance with therapy, thereby improving therapeutic effectiveness.

To date, only two case reports^{10,11} and one pilot study¹², reporting on the simultaneous use of CPAP and oral appliance therapy in OSAS, have been published. These studies included only patients intolerant to CPAP, and in two studies^{10,12} patients were ineffectively treated with an oral appliance. Furthermore, the studies provide insufficient information about comfort and compliance. In one other case report, the use of an oral appliance in combination with noninvasive ventilation in a patient with amyotrophic lateral sclerosis was described¹³.

The aim of this study was to evaluate whether hybrid therapy is an adequate alternative to conventional CPAP in moderate to severe OSAS. For this study, patients being effectively treated with conventional CPAP and who did tolerate their CPAP and were satisfied with it, despite relative high therapeutic pressures (i.e., > 10 cm H₂O) were selected. Primary outcomes were comfort and compliance with hybrid therapy. Secondary outcomes were effectiveness of hybrid therapy and the effect of this treatment on quality of life.

Methods

Subjects

Patients were eligible for the study when they: (1) were diagnosed with moderate to severe OSAS (apnea-hypopnea index (AHI) ≥15/h) during overnight poly(somno)graphy, (2) used

conventional CPAP with pressure ≥ 10 cm H₂O and could tolerate this pressure, (3) were aged >18 years.

Exclusion criteria were (1) previously treated with an oral appliance, (2) dental contraindications for oral appliance therapy (i.e., extensive periodontal disease or tooth decay, active temporomandibular joint disease (including severe bruxism), restrictions in mouth opening (<25 mm) or advancement of the mandible (<5 mm), partial or complete edentulism (<8 teeth in upper or lower jaw))⁵, (3) morphologic abnormalities of the upper airway, (4) current untreated endocrine dysfunction, (5) reported or documented severe cardiac or pulmonary comorbidity, and (6) patients being treated for psychiatric disorders at the moment of inclusion for the study.

Patients were considered effectively treated with conventional CPAP when AHI reduced to $<5/h$ or reduced $\geq 50\%$ from the diagnostic value to an absolute value $<20/h$ ⁵ (confirmed by poly(somno)graphic evaluation), or when subjective obstructive sleep apnea symptoms were absent and CPAP machine software readout showed sufficient suppression of AHI (therefore in the latter category of patients no poly(somno)graphic evaluation had been performed).

Study Design

This study is a longitudinal quantitative as well as a qualitative study without a control group. The oral appliance (Thornton Adjustable Positioner (TAP3, Airway Management Inc., Dallas, TX, USA)) was custom-made for each patient. The Thornton Adjustable Positioner is an oral appliance that consist of two separate parts for both the maxilla and the mandible. The mandibular protrusion can be adjusted with 0.2-mm increments with a propulsion screw, which was incorporated anteriorly in the oral appliance. The maximum range of mandibular protrusion was first determined with a George-Gauge (H-Orthodontics, Michigan City, IN, USA). When initiating oral appliance therapy, the mandible was set at 70% of the patient's maximum protrusion or at 60% when 70% was uncomfortable to the patient.

After adjusting the oral appliance, nose-probes from a CPAP interface were attached to the oral appliance by means of a connection-unit (Figure 1). No headstraps were used for hybrid therapy.

Figure 1. Continuous positive airway pressure (CPAP) with nose-probe interface combined with a Thornton Adjustable Positioner 3.

When starting with hybrid therapy CPAP pressure was set at 6 cm H₂O for all patients. After an adjustment period of about 2–4 weeks, the degree of mandibular protrusion or CPAP pressure was adjusted if necessary, based on patients' reported symptoms, until the desired effectiveness had been reached or until the adjustments became uncomfortable to the patient. Whether the degree of mandibular protrusion or CPAP-pressure had to be adjusted was decided in accordance with the patient. There was, however, not a strict adjustment protocol.

After 3 months of hybrid therapy, current CPAP pressure was assessed and effectiveness of the therapy was measured with home-based polysomnography. Furthermore, patients were asked about their treatment preference regarding comfort, efficacy, and satisfaction when comparing hybrid therapy with conventional CPAP therapy.

At baseline (conventional CPAP) and after 3 months (hybrid therapy) patients filled in questionnaires assessing comfort of, and compliance and satisfaction with their current treatment, excessive daytime sleepiness (Epworth Sleepiness Scale (ESS)¹⁴, quality of life (Short-Form 36-item Health Survey (SF-36)¹⁵, and Functional Outcomes of Sleep Questionnaire (FOSQ)¹⁶, and anxiety and depressive feelings (Hospital Anxiety and Depression Scale (HADS)¹⁷.

The study was approved by the local Ethical Committee (METc University Medical Center Groningen; METc2010/051). All patients gave written informed consent for using their data for this study and publication before inclusion.

Measurements

Polysomnography

Polysomnographic overnight home-based evaluations (Vita-port-4 PSG, Temec Instruments BV, Kerkrade, the Netherlands) were used to diagnose OSAS and to assess the effect of the hybrid therapy at follow-up. Sleep stages were measured with surface electroencephalography, left and right electrooculography, and submental electromyography. Oxygen saturation was recorded with pulse oximetry. Oronasal airflow was recorded with a pressure cannula. Respiratory effort was monitored with thoracic and abdominal strain bands. Apnea was defined as a complete obstruction resulting in a cessation in airflow (i.e., reduction of airflow $\geq 90\%$) ≥ 10 seconds. Hypopnea was defined as a substantial (i.e., $\geq 30\%$) reduction in airflow ≥ 10 seconds when associated with oxygen desaturation ($\geq 4\%$)¹⁸.

Compliance, Satisfaction, and Preference

The number of nights per week and hours per night using therapy were assessed through a self-report questionnaire. Satisfaction with the current therapy was assessed with a visual analog scale of 0–100 mm without anchors. Patients were asked to draw a vertical line crossing the horizontal scale. After 3 months, patients were asked to indicate whether they preferred conventional CPAP or hybrid therapy based on satisfaction with therapy, long-term use, comfort, and effectiveness, (i.e., the experience that the device is effective in reducing sleep apnea symptoms).

Comfort

Complaints with conventional CPAP (e.g., irritation of CPAP mask; leakage; dry eyes; claustrophobia), oral appliance (e.g., tooth or molar pain; painful jaws, joint, muscles), and the combination of both therapies (hybrid therapy) (e.g., hindered by therapy when falling asleep; awakened by poorly fitted or loose equipment) were assessed through a self-report questionnaire. Patients scored how frequently they experienced a specific complaint on a 4-point scale, ranging from never to often (0–3).

Data Analysis

Descriptive statistics are presented as means ± standard deviations or medians and interquartile ranges (IQR) for continuous variables. Categorical variables are presented in terms of proportions. Wilcoxon signed-rank tests were performed to assess the difference between measurements at baseline and after 3 months. Data were analyzed with SPSS 20.0 statistical software. A value of $p < 0.05$ was considered statistically significant.

Results

Seven patients (6 men) participated (mean±SD age 54±8.9 years). Table 1 contains the demographic characteristics of the patients at baseline. Pressure could be lowered from 11.5±1.3 cm H₂O with CPAP to 6.4±0.5 cm H₂O with hybrid therapy. Three patients had their pressure increased from 6 cm H₂O to 7 cm H₂O during the follow-up period on hybrid therapy. In 4 patients, the degree of mandibular protrusion was increased from 60% to 70% of the patient's maximum protrusion (of whom 2 patients also had their pressure increased from 6 cm H₂O to 7 cm H₂O).

Table 1. Demographic characteristics

	n=7
Age (years)	54.0 ± 8.9
Gender (male/female)	6/1
Body mass index (kg/m ²)	37.4 ± 5.5
Neck circumference (cm)	48.1 ± 3.9
Score on Epworth sleepiness scale at diagnosis (0-24)	16.0 ± 4.2
Score on Epworth sleepiness scale under conventional CPAP (0-24)	9.0 ± 5.3

Age and body mass index assessed at the moment of inclusion for the study
CPAP=continuous positive airway pressure

Five patients used hybrid therapy for the full 3 months, of whom one stopped after the study period. Two patients could not cope with the hybrid therapy and stopped before the 3-month endpoint. Four patients preferred hybrid therapy on the long term over conventional CPAP and also reported hybrid therapy as more comfortable and effective, (i.e., the experience that the device is effective in reducing sleep apnea symptoms) than conventional CPAP. The reasons to stop were feelings of dyspnea and anxiety, and being very restless during sleep due to the therapy and having specific oral appliance related

complaints which were indicated as frequently occurring (tooth or molar pain, feeling that teeth are “out of place” in the morning, painful jaws, joints and chewing muscles). The patient who stopped after the study could not get used to hybrid therapy (claustrophobia), and hybrid therapy was not effective in this patient (AHI at follow-up of 51.8/h, Figure 2).

Figure 2. Apnea-hypopnea index for each patient at diagnosis, with conventional continuous positive airway pressure (CPAP) and with hybrid therapy.

There were no differences in compliance between conventional CPAP (median 7.0 nights/week (IQR 6.0–7.0)); 6.5 h/night (IQR 5.0–8.0)) and hybrid therapy (median 7.0 nights/week (IQR 2.8–7.0)); 6.0 h/night (IQR 4.5–8.1)), both $p=1.0$. Satisfaction rates on the visual analog scale did not differ between conventional CPAP (median 90.0 (IQR 60.0–90.0)) and hybrid therapy (median 92.5 (IQR 42.8–96.3)), $p=0.89$. Nevertheless, when explicitly asked to make a choice between both treatment modalities, 4 of 7 patients reported to be more satisfied with hybrid therapy (Table 2).

AHI decreased significantly with hybrid therapy (median AHI 1.5/h (IQR 1.0–33.4)) compared to AHI at diagnosis (median AHI 64.6/h (IQR 31.0–81.0)), $p<0.05$. There was no statistical difference in effectiveness between conventional CPAP and hybrid therapy (median AHI with conventional CPAP was 2.4/h (IQR 0.0–5.0)).

Scores on the Epworth sleepiness scale dropped from 10.3 ± 4.4 ($n=6$) at baseline with conventional CPAP to 9.2 ± 6.2 with hybrid therapy ($p=0.68$). Quality of life, measured with the FOSQ, increased from 15.9 ± 3.2 ($n=5$) with conventional CPAP to 16.3 ± 3.6 with hybrid therapy ($p=0.79$). The physical subscale of the SF-36 increased from 50.9 ± 8.7 ($n=5$) with conventional CPAP to 51.4 ± 6.2 with hybrid therapy ($p=0.73$) and the mental subscale of the SF-36 increased from 42.7 ± 17.2 with conventional CPAP to 47.5 ± 16.3 with hybrid therapy ($p=0.41$). Anxiety and depressive feelings, measured with the HADS, dropped from 12.4 ± 12.6 ($n=5$) with conventional CPAP to 8.0 ± 9.0 with hybrid therapy ($p=0.16$). All results were in the desired direction, but none of the differences were statistically significant.

Six patients filled in the self-report questionnaire on complaints both at baseline (conventional CPAP) and at follow-up (hybrid therapy). Figure 3 displays the percentages of reported complaints for both therapies per category (calculated as the actual number of reported side effects or complaints for that category divided by the maximum expected number of reported complaints, i.e., the situation when all patients would have scored the same category). Mean scores per (specific) complaint were calculated in order to compare complaints for conventional CPAP with hybrid therapy (Figure 4).

Table 2. Overview per patient

	Pressure (cm H ₂ O)		Compliance				Satisfaction (0-10)		Preference
	Conventional CPAP	Hybrid Therapy	Conventional CPAP		Hybrid Therapy		Conventional CPAP	Hybrid Therapy	
			nights/w	h/night	nights/w	h/night			
1. †	12.0	-	7	8.0	-	-	9.0	-	Conventional CPAP
2. ††	11.0	6.0	7	6.5	7	5.0	9.0	9.5	Conventional CPAP
3.	14.0	7.0	2	3.0	3	3.0	6.0	5.7	Hybrid therapy
4.	11.0	7.0	6	5.0	7	6.0	9.0	9.1	Hybrid therapy
5.	12.0	6.0	7	5.5	7	6.0	6.9	9.4	Hybrid therapy
6.	10.5	7.0	7	8.0	7	8.0	10.0	10.0	Hybrid therapy
7. †*	10.0	-	7	8.5	2	8.5	5.5	0.0	Conventional CPAP

†patient 1 and 7 stopped during the study and before the 3 month follow-up; ††patient 2 stopped after 3 months;

* Patient 7 filled in a shortened questionnaire about EDS, satisfaction and comfort with hybrid therapy; CPAP=continuous positive airway pressure

Figure 3. A. Complaints with conventional continuous positive airway pressure (CPAP) and hybrid therapy. B. Complaints specifically related to oral appliance.

Patients had fewer CPAP complaints in combination with the oral appliance (hybrid therapy) than with conventional CPAP alone (Figure 3A). Specific oral appliance related complaints were reported as not frequently occurring (Figure 3B). Most complaints with conventional CPAP, such as stuffy nose, irritation of the mask, painful nose bridge, leakage, dry eyes, dry mucous membrane mouth and nose became less of a problem when using hybrid therapy, while the swallowing of air, and the presence of a headache appeared to increase slightly with hybrid therapy (Figure 4). When patients had to indicate the severity of their complaints on a scale of mild to severe, most complaints with conventional CPAP were indicated as mild (once absent, 5 times mild, and once moderate). Complaints with hybrid therapy were also indicated as mild most of the times (once absent, 3 times mild, once moderate, and once severe).

Figure 4. Mean scores on complaints with conventional continuous positive airway pressure (CPAP) and hybrid therapy.

Complaint therapy: A = hindered by therapy when falling asleep; B = hindered by therapy during sleep; C = awakened by mask fitted or lose equipment. CPAP complaint: 1 = irritation of CPAP mask; 2 = painful nose bridge; 3 = sound CPAP machine; 4 = leakage; 5 = dry eyes; 6 = dry mucous membrane mouth, nose; 7 = stuffy nose; 8 = claustrophobia; 9 = nosebleed; 10 = swallowing of air; 11 = headache.

Discussion

This study showed that CPAP – oral appliance hybrid therapy could be a comfortable and effective alternative to conventional CPAP in many but not all patients with moderate to severe OSAS. Patients were equally compliant with hybrid therapy and conventional CPAP.

Pressure could be lowered from 11.5 ± 1.3 cm H₂O with conventional CPAP to 6.4 ± 0.5 cm H₂O with hybrid therapy. In addition, complaints were less frequently mentioned with hybrid therapy when compared with conventional CPAP.

The case reports by Denbar¹⁰ and Upadhyay et al.¹¹ and the pilot study by El-Solh et al.¹² showed similar positive effects on therapeutic CPAP pressure and AHI reduction. Both studies, however, have some limitations. Patients in the study by El-Solh et al.¹² used the combination therapy for only 3 days. Furthermore, the only patients selected were intolerant of CPAP and were ineffectively treated with an oral appliance. No overnight sleep study was performed at the end. The study of Denbar¹⁰ describes the treatment of one patient over a time period of 4.5 years, of which the last 1.5 years consisted of hybrid therapy. Both conventional CPAP and an oral appliance therapy were unsuccessful for this specific patient. Upadhyay et al.¹¹ describe the treatment of one patient, who was intolerant of CPAP and was declared unfit for uvulopalatopharyngoplasty. The study describes a treatment period of 90 days during which the patient lost 9 kilograms in weight, which could have amplified the positive study results.

It is plausible that ineffectively treated patients or patients who regard their current treatment as uncomfortable are more eager to start, and are more satisfied with a new therapeutic modality. In order to avoid this bias we selected patients who did tolerate their CPAP and were satisfied with it, despite relative high therapeutic pressures (i.e., >10 cm H₂O). Including only patients who tolerate their CPAP therapy raises another possible bias, as those patients might tend to prefer the therapy they know. Our results show however that four patients preferred hybrid therapy over the long term over conventional CPAP.

Pressure could be lowered in all patients (mean 11.5±1.3 cm H₂O with conventional CPAP to mean 6.4±0.5 cm H₂O with hybrid therapy). Pressure was not again titrated before the start of this study. It is therefore possible that the conventional CPAP was not at the minimum efficient pressure as the CPAP pressure was the pressure patients were on before the period with hybrid therapy started. The conventional CPAP pressure was, however, increased until OSAS complaints were no longer present and the sleep study, or CPAP machine software readout showed sufficient suppression of the AHI. A lower efficient pressure is therefore not very likely.

Complaints were indicated as not frequently occurring for conventional CPAP as well as for hybrid therapy. Patients reported less specific CPAP complaints with hybrid therapy than with conventional CPAP, suggesting higher comfort with the hybrid therapy.

Our theory that lower pressure and better comfort could result in a better therapeutic compliance was not confirmed by our data. Moreover, satisfaction scores on the visual analog scale were similar. However, when forced to make a choice for one of the two treatments, four of seven patients preferred hybrid therapy over conventional CPAP. They reported hybrid therapy as more comfortable and effective. These patients continued using the hybrid therapy after completion of the study. Unfortunately, due to the small sample size, no statistics could be applied to assess whether complaints were significantly less with hybrid therapy than with conventional CPAP.

In our study, one patient had his AHI worsened using hybrid therapy. A possible explanation for this could be that this patient had gained weight compared to the time when the OSAS was diagnosed and also when compared to baseline (137 kg with hybrid therapy compared to 123 kg with conventional CPAP).

There are some other limitations to consider for this study. Unfortunately, we did not have polysomnographic data for all patients while using conventional CPAP, making a good comparison on objective effectiveness between conventional CPAP and hybrid therapy difficult. Four patients had polysomnography performed with both treatment modalities; the

other three patients reported no subjective obstructive sleep apnea symptoms, and CPAP machine software readout showed sufficient suppression of AHI. Therefore, no follow-up poly(somno)graphic evaluation was indicated at that moment.

During the study period the degree of mandibular protrusion or CPAP pressure was adjusted when necessary. There was, however, not a strict protocol regarding which one to perform first. To date, there are no data to substantiate which approach is best in titrating hybrid therapy. This should be a point of attention in future studies assessing hybrid therapy.

The results of our study should be interpreted with caution, as this study consists only of a small patient sample and because there was no control group. Furthermore, a follow-up of 3 months may be too short to reveal effects on quality of life data.

Conclusions

In conclusion, although pressure could be lowered substantially, this pilot study did not show large differences between conventional CPAP and hybrid therapy regarding compliance, satisfaction, and both objective and experienced effectiveness. There are, however, some differences in scores on CPAP complaints, which could explain why hybrid therapy is preferred by four of the seven patients. Therefore, CPAP – oral appliance hybrid therapy could be a comfortable and effective alternative to conventional CPAP when high pressure is needed or in case of high-pressure intolerance. Larger, longer term, and preferably randomized studies are needed to answer the question whether hybrid therapy can result in lower pressures leading to a more comfortable and effective treatment for patients with moderate to severe OSAS.

Abbreviations

AHI	apnea-hypopnea index
CPAP	continuous positive airway pressure
IQR	interquartile range
OSAS	obstructive sleep apnea syndrome

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Chapter 7

Usage of positional therapy in adults with obstructive sleep apnea

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Abstract

STUDY OBJECTIVES

Many positional therapy (PT) strategies are available for treating positional obstructive sleep apnea (OSA). PT is primarily supplied to selected patients as a secondary treatment option when other therapies have failed. To our knowledge this is the largest study to date to assess effectiveness and long-term compliance of PT (both commercial waistband and self-made constructions, mimicking the tennis ball technique) as primary treatment in patients with different positional OSA severities.

METHODS

PT was used by 53 patients, of which 40 patients underwent a follow-up polygraphic evaluation under treatment after a median time interval of 12 weeks. Patients were routinely contacted regarding their clinical status and treatment compliance.

RESULTS

PT was successful in 27 out of 40 patients (68%). Overall AHI reduced significantly from a median (interquartile range (IQR)) AHI of 14.5 (10.7–19.6) to 5.9 (3.1–8.5), $p < 0.001$. The commercial waistband and self-made constructions were equally effective (median (IQR) reduction in overall AHI ($\Delta 9.6$ (5.5–11.9) and $\Delta 6.8$ (3.2–11.3) respectively), $p = 0.22$). Short-term compliance was good as most patients used PT more than 7 hours/night (mean $7.2 \pm \text{SD } 1.4$) and more than 6 days/week (mean $6.5 \pm \text{SD } 1.3$). However, after mean 13 ± 5 months, 26 patients (65%) reported they no longer used PT, especially patients with moderate positional OSA (89%).

CONCLUSIONS

On the short-term, PT using the tennis ball technique, is an easy method to treat most patients with positional OSA, showing significant reductions in AHI. Unfortunately, long-term compliance is low and close follow-up of patients on PT with regard to their compliance is necessary.

Keywords: compliance; effectiveness; obstructive sleep apnea; positional therapy; sleep related breathing disorder

Brief Summary

To our knowledge this is the largest study to date to assess effectiveness and long-term compliance of positional therapy as a primary treatment option in patients with different severities of positional OSA. Furthermore, in this study both a commercial fabricated waistband and self-made constructions mimicking the tennis ball technique were assessed.

After reading this article, readers should be able to know the short-term effectiveness of and long-term compliance with positional therapy. Positional therapy is an effective method to treat patients with positional OSA on the short-term. Long-term compliance is low especially in patients with moderate OSA at baseline. More comfortable devices such as vibrating devices might be more useful to treat positional OSA.

Introduction

Obstructive sleep apnea syndrome (OSAS) is a common sleep-related breathing disorder affecting 14% of middle-aged men and 5% of women¹. OSAS is characterized by repetitive upper airway collapse during sleep, resulting in a complete (apnea) or partial (hypopnea) obstruction in airflow, reduced oxygen saturation levels and disruptive snoring. The increased respiratory effort to restore oxygen levels result in activation of the sympathetic nervous system, brief awakenings from sleep, leading to sleep fragmentation and excessive daytime sleepiness (EDS)^{2,3}.

The collapsibility of the upper airway is increased in the supine sleeping position, possibly due to the effect of gravity and altered size and shape of the upper airway in this position⁴⁻⁷. As a result the total number of apneas and hypopneas per hour of sleep (i.e., apnea-hypopnea index (AHI)) and severity of the respiratory events usually increases in supine position. According to the American Academy of Sleep Medicine (AASM) definition positional obstructive sleep apnea (OSA) can be defined as a lower AHI in the non-supine position than in the supine position⁸. In practice positional OSA is defined as an AHI at least twice as high in supine position as in other positions^{9,10}. When using this definition about half of all patients with OSA have positional OSA¹⁰, while in patients with mild (AHI 5–15 events/h) to moderate (AHI 15–30 events/h) OSA this percentage is even higher¹⁰. When using a more stringent definition, requiring an AHI that normalizes (AHI <5 events/h) in the non-supine posture, prevalence is still 35%¹¹.

Throughout the years, many PT strategies have been designed to prevent patients from sleeping on their back¹², such as an alarm system¹³, a backpack with ball¹⁴, behavioral therapy¹⁵, a pillow with straps¹⁶, the so-called tennis ball technique^{17,18}, a recently developed neck-worn vibrating device^{19,20}, and a chest-worn vibrating device^{21,22}.

Oksenberg and Gadot²³ argue that PT might be a simple solution for patients with mild to moderate positional OSA. While most devices appear effective in the beginning and compliance on a short-term (<3 months) seems satisfactory, long-term (>6 months) efficacy is unknown and compliance is poor²⁴. To date most studies have a short follow-up period and in general small patient samples. Furthermore, in most studies the devices are supplied to selected patients as a secondary treatment option when continuous positive airway pressure (CPAP) and oral appliance therapy have failed.

To our knowledge this is the largest study to date to assess effectiveness and long-term compliance of PT as a primary treatment option in patients with different severities of positional OSA. In this observational study both a commercial fabricated waistband and self-made constructions mimicking the tennis ball technique were assessed.

Methods

This study is a retrospective observational study. Data were collected based on patient files. Therefore, there is no control group and no sample size calculation was performed. Patients were seen by a nurse practitioner at the outpatient clinic, and had follow-up visits scheduled based on usual care. The (telephone) visits followed a semi-structured protocol using structured and predefined questions including questions about the clinical status of the patient and treatment compliance.

Patients and Treatment

Patients suspected of having OSA were referred to the University Sleep Apnea Center (USAC) Groningen, University Medical Center Groningen (UMCG), Groningen, the Netherlands. All patients diagnosed with positional OSA during an overnight polygraphic or polysomnographic evaluation received information about the possible treatment modalities (PT, oral appliance therapy, CPAP or surgery if indicated). It was up to the patient which treatment option to use. When patients chose to start with PT, they were given information about the commercial waistband (Werkmeister SnurkStop, Soft Medic Veendam, the Netherlands, Figure 1). As costs for the commercial waistband are not reimbursed by the health insurance companies, patients were allowed to make a self-made construction (tennis ball or other stiff product sewn into the backside of a shirt or pyjamas). All devices mimicked the so-called tennis ball technique.

Figure 1. Werkmeister SnurkStop.

A second group consisting of patients who failed on CPAP or oral appliance therapy, and had positional OSA based on their diagnostic sleep study, were advised to use PT afterwards. Patients with known significant cardiovascular diseases (heart failure, coronary disease, or severe cardiac arrhythmias) were excluded from PT as primary treatment option and received CPAP therapy.

Measurements

OSA was diagnosed by polygraphy (PG) (Embletta-GOLD Medcare) or polysomnography (PSG) (Vitaport-4 PSG, Temec Instruments BV, Kerkrade, the Netherlands) during overnight home-based monitoring. Follow-up measurement under treatment was performed by PG.

During PSG, 6-channel surface electroencephalography, left and right electrooculography, and submental electromyography were used to stage sleep. Oxygen saturation was recorded with pulse oximetry. Cardiac function was monitored by electrocardiography. Oronasal airflow was recorded with a pressure cannula. Respiratory effort was monitored with thoracic and abdominal strain gauges. Electromyography of the tibialis anterior muscle was measured to screen for periodic limb movements. Body position was measured with a position meter. During PG, the same assessments were done but without the electroencephalography. Apnea was defined as a complete obstruction resulting in a cessation in airflow (reduction of airflow $\geq 90\%$) of ≥ 10 seconds. Hypopnea was defined as a

substantial ($\geq 30\%$) reduction in airflow of ≥ 10 seconds when associated with oxygen desaturation ($\geq 4\%$)²⁵. Severity of OSA was classified by AHI during the poly(somno)graphic sleep study. Accordingly, patients were classified either as suffering from mild (5–15 events/h), moderate (15–30 events/h), or severe (AHI >30 events/h) OSA⁸. Positional OSA was defined as an AHI at least twice as high in supine position as in other positions (usually lateral position)^{9,10}.

A follow-up polygraphic evaluation (PG) under treatment was performed to assess the effectiveness of PT, including differences between baseline and follow-up percentages in supine position, AHI, minimal oxygen saturation, and maximal duration of apnoeic events. The sleep physicians scoring the PGs were not blinded on which therapy the patient was using as the sleep study was part of usual care. EDS was measured with the Epworth Sleepiness Scale (ESS), a questionnaire filled in by the patient, which assesses the propensity to fall asleep in eight different situations. ESS was scored both at baseline and follow-up.

Treatment was considered successful when AHI was <5 events/h or reduced $\geq 50\%$ from the baseline value to an absolute value <20 events/h in patients without subjective OSA symptoms²⁶. Patients were routinely contacted by the nurse practitioner about their clinical status and their compliance with the treatment. We considered 3 months results as short-term and results after 6 months as long-term.

Statistical Analysis

Descriptive statistics are presented as mean $\pm$ standard deviation or median and interquartile range (IQR) for continuous variables (depending on the distribution of the variables). Categorical variables are presented in terms of proportions. To test for normality Kolmogorov-Smirnov tests were performed. Paired t-tests and Wilcoxon signed-rank tests were performed to assess the difference between baseline and follow-up values. Independent t-tests and Mann-Whitney U-tests were performed to assess baseline differences between groups, and to compare changes from baseline between groups. Data were analyzed with SPSS 18.0 statistical software. A value of $p < 0.05$ was considered statistically significant. As this was a retrospective observational study not deviating from standard medical care approval from the ethics committee was not obligatory. Patient confidentiality was warranted. All patients gave informed consent for using their data for this study and publication.

Results

Between April 2009 and April 2011, 89 patients were diagnosed with positional OSA (Figure 2). Forty-six used PT as primary treatment option, while 43 chose a different treatment: CPAP $n=19$, oral appliance $n=5$, ear nose and throat surgery $n=6$, other/no therapy $n=13$. Seven patients used PT as secondary treatment option after another treatment had failed (Figure 2). In total 53 patients used PT (Figure 3).

Forty patients (32 polygraphic (PG) and 8 polysomnographic (PSG) evaluations at baseline) underwent follow-up PG (20 mild, 18 moderate, 2 severe OSA; 85% men, mean age 51.1 ± 8.3 years) to assess the effectiveness of PT. The PG under treatment was scheduled in consultation with the patient with a median (IQR) time interval of 12 (9–16) weeks.

Thirteen patients had no follow-up PG: n=6 cancelled the sleep study or did not show up and were lost to follow-up (4 mild, 2 moderate OSA), n=7 stopped using PT before the follow-up PG (dissatisfied with PT n=6, no specific reason mentioned for stopping PT n=1) and received other treatment (CPAP n=3; oral appliance n=2, ear nose and throat surgery n=2). There were no baseline differences in overall AHI, ESS score, and percentage supine position between these 13 patients and the 40 patients with follow-up PG.

Figure 2. Patients with positional obstructive sleep apnea syndrome.
AHI=apnea-hypopnea index; CPAP=continuous positive airway pressure; OSA=obstructive sleep apnea.

Figure 3. Patients using positional therapy.

CPAP=continuous positive airway pressure; OSA=obstructive sleep apnea.

Effectiveness

Table 1 shows the baseline and follow-up data and the results of the statistical analysis for the total group (n=40) and for both kinds of PT (commercial waistband n=20; and self-made construction n=20). The cost of a commercial waistband not being reimbursed was the reason for 20 patients to make their own waistband.

Table 1. Baseline and follow-up data of patients using positional therapy.

	Baseline	Follow-up		p-value†	
	(n=40)	Total group (n=40)	Commercial device (n=20)		Self-made construction (n=20)
BMI (kg/m ²)*	28.0 ± 4.1	27.9 ± 4.0	28.5 ± 4.8	27.2 ± 3.1	0.29
Analyzed time (min)*	452.4 ± 59.1	443.6 ± 81.2	428.6 ± 56.5	458.6 ± 99.4	0.45
Time spent in supine posture (min)†	155.3 (97.8-193.7)	33.5 (0.5-66.9)	30.5 (0.5-48.8)	35.6 (0.3-75.2)	<0.001
Time spent in supine posture (%)†	32.4 (23.2-43.9)	8.7 (0.1-15.2)	7.0 (0.1-10.9)	9.1 (0.1-15.9)	<0.001
Overall AHI (events/hour)†	14.5 (10.7-19.6)	5.9 (3.1-8.5)	5.8 (3.3-7.8)	5.9 (2.5-13.5)	<0.001
Supine AHI (events/hour)†	38.0 (24.0-52.4)	8.5 (0-21.5)	12.0 (0-32.4)	6.3 (0-14.6)	<0.001
Non-supine AHI (events/hour)†	3.9 (2.2-7.1)	4.3 (1.4-8.9)	3.6 (1.2-7.0)	5.9 (1.7-17.2)	0.21
Minimal oxygen saturation (%)†	86 (82-87)	87 (84-89)	87 (80-89)	88 (85-90)	0.01
Maximal duration event (sec)*	63.0 ± 23.8	52.0 ± 25.3	50.7 ± 20.9	53.6 ± 28.7	0.02
Epworth sleepiness scale (0-24)*	12.2 ± 5.4	10.2 ± 5.5	9.1 ± 4.9	11.3 ± 6.0	<0.01

The table does not include the 13 patients who started on PT but who did not have follow-up PG
Data are presented as mean ± SD or median (IQR); * Paired t-test; † Wilcoxon signed-rank test; ‡ baseline vs. follow-up total group
BMI=body mass index; AHI=apnea-hypopnea index

Table 2. Comparing the commercial device with self-made constructions

	Commercial device (n=20)	Self-made construction (n=20)	p-value
Δ BMI (kg/m ²)†	0.0 (0.0-0.3)	0.0 (-0.2-0.1)	0.61
Δ Analyzed time (min)*	9.6 ± 53.7	8.2 ± 91.4	0.95
Δ Time spent in supine posture (min)*	127.5 ± 102.0	121.7 ± 95.8	0.86
Δ Time spent in supine posture (%)*	28.1 ± 23.0	24.7 ± 20.8	0.63
Δ Overall AHI (events/hour)†	9.6 (5.5-11.9)	6.8 (3.2-11.3)	0.22
Δ Supine AHI (events/hour)*	18.7 ± 30.5	27.8 ± 28.6	0.35
Δ Non-supine AHI (events/hour)†	-1.0 (-3.0-2.4)	-0.7 (-11.3-1.2)	0.41
Δ Minimal oxygen saturation (%)*	-0.7 ± 6.1	-3.0 ± 4.1	0.19
Δ Maximal duration event (sec)*	10.8 ± 23.7	11.1 ± 31.9	0.98
Δ Epworth sleepiness scale (0-24)*	2.8 ± 4.1	1.3 ± 2.8	0.19

The table does not include the 13 patients who started on PT but who did not have follow-up PG
 Data are presented as mean ± SD or median (IQR); *Independent t-test; † Mann-Whitney U-test
 BMI=body mass index; AHI=apnea-hypopnea index

PT effectively reduced the time spent in supine sleeping position from median (IQR) 155.3 (97.8–193.7) minutes at baseline to 33.5 (0.5–66.9) minutes, $p<0.001$. At baseline all patients spent at least 30 minutes in both the supine and non-supine position. Overall AHI reduced from a median (IQR) AHI of 14.5 (10.7–19.6) events/h to 5.9 (3.1–8.5) events/h, $p<0.001$. Baseline overall AHI was not significantly different between both groups ($p=0.99$). Furthermore, supine AHI, maximal duration of the respiratory events, and ESS score significantly reduced when using PT (Table 1). Also oxygen saturation increased significantly under treatment.

PT for the short-term was successful in 27 (commercial waistband $n=14$; and self-made construction $n=13$) of 40 patients (68%): these 27 patients showed a reduction in AHI of $\geq 50\%$ from the baseline value to a value <20 events/h; of these 16 patients showed an AHI <5 events/h. Results per patient on overall AHI are shown in Figures 4A, 4B, and 4C. PT was comparably effective in mild ($n=20$; 65% successful) and moderate OSA ($n=18$; 67% successful). In severe OSA all patients ($n=2$; 100% successful) were treated effectively. In 2 patients with mild and 2 with moderate OSA, AHI worsened despite using PT. All those patients made their own PT construction, of which 3 were successful in reducing the time spent in supine position (2 completely eliminated the supine position) without leading to a reduction in AHI.

Figure 4. Dotted lines represent commercial waistbands, straight lines self-made constructions. A. Overall apnea-hypopnea index per patient with mild obstructive sleep apnea at baseline. B. Overall apnea-hypopnea index per patient with moderate obstructive sleep apnea at baseline. C. Overall apnea-hypopnea index per patient with severe obstructive sleep apnea at baseline.

The commercial waistband and self-made constructions showed no significant difference in overall AHI reduction, median (IQR) $\Delta 9.6$ (5.5–11.9 events/h) and $\Delta 6.8$ (3.2–11.3 events/h), respectively, $p=0.22$. Patients using the commercial waistband had larger reductions in the time spent in supine position and had larger reductions in ESS scores than patients using a self-made construction, but these differences were not significant (Table 2). There were no baseline differences in demographic characteristics between patients using the commercial waistband and patients using a self-made construction.

Compliance

During the first weeks compliance was considered good, as most patients used their device >7 h/night (mean 7.2 ± 1.4) and >6 days/week (mean 6.5 ± 1.3). However, 13 ± 5 months after starting PT, 26 patients (65%, commercial waistband $n=15$, self-made construction $n=11$) reported that they had stopped using PT (Figure 3). In mild positional OSA patients, 9 of 20 stopped, in moderate 16 out of 18, and in severe 1 of the 2 patients. Of the patients, who were effectively treated, 60% had stopped using PT, whereas of the patients not effectively treated 77% had stopped. However, this difference was not statistically significant. In total 16 patients received other treatment after PT, such as CPAP ($n=8$), an oral appliance ($n=4$) or ear nose and throat surgery ($n=4$) (Figure 3). Two patients who initially stopped PT restarted using the device. Three patients started other treatment in addition to their PT.

Discussion

To our knowledge this is the largest study to date to assess effectiveness and long-term compliance of PT (both commercial waistband and self-made constructions) as a primary treatment option in patients with different severities of positional OSA. The largest study sample so far was by Oksenberg et al. ($n=78$)¹⁸. This was however a questionnaire study, and only 12 patients had a follow-up sleep study to assess effectiveness.

Effectiveness

Our short-term results show that PT with the so-called tennis ball technique (both commercial waistband and self-made constructions) effectively reduces the time spent in supine sleeping position in patients with positional OSA. Furthermore, AHI, severity of the respiratory events, and EDS were significantly reduced when using PT.

PT was successful in 27 of 40 patients (68%). Body mass index (BMI) was stable during treatment, which indicates that the positive findings are not the result of weight loss, but can be ascribed to PT.

In four patients, AHI worsened despite using PT. Although we saw that in three patients the self-made constructions were effective in reducing time spent in supine position, AHI was not improved, which can be ascribed to the increased number of apneas and/or hypopneas in the non-supine position during the follow-up PG. Several factors could have influenced non-supine AHI, such as alcohol use, cigarette smoking²⁷, and medication use. Unfortunately we have no reliable data about these factors on the specific day/evening of the sleep study.

Our short-term results are in accordance with other studies assessing PT. Most studies report positive results on the time spent in supine sleeping position, severity of the respiratory events, and a significant reduction in AHI^{14,16,18,19,21,28–30}.

In our study, a commercial waistband or a self-made construction was used by patients. As far as we know, there are no other studies comparing self-made constructions with commercially fabricated devices. Although the commercial waist-band showed a slightly larger reduction in overall AHI, a larger reduction in the time spent in the supine position and a larger reduction in ESS score at the follow-up PG, these differences were not statistically significant and we conclude that both types of PT can be considered equally effective.

Compliance

In our study short-term compliance was good as most patients used their device more than 7 hours/night (mean 7.2 ± 1.4) and more than 6 days/week (mean 6.5 ± 1.3). Short-term compliance was assessed subjectively which could mean that treatment use was over- or underestimated. Though, our results are comparable with the compliance rates reported by Heinzer et al.²⁸ who assessed compliance with their device objectively by placing an actigraphic recorder inside. Long-term results regarding compliance were considered disappointing, as only 14 of 40 patients were still using their device 13 $\pm$ 5 months after starting PT. Compliance was also low in the 13 patients without follow-up PG. Of these 13 patients, 7 stopped using PT before the follow-up PG. This means that in total, 33 of the initial 53 patients (62%) who started PT stopped using this treatment modality.

This was particularly notable in patients with moderate positional OSA at baseline, as 16 of 18 patients (89%) stopped using PT. Patients were classified as “moderate” due to the fact that they spent more time in supine sleeping position, thereby increasing the overall AHI. Despite PT effectively correcting supine sleeping position for both mild and moderate OSA groups, residual overall AHI (due to an increase in the non-supine component of the AHI) stayed higher at follow-up only in patients with initial moderate OSA. Factors other than position might have influenced AHI, such as anatomical factors or a central component of the apneas and/or hypopneas. Sleep endoscopy is not a standard procedure for these patients in our medical center. Therefore, we cannot confirm anatomical differences between patients with initial mild and moderate positional OSA. Finally, it is possible that patients experienced insufficient reduction in AHI to feel better, resulting in the higher percentage of compliance failures in patients with moderate positional OSA.

It could be expected that successful treatment increases compliance. This was, however, not the case in our study, as 60% of patients who were successfully treated, stopped using PT. Apparently, compliance is independent of treatment effectiveness; more behavioral factors and comfort might play an important role in continued PT use.

While short-term non-compliance with therapy is a common and well-known problem, as with CPAP, there is little known about long-term compliance with PT. Bignold et al.²⁴ assessed long-term compliance with the tennis ball technique through a questionnaire study. They found that compliance after 2.5 ± 0 years was poor, as 81% of the patients no longer used the device. However, as a large proportion did not return the questionnaire (non-responders) there is a possible responder bias. In the study by Oksenberg et al.¹⁸, 62% of the patients stopped using the device. Also in this study a large proportion of the patients did not respond (36%) to the questionnaire.

Van Maanen et al.¹⁹ tried to develop a more comfortable device not disturbing sleep architecture and sleep quality. However, the total sleep time of the patients significantly decreased when using the neck-worn vibrating device. Furthermore, the number of awakenings increased and sleep efficiency decreased with the particular device. Compliance was unfortunately not assessed in this study. In another study by van Maanen et al.²¹, compliance with a chest-worn vibrating device was very high with 92.7% after 29±2 days of usage. After 6 months, compliance was 64.4%²². This type of device, a chest- or neck-worn vibrator, could be a solution for positional OSA as this device might be more comfortable to wear than a device using the tennis ball technique. Compliance with PT using the tennis ball technique could, for example, be limited as a result of the bulkiness of the device resulting in back pain and discomfort, which could lead to disruption of sleep and low sleep quality.

A weakness of the present study is that PG was used at follow-up instead of PSG, and we cannot state with certainty if the patients were sleeping or not. However, in our study, analyzed bedtime remained unchanged, indicating that all parameters were assessed during the same length of time with and without the device. In future studies it would be preferred to use PSG for both baseline and follow-up measurement to compare sleep quality with and without therapy.

Unfortunately, 13 patients did not undergo follow-up PG, and therefore we cannot compare effectiveness in these patients with the patients who did attend their follow-up sleep study. This possible responder bias could have influenced our results, but it is unlikely that these patients react differently in terms of AHI reduction compared to the patients who underwent follow-up PG.

In conclusion, this study shows that on the short-term PT (both self-made construction and commercial band), is an easy and effective method in most patients with positional OSA. However, as long-term compliance is low, close follow-up of patients with regard to their compliance is necessary, especially in patients with moderate-to-severe OSA, as these patients are more prone to stop using PT. Otherwise, PT using the tennis ball technique might not be the best solution in treating patients with OSA.

More comfortable devices such as vibrating devices might be more useful in the treatment of positional OSA, but long-term compliance and effectiveness of these devices is unknown. As it was stressed recently³¹, high-quality long-term research on this topic is needed as PT still provides a promising treatment option.

Abbreviations

AASM	American Academy of Sleep Medicine
AHI	apnea-hypopnea index
BMI	body mass index
CPAP	continuous positive airway pressure
EDS	excessive daytime sleepiness
ESS	Epworth Sleepiness Scale
IQR	interquartile range
OSA	obstructive sleep apnea
OSAS	obstructive sleep apnea syndrome
PG	polygraphy
PSG	polysomnography
PT	positional therapy

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Chapter 8

Summary

In this thesis diagnostic and therapeutic options for (the management of) sleep apnea are presented. In **Chapter 2** the results of a sleep-screening tool in patients with stable heart failure (HF) are outlined. In **chapters 3, 4, 5, 6 and 7** several therapeutic options for mild, moderate, and severe OSA are described.

Sleep apnea is an important comorbidity in HF-patients and is associated with adverse outcomes. Diagnosing sleep apnea is difficult and polysomnography (PSG), considered to be the criterion standard, is not widely available. In **Chapter 2**, the validity and predictive value of a portable two-channel sleep-screening tool in the identification of sleep apnea in patients with stable HF was assessed. One hundred patients with stable HF had simultaneous recordings of home-based PSG and the screening tool (Apnealink). Agreement between the sleep-screening tool and PSG was good (intraclass correlation coefficient 0.85, 95% confidence interval 0.78–0.90). The best agreement between the sleep-screening tool and PSG was observed at a cutoff value of $AHI_{PSG} \geq 15$. This cutoff value was retrospectively based on the ROC curves (highest combined sensitivity and specificity) for different chosen AHI_{PSG} cutoff points, thereby making it explorative in nature. We suggest that the sleep-screening tool can be used in the selection of those patients with and without sleep apnea, especially at $AHI_{PSG} \geq 15$. The screening tool was useful in excluding the presence of sleep apnea in HF-patients, thereby restricting referral only to the high-risk patients. This should result in increased cost savings, as these patients do not need to undergo a full PSG.

Obstructive sleep apnea (OSA) is associated with increased cardiovascular morbidity and mortality. To date, research has mainly focused on the effects of oral appliance therapy (OAT) on blood pressure, while systematic reviews assessing a more complete spectrum of cardiovascular outcomes are lacking. Therefore, we performed a systematic review summarizing the current literature on the effects of OAT on a broader spectrum of cardiovascular outcomes; these include heart rate, heart rate variability, endothelial function, arterial stiffness, circulating cardiovascular biomarkers, cardiac function, and cardiovascular death (**Chapter 3**). The systematic review and meta-analysis revealed that OAT has small but positive effects on mean daytime systolic and diastolic blood pressure when compared to baseline, and that OAT and continuous positive airway pressure (CPAP) are equally effective in reducing blood pressure. In addition, based on two randomized controlled trials (RCTs), we reported that daytime heart rate improved with OAT compared to inactive/placebo oral appliances. Quality of evidence concerning the other cardiovascular outcomes, such as heart rate variability, circulating cardiovascular biomarkers, cardiac function, endothelial function, and arterial stiffness was low, as studies assessing the effects of OAT on these parameters generally involved small numbers of patients and were heterogeneous and inconclusive. Furthermore, conclusions are mainly based on studies with mild to moderate OSA-patients, thereby underrepresenting the more severe cases of OSA. Cardiovascular events and mortality were assessed in an observational study showing that OAT was as effective as CPAP in reducing cardiovascular death. The results of this review underscore the need for more well designed RCTs applying high quality measurement tools to evaluate the effect of OAT on cardiovascular outcomes.

The results of our RCT comparing the clinical effectiveness, cost-effectiveness, and objective compliance of an oral appliance (a titratable bibloc mandibular advancement device (MAD)) versus CPAP in patients with moderate OSA, were described in **Chapters 4 and 5**.

Justification to advise clinicians in prescribing MAD or CPAP therapy in moderate OSA remains complex. Therefore, a multicentre RCT (including a cost-effectiveness analysis) with two open parallel arms was performed in patients with an AHI of 15 to 30. Patients were randomized to either MAD or CPAP.

In **Chapter 4** the clinical- and cost-effectiveness results of this study were described. For 85 randomized patients, incremental cost-effectiveness and -utility ratios (ICER/ICUR) were calculated from a societal perspective in terms of AHI reduction and quality adjusted life years (QALYs, based on the EuroQol-5D questionnaire) after 3 and 12 months. A total of 18 patients switched therapy (n=10 from MAD to CPAP therapy, n=8 from CPAP to MAD therapy) and 19 patients dropped out during the study (n=14 MAD, n=5 CPAP). Although both MAD (n=43) and CPAP (n=42) therapy significantly reduced the AHI after 3 and 12 months, CPAP therapy was more effective than MAD therapy when considering AHI reduction. Furthermore, both devices resulted in positive effects on excessive daytime sleepiness and sleep-related functioning and quality of life measurements. Obesity related measures, such as BMI, waist circumference, and fat percentage increased only in patients from the CPAP group. Societal costs, including direct medical, direct non-medical and indirect costs (loss of productivity due to work absenteeism), were comparable for both therapies after 3 months of treatment (mean difference was €50 higher for MAD), while societal costs after 12 months were slightly higher for MAD therapy than for CPAP therapy (mean difference €2,156). Due to the superiority of CPAP in reducing AHI compared to MAD therapy, MAD was less cost-effective than CPAP therapy after 3 and 12 months (ICER -€6 (-€219 to €200)) and (ICER -€305 (-€3,003 to €1,572) per AHI point improvement, respectively). By contrast, cost-utility based on QALYs was more favorable with MAD compared to CPAP therapy (ICUR €3,053 (-€170,350 to €143,934)) and (€33,701 (-€191,106 to €562,271) per QALY gained, respectively).

While all patients in the CPAP group switched to MAD (n=8) due to compliance failure (not able to comply with the CPAP device), patients in the MAD group switched to CPAP therapy mainly as a result of treatment failure (insufficient reduction in AHI, n=9/10). Based on the results of our RCT it can be concluded that CPAP therapy is the first-choice treatment option in moderate OSA, despite a higher percentage of compliance failures in the CPAP group, and that MAD therapy is a good alternative when patients refuse CPAP therapy. Furthermore, considering the fact that in terms of QALY MAD therapy was more favourable, MAD therapy is a validated option when patients do not prefer CPAP.

The comparable health effects of MAD and CPAP therapy have been attributed to higher compliance with MAD compared with CPAP therapy. However, a direct comparison of objective compliance between MAD and CPAP has not yet been performed. In **Chapter 5**, the results of long-term objective compliance with MAD versus CPAP therapy in patients with moderate OSA were described. Compliance was monitored for 12 months in 59 patients with moderate OSA (the patients from two of the three participating centers) as part of the RCT described in **Chapter 4**. Objective compliance with MAD was registered using a microsensor, whereas for CPAP it was determined using the built-in registration software

with read-out on SD-card. For both therapies, subjective compliance was assessed using a questionnaire. Final analyses were performed in the 40 patients who completed the study with the therapy to which they were randomly assigned. Compliance rates (hours/night) did not significantly differ between patient groups using MAD or CPAP therapy after both 3 (7.4 (IQR 5.2–8.2) hours with MAD versus 6.8 (IQR 5.7–7.6) hours with CPAP) and 12 months (6.9 (IQR 3.5–7.9) hours with MAD versus 6.8 (IQR 5.2–7.6) hours with CPAP). In addition, compliance rates were consistent over time for both devices. Subjective compliance was significantly higher with MAD than CPAP during all follow-ups. Subjective compliance with CPAP was significantly lower than objective CPAP compliance at the sixth and twelfth month, in other words, patients using CPAP underestimated their therapeutic compliance. It can be concluded that when patients have accepted CPAP therapy, compliance rates are comparable to MAD therapy.

Patients using CPAP with high pressures (≥ 10 cm H₂O) often report pressure-related discomfort. Both a lower pressure and increased comfort may improve patients' compliance with CPAP-therapy and as such therapeutic effectiveness. Combining CPAP with an oral appliance (hybrid therapy) could be an effective alternative therapy in moderate to severe OSA patients. To evaluate this option, we included seven patients who tolerated their CPAP despite high pressures (≥ 10 cm H₂O) and were fitted with hybrid therapy (**Chapter 6**). The mandible was set at 70% of the patient's maximum protrusion, and CPAP pressure was set at 6 cm H₂O. When OSA complaints persisted, CPAP pressure was increased. Results from the pilot study showed that although pressure could be lowered substantially (from mean 11.5 ± 1.3 cm H₂O with conventional CPAP to mean 6.4 ± 0.5 cm H₂O with hybrid therapy), there were no differences between baseline (conventional CPAP) and follow-up (hybrid therapy) scores in compliance, satisfaction, daytime sleepiness, and quality of life. However, more than half of the patients (4 out of 7) reported hybrid therapy to be more comfortable and effective and preferred it over conventional CPAP. Effectiveness of hybrid therapy was (sufficiently) effective as the AHI significantly decreased from median AHI 64.6/h (IQR 31.0–81.0) at diagnosis to median AHI 1.5/h (IQR 1.0–33.4) after being subjected to hybrid therapy. There was no significant difference in effectiveness between conventional CPAP and hybrid therapy (median AHI with conventional CPAP was 2.4/h (IQR 0.0–5.0)). The results of this pilot study suggest that hybrid therapy is an effective, comfortable, and potentially valuable treatment option in addition to conventional CPAP in moderate to severe OSA, especially when patients experience discomfort due to high CPAP pressures.

Patients suffering from positional OSA, which is defined by presenting with an AHI at least twice as high in supine position as in other positions, might benefit from positional therapy (PT). PT is primarily applied to a select group of patients as a secondary treatment option when other therapies have failed. Many PT strategies are available for treating positional OSA. To assess the effectiveness and long-term compliance of a commercial waistband and self-made constructions, mimicking the tennis ball technique, as a primary treatment in patients with mild, moderate, and severe OSA, a retrospective observational study was performed (**Chapter 7**). PT was applied in 53 patients, of which 40 patients (n=20 commercial waistband, n=20 self-made constructions) underwent a follow-up polygraphic evaluation during treatment after a median time interval of 12 weeks. Patients were routinely contacted regarding their clinical status and treatment compliance.

PT was successful in 27 out of 40 patients. It effectively reduced the time spent in supine sleeping position and overall AHI was significantly reduced from a median (IQR) AHI of 14.5 (10.7–19.6) to 5.9 (3.1–8.5). The commercial waistband and self-made constructions were equally effective in terms of AHI reduction. Furthermore, excessive daytime sleepiness (EDS) was significantly reduced by PT. Short-term compliance was good as most patients used PT more than 7 hours/night and more than 6 days/week. However, after mean 13 ± 5 months, 26 patients (65%), a group largely consisting of patients with moderate positional OSA (89%), reported they no longer applied PT. In conclusion, considering short-term effects, PT (using the tennis ball technique) seemed an easy and effective method to treat most patients with positional OSA, showing significant reductions in AHI. However, long-term compliance was low, due to the high discontinuation rate. Future studies are warranted to evaluate the effectiveness of other, perhaps more comfortable (e.g. vibrating), devices with regards to short- and long-term PT compliance and the treatment of positional OSA.

Chapter 9

General discussion and future perspectives

In the treatment of sleep apnea several adequate options are available. The choice of therapy primarily depends on the type of sleep apnea (central or obstructive) and the severity of the disorder, objectively based on the results of the polysomnography (PSG) (mild (apnea-hypopnea index (AHI) 5-15 events/h), moderate (AHI 15-30 events/h), or severe (AHI>30 events/h)), in combination with the severity of excessive daytime sleepiness, the subjectively reported complaints in daily functioning, and medical and social history.

The general aim of this thesis was to evaluate therapeutic options in mild, moderate, and severe obstructive sleep apnea (OSA). Furthermore, a sleep-screening tool was assessed for diagnosing sleep apnea in a group of heart failure (HF) patients.

In this general discussion, results of the chapters are discussed in a broader perspective and general conclusions are drawn. Future perspectives regarding research in central and obstructive sleep apnea are provided at the end of this chapter.

Screening and diagnostic tools

A large number of subjects in the general population show signs and symptoms indicative of sleep apnea. However, it is difficult to recognize obstructive and central sleep apnea based on clinical signs and symptoms alone. Thus, observed episodes of breathing cessation during sleep, snoring, fatigue, excessive daytime sleepiness, morning headaches, suggest but do not always predict sleep apnea. Due to similarities in symptoms with other disorders as well as the broad spectrum of possible signs and symptoms within sleep apnea itself, differentiating between patients with and without sleep apnea is difficult. In addition, despite known risk factors such as obesity, a large neck circumference, central body fat distribution, male sex, and increased age, sleep apnea remains under-recognized. Some screening questionnaires have shown acceptable sensitivity and specificity in the sleep clinic population¹⁻³. However, most questionnaires and prediction models perform much worse in the general population. Therefore, it remains a challenging task to identify whom to refer for further diagnostic evaluation of sleep apnea.

Even though PSG is the gold standard for the diagnosis of sleep apnea, it too has its drawbacks and limitations: it is a time-consuming, costly, and specialized procedure. Furthermore, PSG results can vary between nights due to factors such as (the use of) alcohol or sedative medication, and natural variation in the amount of apneas and/or hypopneas per night. Hence, performing PSG measurements on multiple (preferably, consecutive) nights would be desired. Unfortunately, patient burden outweighs the benefit of such monitoring.

Based on the on-going underdiagnosis and the disadvantages of the existing screening tools, including PSG, the quest for cheaper alternative screening and diagnostic tools continues^{4,5}. In **Chapter 2** we discussed the validity and predictive value of a two-channel screening tool and found that it was useful in excluding sleep apnea in HF-patients, thereby restricting referral exclusively to high-risk patients and resulting in potential cost savings, as the excluded patients do not need to undergo a full PSG. To date, no consensus has been reached on the cutoff value to be considered (e.g., $AHI_{\text{screening}} \geq 5$, ≥ 10 , or ≥ 15) for referral for further evaluation. The best validity with the two-channel screening tool was found when a cutoff of $AHI \geq 15$ was applied. By implementing this cutoff value ($AHI \geq 15$), patients with mild sleep apnea would not have been referred for further evaluation and these patients would not have received treatment. In case of an HF population, as in our study, where CSA is expected to be the most prevalent type of sleep apnea, this cutoff is rational and justified as the most frequently used cutoff point for starting treatment in CSA is $AHI \geq 15$. In case of

OSA, however, patients would be prevented from receiving appropriate treatment. Fortunately, tools that also record respiratory effort have been developed, allowing to differentiate between central and obstructive events. This differentiation gives the caregiver the opportunity to apply different AHI cutoff values for patients with CSA and OSA, and referral for further evaluation and appropriate treatment can be initiated.

Treatment options

The treatment options studied in this thesis are oral appliance therapy (mandibular advancement devices (MAD)), continuous positive airway pressure (CPAP), hybrid therapy (a combination of MAD and CPAP), and positional therapy (PT).

Informed decision-making in prescribing appropriate treatment requires information on benefits and costs associated with treatment, long-term effects, and compliance.

Furthermore, there are some general issues applicable to sleep apnea research, such as selection bias, generalization of results, and the choice of endpoints and how it affects research outcomes and conclusions. These aspects will be addressed in the following paragraphs in relation to the results of the studies described in this thesis.

Benefits and costs

Cost-effectiveness and -utility research assesses both treatment effects and costs. In public health research, costs are predominantly determined from a societal perspective as it is important to include all possible costs for a treatment, irrespective of who is paying for it.

Therefore, in our study on the clinical- and cost-effectiveness of MAD versus CPAP therapy in moderate OSA (**Chapter 4**), costs were assessed from a societal perspective, including direct medical costs (costs of treatment, outpatient hospital visits, hospital stay, and visits to general practitioner and other health care providers), direct costs outside of the health care sector (i.e. direct non-medical costs, such as travel expenses and parking costs), and indirect costs (income missed from being absent from paid work). When performing our RCT, we made *a priori* choices that could have influenced our results. Only patients willing to be randomized to either MAD or CPAP therapy were considered eligible, thereby reducing the generalizability to regular care settings where patients, in most cases, can choose their preferred treatment. In addition, we made some decisions beforehand potentially affecting costs. First, we chose to use one specific type of MAD device, which limited the variation in the costs and prevented the option to resort to other devices. Of note, prices of other devices are not substantially different and therefore this parameter was not likely to influence the results. Second, in our RCT, a follow-up time of 12 months was chosen, while in most cost-effectiveness models follow-up periods are extended to 5 or 10 years (or even a lifetime). Inherent to performing an RCT, data are collected during the study period, making it very difficult to extend the follow-up time as this automatically results in a higher burden for the patient. It would be very valuable to increase follow-up periods of RCTs in future research in order to incorporate maintenance costs, which might be different for MAD and CPAP therapy.

Long-term effects

In addition to being aware of 'long-term' costs, it is of great value to expand our knowledge on long-term treatment effects. For example, there is accumulating evidence that OSA is associated with increased cardiovascular morbidity and mortality with a worse prognosis for patients with increasing OSA severity. OSA treatment might improve prognosis, especially in moderate to severe OSA, as in mild OSA no association between sleep apnea and cardiovascular and neurocognitive impairment is apparent⁶. A large body of literature on the effects of CPAP on cardiovascular outcomes indicates that CPAP reduces systolic and diastolic blood pressure⁷ and has a positive effect on inflammation⁸, arterial stiffness^{9,10}, and cardiovascular morbidity and mortality^{11,12}. Based on our systematic review (**Chapter 3**), it can be speculated that oral appliance therapy (including MAD) also yields a reduction in cardiovascular morbidity and mortality in OSA patients by marginally but positively affecting mean daytime SBP and DBP. Oral appliance therapy and CPAP appear equally effective in reducing blood pressure. However, for other cardiovascular biomarkers, studies generally involved small numbers of patients and were heterogeneous and inconclusive. It can be concluded that to date a paucity in the data on long-term effects of CPAP and especially MAD therapy still exists and that the long-term clinical implications and cardiovascular and health effects, including quality of life, of the treatment of OSA remain unclear. Studies on the long-term effects of alternative treatment options, such as PT and combination therapies (e.g. MAD and CPAP or MAD and PT simultaneously), are still lacking.

More well designed RCTs are warranted to evaluate the effects of OSA and CSA treatment on cardiovascular and other health related outcomes within the full spectrum of OSA severity. Additionally, large consortia and databases are needed to be able to pool individual data and identify effects in different subgroups of OSA patients.

Choice of endpoints

Which endpoints should be chosen when evaluating the effects of sleep apnea treatment? This choice has a prominent effect on the results and conclusions of the study. There is debate about whether to choose an objective, clinically measurable outcome or a subjective, quality of life outcome; the latter has become increasingly important. To put it in other words: a patient is more than an AHI. The severity of sleep apnea during a particular night only reveals a small piece of the puzzle. There is another downside to AHI: when considering the formula used to calculate AHI, every apnea and/or hypopnea contributes to AHI to a similar extent. Alternatively, total duration of apneas and/or hypopneas per minute or hour, or the amount of time spent under a certain oxygenation threshold, might be better outcome measurements than AHI. In cardiovascular research, the oxygen desaturation index (ODI) might provide more predictive information as it scores the events of reductions in blood oxygen levels regardless of whether a cessation in airflow occurs. For example, data from the European sleep apnoea database (ESADA) cohort showed that ODI, and not AHI, was an independent predictor of prevalent hypertension¹³.

In conclusion, it is important to appreciate the impact of the primary endpoint chosen. As outlined in **Chapter 4**, the difference between the cost-effectiveness and cost-utility analysis was primarily determined by the way that outcomes were valued. We found that CPAP was more cost-effective in terms of AHI reduction, while MAD was superior in terms of quality adjusted life years (QALYs). The answer to which endpoint is more valuable remains

complex and for now inconclusive as knowledge of the long-term effects is currently unavailable.

Compliance

Although a treatment can be very effective in terms of the chosen clinical and/or quality of life endpoint, patients need to be compliant with the device or therapy in order to achieve beneficial effects.

The comparable results on behavioral and other health related outcomes of MAD versus CPAP was attributed to a suggested higher compliance with MAD than with CPAP. It was thought that the suggested higher compliance of MAD could 'compensate' for its lower efficacy. This conclusion was based on studies comparing the objectively measured use of CPAP with the subjectively measured use of MAD, as for a long time researchers were not able to objectively monitor MAD therapy. Nowadays, microsensors are available, allowing the measurement of objective compliance for both CPAP and MAD.

Based on the results of our RCT (**Chapter 5**), we concluded that objective compliance with MAD and CPAP was comparable and fairly consistent over a period of 12 months. In particular the observed higher CPAP compliance in our RCT as compared to earlier studies contributed to this outcome. Although surprising, this result might be explained by the fact that patients in our study were not blinded and were aware of the fact that compliance was monitored. Consequently, this open approach may have resulted in patients using their device more frequently for longer periods of time. For CPAP, this could have led to a higher compliance rate in comparison with other studies. Furthermore, patients were willing to receive either MAD or CPAP potentially leading to a selection of patients who are more compliant than patients not included in clinical trials.

As microsensors are now available, additional research can be performed to substantiate the conclusions of our study.

Alternative therapy

Compliance also played an important role in the studies on hybrid therapy, where we compared CPAP alone with a combination therapy of MAD and CPAP (**Chapter 6**), and positional therapy (**Chapter 7**).

In general, research strives to explore new opportunities. The combination of therapies might improve compliance and subsequently clinical efficacy and might therefore serve as a solution when other therapies have failed. For example, in **Chapter 6** we assessed the effectiveness and compliance of hybrid therapy, a combination of MAD and CPAP therapy. Despite the fact that our hypothesis that lower pressure and better comfort could result in a better therapeutic compliance was not confirmed by our data (compliance was comparable between conventional CPAP and hybrid therapy), we did make some interesting observations that were promising for future research. Pressure could indeed be lowered while maintaining a positive therapeutic effect and complaints were less frequently mentioned with hybrid therapy than with conventional CPAP. Therefore, hybrid therapy could be a comfortable alternative to conventional CPAP in patients requiring high CPAP pressures and possibly in patients that have trouble accepting CPAP. To date, literature on hybrid therapy is very limited and larger, more long-term, and preferably randomized

studies are needed to augment our knowledge of long-term efficacy and compliance of this combination therapy.

Other types of combination therapies have also been applied. As there is accumulating evidence that CPAP therapy results in increases of central obesity parameters (as was confirmed in our RCT described in **Chapter 4**), combining CPAP with physical therapy or a weight-loss program seems a logical step. Chirinos and colleagues found that in obese, moderate to severe OSA patients, who were compliant to the 'CPAP *plus* weight loss intervention', reductions in blood pressure were more pronounced than in the groups receiving either intervention alone¹⁴. Another study assessed the effects of MAD in combination with positional therapy and results indicated that this combination therapy results in a higher therapeutic efficacy¹⁵. A major downside of combining two treatment options is the cost aspect. Obviously, two treatments are more expensive than just one treatment modality. Therefore, the suggested larger and more long-term RCTs mentioned above should also include a cost-effectiveness analysis.

Positional OSA is abundantly prevalent among patients diagnosed with OSA and a large proportion of these patients could therefore be treated with positional therapy¹⁶. However, long-term compliance with conventional positional therapies is rather low¹⁷, which is in agreement with the conclusions from our retrospective study on positional therapy (**Chapter 7**). A large proportion of patients stopped using their device. We found that continued use of therapy was independent of (perceived) treatment efficacy and that the discomfort and resulting sleep disruption likely outweighs the positive clinical effects. Another limiting factor is the inability to objectively measure compliance of positional therapy. Manufacturers proclaim that the newest generation of positional devices are more comfortable and able to objectively monitor compliance. These 'new' vibrating devices show encouraging results in terms of efficacy and compliance¹⁸. However, large high quality RCTs with long-term follow-up, including cost-effectiveness analysis, are currently lacking and therefore warranted to validate implementation of this novel approach to treat positional OSA¹⁸.

Despite the efforts to make treatment as effective and simultaneously as comfortable as possible to increase compliance, therapy efficacy and compliance will, unfortunately, rarely reach 100 percent. However, the best combination of efficacy and compliance should be pursued. Grote et al.¹⁹ introduced the concept of 'mean disease alleviation', which combines those two elements; it might be worthwhile to assess the concept of 'mean disease alleviation' in future research to incorporate the effect of compliance in therapeutic (long-term) efficacy.

Concluding remarks

Based on the results of the studies described in this thesis in addition to existing literature in the field of diagnostic and treatment options in obstructive and central sleep apnea, we can conclude that:

- 1) The quest for valid screening and diagnostic tools for OSA in the general population in order to minimize the number of underdiagnosed patients is still ongoing. Fortunately, in the sleep clinic and in specific subgroups, such as heart-failure patients, sufficient tools already exist that can aid the caregiver in proper decision making.
- 2) When assessing the different treatment options for patients with moderate OSA as addressed in this thesis, CPAP is more cost-effective than MAD in terms of AHI reduction, whereas MAD has a more pronounced positive effect in terms of QALY. Furthermore, both treatment options showed comparable compliance rates even after 12 months of therapy. Hybrid therapy and positional therapy could be effective alternative treatment options in a select group of OSA patients.
- 3) Overall, OSA and CSA research faces problems with regards to the generalizability of study results, due to the fact that most studies include small numbers of selected patients within a limited range of sleep apnea severity.

Future research

Based on those general issues in combination with the findings of this thesis, future research aimed at the following could prove useful:

- long-term effects of therapies (MAD, CPAP, hybrid therapy, positional therapy) on cardiovascular outcomes, including morbidity and mortality, quality of life, and costs
- combining cohorts and research outcomes in large databases allowing for statistical correction of confounders and detailed insight in highly selected subgroups of patients
- searching for alternatives in addition to AHI as an outcome measure, and assessing the usefulness of ODI
- combining objective outcomes (efficacy) with subjective outcomes (quality of life) and compliance, e.g. by implementing 'mean disease alleviation'

We believe that incorporating those elements in future research will render new insight and evidence in order to provide justified treatment advice and to offer personalised medical care in patients with OSA and CSA.

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Chapter 10

Nederlandse samenvatting

Slaapapneu is een slaapgerelateerde ademhalingsstoornis en wordt gekenmerkt door herhaaldelijke ademstops tijdens de slaap. Er worden twee hoofdtypen van het ziektebeeld onderscheiden: obstructief slaapapneu (OSA) en centraal slaapapneu (CSA).

OSA wordt gekenmerkt door herhaaldelijke obstructies van de bovenste luchtweg, en gaat veelal gepaard met snurken. Het komt voor bij ongeveer 14% van de mannen en 5% van de vrouwen van middelbare leeftijd. Tijdens deze obstructies ontstaat er een volledige ademstilstand (apneu) dan wel een verminderde luchtstroom (hypopneu) en daarmee samenhangend een zuurstofsaturatiedaling in het bloed. De zuurstofsaturatiedalingen resulteren achtereenvolgens in het activeren van het sympathische zenuwstelsel, korte ontwakingsreacties (arousals) en uiteindelijk een gefragmenteerde slaap. Deze gebroken en kwalitatief inefficiënte slaap heeft tot gevolg dat de patiënten overdag vaak last hebben van overmatige slaperigheid en concentratieverlies. Het cognitief functioneren en de kwaliteit van leven kunnen hierdoor verminderen. Overgewicht, een vergrote nekomvang en een verhoogd vetpercentage zijn bekende risicofactoren voor het hebben van OSA. Daarnaast neemt de kans op OSA toe met de leeftijd en hebben mannen ten opzichte van vrouwen een verhoogd risico op het krijgen van OSA. Er is steeds meer bewijs voor een causaal verband tussen OSA en het ontwikkelen van hypertensie en het krijgen van hartritmestoornissen, een hartinfarct en een beroerte.

Bij CSA stopt of vermindert de ademhaling tijdelijk doordat er geen signaal wordt gegeven vanuit de hersenen naar de ademhalingsspieren. Bij CSA zijn er dus geen adempogingen tijdens de ademstops, dit in tegenstelling tot OSA, waar dit wel het geval is. Cheyne-Stokes ademhaling is de meest voorkomende vorm van CSA en wordt met name gestuurd door veranderingen in de partiële druk van koolstofdioxide ($p\text{CO}_2$). Cheyne-Stokes ademhaling heeft een kenmerkend crescendo-decrescendo ademhalingspatroon waarbij de hoeveelheid lucht per ademhaling langzaam toeneemt en weer afneemt, waarna een ademstop ontstaat. Cheyne-Stokes ademhaling is vaak een gevolg van hartfalen.

Gezien het feit dat slaapapneu een belangrijke risicofactor is voor ziekteverzuim, arbeidsongeschiktheid en hart- en vaatziekten is het cruciaal dat patiënten met slaapapneu in een vroeg stadium worden gediagnosticeerd en dat zij een effectieve behandeling krijgen. Omdat slaapapneu grote impact heeft op de gezondheid van de patiënt, maar ook op de maatschappelijke zorgkosten, is het belangrijk dat deze behandeling tevens kosteneffectief is. Een kosteneffectieve behandeling leidt nu of in de toekomst tot kostenbesparing, of geeft tenminste goede gezondheidswinst tegen aanvaardbare kosten.

OSA en CSA worden vastgesteld door middel van een slaaponderzoek (polygrafie; PG of polysomnografie; PSG). De ernst wordt veelal uitgedrukt in de 'apneu-hypopneu index' (afgekort AHI = het gemiddelde aantal apneus en/of hypopneus per uur slaap). OSA kan worden ingedeeld in mild (AHI 5 tot 15 events/uur), matig (AHI 15 tot 30 events/uur) of ernstig (AHI >30 events/uur).

De behandelaar en patiënt hebben de beschikking over verschillende therapieën, zoals conservatieve behandeling (leefstijladviezen, positietherapie), chirurgische ingrepen, en behandeling door middel van een mandibulair repositieapparaat (MRA) of continue positieve luchtwegdruk (CPAP). De keuze voor een behandeling hangt met name af van de ernst van het slaapapneu, maar ook het type slaapapneu, obstructief dan wel centraal.

Het doel van deze thesis is het evalueren van de diagnostische en therapeutische opties bij mild, matig en ernstig centraal en obstructief slaapapneu, waarbij de focus voornamelijk ligt bij MRA- en CPAP-therapie voor OSA.

Zoals gezegd komt slaapapneu, met name CSA met Cheyne-Stokes ademhalen, vaak voor bij mensen met hartfalen. Het is belangrijk om te onderzoeken of patiënten met hartfalen ook slaapapneu hebben, omdat hartfalen in combinatie met slaapapneu een slechtere prognose heeft dan alleen hartfalen. Het diagnosticeren van slaapapneu moet echter gebeuren door geschoold personeel. Daarnaast is een PSG, de gouden standaard, niet altijd en overal toegankelijk. In **Hoofdstuk 2** hebben we daarom de validiteit en de voorspellende waarde van een draagbare en simpele screeningstool (de Apnealink) getest. Hierbij werd gekeken hoe goed deze tool kon vaststellen of een patiënt met hartfalen daarnaast ook slaapapneu had. In totaal kregen honderd patiënten met stabiel hartfalen een meting met zowel een ambulante (waarbij mensen thuis slapen met de apparatuur) PSG als de screeningstool (Apnealink) tijdens dezelfde nacht. De overeenkomst tussen de screeningstool en de PSG was goed met een 'intraclass correlatie coëfficiënt' (ICC) van 0.85 (95% confidence interval 0.78–0.90). De overeenkomst tussen beide technieken was het beste bij een afkapwaarde van $AHI \geq 15$. Deze afkapwaarde werd achteraf bepaald op basis van de 'receiver operating characteristic' (ROC) curves, op basis van het punt in de curves met de hoogste sensitiviteit en specificiteit. Gebaseerd op de resultaten van het onderzoek concluderen wij dat de Apnealink kan worden gebruikt voor het selecteren van mensen met en zonder slaapapneu, met name bij een afkapwaarde van $AHI \geq 15$. De Apnealink kan met name de aanwezigheid van slaapapneu uitsluiten bij patiënten met hartfalen. Hierdoor kan het aantal patiënten dat wordt doorverwezen voor een PSG worden verminderd, hetgeen uiteindelijk kan lijden tot een kostenbesparing.

Er is steeds meer bewijs voor een causaal verband tussen OSA en het ontwikkelen van hart- en vaatziekten. Studies waarin de cardiovasculaire effecten van MRA worden onderzocht, hebben zich tot nu toe vooral gericht op de effecten op de bloeddruk, terwijl systematische reviews die een completer cardiovasculair spectrum evalueren, ontbreken. In **Hoofdstuk 3** hebben we een systematisch review uitgevoerd. De huidige literatuur werd samenvat op het gebied van de effecten van een MRA op een breed cardiovasculair gebied; hartritme, hartritmevariabiliteit, endotheel functie, vaatstijfheid, cardiovasculaire biomarkers, hartfunctie en cardiovasculaire mortaliteit. De systematische review en meta-analyse liet zien dat een MRA een minimaal, maar positief effect heeft op de gemiddelde systolische en diastolische bloeddruk overdag wanneer dit wordt vergeleken met de bloeddruk op baseline zonder behandeling. MRA en CPAP zijn vergelijkbaar voor wat betreft de reductie in bloeddruk. Daarnaast zagen we, op basis van twee gerandomiseerde trials, dat het hartritme overdag verbeterde met een MRA wanneer dit werd vergeleken met inactieve/placebo behandeling. De bewijslast betreffende andere cardiovasculaire uitkomstmaten, zoals hartritmevariabiliteit, endotheel functie, vaatstijfheid, cardiovasculaire biomarkers en de hartfunctie was zeer mager. De studies die de effecten van MRA op deze parameters beschreven bestonden in het algemeen uit kleine aantallen patiënten en waren heterogeen wat betreft patiëntkarakteristieken en gehanteerde meetinstrumenten, en niet eenduidig in de uitkomsten. De resultaten van de systematische review waren met name gebaseerd op de data van patiënten met mild tot matig OSA, waardoor de effecten bij ernstig OSA op

cardiovasculair gebied nog grotendeels onduidelijk blijven. Cardiovasculaire gebeurtenissen en mortaliteit werden geanalyseerd in één observationele studie. Deze studie liet zien dat een MRA even effectief was als CPAP in het verlagen van het risico op fatale cardiovasculaire events bij patiënten met een ernstig OSA. De resultaten van deze systematische review ondersteunen het belang van goed ontworpen gerandomiseerde studies die gebruik maken van meetinstrumenten van hoge kwaliteit. Op deze manier kunnen de hiaten op het gebied van de cardiovasculaire effecten van MRA-therapie worden opgevuld.

De resultaten van een gerandomiseerde trial, waarin de klinische effectiviteit, kosteneffectiviteit en therapietrouw van de MRA werd vergeleken met CPAP bij patiënten met matig OSA, worden beschreven in **Hoofdstuk 4 en 5**.

Wanneer sprake is van matig OSA kan de behandelaar zowel MRA- als CPAP-therapie voorschrijven, omdat beide behandelopties effectief zijn in het reduceren van de AHI in deze groep. Echter, een gedegen en compleet advies blijft lastig aangezien data over de kosteneffectiviteit en de cardiovasculaire effecten van beide behandelopties specifiek voor matig OSA ontbreken. Daarom werd een multicenter gerandomiseerde trial uitgevoerd inclusief een kosteneffectiviteits analyse. Patiënten met een matig OSA (AHI 15 tot 30 events/uur) kregen op basis van loting een MRA dan wel CPAP. In **Hoofdstuk 4** worden de klinische- en kosteneffectiviteitsresultaten van de studie beschreven. Voor 85 patiënten werden de 'incremental cost-effectiveness en -utiliteits ratios' (ICER/ICUR) berekend vanuit een sociaal perspectief, uitgedrukt in respectievelijk AHI reductie en 'quality adjusted life years' (QALY's, gebaseerd op de EuroQol-5D vragenlijst) na 3 en 12 maanden. In totaal veranderden 18 patiënten van therapie (n=10 van MRA naar CPAP-therapie, n=8 van CPAP naar MRA-therapie) en vielen 19 patiënten uit of stopten gedurende de studie (n=14 MRA, n=5 CPAP). Zowel MRA (n=43) als CPAP (n=42) therapie resulteerde in een significante daling van de AHI na zowel 3 als 12 maanden. De AHI reductie was echter significant groter met CPAP-therapie dan met de MRA. Daarnaast hadden beide behandelopties een positief effect op de slaperigheid overdag, het functioneren overdag en de kwaliteit van leven. De maatschappelijke kosten, inclusief direct medische en niet-medische kosten en indirecte kosten (productiviteitsverlies door werkverzuim), waren vergelijkbaar voor beide behandelopties na 3 maanden van behandeling (gemiddelde verschil €50 hoger voor MRA), terwijl de maatschappelijke kosten na 12 maanden iets hoger waren voor MRA-therapie dan voor CPAP-therapie (gemiddelde verschil €2,156). CPAP-therapie was superieur in het reduceren van de AHI ten opzichte van MRA en bovendien goedkoper, zodat de MRA minder kosteneffectief dan CPAP was na 12 maanden behandeling (ICER -€305 (-€3,003 tot €1,572) per één punt AHI reductie). Dit in tegenstelling tot de kostenutiliteit gebaseerd op de QALY's, waarbij MRA-therapie beter presteerde dan CPAP-therapie (€33,701 (-€191,106 tot €562,271) per gewonnen QALY). Waar alle patiënten in de CPAP-groep overstapten naar MRA (n=8) vanwege problemen met de CPAP ('compliance failure'), stapten patiënten in de MRA-groep voornamelijk over naar CPAP-therapie vanwege een gebrek aan behandel effect ('treatment failure'; onvoldoende reductie in AHI, n=9/10). Op basis van de resultaten van deze gerandomiseerde trial concluderen we dat CPAP-therapie de behandeling van eerste keus blijft bij patiënten met matig OSA, ondanks het hogere percentage van compliantieproblemen met CPAP. MRA is daarbij een goed alternatief wanneer patiënten problemen ervaren met CPAP-therapie dan wel weigeren te starten met CPAP-therapie,

zeker gezien de positieve resultaten van MRA wat betreft de verbetering in QALY ten opzichte van CPAP-therapie.

De vergelijkbare gezondheidseffecten van MRA en CPAP worden traditioneel toegeschreven aan een hogere therapietrouw met MRA vergeleken met CPAP-therapie. Echter, een directe vergelijking van de objectieve therapietrouw van patiënten die een MRA gebruiken met patiënten die CPAP gebruiken was nog niet uitgevoerd. In **Hoofdstuk 5** wordt de objectieve therapietrouw van patiënten met MRA vergeleken met die van patiënten met CPAP. De therapietrouw van 59 patiënten met matig OSA (patiënten van twee van de drie deelnemende centra) werd 12 maanden lang gemonitord als onderdeel van de in **Hoofdstuk 4** beschreven gerandomiseerde trial. De objectieve therapietrouw met MRA werd geregistreerd met een microsensor, die was geïntegreerd in de MRA-beugel. De therapietrouw met CPAP werd bepaald aan de hand van de uitlezing van de data die was opgeslagen op de SD-kaart. Subjectieve therapietrouw werd voor beide behandelopties uitgevraagd door middel van een vragenlijst. De uiteindelijke analyses werden uitgevoerd in de groep patiënten die de studie volgens protocol hadden volbracht (in totaal 40 patiënten). Het gebruik, objectief gemeten in uren/nacht, verschilde niet significant tussen patiënten die MRA gebruikten en patiënten die CPAP gebruikten na zowel 3 maanden (7.4 (IQR 5.2–8.2) uren/nacht met MRA versus 6.8 (IQR 5.7–7.6) uren/nacht met CPAP) als na 12 maanden (6.9 (IQR 3.5–7.9) uren/nacht met MRA versus 6.8 (IQR 5.2–7.6) uren/nacht met CPAP). Verder bleek dat het gebruik van beide behandelopties consistent was over de tijd. Er was echter wel een verschil in de subjectieve therapietrouw: patiënten met een MRA schatten hun gebruiksuren per nacht hoger in dan patiënten met CPAP. Bovendien was de subjectieve therapietrouw met CPAP significant lager dan de objectief gemeten therapietrouw met CPAP tijdens de zesde en de twaalfde maand van de behandeling. In andere woorden, patiënten die CPAP gebruikten onderschatten hun gebruik. Het kan worden geconcludeerd dat wanneer patiënten de CPAP accepteren als therapie, het gebruik vergelijkbaar is met patiënten die MRA gebruiken.

Patiënten die CPAP met hoge druk gebruiken (≥ 10 cm H₂O) rapporteren regelmatig ongemak gerelateerd aan deze hoge druk. Zowel het verlagen van de druk als een betere comfort zou de therapietrouw van CPAP-patiënten kunnen vergroten, met als mogelijk gevolg een toegenomen therapeutisch effect. Het combineren van CPAP met een MRA (hybride therapie) zou zowel een drukverlaging als een beter comfort kunnen opleveren en daarmee mogelijk een effectieve alternatieve therapie kunnen zijn voor patiënten met een matig tot ernstig OSA. Om dit te evalueren hebben we zeven patiënten geïnccludeerd, die tevreden waren met de CPAP ondanks de relatief hoge druk (≥ 10 cm H₂O). Deze patiënten ontvingen allemaal een op maat gemaakte hybride therapie (**Hoofdstuk 6**). Bij aanvang werd de onderkaak op 70% van de maximale protrusie (voorwaartse beweging van de onderkaak) gezet en werd de druk van de CPAP op 6 cm H₂O gezet. Wanneer OSA-gerelateerde klachten persisteerden werd de druk verhoogd. Bij de nameting met de hybride therapie zagen we geen veranderingen wat betreft therapietrouw, tevredenheid, slaperigheid overdag en kwaliteit van leven ten opzichte van de baseline meting met de conventionele CPAP, ondanks het feit dat de druk wel substantieel verlaagd kon worden (van een gemiddelde 11.5 ± 1.3 cm H₂O met conventionele CPAP naar een gemiddelde van 6.4 ± 0.5 cm H₂O met hybride therapie). Echter, wanneer hier expliciet naar werd gevraagd gaven vier van de

zeven patiënten aan hybride therapie comfortabeler en effectiever te vinden dan conventionele CPAP en prefereerden zij de hybride therapie boven de conventionele CPAP. Met de hybride therapie daalde de AHI significant van een mediane AHI van 64.6 events/uur (IQR 31.0–81.0), gemeten bij de diagnosestelling, naar AHI 1.5 events/uur (IQR 1.0–33.4). Daarnaast was de hybride therapie even effectief in het reduceren van de AHI als conventionele CPAP (de mediane AHI met conventionele CPAP was 2.4 events/uur (IQR 0.0–5.0)). De resultaten van deze pilotstudie geven aan dat hybride therapie een effectieve en comfortabele therapie is. Hybride therapie is daarmee mogelijk een waardevolle toevoeging aan het scala van behandelopties van matig tot ernstig OSA, zeker wanneer patiënten ongemak ervaren door een hoge CPAP druk.

Patiënten met positie afhankelijk OSA, waarbij de AHI in rugligging tenminste tweemaal zo hoog is als in andere houdingen, kunnen mogelijk baat hebben bij positietherapie (PT). PT wordt van oudsher met name toegepast bij een selecte groep patiënten als secundaire behandeloptie, wanneer andere behandelingen niet het gewenste effect hebben gehad. In **Hoofdstuk 7** hebben wij in een retrospectieve observationele studie de effectiviteit en therapietrouw van PT (commercieel verkrijgbare band en zelfgemaakte constructies, beide lijkend op de tennisbaltechniek) als primaire behandeloptie onderzocht bij patiënten met mild, matig en ernstig OSA. Drieënvijftig patiënten ontvingen PT, waarvan 40 patiënten (n=20 commerciële band, n=20 zelfgemaakte constructies) een herhalings slaaponderzoek (PG) onder behandeling ondergingen. De verpleegkundig specialist nam routinematig contact op met de patiënten betreffende de gezondheidstoestand en therapietrouw. PT was succesvol bij 27 van de 40 patiënten. De totale tijd dat patiënten op hun rug lagen was beduidend minder en de AHI was significant lager (deze daalde van mediaan (IQR) AHI 14.5 (10.7–19.6) naar 5.9 (3.1–8.5) met PT). De commercieel verkrijgbare band en de zelfgemaakte constructies waren even effectief in het reduceren van de AHI. Daarnaast was de overmatige slaperigheid overdag significant lager met PT. De kortetermijntherapietrouw was goed: meer dan 7 uren/nacht en meer dan 6 dagen/week. Echter, na verloop van tijd (gemiddeld 13±5 maanden later), rapporteerden maar liefst 26 patiënten (65%) dat zij waren gestopt met de therapie. Concluderend kunnen we zeggen dat PT in de eerste weken na diagnose een goede optie kan zijn bij de behandeling van positie afhankelijk OSA. De langetermijntherapietrouw was echter zeer laag. Mogelijk kan PT worden gebruikt gedurende de wachttijd tot de start van een andere behandeling of als optie naast een andere behandeling. Toekomstige studies zijn nodig om de effectiviteit en langetermijntherapietrouw te evalueren van mogelijk meer comfortabele technieken, zoals een apparaatje dat vibreert wanneer iemand op zijn rug gaat liggen.

Samenvattend kan het volgende gezegd worden:

- 1) De zoektocht naar de ultieme methode voor het screenen op slaapapneu in de algemene populatie is nog niet voltooid. Gelukkig bestaan er binnen de slaapklinieksetting methoden die voldoende differentiëren tussen het wel of niet hebben van slaapapneu, die ook gebruikt kunnen worden bij specifieke patiëntengroepen, zoals patiënten met hartfalen. Deze methoden kunnen de zorgverlener bijstaan in het maken van een weloverwogen keuze voor het wel of niet doorverwijzen van een patiënt voor eventuele behandeling.
- 2) Bij de behandeling van matig OSA blijkt CPAP kosteneffectiever dan MRA-therapie wanneer uitgedrukt in de reductie in AHI, terwijl MRA-therapie een meer uitgesproken positief effect heeft op de kwaliteit van leven (gemeten in kwaliteit van leven gecorrigeerd aantal levensjaren) dan CPAP-therapie. Hierbij zagen wij een vergelijkbare therapietrouw van MRA- en CPAP-therapie bij de groep patiënten die een jaar lang dezelfde therapie gebruikten.
- 3) Hybride therapie (combinatie van CPAP- en MRA-therapie) is een veelbelovende, maar nog weinig gebruikte, alternatieve behandeloptie bij patiënten met OSA.

Toekomstig onderzoek zou zich moeten richten op:

- de lange-termijn effecten van therapieën (MRA, CPAP, hybride therapie, positietherapie) op cardiovasculaire uitkomstmaten, inclusief morbiditeit en mortaliteit, kwaliteit van leven en kosten
- het combineren van cohorten en onderzoeksresultaten in grote databases waardoor gecorrigeerd kan worden voor 'confounders' en waardoor geselecteerde subgroepen kunnen worden gevormd en geanalyseerd
- het zoeken naar alternatieve uitkomstmaten naast de AHI, en het analyseren van de toegevoegde waarde van de 'oxygen desaturation index' (ODI)
- het combineren van objectieve uitkomsten (effectiviteit) met subjectieve uitkomsten (kwaliteit van leven) en de therapietrouw, zoals bijvoorbeeld de 'mean disease alleviation' (effectiviteit * therapietrouw)

Wij geloven dat het meenemen van bovenstaande elementen in toekomstig onderzoek zal leiden tot nieuwe inzichten en kennis, waardoor een gedegen behandeladvies kan worden gegeven en gepersonaliseerde medische zorg (therapie op maat) voor patiënten met OSA optimaler wordt toegepast.

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Grietje