Efficacy and tolerability of a custom-made Narval mandibular repositioning device for the treatment of obstructive sleep apnea: ORCADES study 2-year follow-up data

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"Take home" message

Mandibular repositioning device therapy was effective in maintaining improvements in sleep apnoea and quality of life over 2 years of follow-up in patients who refused or were intolerant of continuous positive airway pressure

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ABSTRACT

Objective/Background: Mandibular repositioning device (MRD) therapy is an alternative to continuous positive airway pressure (CPAP). The ORCADES study is assessing the long-term efficacy and tolerability of MRD therapy in OSAS; 2-year follow-up data are presented.

Patients/Methods: OSAS patients who refused or were noncompliant with CPAP were fitted with a custom-made computer-aided design/computer-aided manufacturing (CAD/CAM) bi-block MRD (ResMed, Narval CC™); mandibular advancement was individually titrated. Sleep and respiratory parameters were determined at baseline, 3–6 months and 2 years. The primary endpoint was treatment success (percentage of patients achieving a ≥50% reduction in the apnoea-hypopnoea index [AHI]).

Results: Of 315 enrolled patients, 237 remained on MRD treatment at 2 years and 197 had follow-up data. Treatment success rate at 2 years was 67%; AHI <5/h, <10/h and <15/h was achieved in 30%, 56% and 72% of patients, respectively. On multivariate analysis, ≥50% decrease in AHI at 3–6 months and absence of nocturia at 3–6 months were significant predictors of MRD treatment continuation. Adverse events were generally mild and the majority occurred in the first year of treatment.

Conclusions: Two years' treatment with an MRD was effective and well tolerated in patients with mild to severe OSAS who refused or were intolerant of CPAP.

1. Introduction

Obstructive sleep apnoea syndrome (OSAS) is characterised by recurrent obstructions of upper airways during sleep, which result in sleep fragmentation and intermittent hypoxia [1]. Moderate to severe OSAS is associated with cardiovascular, metabolic and cognitive comorbidities, and sleepiness-related accidents [2-4]. Continuous positive airway pressure (CPAP) remains the gold standard treatment for OSAS [5]. CPAP therapy reduces the apnoea-hypopnoea index (AHI), improves symptoms and quality of life, reduces the risk of motor vehicle crashes [6], and potentially reduces cardiovascular events and mortality [7-9]. However, as many as 30–50% of patients prescribed CPAP are non-compliant with therapy over the long term [10-12].

A mandibular repositioning device (MRD) is recommended as the first alternative to CPAP [13] in patients requiring treatment for OSAS. The MRD prevents recurrent obstruction of the upper airways during sleep by maintaining the mandible in a forward position to enlarge [14] and maintain an open airway [15], and significantly reduces the AHI [16]. Although MRD therapy is not as effective as CPAP in controlling the occurrence of obstructive events [17], this is counterbalanced by better adherence to treatment [18]. Therefore, improvement in symptoms and quality of life after up to 12 months are similar with MRD therapy and CPAP [19]. However, there is a lack of data on the longer term effects of second-line MRD therapy in patients with OSAS.

The multicentre, prospective ORCADES study was designed to investigate the long-term effects of MRD therapy in OSA patients non-compliant with or intolerant of CPAP with follow-up for 5 years. The first analysis of data after 6 months of follow-up showed a significant reduction in AHI and symptoms during MRD therapy, which was well tolerated [16]. Patients were treated either with a custom-made computer-aided design/computer-aided manufacturing (CAD/CAM) bi-block MRD (ResMed, Narval CC™; 84% of patients) or a

non-CAD/CAM MRD device (ResMed, Narval™). Early evaluation suggested that the CAD/CAM device, which allows more accurate adjustment of the vertical opening, was superior to the non-CAD/CAM MRD [16]. Therefore, this 2-year follow-up of the ORCADES trial focusses on patients with OSAS treated with the CAD/CAM MRD.

2. Methods

2.1 Study design

ORCADES was a single-arm prospective observational study that was conducted at 28 centres in France (NCT01326143). Full details of the study design have been reported previously [16]. The study protocol was approved by the relevant ethics committees, and all procedures were conducted in accordance with the Declaration of Helsinki principles. All patients received detailed information and gave written informed consent to participate.

2.2 Patients

Adult patients (age ≥18 years) with OSAS (AHI >30/h, or AHI ≤30/h with excessive daytime sleepiness and/or an Epworth Sleepiness Scale [ESS] score >10) who refused or were noncompliant with CPAP (device usage <3 h/night) and had not previously received MRD treatment were screened by a sleep specialist. Only those without any contraindications to MRD treatment, as confirmed by a dental sleep specialist, were included. Patient should not presented dental, periodontal or articular contraindications. A patient completely edentulous or presenting partial toothless (less than 3 teeth (or implants) by hemi-arch including the canine at the maxillary level, or presenting less than 4 teeth (or implants) by hemi-arch including the canine at the mandibular level was not enrolled in the study.

2.3 MRD titration and follow-up

Patients included in this analysis were treated with a custom-made CAD/CAM MRD device (ResMed, Narval CC™). The device was fitted by a dental specialist; initial mandibular advancement that was adjusted over a 15-mm range (the maximal advancement allowed with MRD depending of the connecting rod size) at subsequent titration visits, to achieve the best balance between clinical efficacy and tolerability. The first evaluation took place 4–6 months after treatment initiation [16], then patients were re-evaluated at the 2-year follow-up visit. MRD replacement during the study was performed based on routine clinical practice.

2.4 Endpoints

The primary endpoint was the treatment success rate, defined as the percentage of patients achieving a ≥50% reduction in AHI at the 2-year follow-up visit. Absolute change in AHI from baseline to 2-year follow-up, and from baseline to 3-6 months and 2 years was also determined. The percentage of patients achieving an AHI below three cut-off values (<5/h, <10/h and 15/h) was calculated, overall and in patient subgroups based on OSAS severity at baseline (mild: AHI 5/h to ≤15/h; moderate: AHI 15/h to ≤30/h; severe: AHI >30/h). Additional nocturnal respiratory endpoints were the oxygen desaturation index (ODI; average number of desaturation episodes per hour, with desaturation defined as a ≥3% decrease in oxygen saturation [SpO_2] from the average value), the lowest SpO_2 (nadir SpO_2), and total time with SpO_2 <90%. In patients who underwent PSG, total sleep time, sleep latency, percentage of slow wave and rapid eye movement (REM) sleep, micro-arousal index and intra-sleep wakefulness were determined. Clinical efficacy, tolerability and device usage were determined as described below.

2.5 Clinical evaluation

Clinical evaluation at the 2-year follow-up included the same endpoints as the 3- to 6-month follow-up [16]. Briefly, somnolence was evaluated using the ESS, and snoring, nocturia, libido disorders and nocturnal mouth breathing were self-reported (yes/no). Patients were asked to rate their sleep quality, state on waking and morning headache on non-graduated 10 cm visual analogue scales (VAS), from "very bad" to "excellent" for sleep quality and state on waking, and from “absence of pain” to “maximal pain” for morning headache. Quality of life was evaluated using the Quebec Sleep Questionnaire (QSQ) [20] and a Pichot fatigue scale questionnaire was administered [21]. Data on MRD-related side effects and their severity were determined by sleep and dental sleep physicians. Self-reported MRD compliance (hours per night; nights per week) was assessed.

2.6 Sleep studies

Evaluation of the AHI was based on ventilatory polygraphy (PG) or polysomnography (PSG). The same test was used in the same patient at baseline, 3–6 months and 2 years. PSG/PG recordings were manually scored according to the American Academy of Sleep Medicine (AASM) guidelines [22]. Obstructive apnoea was defined as a ≥10-s cessation of airflow on the pressure nasal cannula, with or without association with an oro-nasal thermal sensor. Hypopnoea was defined as a ≥50% reduction in airflow, or a <50% airflow reduction on the nasal pressure cannula accompanied by a ≥3% decrease in arterial oxyhaemoglobin saturation (SpO2) recorded using finger pulse oximetry or an arousal.

2.7 Statistical analysis

The intention-to-treat (ITT) population for this analysis included all patients using a CAD/CAM MRD device. Values are presented as median and interquartile range (IQR) for quantitative variables, and number and percentage for qualitative variables. Quantitative

changes from baseline to the 2-year follow-up visit were compared using unpaired or paired Student's t-test or the Wilcoxon–Mann–Whitney nonparametric test depending on normality of distribution and group comparison. Qualitative changes were described using frequency distribution and compared using Fisher's exact test or Chi-squared test. Change over time in AHI, 3% ODI, time with SpO_2 <90%, ESS score, symptoms (snoring, nocturia, libido disorders, nocturnal mouth breathing), QSQ global and sub-scores, and Pichot questionnaire results was determined using a repeated measures ANOVA; if significant this was followed by a Tuckey's test to compare visits two by two. Comparisons between patient subgroups based on baseline OSAS severity, gender and body mass index (BMI) were assessed using the Student's t-test, ANOVA or Wilcoxon–Mann–Whitney test. Two logistic models were created and backward stepwise regression analysis was used to determine independent factors associated with continuation of treatment until the 2-year follow-up in the ITT population (first model) and achievement of AHI <10/h at 2-year follow-up in patients with available 2-year AHI data (model 2). For both models, variables with a p-value <0.10 in univariate analysis were entered in the stepwise logistic regressions, and variables with a p-value <0.05 were retained in the final multivariate models. Statistical analyses were performed using SAS version 9.

3. Results

3.1 Population

A total of 540 patients were screened, 165 patients were excluded and 315 were treated with a CAD/CAM MRD (Figure 1). The majority of patients were male (76%), 20% were obese and 51% had previously been treated with CPAP (Table 1). The number [IQR] of initial MRD titrations was of 2.0 [1.0, 3.0], and final mandibular advancement was 7.0 [6.0; 8.0] mm. The 2-year follow-up visit was completed for 197 of the 237 patients who remained on treatment,

with a median follow-up of 24 [25; 28] months; the 2-year follow-up visit was pending for the remaining 40 patients. Median changes from baseline in weight (0 [–3; 2] kg), BMI (0.28 [–0.73; 0.99] kg/m^2), neck circumference (0 [–1; 1] cm) and waist circumference (0 [–2; 4] cm) were not statistically significant and only seven patients needed to have their MRD replaced before the 2-year follow-up visit.

3.2 Withdrawals

A total of 78 patients (25%) were withdrawn before the 2-year follow-up visit, mainly due to side effects (30 patients), or lack of efficacy (21 patients) (Figure 1). The overall proportion of withdrawals did not vary by baseline OSAS severity and gender, but the rate of withdrawal due to adverse events was higher in females than in males (65% vs 32%; p=0.0098). Withdrawal occurred more frequently in obese versus non-obese patients (40% vs 21%; p=0.0024) and obese patients were withdrawn more often for lack of efficacy than non-obese patients (44% vs 19%; p=0.0195). The majority of withdrawals (83%) occurred within the first 6 months of MRD therapy (Figure 2).

3.3 Sleep study data

AHI data were available for 191 patients (132 underwent PG and 59 had PSG). A 50% reduction in the AHI was achieved in 67% of participants. The proportion of patients achieving an AHI of <15/h, <10/h and <5/h was 72%, 56% and 30%, respectively (Figure 3). After 2 years, the reduction in AHI from baseline was –15 [-23; -7]/h (–64 [–83; –42]%). AHI, 3% ODI, time with SpO_2< 90% and nadir SpO_2 values decreased significantly from baseline to 2-year follow-up (Table 2). In the 59 patients with 2-year PSG data, the change from baseline in median sleep latency was –5 [–24; 2] minutes (p=0.0014) and in micro-

arousal index was –8 [–13; 1]/h (p=0.0001). No changes in the percentage of slow wave and REM sleep were observed.

3.4 Symptoms and quality of life

A total of 81% of patients had an ESS score <10 at the 2-year follow-up. The ESS score decreased from 11 [8; 15] at baseline to 7 [5; 10] at 3–6 months and 7 [4; 9] at 2 years (p<0.0001); reductions were similar across OSAS severity subgroups. The QSQ global score increased from 144.0 [111.0; 173.0] at baseline to 180.5 [153.0; 201.0] at 3-6 months and 191.5 [94.0; 205.0] at 2 years (p<0.001), and the Pichot score decreased from 14.0 [7.0; 20.0] at baseline to 7.0 [3.0; 14.0] at 3–6 months and 6.0 [3.0; 11.0] at 2 years (p<0.001). Changes over time in symptoms and QSQ subscores are shown in Figure 4.

3.5 Device usage

At the 2-year follow-up, median [IQR] MRD usage was 7 [7; 7] nights/week and 7 [6; 8] hours/night; 95% of patients used their MRD for ≥4 hours/night on 4 nights/week, and 85% for ≥4 hours/night on 7 days/week. Device usage was similar across patient subgroups based on OSA severity, gender or BMI.

3.6 Predictive factors

A number of factors were significant predictors of either treatment continuation or AHI <10/h at 2 years in the univariate analysis (Table 3). Only two variables remained significant predictors of treatment continuation in the multivariate analysis: a 50% decrease in AHI at 3–6 months' follow-up and the absence of nocturia at 3–6 months' follow-up (Figure 5). There were also two significant predictors of AHI <10/h at the 2-year follow-up: smaller initial AI and the absence of previous CPAP treatment (Figure 5).

3.7 Tolerability

At least one adverse event was reported by 59% of patients. The most common event was TMJ disorder (Table 4). Of the 509 adverse events recorded by the 2-year follow-up, 137 (27%) were reported in the first 6 months of therapy and 64 (13%) were reported in the first year. Only 13% of all events were classified as severe (Table 4). 30 patients withdrawn the study for side effects before the 2 year evaluation, as follow: dental pain (7 pts), TMJ disorder (7 pts), gingival pain (5 pts), occlusion change (2 pts), tooth loosening (1 pt), mouth pain (1 pt), discomfort (1 pt), mouth dryness (1 pt), nausea (1 pt), suspected allergy (1 pt) and other reasons (3 pts).

4. Discussion

Two-year follow-up data from the multicentre, prospective ORCADES study showed that MRD therapy remained effective and well-tolerated in patients with mild to severe OSAS who refused, were intolerant of, or non-compliant with CPAP.

Non-compliance with CPAP is an important concern in OSAS management [11]. MRD therapy is recommended as a potential first-line treatment option for mild to moderate OSA patients without cardiovascular comorbidities, but guidelines also acknowledge that an MRD provides a non-surgical second-line treatment option and is better than no treatment for adult patients intolerant of CPAP or who prefer alternate therapy [23]. Several studies have investigated the long-term effects of MRD in OSAS, but mainly included only a small number of mild to moderate OSAS patients [24-29]. Larger comparative [19, 30-32] or noncomparative [24, 26, 33, 34] trials evaluated an MRD as first-line therapy, but only one reported long-term data in CPAP-intolerant patients [35].

The purpose of the 5-year ORCADES study is to provide long-term evaluation of MRD as second-line treatment of OSAS in patients with a range of disease severity. The large number of patients included (n=315) and continuing treatment at 2 years (n=237), the selection of a homogeneous population intolerant of or refusing CPAP, and the high proportion of individuals with severe disease are important strengths of this study. In addition, particular attention was payed to adapting the study design to follow the most recent guidelines on MRD treatment [23]. Sleep and dental maxillofacial specialists were both involved to ensure selection of the right patients and to exclude those with contraindications for MRD therapy. The CAD/CAM MRD was a custom-made titratable device and a titration period was included to achieve mandibular propulsion that maximised resolution of symptoms, tolerability and AHI reduction before patients entered the long-term follow-up. In addition, this 2-year interim analysis provided important information to improve understanding of therapy withdrawal and adverse event rate evolution over time at a time point in therapy where patients should, in theory, renew their MRD.

As well as these strengths, the study also has a number of limitations. The most important is the observational, registry-based design, without random allocation to treatment. However, patient management in this setting is representative of routine clinical practice and our findings are similar to those of another observational cohort study [36]. The findings are therefore likely to have good external validity. Seventy-eight patients withdrew from our study before the 2-year assessment and 40 were still awaiting assessment. This left a total of 191 patients (60% of the ITT population) who had an AHI evaluation at 2 years, something that could influence the study results and their interpretation. The reduction in patient numbers over time highlights the difficulty in maintaining adherence to chronic therapy and retaining patients in a clinical pathway, even when therapy is reimbursed. Such difficulties have been described previously [36, 37] and were taken into account in our multivariate

model analysis of treatment continuation, where non-analysed patients were considered as treatment failures. It is also important to acknowledge that two different types of patients were enrolled in the study: those intolerant of CPAP therapy and those who refused CPAP. This could have influenced the study findings, as indicated in the univariate analysis on treatment success (AHI <10/h). More research is needed to differentiate and identify specific traits of these two populations. Another study limitation to mention is that two types of sleep test (PG and PSG) were used in the study to evaluate respiratory events, however each patient was evaluated with the same sleep test all along the study which limits discrepancy.

In our study, we defined the rate of treatment success as a 50% reduction in AHI because it is an endpoint that has been widely used in non-CPAP surgical intervention and MRD studies [31, 38, 39], thus allowing easy comparison of findings, and is suited to evaluating MRD efficacy related to quality of sleep [39]. The treatment success rate in this analysis (67%), without any difference between OSAS severity subgroups, is consistent with previous long-term studies [13]. To improve sensitivity and clinical relevance, we also performed analyses using three different residual AHI thresholds (<15/h, <10/h and <5/h). Residual AHI <10/h is commonly related to long-term control of symptoms [40], and was observed in 56% of patients. In our study, 72% of patients had an AHI <15/h, which has been associated with a reduction in the risk of new-onset hypertension [40]. The AHI findings were consistent with the maintenance of good OSAS symptom control, good sleep quality and good quality of life, including all domains of the QSQ. In the subgroup of patients with severe OSAS at baseline, the proportion of patients achieving an AHI <10/h and <15/h was 37% and 53%, respectively, suggesting that long-term MRD treatment is a good alternative to CPAP for some of these patients. An AHI <5/h is often used to evaluate CPAP efficacy [41], and was achieved by 30% of patients during MRD therapy. However, this threshold may not be as appropriate for MRD evaluation based on the findings of relevant MRD studies [40, 42]. Although the AHI

<5/h cut-off was determined to define OSAS based on historical cohorts [43-45], recent data suggest that the prevalence of sleep-disordered breathing in the general population based on an AHI >5/h would be 84% in men and 61% in women [3]. It was suggested that the higher apparent prevalence of sleep-disordered breathing in recent versus historical studies might be explained by the increased sensitivity of current recording techniques and scoring criteria. In addition, revision of the AHI criteria for definition of OSAS may be appropriate based on recent findings of a lack of association between mild OSAS and cardiac morbidity [2, 3].

In our study, MRD therapy was associated with relatively consistent control of the AHI over time. However, there was a slight increase in the median AHI at the two-year follow-up in the absence of weight gain [28] and irrespective of OSAS severity (Figure 3). Only seven patients had an MRD replacement before the 2-year follow-up, and it is possible that the slight increase in AHI could simply be due to a worn device even though long-term increases in the AHI over a median follow-up of 16.6 years have been reported in a small group of patients using an optimally titrated MRD in the absence of weight change [26]. It is important to note that increasing age and bite changes over time could influence long-term assessments of MRD effectiveness [13]. These factors will be taken into account for the 5-year follow-up of the ORCADES study.

Baseline AI and absence of previous CPAP treatment were independent predictors of a complete response to MRD treatment (AHI <10/h). Baseline AI and others factors such as gender or positional OSAS have previously been reported to be related to MRD efficacy [16, 46, 47]. Conversely, the absence of previous CPAP treatment has not previously been associated with long-term AHI reduction on MRD to the best of our knowledge, although it was predictive of MRD treatment continuation in one observational study [36]. This suggests that patients intolerant of CPAP may be at greater risk of not having a long-term response to MRD therapy. However, even if treatment may be slightly less efficient over the long-term,

use of an MRD could help retain these vulnerable patients in the care network. This was supported by our observation that some patients accepted a return to CPAP therapy after MRD treatment cessation. Absence of nocturia and a 50% reduction in AHI at short-term follow-up were independent predictors of long-term MRD therapy continuation; of these, relapse of nocturia has previously been associated with MRD treatment cessation [36].

The CAD/CAM MRD used in this study was well tolerated. The majority of adverse events were of mild intensity, most were observed within the first 6 months of treatment, and the majority of withdrawals (83%) occurred within 6 months of MRD therapy initiation. Taken together with the predictors of therapy continuation found in our study, this highlights the importance of optimal early control of AHI and symptoms and early identification and management of adverse events for achievement and maintenance of MRD efficacy and compliance.

This second interim analysis of the 5-year ORCADES study showed that 2 years of MRD therapy was effective and well-tolerated in patients with mild to severe OSAS who refused or were intolerant of CPAP. Long-term maintenance of a complete response to MRD therapy was significantly more likely in patients who refused CPAP compared with those who were intolerant or noncompliant with CPAP.

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C.R.O. Clinact (France) mandated by ResMed performed the collection, quality control, management and analysis of the data. The Executive Steering Committee had full access to all of the data and takes responsibility for the integrity and accuracy of the data analysis.

References

[1] Levy P, Kohler M, McNicholas WT, Barbe F, McEvoy RD, Somers VK, et al. Obstructive sleep apnoea syndrome. Nat Rev Dis Primers. 2015;1:15015.

[2] Campos-Rodriguez F, Martinez-Garcia MA, de la Cruz-Moron I, Almeida-Gonzalez C, Catalan-Serra P, Montserrat JM. Cardiovascular mortality in women with obstructive sleep apnea with or without continuous positive airway pressure treatment: a cohort study. Ann Intern Med. 2012;156:115-22.

[3] Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med. 2015;3:310-8.

[4] Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. Lancet. 2014;383:736-47.

[5] Barbe F, Duran-Cantolla J, Sanchez-de-la-Torre M, Martinez-Alonso M, Carmona C, Barcelo A, et al. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. JAMA. 2012;307:2161-8.

[6] Tregear S, Reston J, Schoelles K, Phillips B. Continuous positive airway pressure reduces risk of motor vehicle crash among drivers with obstructive sleep apnea: systematic review and meta-analysis. Sleep. 2010;33:1373-80.

[7] Drager LF, McEvoy RD, Barbe F, Lorenzi-Filho G, Redline S. Sleep Apnea and Cardiovascular Disease: Lessons From Recent Trials and Need for Team Science. Circulation. 2017;136:1840-50.

[8] Sanchez-de-la-Torre M, Campos-Rodriguez F, Barbe F. Obstructive sleep apnoea and cardiovascular disease. Lancet Respir Med. 2013;1:61-72.

[9] Marin JM, Agusti A, Villar I, Forner M, Nieto D, Carrizo SJ, et al. Association between treated and untreated obstructive sleep apnea and risk of hypertension. JAMA. 2012;307:2169-76.

[10] Meurice JC, Dore P, Paquereau J, Neau JP, Ingrand P, Chavagnat JJ, et al. Predictive factors of long-term compliance with nasal continuous positive airway pressure treatment in sleep apnea syndrome. Chest. 1994;105:429-33.

[11] Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. Proc Am Thorac Soc. 2008;5:173-8.

[12] Wolkove N, Baltzan M, Kamel H, Dabrusin R, Palayew M. Long-term compliance with continuous positive airway pressure in patients with obstructive sleep apnea. Can Respir J. 2008;15:365-9.

[13] Marklund M. Update on Oral Appliance Therapy for OSA. Curr Sleep Med Rep. 2017;3:143-51.

[14] Chan AS, Sutherland K, Schwab RJ, Zeng B, Petocz P, Lee RW, et al. The effect of mandibular advancement on upper airway structure in obstructive sleep apnoea. Thorax. 2010;65:726-32.

[15] Kato J, Isono S, Tanaka A, Watanabe T, Araki D, Tanzawa H, et al. Dose-dependent effects of mandibular advancement on pharyngeal mechanics and nocturnal oxygenation in patients with sleep-disordered breathing. Chest. 2000;117:1065-72.

[16] Vecchierini MF, Attali V, Collet JM, d'Ortho MP, El Chater P, Kerbrat JB, et al. A custom-made mandibular repositioning device for obstructive sleep apnoea-hypopnoea syndrome: the ORCADES study. Sleep Med. 2016;19:131-40.

[17] Sharples LD, Clutterbuck-James AL, Glover MJ, Bennett MS, Chadwick R, Pittman MA, et al. Meta-analysis of randomised controlled trials of oral mandibular advancement

devices and continuous positive airway pressure for obstructive sleep apnoea-hypopnoea. Sleep Med Rev. 2016;27:108-24.

[18] Almeida FR, Henrich N, Marra C, Lynd LD, Lowe AA, Tsuda H, et al. Patient preferences and experiences of CPAP and oral appliances for the treatment of obstructive sleep apnea: a qualitative analysis. Sleep Breath. 2013;17:659-66.

[19] Aarab G, Lobbezoo F, Heymans MW, Hamburger HL, Naeije M. Long-term follow-up of a randomized controlled trial of oral appliance therapy in obstructive sleep apnea. Respiration. 2011;82:162-8.

[20] Lacasse Y, Bureau MP, Series F. A new standardised and self-administered quality of life questionnaire specific to obstructive sleep apnoea. Thorax. 2004;59:494-9.

[21] Pichot P, Brun JP. [Brief self-evaluation questionnaire for depressive, asthenic and anxious dimensions]. Ann Med Psychol (Paris). 1984;142:862-5.

[22] Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep. 1999;22:667-89.

[23] Ramar K, Dort LC, Katz SG, Lettieri CJ, Harrod CG, Thomas SM, et al. Clinical Practice Guideline for the Treatment of Obstructive Sleep Apnea and Snoring with Oral Appliance Therapy: An Update for 2015. J Clin Sleep Med. 2015;11:773-827.

[24] Fransson AM, Tegelberg A, Leissner L, Wenneberg B, Isacsson G. Effects of a mandibular protruding device on the sleep of patients with obstructive sleep apnea and snoring problems: a 2-year follow-up. Sleep Breath. 2003;7:131-41.

[25] Gong X, Zhang J, Zhao Y, Gao X. Long-term therapeutic efficacy of oral appliances in treatment of obstructive sleep apnea-hypopnea syndrome. Angle Orthod. 2013;83:653-8.

[26] Marklund M. Long-term efficacy of an oral appliance in early treated patients with obstructive sleep apnea. Sleep Breath. 2016;20:689-94.

[27] Rose EC, Barthlen GM, Staats R, Jonas IE. Therapeutic efficacy of an oral appliance in the treatment of obstructive sleep apnea: a 2-year follow-up. Am J Orthod Dentofacial Orthop. 2002;121:273-9.

[28] Wiman Eriksson E, Leissner L, Isacsson G, Fransson A. A prospective 10-year follow-up polygraphic study of patients treated with a mandibular protruding device. Sleep Breath. 2015;19:393-401.

[29] Gauthier L, Laberge L, Beaudry M, Laforte M, Rompre PH, Lavigne GJ. Mandibular advancement appliances remain effective in lowering respiratory disturbance index for 2.5-4.5 years. Sleep Med. 2011;12:844-9.

[30] Doff MH, Hoekema A, Wijkstra PJ, van der Hoeven JH, Huddleston Slater JJ, de Bont LG, et al. Oral appliance versus continuous positive airway pressure in obstructive sleep apnea syndrome: a 2-year follow-up. Sleep. 2013;36:1289-96.

[31] Walker-Engstrom ML, Tegelberg A, Wilhelmsson B, Ringqvist I. 4-year follow-up of treatment with dental appliance or uvulopalatopharyngoplasty in patients with obstructive sleep apnea: a randomized study. Chest. 2002;121:739-46.

[32] Ghazal A, Sorichter S, Jonas I, Rose EC. A randomized prospective long-term study of two oral appliances for sleep apnoea treatment. J Sleep Res. 2009;18:321-8.

[33] Gupta A, Tripathi A, Sharma P. The long-term effects of mandibular advancement splint on cardiovascular fitness and psychomotor performance in patients with mild to moderate obstructive sleep apnea: a prospective study. Sleep Breath. 2017;21:781-9.

[34] Marklund M, Sahlin C, Stenlund H, Persson M, Franklin KA. Mandibular advancement device in patients with obstructive sleep apnea : long-term effects on apnea and sleep. Chest. 2001;120:162-9.

[35] Anandam A, Patil M, Akinnusi M, Jaoude P, El-Solh AA. Cardiovascular mortality in obstructive sleep apnoea treated with continuous positive airway pressure or oral appliance: an observational study. Respirology. 2013;18:1184-90.

[36] Attali V, Chaumereuil C, Arnulf I, Golmard JL, Tordjman F, Morin L, et al. Predictors of long-term effectiveness to mandibular repositioning device treatment in obstructive sleep apnea patients after 1000 days. Sleep Med. 2016;27-28:107-14.

[37] Iglay K, Cartier SE, Rosen VM, Zarotsky V, Rajpathak SN, Radican L, et al. Meta-analysis of studies examining medication adherence, persistence, and discontinuation of oral antihyperglycemic agents in type 2 diabetes. Curr Med Res Opin. 2015;31:1283-96.

[38] Bettega G, Pepin JL, Veale D, Deschaux C, Raphael B, Levy P. Obstructive sleep apnea syndrome. fifty-one consecutive patients treated by maxillofacial surgery. Am J Respir Crit Care Med. 2000;162:641-9.

[39] Lee WH, Hong SN, Kim HJ, Rhee CS, Lee CH, Yoon IY, et al. A Comparison of Different Success Definitions in Non-Continuous Positive Airway Pressure Treatment for Obstructive Sleep Apnea Using Cardiopulmonary Coupling. J Clin Sleep Med. 2016;12:35-41.

[40] Wee JH, Lim JH, Gelera JE, Rhee CS, Kim JW. Comparison of success criteria based on long-term symptoms and new-onset hypertension in mandibular advancement device treatment for obstructive sleep apnoea: observational cohort study. BMJ Open. 2018;8:e021644.

[41] Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet. 2005;365:1046-53.

[42] Ravesloot MJ, de Vries N. Reliable calculation of the efficacy of non-surgical and surgical treatment of obstructive sleep apnea revisited. Sleep. 2011;34:105-10.

[43] Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Rein J, Vela-Bueno A, et al. Prevalence of sleep-disordered breathing in women: effects of gender. Am J Respir Crit Care Med. 2001;163:608-13.

[44] Duran J, Esnaola S, Rubio R, Iztueta A. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. Am J Respir Crit Care Med. 2001;163:685-9.

[45] Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med. 1993;328:1230-5.

[46] Marklund M, Stenlund H, Franklin KA. Mandibular advancement devices in 630 men and women with obstructive sleep apnea and snoring: tolerability and predictors of treatment success. Chest. 2004;125:1270-8.

[47] Sutherland K, Takaya H, Qian J, Petocz P, Ng AT, Cistulli PA. Oral Appliance Treatment Response and Polysomnographic Phenotypes of Obstructive Sleep Apnea. J Clin Sleep Med. 2015;11:861-8.

TABLES

TABLE 1 Demographic, respiratory and clinical data at baseline for the intention-to-treat population

Baseline characteristics	**Patients (n=315)**
Male, n (%)	239 (76)
Age, years	53.0 [45.0; 61.0]
BMI, kg/m^2	26.7 [24.6; 29.4]
Obese (BMI >30 kg/m^2), n (%)	63 (20)
Waist circumference, cm	97.0 [89.0; 105.0]
Neck circumference, cm	40.0 [38.0; 42.0]
Previously treated with CPAP, n (%)	160 (51)
ESS	11.0 [8.0; 15.0]
ESS >10, n (%)	160 (56)
AHI, /h	27.0 [17.8; 37.2]
Mild OSA, n (%)	50 (16)
Moderate OSA, n (%)	132 (42)
Severe OSA, n (%)	133 (42)
AI, /h	8.5 [3.6; 18.6]
Central AI, /h	0.0 [0.0; 0.5]

Mean SpO_2, %	94.0 [93.0; 98.0]
Minimum SpO_2, %	84.0 [78.0; 87.0]
Time with SpO_2 <90%, min	7.0 [1.0; 22.0]
ODI, /h	17.0 [9.0; 29.0]
Dental status, n (%)	
Good	259 (83)
Acceptable	53 (17)
Periodontal status, n (%)	
Good	254 (81)
Acceptable	58 (19)
Dental mobility, n (%)	
None	295 (95)
Low and limited	17 (5)
Angle malocclusion, n (%)	
Type 1	209 (69)
Type 2	80 (27)
Type 3	13 (4)

Values are median [interquartile range] or number of patients (%)

AHI, apnoea-hypopnoea index; AI, apnoea index; BMI, body mass index; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale; ODI, oxygen desaturation index; SpO_2, oxygen saturation.

TABLE 2 Change in sleep and respiratory parameters over time during MRD therapy.

(n=191)	**Baseline**	**3–6 months**	**2 years**
AHI, /h	26 [18; 35]	6 [3; 11]*	8 [4; 16]*
3% ODI, /h	17 [9; 29]	5 [2; 12]*	8 [3; 15]*
Time with SpO_2 <90%, %	7 [1; 22]	0 [1; 9]**	0 [1; 9]**
Nadir SpO_2, %	84 [87; 94]	87 [90; 95]*	87 [89; 96]*

Values are median [interquartile range].

AHI, apnoea-hypopnoea index; ODI, oxygen desaturation index; SpO_2, oxygen saturation.

*p<0.0001 vs baseline; **p<0.0004 vs baseline.

TABLE 3: Univariate analysis of predictive factors based on continuation of treatment after two years and achievement of reduction of an apnoea-hypopnoea index AHI of <10/h at the 2-year follow-up

Variable	OR (95% CI)	p-value
Continuation of treatment after 2 years (ITT CAD/CAM population, n=315)		
Neck circumference (cm)	0.924 (0.866-0.986)	0.021
Waist circumference (cm)	0.981 (0.962-1.001)	0.058
Obesity (yes/no)	0.591 (0.338; 1.033)	0.065
ESS score >10 (yes/no)	1.674 (1.048-2.675)	0.031
Episodes of breathing cessation during sleep at inclusion (yes/no)	1.817 (1.066-3.098)	0.028
Compliance to with MRD at the last titration visit (days/week)	1.320 (1.086-1.605)	0.005
Compliance to with MRD at the last titration visit (hours/night)	1.327 (1.108-1.558)	0.002
Pain at the last titration visit (yes/no)	0.419 (0.242-0.727)	0.002
50% reduction in AHI at the 3-6 months' follow-up (yes/no)	3.542 (1.930-6.499)	<0.001
Nocturnal mouth breathing at the 3-6 months' follow-up (yes/no)	1.859 (1.115-3.101)	0.017
Absence of snoring at the 3-6 months' follow-up (yes/no)	2.000 (1.089-3.680)	0.026
Absence of nocturia at the 3-6 months' follow-up (yes/no)	1.930 (1.040-3.578)	0.037
Compliance to with MRD at the 3-6 months' follow-up (days/week)	1.387 (1.064-1.807)	0.015
Compliance to with MRD at the 3-6 months' follow-up (hrs/night)	1.270 (1.010-1.514)	0.040
Reduction in AHI to <10/h at the 2-year follow-up (patients with AHI measurement, n=191)		
Neck circumference (cm)	0.914 (0.836-0.999)	0.015

Dental class (class II versus I)	3.542 (1.636-7.668)	<0.0001
Dental class (class III versus I)	5.565 (0.630-49.172)	<0.0001
Maximal propulsion (mm)	1.117 (0.978-1.276)	0.101
Mandibular propulsion as % of maximal propulsion	0.986 (0.974-0.998)	0.077
Initial AHI by severity group (mild versus severe)	5.552 (2.120-14.538)	<0.0001
Initial AHI by severity group (moderate versus severe)	3.574 (1.857-6.878)	<0.0001
Initial AI (number/h)	0.941 (0.913-0.970)	<0.0001
Initial dorsal AHI (number/h)	0.981 (0.959-1.004)	0.1026
Positional OSA (yes/no)	2.412 (0.941-6.184)	0.063
Absence of previous CPAP treatment by CPAP (yes/no)	3.153 (1.735-5.729)	0.0001

TABLE 4 Adverse events at the 2-year follow-up visit (n=315)

	Patients, n (%)		
	All	**Severe**	**Requiring patient withdrawal**
TMJ disorder	89 (28.3)	18 (5.7)	7 (2.2)
Gingival pain or gingivitis	61 (19.3)	13 (4.1)	5 (1.6)
Occlusion change	53 (16.8)	1 (0.3)	2 (0.6)
Dental pain	50 (15.9)	6 (1.9)	7 (2.2)
Tooth migration or dental mobility	31 (9.8)	0 (0)	0 (0)
Mouth dryness or hypersalivation	27 (8.6)	0 (0)	1 (0.3)
Mouth pain or irritation	12 (3.8)	2 (0.6)	1 (0.3)
Discomfort	14 (4.4)	1 (0.3)	1 (0.3)
Dental fracture or prothesis loosening	10 (3.2)	7 (2.2)	1 (0.3)
Broken MRD	7 (2.2)	5 (1.6)	4 (1.2)
Nausea or vomiting	4 (1.3)	1 (0.3)	1 (0.3)
Mouth ulcer	4 (1.3)	1 (0.3)	0 (0)
Lack of prothesis retention	4 (1.3)	1 (0.3)	1 (0.3)
Suspected allergy	2 (0.6)	1 (0.3)	2 (0.6)
Other	19 (6.0)	5 (1.6)	3 (0.9)

MRD, mandibular repositioning device; TMJ, temporo-mandibular joint.

Figures

FIGURE 1 Study flow chart. CAD/CAM, computer-aided design, computer-aided manufacturing; CPAP, continuous positive airway pressure; FU, follow-up; ITT, intention-to-treat; MRD, mandibular reposition device.

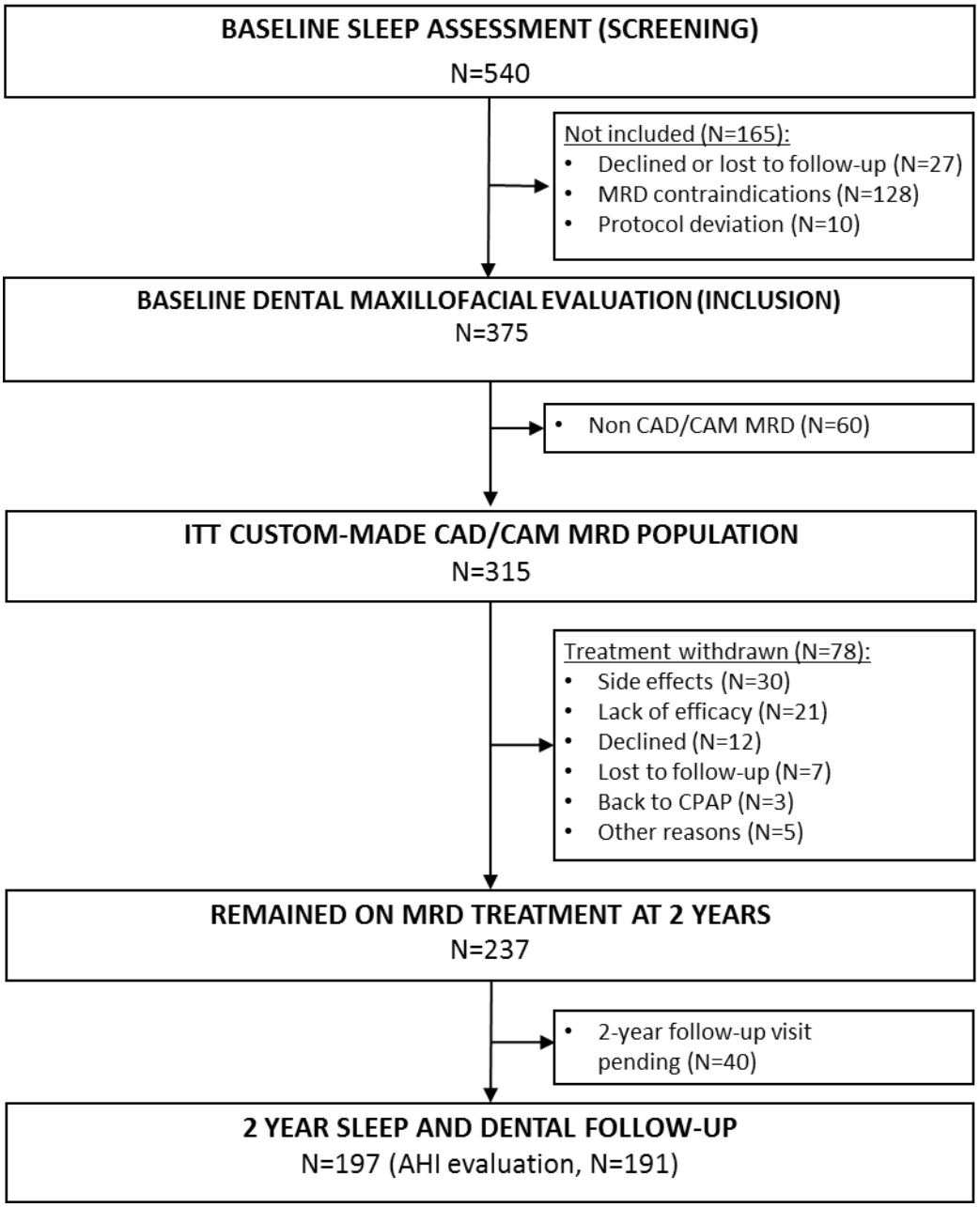


FIGURE 2 Proportion of patients continuing mandibular repositioning device therapy over time

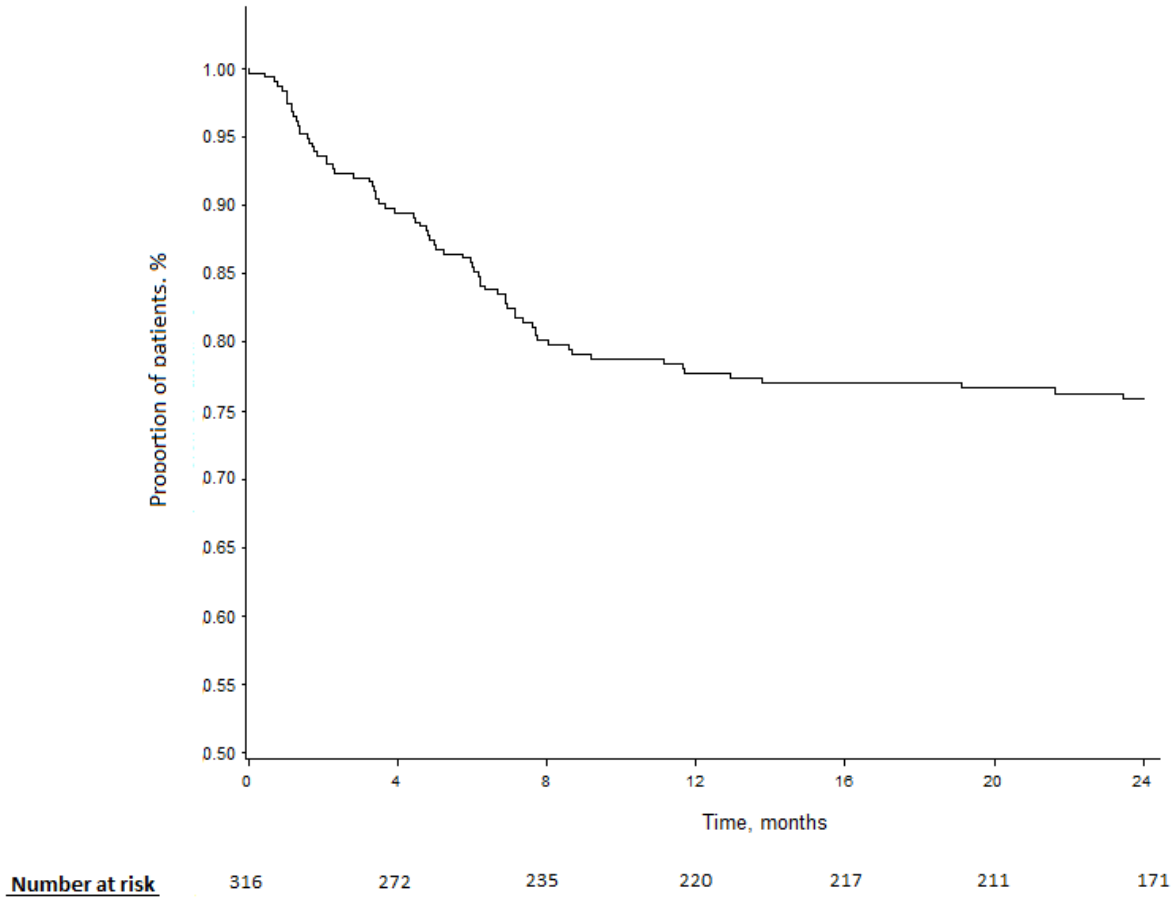


FIGURE 3 Mandibular repositioning device efficacy at 2-year follow-up by obstructive sleep apnoea syndrome (OSAS) severity (**A**) (AHI, apnoea–hypopnoea index; Success rate, percentage of patients with a ≥50% decrease in AHI from baseline to follow-up. Chi-squared test for AHI achieved; *p<0.001). Change in AHI over time by baseline OSAS severity in patients remaining in the study at the 2-year follow-up (**B**) (two-by-two comparisons of AHI (Tuckey's test) for baseline versus 3-6 months and baseline versus 2 years: p<0.0001 for each severity subgroup; for 3–6 months versus 2 years: p=0.0082 for mild OSAS, p=0.0001 for moderate OSAS and p=0.0015 for severe OSAS; *p<0.0001 versus baseline).

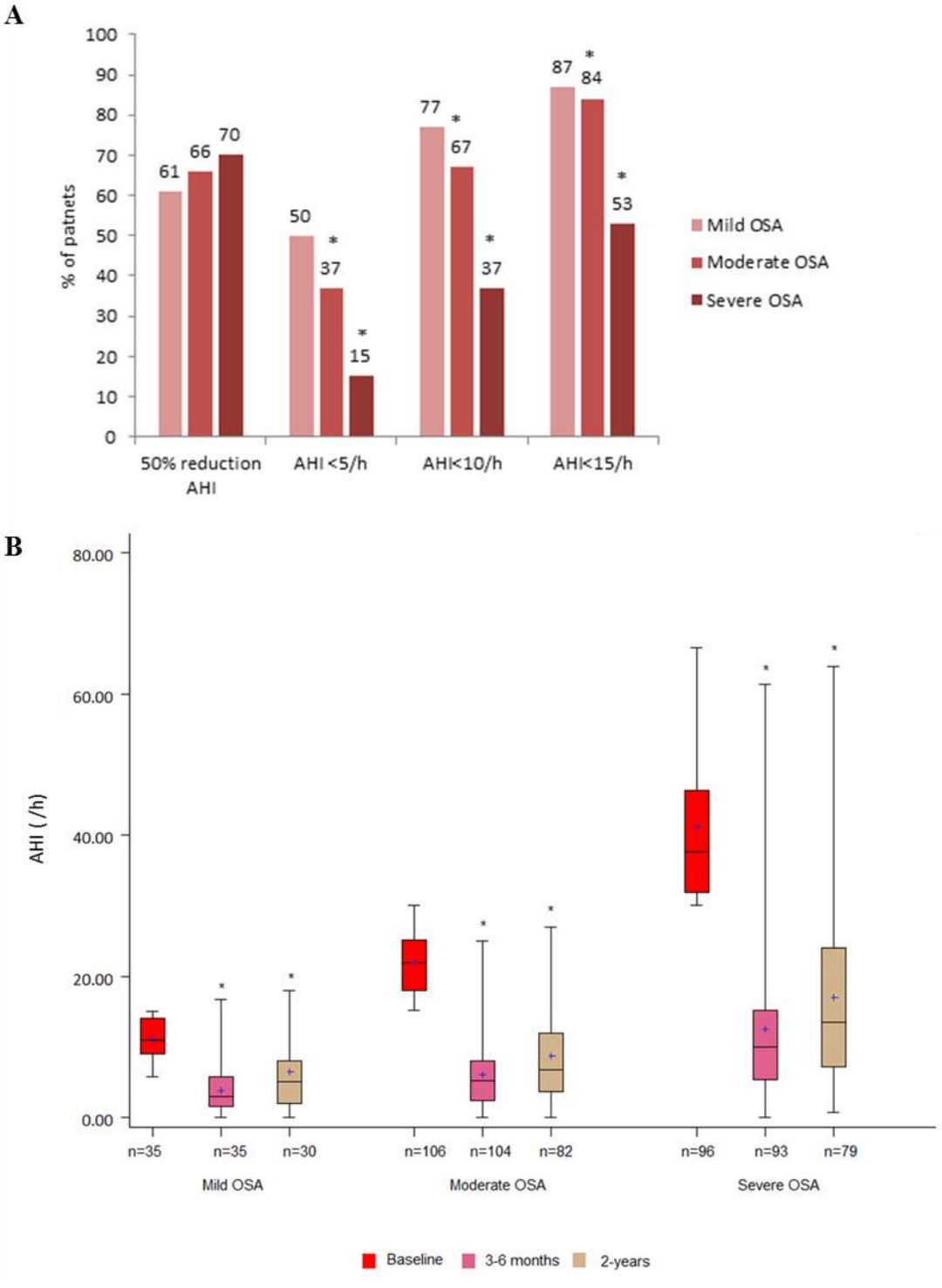


FIGURE 4 Proportion of patients with different symptoms and Epworth Sleepiness Scale (ESS) score >10 (**A**), Quebec Sleep Questionnaire (QSQ) scores (**B**) and visual analogue scale (VAS) scores (**C**) at baseline, and after 3–6 months and 2 years of follow-up.

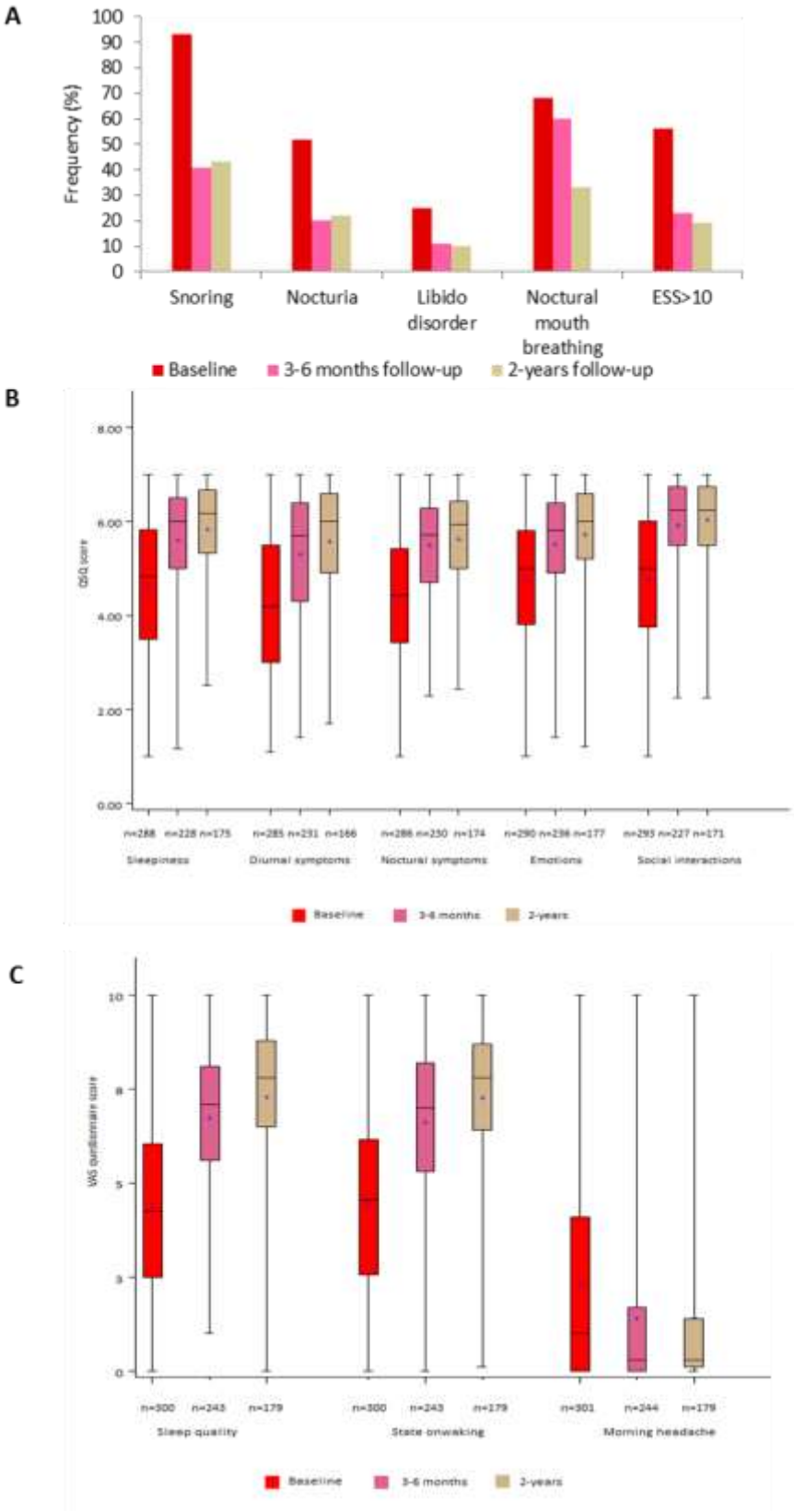
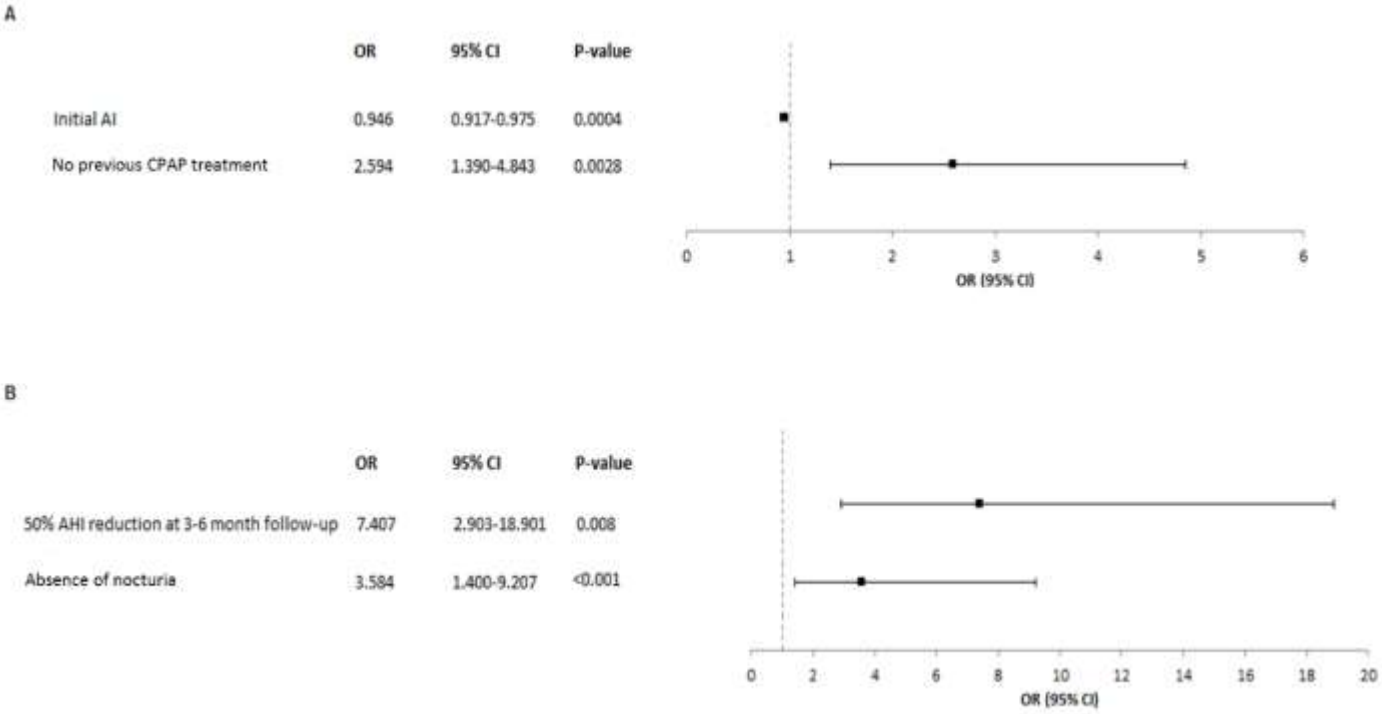


FIGURE 5 Forest plot of multivariate analysis showing predictors of apnoea-hypopnoea index (AHI) <10/h (**A**) and continuation of treatment (**B**) after two years. AI, apnea index; CI, confidence interval; CPAP, continuous positive airway pressure; OR, odds ratio.



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