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ORIGINAL ARTICLE

Predicting treatment response to mandibular advancement therapy using a titratable thermoplastic device

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Abstract

Objectives Mandibular advancement device (MAD) therapy is the most commonly used second-line treatment for obstructive sleep apnea (OSA), but MAD may be ineffective in a subgroup of patients. We describe the use of a trial of a titratable thermoplastic MAD to predict treatment outcomes with a custom-made MAD.

Materials and methods Patients treated with a thermoplastic MAD as a trial before custom-made MAD manufacturing were included in the study. Sleep recordings and clinical outcomes assessed after 6 months of treatment with each device were compared. Predictive utility of thermoplastic MAD to identify custom-made MAD treatment success defined as a reduction greater than 50% and final apnea-hypopnea index (AHI) less than 10 events/h was evaluated.

Results Thermoplastic MADs were installed in 111 patients, but only 36 patients were finally treated with both devices and were included in the analysis. A significant correlation was observed between the impact of the two devices on the AHI (r=0.85, p<0.0001), oxygen desaturation index (r=0.73, p<0.0001), snoring index (r=0.85, p<0.0001), and Epworth sleepiness scale (r=0.77, p<0.0001). A high positive predictive value (86%) but a low negative predictive value (46%) was observed regarding AHI decrease.

Conclusions Similar impacts of both MADs were observed on major OSA severity markers and symptoms. The ability of thermoplastic MAD to indicate likelihood of success with custom-made MAD will require further controlled studies.

Clinical relevance Thermoplastic MADs could represent a useful and easily implemented tool to predict the likelihood of success of a custom-made MAD as treatment for OSA.

Keywords Sleep apnea · Custom-made mandibular advancement device · Thermoplastic mandibular advancement device

Introduction

Mandibular advancement devices (MAD) have emerged as the principal alternative to continuous positive airway pressure (CPAP) for the treatment of obstructive sleep apnea (OSA) [1, 2]. According to French clinical guidelines, MAD therapy is recommended as an appropriate first-line treatment option for mild to moderate OSA in patients without severe cardiovascular comorbidity or as a second-line option in patients intolerant to CPAP. Despite a lower impact of MADs on decreasing the apnea-hypopnea index (AHI), both treatments have been shown to have a similar impact on clinical outcomes, including sleepiness, and cardiovascular outcomes [3].

Unfortunately, there is significant individual variability in the response rate to MAD therapy, making it difficult for clinicians to select MAD therapy over CPAP [4]. In current clinical practice, patient selection for MAD therapy is largely

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based on AHI severity and demographic data, although these criteria have been shown to have little predictive value [5, 6]. One potential solution is the development of easily applicable strategies to prospectively identify patients likely to benefit from MAD therapy in terms of AHI reduction but also in terms of improvement of patient-centered outcomes.

A pragmatic approach would be to assess the impact of MAD on OSA severity markers and patient-centered outcomes using a temporary, easily implemented, but reliable MAD. MADs are generally customized devices requiring dental impressions and bite registrations performed by a dentist and are associated with expense and time. Thermoplastic heat molded appliances, made from a thermoplastic polymer material that can be easily molded when heated in hot water, would constitute cheaper and simpler alternatives. Under the supervision of a dentist, the patient bites into the softened material, and the device then sets in this configuration while cooling. Recent observational and randomized trials suggest that thermoplastic heat-molded titratable MADs are not inferior to custom-made acrylic MADs in terms of the rate of reduction of OSA severity indices, patient-centered outcomes, and blood pressure improvement [7, 8]. However, thermoplastic devices have a shorter expected lifespan, and the long-term impact of wearing these devices remains unknown. This device was first developed in order to be proposed as temporary means of determining whether mandibular advancement therapy is feasible and effective before ordering a custom-made MAD for long-term use. The ability of a trial thermoplastic MAD to predict success of a custom-made MAD has not yet been evaluated. The purpose of this study was therefore to describe the use of thermoplastic MADs in a real-life observational cohort and to evaluate their ability to predict the rate of reduction of OSA severity indices and patient-centered outcomes with custom-made MAD therapy.

Methods

This observational study was conducted on the Institut de Recherche en Santé Respiratoire des Pays de la Loire [IRSR] sleep cohort [9]. Approval was obtained from the University of Angers ethics committee. All patients included in the IRSR sleep cohort have given their written informed consent.

Study population

OSA patients, for whom MAD therapy was considered a first-line therapy for mild to moderate OSA or a second-line therapy due to CPAP intolerance at Angers University Hospital between June 2014 and December 2018, were assessed for eligibility. Patients were examined by a dentist to assess any contraindication for MAD therapy (e.g., periodontal disease or insufficient dentition). All the patients treated with thermoplastic MAD therapy were included in this study. When a thermoplastic MAD was initiated, the device was titrated and the patient used the MAD for approximately 6 months. When the thermoplastic MAD was considered to be effective, a custom-made MAD was then proposed. Only patients who received both MAD devices and who completed the subsequent sleep evaluations were included in the final analysis.

Device fitting and titration

A titratable thermoplastic MAD (BluePro®; BlueSom, France) was evaluated in this study, together with two titratable custom-made MADs with proven clinical efficacy in the treatment of OSA [1, 2]: the AMO® device (SomnoMed, France) and the Somnodent® device (SomnoMed, France) (Fig. 1). All patients were fitted with the thermoplastic MAD by a dentist and underwent an acclimatization period, during which the mandible was incrementally advanced by 1mm steps every 1 or 2 weeks until the patient was relieved of symptoms or the maximum comfortable limit of advancement had been achieved [7]. The impact of thermoplastic MADs on sleep was evaluated within the following 6 months, and a custom-made MAD was proposed at the end of the 6-month period when the thermoplastic MAD trial was considered to be conclusive. A similar MAD titration and evaluation procedure was used for custom-made MADs.

Outcomes and follow-up

The primary outcome was a change in sleep-disordered breathing severity, as assessed by the AHI, the 3% oxygen desaturation index (ODI), and the snoring index between baseline and treatments with thermoplastic and custom-made MADs. The secondary outcomes included changes in daytime sleepiness, as evaluated by the Epworth sleepiness scale (ESS) [10], and the degree of mandibular protrusion achieved after the titration procedure.

Sleep recordings

At baseline and 6 months after thermoplastic and custom-made MAD therapy, patients underwent type III overnight respiratory recordings (CID 102 LX, Cidelec, Sainte-Gemmes sur Loire, France) [11]. Respiratory events were scored manually using recommended criteria [12]. Patients were classified as responders or non-responders according to the following definition: treatment response greater than 50% reduction in AHI from baseline plus a treatment AHI less than 10 events/h [13, 14].

Fig. 1 Mandibular advancement devices (MADs) used in the study: (**a**) BluePro® (BlueSom, France) thermoplastic MAD, (**b**) SomnoDent® (SomnoMed, France) custom-made MAD, and (**c**) AMO® (SomnoMed, France) custom-made MAD

Statistical analysis

Continuous variables were described as mean (standard deviation [SD]). The normality of distribution was assessed using the Kolmogorov-Smirnov test. Normal variables were analyzed using an unpaired *t*-test for intergroup differences. Non-normal variables were analyzed using the Mann-Whitney test for intergroup differences. The chi-square test and Fisher's exact test were used for categorical variables, as appropriate. Spearman's and Pearson's rank correlation coefficients were used as appropriate to correlate changes in outcomes (deltas between treatment and baseline values) with both MADs. Sensitivity, specificity, and positive and negative predictive values of the thermoplastic MAD as a predictor of success of custom-made MAD treatment were calculated. Receiver operating characteristic (ROC) curves displaying sensitivities and specificities over the continuous range of decision cut-points as well as the overall summary of the area under the curve (AUC) were also provided. All reported *p*-values were two-sided. A *p*-value less than or equal to 0.05 was considered to indicate statistical significance. All statistical analyses were performed with GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, CA, USA.

Results

A flow diagram summarizing patient selection is shown in Fig. 2. Between June 2014 and December 2018, thermoplastic MAD therapy was initiated in 111 OSA patients. Seventy-one of these 111 patients completed the first evaluation including sleep recording and ESS evaluation, 26 discontinued treatment due to intolerance of the devices, 2 discontinued treatment due to a broken device, and 12 patients did not participate in follow-up. The most common side effects motivating discontinuation of thermoplastic MAD therapy were tooth pain (18/26), temporomandibular joint pain (15/26), occlusion changes (9/26), dry mouth (6/26), and excessive salivation (6/26). After sleep recording with a thermoplastic MAD, the device was considered to be ineffective in 10 patients; 7 patients declined to continue with MAD therapy due to side effects; 6 preferred an alternative OSA treatment; 1 patient refused custom-made MAD for financial reasons; and 7 did not participate in follow-up. Finally, 40 patients were treated with custom-made MAD, and 36 underwent the custom-made MAD sleep recording and were included in this analysis.

The 36 patients were classified as responders or non-responders according to the previously described definition (treatment response greater than 50% reduction in AHI from baseline plus a treatment AHI less than 10 events/h). Differences between responders and non-responders in terms of baseline characteristics are described in Table 1. The two groups were similar in terms of anthropomorphic characteristics and prevalence of comorbidities. Non-responders had more pronounced nighttime hypoxemia, as assessed by the time spent with an oxygen saturation below 90%, with no significant difference in terms of baseline AHI.

The impact of thermoplastic and custom-made MADs on sleep outcomes and sleepiness is shown in Table 2 and Fig. 3. There was a highly significant correlation between the impacts of thermoplastic and custom-made MADs on AHI (r=0.85, p<0.0001), ODI (r=0.73, p<0.0001), snoring index (r=0.85, p<0.0001), and ESS (r=0.77, p<0.0001). A significant positive correlation was also found between the final settings of the two MADs (degree of mandibular protrusion) (r=0.49, p=0.0039) (Fig. 4).

A numerical description of predictive accuracy is presented in Table 3, in which the prediction of treatment success or failure with a thermoplastic MAD is cross-referenced with the final therapeutic outcome with a custom-made MAD using the same definition of treatment success for both devices. Due to the selection process, the prevalence of custom-made MAD treatment failure was low (9/36; 25%). The positive predictive value was high (86%), and the negative predictive value was low (46%). A similar analysis was performed to evaluate the accuracy of a thermoplastic MAD to predict the impact of a custom-made MAD on sleepiness using the same definition of treatment success for both devices (treatment ESS < 10). Overall, the predictive accuracy of the thermoplastic MAD was higher for ESS than for AHI (Table 4).

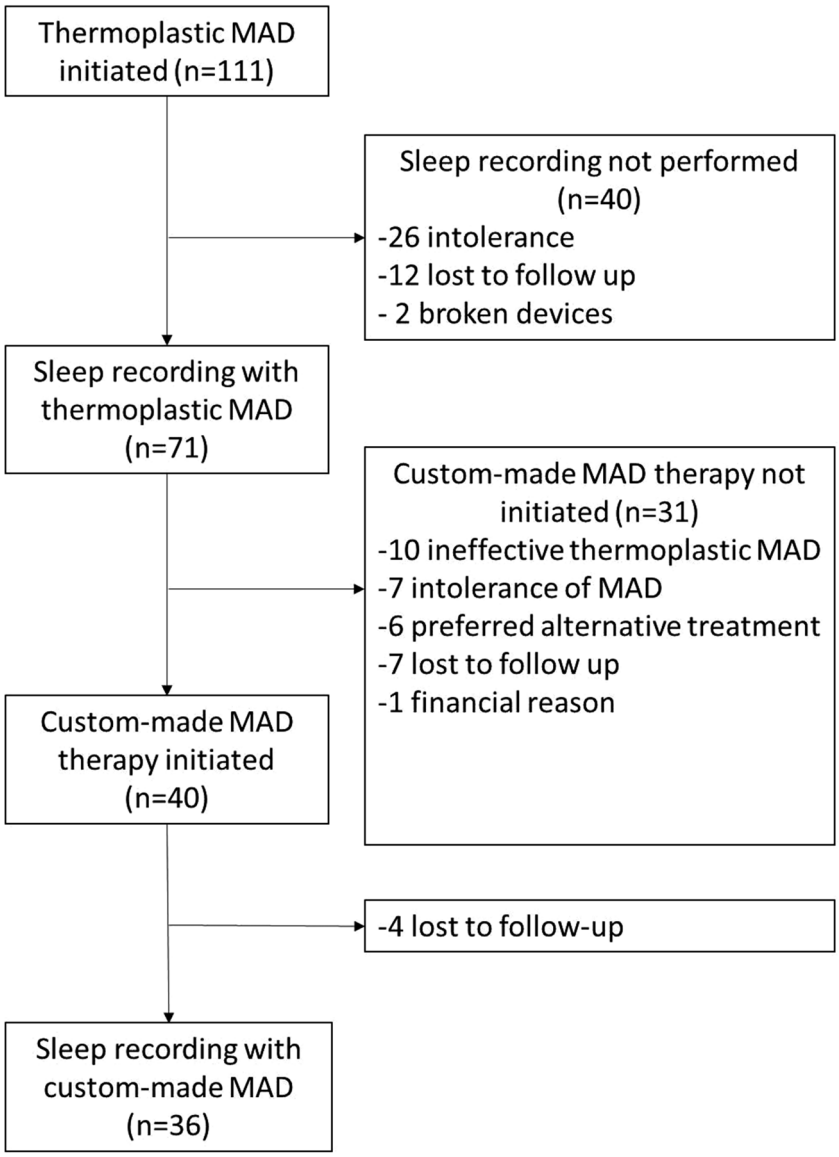

Fig. 2 Patient flow chart

Table 1 Baseline patient demographics and sleep recording data for all patients and for custom-made MAD responders and non-responders

	All	Responders	Non-responders	*p* value[a]
N	36	27	9	
Age, years	54.7 (11.4)	54.0 (11.5)	56.7 (11.8)	0.56
BMI, kg/m^2	26.2 (3.3)	26.1 (3.2)	26.5 (3.4)	0.75
Women, %	19	22	11	0.46
Hypertension, %	20	21	16	0.81
Diabetes, %	8	11	0	0.40
Current smoker, %	40.9	43	37	0.80
Previous CPAP therapy, %	36	35	37	0.89
ESS	9.4 (4.5)	9.3 (4.6)	9.9 (4.7)	0.72
AHI, n/h	27.1 (11.9)	25.8 (11.3)	31.0 (13.5)	0.26
3% ODI, n/h	18.6 (12.1)	16.6 (11.3)	24.7 (12.7)	0.08
T90, %	2.1 (4.0)	1.2 (2.5)	4.7 (6.3)	0.02
Snoring index, n/h	258.2 (198.9)	256.9 (188 .9)	262.2 (239.2)	0.95

Data are expressed as mean (standard deviation) or percentages

BMI body mass index, *CPAP* continuous positive airway pressure, *ESS* Epworth sleepiness score, *AHI* apnea/hypopnea index, *ODI* oxygen desaturation index, *T90*, time spent with SaO_2<90%

[a] Custom-made MAD responders *versus* custom-made MAD non-responders

Table 2 Baseline and follow-up sleep recording data for custom-made MAD responders and non-responders

	Baseline		Thermoplastic MAD		Custom-made MAD	
	Responders	Non-responders	Responders	Non-responders	Responders	Non-responders
ESS	9.3 (4.6)	9.9 (4.7)	6.8 (4.1)#	5.8 (4.9)#	5.9 (3.4)#	6.1 (4.6)#
AHI, n/h	25.8 (11.3)	31.0 (13.5)	7.3 (6.0)#	14.9 (12.8)*#	4.9 (2.9)#	15.3 (8.5)*#
3% ODI, n/h	16.6 (11.3)	24.7 (12.7)	8.3 (4.6)#	12.7 (8.9)#	7.4 (4.3)#	19.2 (18.0)*
T90, %	1.2 (2.5)	4.7 (6.3)	2.5 (10.2)#	1.3 (3.3)#	2.4 (7.2)	6.6 (12.7)
Snoring index, n/h	256(188)	262 (239)	79 (129)#	129 (131)	67 (89)#	71 (84)#

Data are expressed as mean (standard deviation) or percentages

ESS Epworth sleepiness score, *AHI* apnea/hypopnea index, *ODI* oxygen desaturation index, *T90* time spent with SaO_2<90%

*p<0.05 responders versus non-responders

#p<0.05 versus baseline

Finally, the accuracy of thermoplastic MAD, AHI, and ESS (considered a continuous value) to predict custom-made MAD treatment success, defined as a 50% reduction in AHI from baseline plus a treatment AHI less than 10 events/h and a treatment ESS<10, was represented by two ROC curves (Fig. 5) and the corresponding AUC.

Discussion

This study describes the implementation of thermoplastic MAD in a sleep center as a trial prior to manufacture of a custom-made MAD and evaluates the prognostic accuracy of the device not only to predict the impact of MAD on AHI but also on patients' symptoms. We showed that only one-

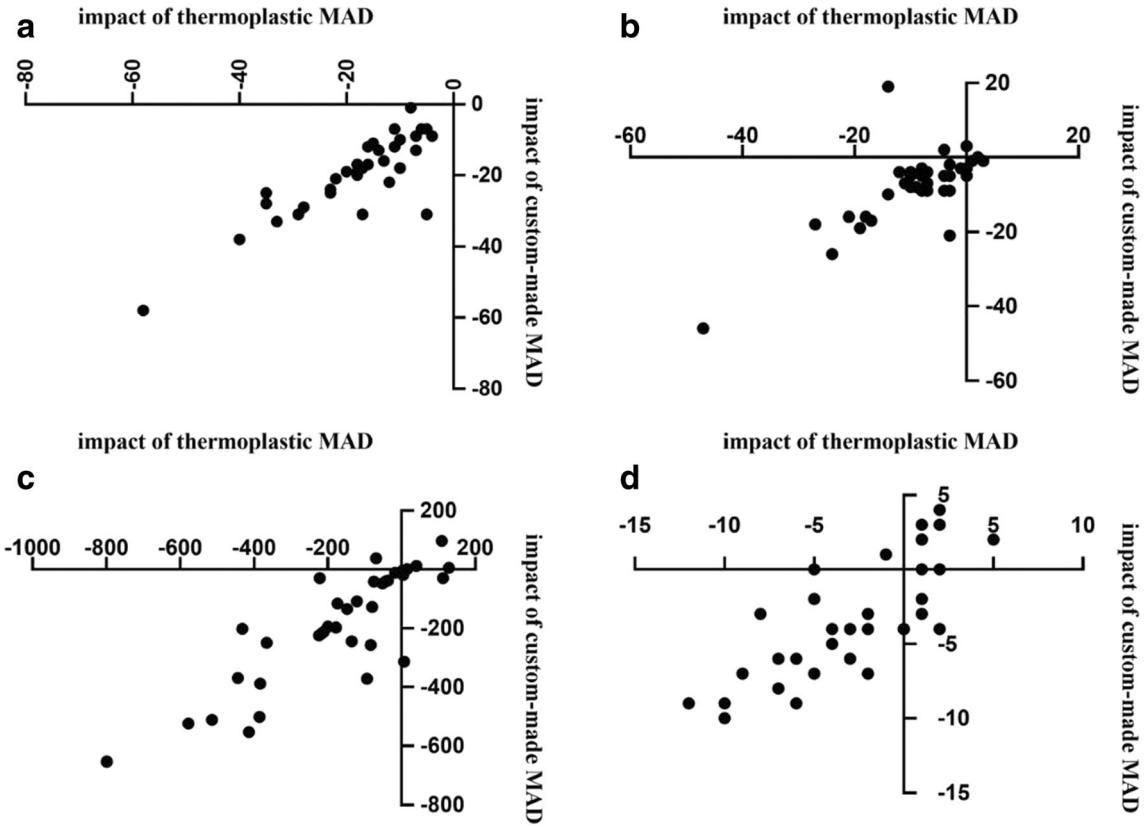

Fig. 3 Correlations between the impact (deltas between baseline and treatment values) of thermoplastic and custom-made MADs on AHI (**a**), ODI (**b**), snoring index (**c**), and ESS (**d**). *MAD* mandibular advancement device, *AHI* apnea/hypopnea index, *ODI* oxygen desaturation index, *ESS* Epworth sleepiness score

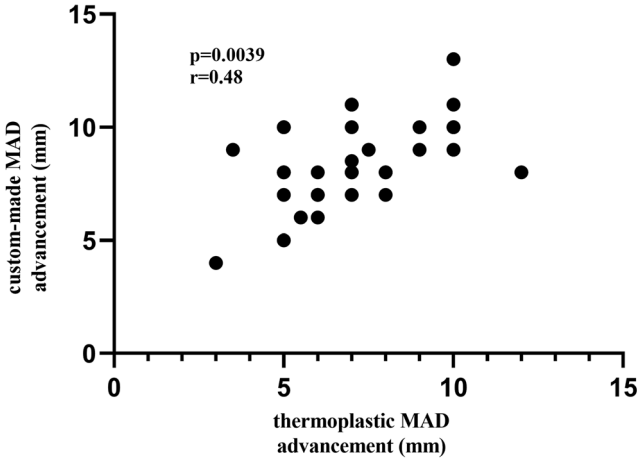

Fig. 4 Correlations between the degrees of mandibular advancement achieved with thermoplastic and custom-made MADs. *MAD* mandibular advancement device

third of patients who initiated thermoplastic MAD therapy continued with a custom-made device. Among patients who underwent evaluation with both devices, a thermoplastic MAD showed a good ability to predict the impact of a custom-made MAD on both major OSA severity markers and sleepiness.

Despite large theoretical indication for MAD therapy as a first-line treatment option for patients with mild-to-moderate or as second-line treatment in patients who are intolerant to or refuse CPAP [15], this treatment option is rarely proposed in comparison with CPAP, which tends to be much more frequently prescribed. The most frequently cited reason to explain this mismatch is the relatively low efficacy of MADs, together with a lack of a reliable prospective selection procedure of the most likely responders [4]. Therefore, a number of elaborate strategies have reported various predictors of MAD treatment outcomes using polysomnographic parameters [14, 16], imaging techniques [17, 18], CPAP pressure [19, 20], spirometry [21], drug-induced sleep endoscopy [22], a remotely controlled mandibular positioner [13], and multisensory catheter parameters [23]. While these methods may be clinically useful, they differ widely in terms of their technical complexity, the need for specialized equipment, medical expertise, and cost and could therefore preclude widespread implementation in the clinical setting.

A thermoplastic MAD trial has many potential advantages over other previously proposed strategies: it is easy to implement; no specific knowledge or equipment is required; it incurs a reasonable cost; and it involves no invasive procedure. Furthermore, we have demonstrated that thermoplastic MADs can not only predict the impact of custom-made MADs on OSA severity markers (AHI, nocturnal oxygenation) but also on patient-centered outcomes including sleepiness or snoring.

The strengths and limitations of the study are inherent to its observational design. On the one hand, this study describes, for the first time, a real-life clinical implementation of thermoplastic MAD therapy proposed as a trial before custom-made MAD manufacture. The follow-up of patients initially treated with thermoplastic MADs showed that a large majority did not receive long-term MAD therapy due to intolerance, side effects, or lack of efficacy. Our data are in accordance with recent observational data showing that a significant proportion of patients discontinue MAD therapy during the first year of treatment [24]. On the other hand, the most significant limitation of this study is its observational nature, as the final analysis of prognostic accuracy was performed on data from a particular selected population. Of the 111 patients initially included, 33 did not undergo custom-made MAD therapy due to intolerance to thermoplastic MADs (26 before and 7 after the first MAD sleep recording). Previous studies comparing similar devices have shown that thermoplastic MAD therapy was associated with similar effectiveness but had significantly higher side effect scores [7, 8]. More importantly, it is still unknown whether the same patient will experience similar side effects with different devices. It can therefore be hypothesized that side effects experienced during a thermoplastic MAD trial might limit the patient's access to a custom-

Table 3 Numerical matrix describing the qualitative prediction of success of a thermoplastic MAD to forecast the success of a custom-made MAD on AHI

	Predicted success with thermoplastic MAD	Predicted failure with thermoplastic MAD		
Custom-made MAD success	20	7	PPV=86%	Sensitivity=74%
Custom-made MAD failure	3	6	NPV=46%	Specificity=66%

Treatment success was defined as a greater than 50% reduction in AHI from baseline plus a treatment AHI of less than 10 events/h for both thermoplastic and custom-made MADs. The table presents the number of participants in each of four categories: "true" positive (predicted success and custom-made MAD success), "true" negative (predicted failure and custom-made MAD failure), "false" positive (predicted success and custom-made MAD failure), and "false" negative (predicted failure and custom-made MAD success) at the final protrusive position. The parameters of predictive accuracy are provided

AHI apnea/hypopnea index, *MAD* mandibular advancement device, *PPV* positive predictive value, *NPV*, negative predictive value

Table 4 Numerical matrix describing the qualitative prediction of success of thermoplastic MAD to forecast custom-made MAD success on ESS

	Predicted success with thermoplastic MAD	Predicted failure with thermoplastic MAD		
Custom-made MAD success	26	2	PPV=96%	Sensitivity= 92%
Custom-made MAD failure	1	4	NPV=66%	Specificity= 80%

Treatment response success was defined as a treatment ESS<10 for both thermoplastic and custom-made MADs. The table presents the number of participants in each of four categories: "true" positive (predicted success and custom-made MAD success), "true" negative (predicted failure and custom-made MAD failure), "false" positive (predicted success and custom-made MAD failure), and "false" negative (predicted failure and custom-made MAD success) at the final protrusive position. The parameters of predictive accuracy are provided

ESS Epworth sleepiness scale, *MAD* mandibular advancement device, *PPV* positive predictive value, *NPV* negative predictive value

made MAD, which could be better tolerated. Alternatively, a trial with a thermoplastic MAD could also predict intolerance of MAD therapy, thereby avoiding the production of a useless custom-made MAD. Further controlled studies proposing a trial of both devices for all included patients are necessary to distinguish between these two opposing hypotheses.

One important finding of the study is the low negative predictive value observed regarding the ability of the thermoplastic MAD to predict custom-made MAD failure. This raises the question if thermoplastic MAD pre-treatment trial should be recommended to identify poor MAD responders in clinical practice. Due to the observational design of the study, this analysis is based on a very selected population making it difficult to draw any definitive conclusion. Indeed, the success rate among the 36 patients is particularly high in comparison with previous studies [1, 2, 13, 14] which probably means that most of the MAD non-responders have been excluded during the thermoplastic MAD trial. Consequently, the small number of patients presenting treatment failure may have affected the relatively low negative predictive value based on the AHI.

In conclusion, despite several limitations inherent to its observational design, this study is the first to describe the use of a thermoplastic MAD in clinical practice. Thermoplastic MAD is an easily implemented tool that could be useful to predict intolerance and to evaluate the likelihood of success with MAD therapy before opting for the more time-consuming procedure of manufacturing a custom-made MAD. At this step, the limited available data regarding the predictive accuracy of this strategy make it difficult to draw any definitive conclusions for clinical practice. Further controlled studies evaluating the performance of both devices in an unselected OSA population are required to evaluate the effectiveness of this strategy.

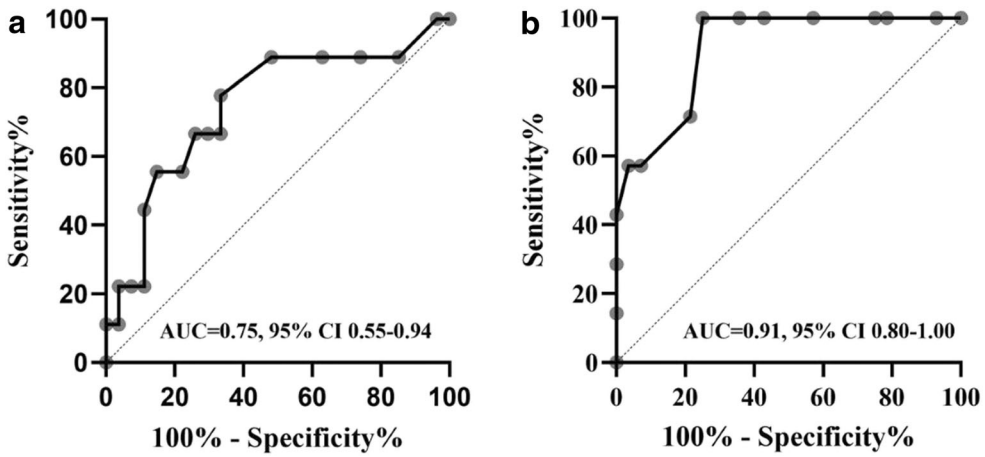

Fig. 5 Receiver operating characteristics (ROC) curves displaying the sensitivities and specificities over the continuous range of AHI (**a**) and ESS (**b**) scores during thermoplastic MAD therapy as a predictor of custom-made MAD success in terms of decreased AHI (**a**) and ESS (**b**). Custom-made MAD success in terms of AHI was defined as a greater than 50% reduction in AHI from baseline plus a treatment AHI less than 10 events/h. Custom-made MAD response success in terms of ESS was defined as a treatment ESS<10. *MAD* mandibular advancement device, *AHI* apnea/hypopnea index, *ESS* Epworth sleepiness score, *AUC* area under curve, *CI* confidence interval

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Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approval was obtained from the University of Angers Ethics Committee and the "Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé" (07.207bis).

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of Interest WT and NM report non-financial support from ASTEN. FG reports grants and personal fees from RESMED, personal fees and non-financial support from SEFAM, personal fees from CIDELEC, personal fees and non-financial support from NOVARTIS, personal fees from ACTELION, non-financial support from BOEHRINGER INGELHEIM, personal fees and non-financial support from AIR LIQUIDE SANTE, non-financial support from ASTEN, and personal fees and non-financial support from NYXOAH unrelated to the submitted work.

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