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A Comparison of Success Criteria based on Long-Term Symptoms and New-onset Hypertension in Mandibular Advancement Device Treatment for Obstructive Sleep Apnea

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Abstract

Objective: To identify adequate criteria to determine the success or failure of mandibular advancement device (MAD) treatment for obstructive sleep apnea (OSA) based on long-term symptoms and new-onset hypertension.

Design: Prospective cohort study

Setting: A tertiary care hospital setting in South Korea

Participants: Patients (age > 18 years) who were diagnosed with OSA by a polysomnography (PSG) or Watch peripheral arterial tonometry (PAT), and who had been treated with MAD between January 2007 and December 2014 were enrolled.

Primary and secondary outcome measures: Patients underwent PSG or Watch PAT twice; before and 3 months after the application of MAD. The patients were categorized into success and failure groups using 7 different criteria. MAD compliance, witnessed apnea and snoring, Epworth sleepiness scale score, and occurrence of new-onset hypertension were surveyed via telephonic interview to determine the criteria that could identify success and failure of MAD.

Results: A total of 97 patients were included. The mean follow-up duration was 60.5 months, and the mean apnea-hypopnea index (AHI) was 35.5/h. Two of the 7 criteria could significantly differentiate the success and failure groups based on long-term symptoms, including (1) AHI < 10/h with MAD, and (2) AHI < 10/h and AHI reduction of >50% with MAD. Kaplan-Meier survival analysis showed that one criterion of AHI < 15/h with MAD could differentiate the success and failure groups based on new-onset hypertension (P = 0.035). The receiver operating characteristic curve analysis indicated that the cutoff AHI for new-onset hypertension was 16.8/h (71.4% sensitivity and 75.0% specificity).

Conclusion: Our long-term follow-up survey for symptoms and new-onset hypertension

suggested that some of the polysomnographical success criteria, i.e., AHI < 10/h with MAD, AHI < 10/h with MAD and AHI reduction of >50%, and AHI < 15/h with MAD may be useful in distinguishing the success group from failure one. Further prospective longitudinal studies are warranted to validate these criteria.

Key Words: Obstructive sleep apnea, Mandibular advancement, Hypertension

Strengths and limitations of this study

- Strength of this study is that prospective cohort study to identify the optimal polysomnographic success criteria for mandibular advancement device treatment based on long-term subjective symptom changes or occurrence of new-onset hypertension.
- This study was limited in its telephonic interview-based study design.
- Diagnosis of hypertension was estimated based on a physician diagnosed disease.
- Potential interviewer bias and respondent's recall bias may exist.

INTRODUCTION

Obstructive sleep apnea (OSA) is associated with many chronic diseases such as cardiovascular diseases,[1] cerebrovascular diseases,[2] metabolic syndrome,[3] and neurocognitive dysfunction.[4] Furthermore, it may be a risk factor for the future development of hypertension.[5, 6] A short-term randomized controlled trial showed that the treatment for OSA reduces cardiovascular morbidity.[7] Therefore, it is important to focus on effective treatments for OSA to reduce its associated comorbidities.

The mandibular advancement device (MAD) is generally indicated for use in patients with mild-to-moderate OSA.[8] However, MAD treatment is not always inferior to continuous positive airway pressure (CPAP) therapy, and has been reported to show better compliance than CPAP.[9] MAD treatment has shown beneficial effects on the number of obstructive breathing events, arterial oxygen saturation levels, and arousal frequency.[10, 11] Furthermore, a meta-analysis of several observational and randomized controlled trials showed that MAD reduces blood pressure in patients with OSA.[12] Although MAD is frequently prescribed by sleep specialists due to its efficacy, there is no validated standard criterion for determining the success or failure of this treatment for OSA based on long-term subjective symptomatic improvement or occurrence of medical comorbidities. Theoretically, an apnea-hypopnea index (AHI) < 15 or AHI < 5 without symptoms such as witnessed snoring, apnea, and daytime sleepiness are required for treatment success. However, these polysomnography (PSG)-based definitions of success do not always agree with subjective improvement experienced by patients. Furthermore, the literature provides various criteria for defining treatment success. One recent study reported that the success rate of OSA treatment with MAD can vary remarkably according to the success criteria.[13] However, success or failure

cannot be defined by PSG findings alone. A long-term observation of symptom improvement or occurrence of complications is necessary to identify the relationship between success/failure and PSG findings with MAD.

To the best of our knowledge, no long-term follow-up study based on subjective symptom changes or occurrence of new-onset hypertension has thus far identified the optimal PSG success criteria for MAD treatment. Therefore, in the present study, we aimed to determine adequate success criteria for MAD treatment of OSA on the basis of long-term symptoms and occurrence of new-onset hypertension.

METHODS

Patients

This study included patients (age > 18 years) who were diagnosed with OSA (AHI ≥ 5/h and symptoms of snoring, fragmented sleep, witnessed apnea, or daytime sleepiness) by an attended, full-night, in-laboratory PSG or Watch peripheral arterial tonometry (PAT), and who had been treated with MAD at our sleep clinic between January 2007 and December 2014. The MAD was designed to hold the mandible fixed at 60% of the maximum protrusion without an open bite. All the patients were regularly followed up to evaluate any dental or temporomandibular joint problems and to adjust the advancement length. Data regarding demographic parameters, including body mass index (BMI), daytime sleepiness (by the Epworth Sleepiness Scale [ESS]), medical diseases, and current medication use were collected. Patients underwent PSG or Watch PAT twice; before and 3 months after the application of MAD.

Patients with the following conditions were excluded: central sleep apnea; regular use of

sedatives or narcotics; preexisting pulmonary or psychiatric diseases; and any contraindication for MAD such as poor teeth, periodontitis, and temporo-mandibular joint disorders. This study was approved by the Seoul National University Bundang Hospital Institutional Review Board, and the study was conducted according to the principles expressed in the Declaration of Helsinki.

Criteria of Treatment Success

The following six criteria for OSA treatment success which have been used in the literature were analyzed, as described in our previous study[14]: AHI < 10/h with MAD; AHI < 20/h with MAD; AHI < 10/h and AHI reduction of >50% with MAD; AHI < 15/h and AHI reduction of >50% with MAD; AHI < 20/h and AHI reduction of >50% with MAD; and AHI reduction of >50% with MAD. We added another criterion of AHI < 15/h with MAD, which is the cutoff AHI to differentiate mild from moderate OSA. Thereafter, patients were categorized into the success and failure groups based on each of the 7 criteria (Table 1).

Collection of Follow-up Data

Follow-up data were obtained via telephonic interviews using a specially designed questionnaire. For data on MAD compliance, time of use per night and number of nights per week were assessed. Good compliance was defined as the use of MAD > 4 h/night for ≥ 5 days/week.[15] Witnessed apnea and snoring were asked to score on a scale from 0 (no symptom) to 10 (very bad) and the ESS score was used to assess the likelihood of falling asleep in 8 different situations. In addition, occurrence of physician-diagnosed new-onset hypertension since commencement of MAD treatment was assessed based on electronic

medical system and telephonic interview.

Statistical Analysis

All statistical analyses were performed using SPSS version 18 (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as the mean ± standard deviation, and categorical variables are expressed as proportions. Paired *t*-tests were used to compare the sleep-related parameters before and after MAD application in all patients. Unpaired *t*-tests were used to examine the differences in witnessed apnea, snoring, and ESS score between the success and failure groups. A repeated-measures ANOVA was used to assess changes in variables from pretreatment to posttreatment between groups. Survival analysis was used to compare the time elapsed from MAD prescription to newly diagnosed hypertension between groups. Survival analysis was conducted using Kaplan-Meier survival curves. With regard to the posttreatment AHI value as a parameter for differentiating patients with new-onset hypertension from healthy subjects, sensitivity and specificity values for optimal cutoff were calculated using the receiver operating characteristic (ROC) curve. A P value < 0.05 was considered statistically significant.

RESULTS

A total of 97 patients (77 [79.4%] men and 20 [20.6%] women) were enrolled, and their characteristics are presented in Table 2. The mean follow-up duration was 60.5 ± 26.6 months (range, 8–107 months). The baseline age, BMI, and AHI was 50.8 ± 9.9 years (range, 19–68 years), 25.8 ± 2.8 kg/m^2, and 35.5 ± 19.8/h, respectively. According to Cartwright's criteria,[16] 90 patients had position-dependent OSA and 7 patients had position-independent OSA.

Short-term PSG Follow-up with MAD

Table 3 summarizes the sleep-related parameters before and 3 months after application of the MAD. After treatment, there was significant improvement in AHI ($P < 0.001$), apnea index ($P < 0.001$), supine AHI ($P < 0.001$), lateral AHI ($P = 0.004$), lowest O_2 saturation ($P < 0.001$), oxygen desaturation index ($P < 0.001$), and the percentage of sleep time with snoring ($P < 0.001$).

Long-term Symptomatic Changes

Table 4 shows the changes in witnessed apnea, snoring, and ESS after MAD treatment in the success and failure groups according to the 7 criteria. The highest rate of treatment success was 74.2% (72/97 patients) when using criterion 3 (AHI < 20/h with MAD) and lowest at 45.4% (45/97 patients) when using criterion 4 (AHI < 10/h with MAD and AHI reduction of >50%).

With criteria 2 (AHI < 15/h with MAD), 3 (AHI < 20/h with MAD), and 5 (AHI < 15/h with MAD and AHI reduction of >50%), there was no significant difference in the improvement of symptoms between the success and failure groups. With criteria 6 (AHI reduction of >50% with MAD) and 7 (AHI < 20/h with MAD and AHI reduction of >50%), only ESS improved to a larger extent than that in the success group. In contrast, there was a significantly larger improvement in the witnessed apnea, snoring, and ESS from pretreatment to posttreatment in the success group as compared to the failure group when using criterion 1 (AHI < 10/h with MAD) and criterion 4 (AHI < 10/h with MAD and AHI reduction of >50%).

Survival Analysis for New-onset Hypertension

Among the 97 patients, 34 (35.1%) had hypertension before treatment and 7 patients were newly diagnosed with hypertension during the follow-up. Kaplan-Meier survival analysis showed that criterion 2 (AHI < 15/h with MAD) could significantly differentiate between success and failure on the basis of new-onset hypertension ($P = 0.045$) (Fig. 1).

ROC Curve Analysis for New-onset Hypertension

For assuming posttreatment AHI value as a parameter differentiating patient with new-onset hypertension from healthy ones, the ROC curve analysis indicated that the cutoff AHI was 16.8/h, with an area under the curve of 0.704 ($P = 0.080$), a sensitivity of 71.4%, and a specificity of 75.0% (Fig. 2).

DISCUSSION

To our knowledge, this is the first study to identify adequate criteria to determine the success or failure of MAD as a treatment based on long-term symptom improvement and occurrence of new-onset hypertension in OSA. The most commonly used criterion for surgical success for OSA is postoperative AHI < 20/h and AHI reduction of > 50%.[17] CPAP therapy is a standard treatment of OSA and considered to be successful if the AHI reduces to < 5/h with CPAP.[18] Although MAD is one of the treatment options of OSA, there is no standardized criterion to define successful outcome of MAD treatment. Although one study emphasized the need to establish a uniform definition of treatment success of OSA by using the MAD, they did not suggest an adequate criterion.[13]

Generally, the effectiveness of treatments for OSA is reported as change in AHI. However, it

is unclear whether symptoms or co-morbidities persist when AHI is improved by such treatment. Recent evidence indicates that there is no correlation between AHI and clinical outcomes[19-21] and emphasizes subjective sleepiness, snoring, quality of life, and prevention of deleterious effects on comorbidities. Furthermore, several studies have demonstrated a discrepancy between statistically significant outcomes and clinically relevant outcomes. One review[22] highlighted the importance of "highly effective treatment" over "sub-therapeutic treatment" as a necessity for improved health outcomes in OSA. Thus, we focused on the long-term sleep-related symptomatic changes and occurrence of new-onset hypertension.

We found that two success criteria based on the AHI change with MAD —AHI < 10/h with MAD and AHI < 10/h with MAD and AHI reduction of >50%— could differentiate between success and failure on the basis of all three long-term OSA-related symptoms such as witnessed apnea, snoring, and daytime sleepiness. Given that PSG-based assessment of treatment response may not always agree with subjective improvement experienced by patients, these criteria may be helpful when sleep doctors interpret subjective symptomatic changes after application of MAD.

This study also showed that the criterion of AHI < 15/h with MAD differentiated success from failure on the basis of new-onset hypertension. OSA is known to be an independent risk factor for the development of hypertension.[5, 23, 24] In contrast, in a sleep heart health cohort study, sleep-disordered breathing was a not a significant independent predictor of incident hypertension after adjusting for BMI. However, in a subgroup analysis, sleep-disordered breathing predicted future hypertension among women and less obese persons (BMI ≤27.3 kg/m^2).[25] In our study, all patients were Asians, who are generally less obese than the Western population. A meta-analysis showed that MAD treatment for OSA

improves blood pressure control and suggested that blood pressure reduction may portend significant risk reduction for prevalent comorbidities such as hypertension.[12] A recent study reported that the effects of an adjustable MAD were not significantly different to CPAP in terms of 24-h mean ambulatory blood pressure, daytime sleepiness, and disease-specific and general quality of life.[26] Furthermore, the latest guideline for oral appliance use in OSA by the American Academy of Sleep Medicine (AASM) and American Academy of Dental Sleep Medicine (AADSM) shows a modest impact on reducing blood pressure.[27]

In the current study, nearly half of the patients had severe OSA. The guideline of the AASM on OSA treatment suggests that MAD should primarily be used in patients with mild-to-moderate OSA.[9] However, in a previous study, patients with severe OSA had comparable successful outcomes to those with moderate OSA who received MAD treatment.[28] In particular, in the group with moderate-to-severe OSA, patients with position-dependent OSA had better treatment outcomes with an MAD than patients with position-independent OSA.[29] In present study, most patients (92.8%) had position-dependent OSA. In addition, recent meta-analysis by AASM/AADSM showed significant efficacy across all level of OSA severity in adult patients using oral appliance.[27]

However, our study was limited in its telephonic interview-based study design. There was a period between the follow-up sleep apnea/hypopnea test and the telephonic interview. The efficacy of the MAD may be changed or there may be some other changes in body weight or compliance that may influence the symptomatic benefit. Therefore, we adjusted the effects for the age, sex, body mass index, and compliance in the statistical analyses. In this study, diagnosis of hypertension was estimated based on a physician diagnosed disease. However, even in sleep heart health study, they reported the association between sleep disordered

breathing and self-reported cardiovascular disease.[6] In addition, subjective compliance was assessed using self-report. Objective compliance can be measured when using MAD that embedded temperature-sensitive microsensor. However, a previous study has reported a high agreement between self-reported and objectively measured compliance.[30] Considering that most previous studies have focused on simple comparisons between AHI without or with MAD, this study may have another clinical implication, as it highlights the relationships between the AHI changes with MAD and long-term symptoms improvement or occurrence of one of medical comorbidities.

In conclusion, the present study demonstrated that AHI < 10/h with MAD or AHI < 10/h and AHI reduction of >50% with MAD may be useful as criteria to distinguish successful patients from unsuccessful ones on the basis of long-term symptom improvement. In addition, AHI < 15/h with MAD may be a criterion to differentiate between success and failure groups on the basis of new-onset hypertension. Future prospective studies are warranted to validate our proposed success criteria.

Contributors: JH Wee, CS Rhee, and JW Kim conceived the study design. JH Lim and J Gelera coordinated the study. JH Wee and JH Lim completed data collection and made the statistical analysis. JH Wee and JW Kim conducted interpretation of results and drafted the manuscript. CS Rhee and JW Kim revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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FIGURE LEGENDS

Figure 1. Kaplan-Meier survival curves for new-onset of hypertension in success and failure groups.

Figure 2. Receiver operating characteristic curve of apnea hypopnea index with mandibular advancement device for new-onset of hypertension.

TABLES

Table 1. The criteria for success of OSA treatment

Criteria	Definition of success
Criterion 1	AHI < 10/h with MAD
Criterion 2	AHI < 15/h with MAD
Criterion 3	AHI < 20/h with MAD
Criterion 4	AHI < 10/h and AHI reduction of > 50% with MAD
Criterion 5	AHI < 15/h and AHI reduction of > 50% with MAD
Criterion 6	AHI < 20/h and AHI reduction or > 50% with MAD
Criterion 7	AHI reduction of > 50% with MAD

AHI, apnea hypopnea index; MAD, mandibular advancement device

Table 2. Characteristics of 97 subjects treated with a mandibular advancement device

Characteristics	Measure at Baseline
Sex, n (%)	
Male	77 (79.4)
Female	20 (20.6)
Age, years, mean (SD)	50.8 (9.9)
BMI, kg/m^2, mean (SD)	25.8 (2.8)
Follow up duration, months, mean (SD)	60.5 (26.6)
Compliance, n (%)	
Good	20 (20.6)
Poor	77 (79.4)
Apnea-hypopnea index, mean (SD)	35.5 (19.8)
Severity Categories, n (%)	
None (0 - 4.9 events/h)	0 (0.0)
Mild (5 -14.9 events/h)	11 (11.3)
Moderate (15 -29.9 events/h)	38 (39.2)
Severe (≥ 30 events/h)	48 (49.5)
Positional dependency, n (%)	
Position-dependent OSA	90 (92.8)
Position-nondependent OSA	7 (7.2)

SD, standard deviation; BMI, body mass index; OSA, obstructive sleep apnea

Table 3. Changes in the sleep-related parameters before and after treatment with a mandibular advancement device

Polysomnographic index, mean (SD)	Baseline	After treatment	*P-value
Apnea-hypopnea index (/hour)	35.5 (19.8)	15.2 (13.7)	< 0.001
Apnea index (/hour)	26.8 (20.1)	7.7 (10.8)	< 0.001
Supine apnea-hypopnea index (/hour)	50.1 (23.5)	20.1 (19.8)	< 0.001
Lateral apnea-hypopnea index (/hour)	8.1 (15.1)	3.5 (8.6)	0.004
Lowest O_2 saturation (%)	78.0 (10.8)	83.3 (7.6)	< 0.001
Oxygen desaturation index (/hour)	28.7 (19.6)	11.4 (12.3)	< 0.001
Snoring (%)	36.1 (18.1)	27.4 (21.6)	< 0.001

SD, standard deviation; * P-value for the paired t-test

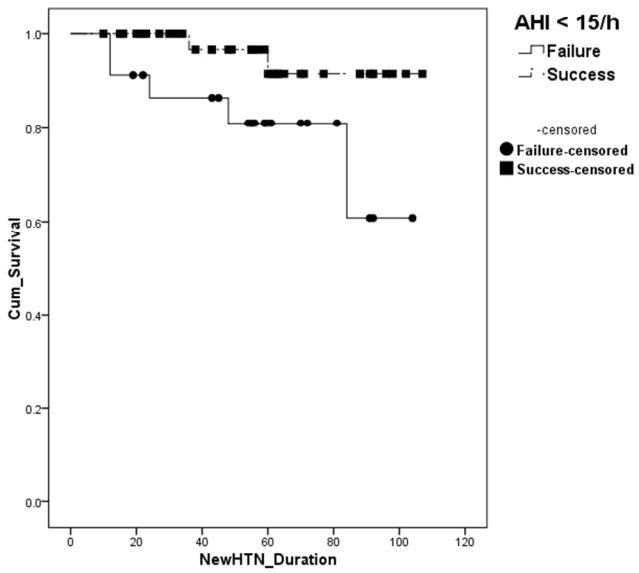
Table 4. Change in the witnessed apnea, snoring, and Epworth sleepiness scale score after mandibular advancement device treatment in the success and failure groups according to the 7 criteria

Criteria	No.	Witnessed Apnea			Witnessed Snoring			Epworth sleepiness scale		
		Pre MAD	Post MAD	*P*-value†	Pre MAD	Post MAD	*P*-value†	Pre MAD	Post MAD	*P*-value†
AHI < 10/h with MAD										
Success	45	6.64	2.82*		6.96	2.93*		8.60*	3.90*	
Failure	52	6.83	3.63*	0.047†	7.29	3.92*	0.022†	11.26*	6.50*	0.003†
AHI < 15/h with MAD										
Success	60	6.75	3.13		7.07	3.25		9.59	4.65*	
Failure	37	6.73	3.46	0.999	7.24	3.81	0.671	10.75	6.38*	0.524
AHI < 20/h with MAD										
Success	72	6.74	3.10		7.13	3.38		9.81	4.89	
Failure	25	6.76	3.72	0.534	7.16	3.72	0.717	10.61	6.39	0.688
AHI < 10/h with MAD & AHI reduction of > 50%										
Success	44	6.64	2.77*		6.95	2.89*		8.64*	3.59*	
Failure	53	6.83	3.66*	0.033†	7.28	3.94*	0.016†	11.17*	6.70*	0.001†
AHI < 15/h with MAD & AHI reduction of > 50%										
Success	59	6.78	3.14		7.03	3.24		9.43	4.58*	
Failure	39	6.68	3.45	0.793	7.29	3.82	0.528	10.97	6.42*	0.295
AHI < 20/h with MAD & AHI reduction of > 50%										
Success	61	6.77	2.95*		7.13	3.16*		9.54	4.24*	
Failure	36	6.69	3.78*	0.240	7.14	3.97*	0.322	10.84	7.06*	0.033†
AHI reduction of > 50% with MAD										
Success	66	6.79	3.02		7.12	3.20*		9.59	4.20*	
Failure	31	6.65	3.77	0.391	7.16	4.03*	0.252	10.79	7.67*	0.009†

* *P*-value < 0.05 for the unpaired t-test

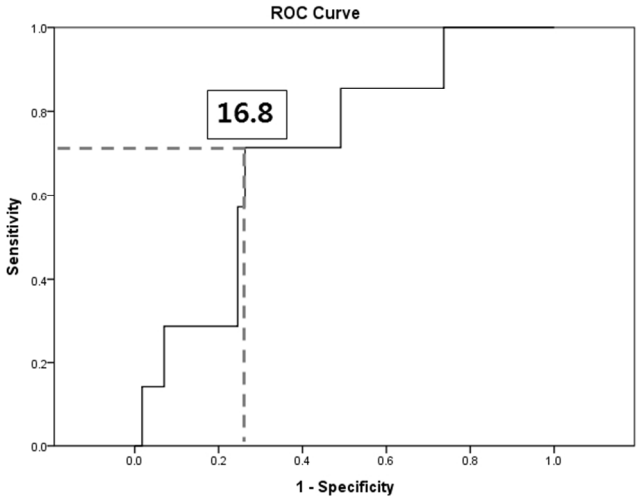
† *P*-value < 0.05 for the repeated measure ANOVA (adjusted for the age, sex, body mass index, and compliance)

MAD, mandibular advancement device; AHI, apnea hypopnea index



Kaplan-Meier survival curves for new-onset of hypertension in success and failure groups.

254x190mm (96 x 96 DPI)



Receiver operating characteristic curve of apnea hypopnea index with mandibular advancement device for new-onset of hypertension.

254x190mm (96 x 96 DPI)

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A Comparison of Success Criteria based on Long-Term Symptoms and New-onset Hypertension in Mandibular Advancement Device Treatment for Obstructive Sleep Apnea: Observational Cohort Study

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A Comparison of Success Criteria based on Long-Term Symptoms and New-onset Hypertension in Mandibular Advancement Device Treatment for Obstructive Sleep Apnea: Observational Cohort Study

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Abstract

Objective: To identify adequate criteria to determine the success or failure of mandibular advancement device (MAD) treatment for obstructive sleep apnea (OSA) based on long-term symptoms and new-onset hypertension.

Design: Observational cohort study

Setting: A tertiary care hospital setting in South Korea

Participants: Patients (age > 18 years) who were diagnosed with OSA by a polysomnography (PSG) or Watch peripheral arterial tonometry (PAT), and who had been treated with MAD between January 2007 and December 2014 were enrolled.

Primary and secondary outcome measures: Patients underwent PSG or Watch PAT twice; before and 3 months after the application of MAD. The patients were categorized into success and failure groups using 7 different criteria. MAD compliance, witnessed apnea and snoring, Epworth sleepiness scale score, and occurrence of new-onset hypertension were surveyed via telephonic interview to determine the criteria that could identify success and failure of MAD.

Results: A total of 97 patients were included. The mean follow-up duration was 60.5 months, and the mean apnea-hypopnea index (AHI) was 35.5/h. Two of the 7 criteria could significantly differentiate the success and failure groups based on long-term symptoms, including (1) AHI < 10/h with MAD, and (2) AHI < 10/h and AHI reduction of >50% with MAD. Kaplan-Meier survival analysis showed that one criterion of AHI < 15/h with MAD could differentiate the success and failure groups based on new-onset hypertension (P = 0.035). The receiver operating characteristic curve analysis indicated that the cutoff AHI for new-onset hypertension was 16.8/h (71.4% sensitivity and 75.0% specificity).

Conclusion: Our long-term follow-up survey for symptoms and new-onset hypertension

suggested that some of the polysomnographical success criteria, i.e., AHI < 10/h with MAD, AHI < 10/h and AHI reduction of >50% with MAD, and AHI < 15/h with MAD may be useful in distinguishing the success group from failure one. Further prospective longitudinal studies are warranted to validate these criteria.

Key Words: Obstructive sleep apnea, Mandibular advancement, Hypertension

Strengths and limitations of this study

- Strength of this study is that observational cohort study to identify the optimal polysomnographic success criteria for mandibular advancement device treatment based on long-term subjective symptom changes or occurrence of new-onset hypertension.
- This study was limited in its telephonic interview-based study design.
- Diagnosis of hypertension was estimated based on a physician diagnosed disease.
- Potential interviewer bias and respondent's recall bias may exist.

INTRODUCTION

Obstructive sleep apnea (OSA) is associated with many chronic diseases[1] such as cardiovascular diseases,[2] cerebrovascular diseases,[3] metabolic syndrome,[4] and neurocognitive dysfunction.[5] Furthermore, it may be a risk factor for the future development of hypertension.[6, 7] A short-term randomized controlled trial showed that continuous positive airway pressure (CPAP) treatment for OSA reduces cardiovascular morbidity.[8] Therefore, it is important to focus on effective treatments for OSA to reduce its associated comorbidities.

The mandibular advancement device (MAD) is generally indicated for use in patients with mild-to-moderate OSA.[9] However, MAD treatment is not always inferior to CPAP therapy, and has been reported to show better compliance than CPAP.[10, 11] MAD treatment has shown beneficial effects on the number of obstructive breathing events, arterial oxygen saturation levels, and arousal frequency.[12] Furthermore, meta-analysis of several observational and randomized controlled trials showed that MAD reduces blood pressure in patients with OSA.[13, 14] Although MAD is frequently prescribed by sleep specialists due to its efficacy, there is no validated standard criterion for determining the success or failure of this treatment for OSA based on long-term subjective symptomatic improvement or occurrence of medical comorbidities. Theoretically, an apnea-hypopnea index (AHI) < 15 or AHI < 5 without symptoms such as witnessed snoring, apnea, and daytime sleepiness are required for treatment success. However, these polysomnography (PSG)-based definitions of success do not always agree with subjective improvement experienced by patients. Furthermore, the literature provides various criteria for defining treatment success. One recent study reported that the success rate of OSA treatment with MAD can vary remarkably according to the success criteria.[15] However, success or failure cannot be defined by PSG findings alone. A

long-term observation of symptom improvement or occurrence of complications is necessary to identify the relationship between success/failure and PSG findings with MAD.

To the best of our knowledge, no long-term follow-up study based on subjective symptom changes or occurrence of new-onset hypertension has thus far identified the optimal PSG success criteria for MAD treatment. Therefore, in the present study, we aimed to determine adequate success criteria for MAD treatment of OSA on the basis of long-term symptoms and occurrence of new-onset hypertension.

METHODS

Patients

This observational cohort study included consecutive patients (age > 18 years) who were diagnosed with OSA (AHI ≥ 5/h and symptoms of snoring, fragmented sleep, witnessed apnea, or daytime sleepiness) by an attended, full-night, in-laboratory PSG or Watch peripheral arterial tonometry (PAT), and who had been treated with MAD at our sleep clinic between January 2007 and December 2014. The MAD was designed to hold the mandible fixed at 60% of the maximum protrusion. All the patients were regularly followed up to evaluate any dental or temporomandibular joint problems and to adjust the advancement length. Data regarding demographic parameters, including body mass index (BMI), daytime sleepiness (by the Epworth Sleepiness Scale [ESS]), medical diseases, and current medication use were collected. Blood pressure was measured at the start of MAD treatment. Patients underwent PSG or Watch PAT twice; before and 3 months after the application of MAD.

Patients with the following conditions were excluded for MAD treatment: central sleep apnea; regular use of sedatives or narcotics; preexisting pulmonary or psychiatric diseases;

and any contraindication for MAD such as poor teeth, periodontitis, and temporo-mandibular joint disorders. Patients who were not available for telephone interviews or have missing data for any of the variables were excluded from the study. This study was approved by the Seoul National University Bundang Hospital Institutional Review Board, and the study was conducted according to the principles expressed in the Declaration of Helsinki.

Criteria of Treatment Success

The following six criteria for OSA treatment success which have been used in the literature were analyzed, as described in our previous study[16]: AHI < 10/h with MAD; AHI < 20/h with MAD; AHI < 10/h and AHI reduction of >50% with MAD; AHI < 15/h and AHI reduction of >50% with MAD; AHI < 20/h and AHI reduction of >50% with MAD; and AHI reduction of >50% with MAD. We added another criterion of AHI < 15/h with MAD, which is the cutoff AHI to differentiate mild from moderate OSA. Thereafter, patients were categorized into the success and failure groups based on each of the 7 criteria (Table 1).

Collection of Follow-up Data

Follow-up data were obtained via telephonic interviews using a specially designed questionnaire. Telephonic interview was performed at least twice for each patient with the same questionnaires to confirm their answers. For data on MAD compliance, time of use per night and number of nights per week were assessed. Good compliance was defined as the use of MAD > 4 h/night for ≥ 5 days/week.[17] Witnessed apnea and snoring were asked to score on a scale from 0 (no symptom) to 10 (very bad) and the ESS score was used to assess the likelihood of falling asleep in 8 different situations. In addition, occurrence of physician-

diagnosed new-onset hypertension and anti-hypertensive medications since commencement of MAD treatment was assessed based on longitudinal review of our electronic medical system and telephonic interview.

Statistical Analysis

All statistical analyses were performed using SPSS version 18 (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as the mean ± standard deviation, and categorical variables are expressed as proportions. Paired *t*-tests were used to compare the sleep-related parameters before and after MAD application in all patients. Unpaired *t*-tests were used to examine the differences in witnessed apnea, snoring, and ESS score between the success and failure groups. A repeated-measure ANOVA was used to assess changes in variables from pretreatment to posttreatment between groups. Survival analysis was used to compare the time elapsed from MAD prescription to newly diagnosed hypertension between groups. Survival analysis was conducted using Kaplan-Meier survival curves. With regard to the posttreatment AHI value as a parameter for differentiating patients with new-onset hypertension from healthy subjects, sensitivity and specificity values for optimal cutoff were calculated using the receiver operating characteristic (ROC) curve. A P value < 0.05 was considered statistically significant.

Patient and Public involvement

Patients were not involved in setting the research question and in the design of the study. We introduced the purpose of this research to the patients. Informed consents were sought from all the participants. All the participants completed this survey on the voluntary basis. Small

gifts were given to the participants who completed this telephonic interview. No patient was asked for advice on interpretation or writing up of results. The results of the research will not be disseminated to the patients.

RESULTS

Out of 214 MAD-treated patients who underwent the follow-up sleep study, 107 were not available for telephone interviews because of phone number change or rejection or had missing data. Thus, a total of 97 patients (77 [79.4%] men and 20 [20.6%] women) were enrolled, and their characteristics are presented in Table 2. The baseline age, BMI, and AHI was 50.8 ± 9.9 years (range, 19–68 years), 25.8 ± 2.8 kg/m^2, and 35.5 ± 19.8/h, respectively. According to Cartwright's criteria,[18] 90 patients had position-dependent OSA and 7 patients had position-independent OSA.

Short-term PSG Follow-up with MAD

Table 3 summarizes the sleep-related parameters before and 3 months after application of the MAD. After treatment, there was significant improvement in AHI ($P < 0.001$), apnea index ($P < 0.001$), supine AHI ($P < 0.001$), lateral AHI ($P = 0.004$), lowest O_2 saturation ($P < 0.001$), oxygen desaturation index ($P < 0.001$), and the percentage of sleep time with snoring ($P < 0.001$).

Long-term Symptomatic Changes

The mean follow-up duration was 60.5 ± 26.6 months (range, 8–107 months). Table 4 shows the changes in witnessed apnea, snoring, and ESS after MAD treatment in the success and

failure groups according to the 7 criteria. The highest rate of treatment success was 74.2% (72/97 patients) when using criterion 3 (AHI < 20/h with MAD) and lowest at 45.4% (45/97 patients) when using criterion 4 (AHI < 10/h and AHI reduction of >50% with MAD).

Repeated-measure ANOVA analyses adjusted for age, sex, BMI, and compliance identified adequate criteria in determining the success or failure of MAD based on long-term symptom improvement. With criteria 2 (AHI < 15/h with MAD), 3 (AHI < 20/h with MAD), and 5 (AHI < 15/h and AHI reduction of >50% with MAD), there was no significant difference in the improvement of symptoms between the success and failure groups. With criteria 6 (AHI reduction of >50% with MAD) and 7 (AHI < 20/h and AHI reduction of >50% with MAD), only ESS improved to a larger extent than that in the success group. In contrast, there was a significantly larger improvement in the witnessed apnea, snoring, and ESS from pretreatment to posttreatment in the success group as compared to the failure group when using criterion 1 (AHI < 10/h with MAD) and criterion 4 (AHI < 10/h and AHI reduction of >50% with MAD).

Survival Analysis for New-onset Hypertension

Among the 97 patients, 34 (35.1%) had hypertension before treatment and 7 patients were newly diagnosed with hypertension during the follow-up and all of the 7 patients showed poor compliance. Kaplan-Meier survival analyses were performed for all the 7 success criteria and the analysis showed that only criterion 2 (AHI < 15/h with MAD) could significantly differentiate between success and failure on the basis of new-onset hypertension ($P = 0.045$) (Fig. 1).

ROC Curve Analysis for New-onset Hypertension

For assuming posttreatment AHI value as a parameter differentiating patient with new-onset hypertension from healthy ones, the ROC curve analysis indicated that the cutoff AHI was 16.8/h, with an area under the curve of 0.704 ($P = 0.080$), a sensitivity of 71.4%, and a specificity of 75.0% (Fig. 2).

DISCUSSION

To our knowledge, this is the first study to identify adequate criteria to determine the success or failure of MAD as a treatment based on long-term symptom improvement and occurrence of new-onset hypertension in OSA. The most commonly used criterion for surgical success for OSA is postoperative AHI < 20/h and AHI reduction of > 50%.[19] CPAP therapy is a standard treatment of OSA and considered to be successful if the AHI reduces to < 5/h with CPAP.[20] Although MAD is one of the treatment options of OSA, there is no standardized criterion to define successful outcome of MAD treatment. Although one study emphasized the need to establish a uniform definition of treatment success of OSA by using the MAD, they did not suggest an adequate criterion.[15]

Generally, the effectiveness of treatments for OSA is reported as change in AHI. However, it is unclear whether symptoms or co-morbidities persist when AHI is improved by such treatment. Recent evidence indicates that there is no correlation between AHI and clinical outcomes[21-23] and emphasizes subjective sleepiness, snoring, quality of life, and prevention of deleterious effects on comorbidities. Furthermore, several studies have demonstrated a discrepancy between statistically significant outcomes and clinically relevant outcomes. One review[24] highlighted the importance of "highly effective treatment" over "sub-therapeutic treatment" as a necessity for improved health outcomes in OSA. Thus, we focused on the

long-term sleep-related symptomatic changes and occurrence of new-onset hypertension.

We found that two success criteria based on the AHI change with MAD —AHI < 10/h with MAD and AHI < 10/h and AHI reduction of >50% with MAD — could differentiate between success and failure on the basis of all three long-term OSA-related symptoms such as witnessed apnea, snoring, and daytime sleepiness. Given that PSG-based assessment of treatment response may not always agree with subjective improvement experienced by patients, these criteria may be helpful when sleep doctors interpret subjective symptomatic changes after application of MAD.

This study also showed that the criterion of AHI < 15/h with MAD differentiated success from failure on the basis of new-onset hypertension. OSA is known to be an independent risk factor for the development of hypertension.[6, 25, 26] In contrast, in a sleep heart health cohort study, sleep-disordered breathing was a not a significant independent predictor of incident hypertension after adjusting for BMI. However, in a subgroup analysis, sleep-disordered breathing predicted future hypertension among women and less obese persons (BMI ≤27.3 kg/m^2).[27] In our study, all patients were Asians, who are generally less obese than the Western population. A meta-analysis showed that MAD treatment for OSA improves blood pressure control and suggested that blood pressure reduction may portend significant risk reduction for prevalent comorbidities such as hypertension.[13] A recent study reported that the effects of an adjustable MAD were not significantly different to CPAP in terms of 24-h mean ambulatory blood pressure, daytime sleepiness, and disease-specific and general quality of life.[11] Furthermore, the latest guideline for oral appliance use in OSA by the American Academy of Sleep Medicine (AASM) and American Academy of Dental Sleep Medicine (AADSM) shows a modest impact on reducing blood pressure.[12]

In the current study, nearly half of the patients had severe OSA. The guideline of the AASM on OSA treatment suggests that MAD should primarily be used in patients with mild-to-moderate OSA.[10] However, in a previous study, patients with severe OSA had comparable successful outcomes to those with moderate OSA who received MAD treatment.[28] In particular, in the group with moderate-to-severe OSA, patients with position-dependent OSA had better treatment outcomes with an MAD than patients with position-independent OSA.[29] In present study, most patients (92.8%) had position-dependent OSA. In addition, recent meta-analysis by AASM/AADSM showed significant efficacy across all level of OSA severity in adult patients using oral appliance.[12]

However, our study was limited in its telephonic interview-based study design. There was a period between the follow-up sleep apnea/hypopnea test and the telephonic interview. Potential interviewer bias and respondent's recall bias may exist. The efficacy of the MAD may be changed or there may be some other changes in body weight or compliance that may influence the symptomatic benefit. Therefore, we adjusted the effects for the age, sex, body mass index, and compliance in the statistical analyses. In this study, diagnosis of hypertension was estimated based on a physician diagnosed disease. However, even in sleep heart health study, they reported the association between sleep disordered breathing and self-reported cardiovascular disease.[7] In addition, subjective compliance was assessed using self-report. Objective compliance can be measured when using MAD that embedded temperature-sensitive microsensor. However, a previous study has reported a high agreement between self-reported and objectively measured compliance.[30] Considering that most previous studies have focused on simple comparisons between AHI without or with MAD, this study may have another clinical implication, as it highlights the relationships between the AHI changes

with MAD and long-term symptoms improvement or occurrence of one of medical comorbidities. Patients underwent PSG or Watch PAT. Although the same sleep studies were performed for pre- and post-treatment in terms of each patient, there is still a limitation in the reliability of using Watch PAT. A previous study showed that Watch PAT has a limited value in detecting mild OSA while it is useful in detecting moderate to severe OSA.[31]

In conclusion, the present study demonstrated that AHI < 10/h with MAD or AHI < 10/h and AHI reduction of >50% with MAD may be useful as criteria to distinguish successful patients from unsuccessful ones on the basis of long-term symptom improvement. In addition, AHI < 15/h with MAD may be a criterion to differentiate between success and failure groups on the basis of new-onset hypertension. Future prospective studies are warranted to validate our proposed success criteria.

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Contributors: JH Wee, CS Rhee, and JW Kim conceived the study design. JH Lim and J Gelera coordinated the study. JH Wee and JH Lim completed data collection and made the statistical analysis. JH Wee and JW Kim conducted interpretation of results and drafted the manuscript. CS Rhee and JW Kim revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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FIGURE LEGENDS

Figure 1. Kaplan-Meier survival curves for new-onset of hypertension in success and failure groups.

Figure 2. Receiver operating characteristic curve of apnea hypopnea index with mandibular advancement device for new-onset of hypertension.

TABLES

Table 1. The criteria for success of OSA treatment

Criteria	Definition of success
Criterion 1	AHI < 10/h with MAD
Criterion 2	AHI < 15/h with MAD
Criterion 3	AHI < 20/h with MAD
Criterion 4	AHI < 10/h and AHI reduction of > 50% with MAD
Criterion 5	AHI < 15/h and AHI reduction of > 50% with MAD
Criterion 6	AHI < 20/h and AHI reduction or > 50% with MAD
Criterion 7	AHI reduction of > 50% with MAD

AHI, apnea hypopnea index; MAD, mandibular advancement device

Table 2. Characteristics of 97 subjects treated with a mandibular advancement device

Characteristics	Measure at Baseline
Sex, n (%)	
Male	77 (79.4)
Female	20 (20.6)
Age, years, mean (SD)	50.8 (9.9)
BMI, kg/m^2, mean (SD)	25.8 (2.8)
Follow up duration, months, mean (SD)	60.5 (26.6)
Compliance, n (%)	
Good	20 (20.6)
Poor	77 (79.4)
Apnea-hypopnea index, mean (SD)	35.5 (19.8)
Severity Categories, n (%)	
None (0 - 4.9 events/h)	0 (0.0)
Mild (5 -14.9 events/h)	11 (11.3)
Moderate (15 -29.9 events/h)	38 (39.2)
Severe (≥ 30 events/h)	48 (49.5)
Positional dependency, n (%)	
Position-dependent OSA	90 (92.8)
Position-nondependent OSA	7 (7.2)

SD, standard deviation; BMI, body mass index; OSA, obstructive sleep apnea

Table 3. Changes in the sleep-related parameters before and after treatment with a mandibular advancement device

Polysomnographic index, mean (SD)	Baseline	After treatment	*P-value
Apnea-hypopnea index (/hour)	35.5 (19.8)	15.2 (13.7)	< 0.001
Apnea index (/hour)	26.8 (20.1)	7.7 (10.8)	< 0.001
Supine apnea-hypopnea index (/hour)	50.1 (23.5)	20.1 (19.8)	< 0.001
Lateral apnea-hypopnea index (/hour)	8.1 (15.1)	3.5 (8.6)	0.004
Lowest O_2 saturation (%)	78.0 (10.8)	83.3 (7.6)	< 0.001
Oxygen desaturation index (/hour)	28.7 (19.6)	11.4 (12.3)	< 0.001
Snoring (%)	36.1 (18.1)	27.4 (21.6)	< 0.001

SD, standard deviation; * P-value for the paired t-test

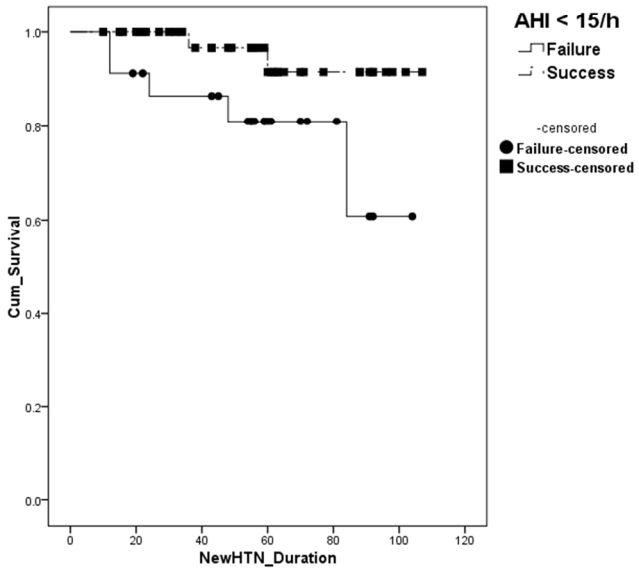
Table 4. Change in the witnessed apnea, snoring, and Epworth sleepiness scale score after mandibular advancement device treatment in the success and failure groups according to the 7 criteria

Criteria	No.	Witnessed Apnea			Witnessed Snoring			Epworth sleepiness scale		
		Pre MAD	Post MAD	*P*-value†	Pre MAD	Post MAD	*P*-value†	Pre MAD	Post MAD	*P*-value†
AHI < 10/h with MAD										
Success	45	6.64	2.82*		6.96	2.93*		8.60*	3.90*	
Failure	52	6.83	3.63*	0.047†	7.29	3.92*	0.022†	11.26*	6.50*	0.003†
AHI < 15/h with MAD										
Success	60	6.75	3.13		7.07	3.25		9.59	4.65*	
Failure	37	6.73	3.46	0.999	7.24	3.81	0.671	10.75	6.38*	0.524
AHI < 20/h with MAD										
Success	72	6.74	3.10		7.13	3.38		9.81	4.89	
Failure	25	6.76	3.72	0.534	7.16	3.72	0.717	10.61	6.39	0.688
AHI < 10/h & AHI reduction of > 50% with MAD										
Success	44	6.64	2.77*		6.95	2.89*		8.64*	3.59*	
Failure	53	6.83	3.66*	0.033†	7.28	3.94*	0.016†	11.17*	6.70*	0.001†
AHI < 15/h & AHI reduction of > 50% with MAD										
Success	59	6.78	3.14		7.03	3.24		9.43	4.58*	
Failure	39	6.68	3.45	0.793	7.29	3.82	0.528	10.97	6.42*	0.295
AHI < 20/h & AHI reduction of > 50% with MAD										
Success	61	6.77	2.95*		7.13	3.16*		9.54	4.24*	
Failure	36	6.69	3.78*	0.240	7.14	3.97*	0.322	10.84	7.06*	0.033†
AHI reduction of > 50% with MAD										
Success	66	6.79	3.02		7.12	3.20*		9.59	4.20*	
Failure	31	6.65	3.77	0.391	7.16	4.03*	0.252	10.79	7.67*	0.009†

* *P*-value < 0.05 for the unpaired t-test

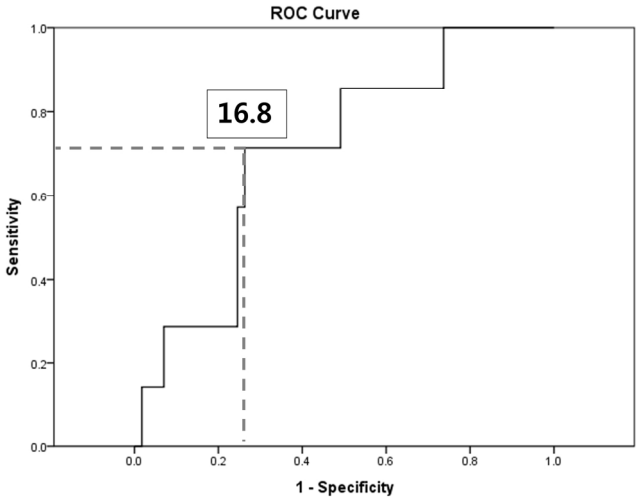
† *P*-value < 0.05 for the repeated measure ANOVA (adjusted for the age, sex, body mass index, and compliance)

MAD, mandibular advancement device; AHI, apnea hypopnea index



Kaplan-Meier survival curves for new-onset of hypertension in success and failure groups.

190x142mm (300 x 300 DPI)



Receiver operating characteristic curve of apnea hypopnea index with mandibular advancement device for new-onset of hypertension.

190x142mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Check Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 6
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 7
Methods			
Study design	4	Present key elements of study design early in the paper	Page 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 7-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 7-8
Bias	9	Describe any efforts to address potential sources of bias	Page 8
Study size	10	Explain how the study size was arrived at	Page 9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 9
		(*b*) Describe any methods used to examine subgroups and interactions	Page 9
		(*c*) Explain how missing data were addressed	Page 8-9
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	Page 9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 9
		(b) Give reasons for non-participation at each stage	Page 9
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 2
		(b) Indicate number of participants with missing data for each	Not

		variable of interest	applicable
		(c) Summarise follow-up time (eg, average and total amount)	Page 9-10
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 9-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 4
		(*b*) Report category boundaries when continuous variables were categorized	Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 11
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.