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ORIGINAL ARTICLE

Cardiovascular mortality in obstructive sleep apnoea treated with continuous positive airway pressure or oral appliance: An observational study

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ABSTRACT

Background and objective: **The objective of this study was to evaluate the long-term cardiovascular mortality in patients with severe obstructive sleep apnoea (OSA) treated with either continuous positive airway pressure (CPAP) or mandibular advancing device (MAD).**
Methods: **A non-concurrent cohort study of 570 subjects with severe OSA (apnoea/hypopnoea index (AHI) ≥ 30/h) and a control group of 269 subjects (AHI < 5/h) were followed up for a median of 79 months (interquartile range 76–88 months). All patients received CPAP initially. MAD was offered for those who were non-adherent to CPAP. The endpoint was cardiovascular death.**
Results: **Two hundred and eight control subjects, 177 patients treated with CPAP, 72 with MAD and 212 who declined treatment were analysed. Forty-two patients had a fatal cardiovascular event during the course of the study. The non-apnoeic group had the lowest cardiovascular death rate (0.28 per 100 person-years (95% confidence interval (CI): 0.08–0.71)) followed by the CPAP-treated (0.56 per 100 person-years (95% CI: 0.20–1.23)) and the MAD-treated OSA group (0.61 per 100 person-years (95% CI: 0.13–1.78)), with the highest cardiovascular mortality rate observed in the untreated OSA group (2.1 per 100 person-years (95% CI: 1.37–2.92)). Although residual AHI for MAD-treated patients was significantly higher than CPAP-treated patients (16.3 ± 5.1/h vs. 4.5 ± 2.3/h; $P < 0.001$), there was no difference in cardiovascular death rate between the two groups (hazard ratio 1.08 (95% CI: 0.55–1.74); $P = 0.71$).**
Conclusions: **Both CPAP and MAD may be equally effective therapy in reducing the risk of fatal cardiovascular events in patients with severe OSA.**

SUMMARY AT A GLANCE

This study suggests for the first time that oral appliances may confer reduction in cardiovascular mortality for patients with severe obstructive sleep apnoea intolerant to continuous positive airway pressure.

Key words: cardiovascular mortality, continuous positive airway pressure, obstructive sleep apnoea, oral appliance, outcome.

Abbreviations: CI, confidence interval; CPAP, continuous positive airway pressure; MAD, mandibular advancing device; OSA, obstructive sleep apnoea.

INTRODUCTION

Continuous positive airway pressure (CPAP) is the gold standard treatment for severe obstructive sleep apnoea (OSA). Randomized trials have shown CPAP benefits in daytime sleepiness, blood pressure, quality of life and endothelial dysfunction.[1–3] Large-scale studies have demonstrated that CPAP reduces also the risk of fatal and non-fatal cardiovascular events in severe OSA.[4,5] However, the clinical effectiveness of CPAP is often limited by poor patient and partner acceptance and suboptimal compliance.[6] Mandibular advancing device (MAD) therapy has emerged as a non-invasive alternative to CPAP for the treatment of snoring and mild to moderate OSA.[7,8] Although less efficacious than CPAP in ameliorating polysomnographic indices, oral appliances are generally more preferred by patients than CPAP.[9] Prospective studies have shown efficacy of MAD in reducing respiratory disturbance index, blood pressure, and improved sleepiness, sleep quality, and subject's and bed partner's satisfaction.[10–14] A major drawback of these clinical investigations is the limited

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participation of subjects with severe OSA. To our knowledge, the long-term impact of MAD versus CPAP treatment on the incidence of cardiovascular events in patients with severe OSA has not been delineated. We sought to investigate whether OA therapy is inferior to CPAP in reducing cardiovascular mortality in patients with severe OSA.

METHODS

Study population

This is a non-concurrent cohort study of subjects who frequented our sleep clinics at the Erie County Medical Center between February 2002 and January 2004. The sleep cohort comprised patients referred for evaluation of sleep-breathing disorders who had undergone an overnight polysomnography. Inclusion criteria were patients age 25–75 years with documented severe OSA by polysomnography (apnoea/hypopnoea index (AHI) $\geq$ 30/h). Exclusion criteria included previously diagnosed or treated patients with sleep apnoea, history of congestive heart failure or documented ejection fraction $\leq$40% by echocardiography or ventricular angiography, or predominance of central respiratory events (more than 50% recorded time). Patients with mild or moderate OSA (AHI (5/h–29/h)) were excluded from the analysis. Patients who had an upper airway surgery as a treatment for OSA were not included in the analysis. Subjects with AHI < 5/h constituted the control group. The study was approved by the local ethics committee, which waived the need for an informed consent.

Baseline assessment

Two physicians (M.A. and A.E.S.) examined all patients at baseline and during follow-up. Collected data included demographic, anthropometric and clinical characteristics, smoking status (current (more than 10 cigarettes per day) or past/never smoker), diabetes mellitus, hypertension (defined according to international guidelines[15] or through the use of antihypertensive drugs), hypercholesterolemia (defined as >250 mg/dL in blood serum or current use of lipid-lowering agents), medication use including antihypertensive drugs, lipid-lowering agents, antiplatelet therapy and anticoagulants.

Sleep studies

Full overnight polysomnography was done in according to international recommendations.[16] The AHI was calculated from the polysomnographic data, using widely accepted criteria.[17] The diagnosis of OSA was made if the sum of the obstructive apnoeas and hypopnoeas per hour was $\geq$5. Severity of OSA was judged from AHI data, and graded as mild OSA ($5 \leq$ AHI < 15/h), moderate OSA ($15 \leq$ AHI < 30/h) and severe OSA (AHI $\geq$ 30/h).

Follow-up

Once the diagnosis of OSA was established, nasal CPAP was prescribed to all patients following CPAP titration study. A respiratory therapist provided education about the basic operation and care of the PAP device and the mask. An educational brochure on OSA and CPAP treatment was given to each patient during the education session. The respiratory therapist would then select and fit a comfortable CPAP mask from a wide range of choices. All patients were followed up in our clinic at 1, 3 and 6 months during the first year and every 12 months thereafter. For those patients who were intolerant to CPAP, an oral appliance was prescribed except for those edentulous or with inadequate number of sound teeth, severe periodontitis and/or history of temporomandibular joint disease. Subjects received a custom-made MAD that has a maximum protrusion of 12 mm, in 0.25-mm increments. A repeat polysomnography was performed at the point of maximal advancement as tolerated by the patient to assess efficacy. During each visit, a standardized data collection form was completed to inquire about technical problems with the CPAP machine and monitor adherence, and record the occurrence and date of new vascular events.

Adherence with CPAP was defined as the use of the device for more than 4 h (at least 70% of the days) per night. If after a reinforcement period of 3 months, the patient was still non-adherent to CPAP, alternative therapy (oral appliance or upper airway surgery) was offered.

Clinical endpoints

The primary endpoint of this study was the occurrence of fatal cardiovascular events. Fatal events were defined as death from a stroke, myocardial infarction, sudden cardiac arrest or cardiac arrhythmias. Occurrence of these events was verified by reviewing the computerized records including emergency room visits and hospital discharges. Date, death and underlying contributory causes of death were obtained from medical records and the New York Vital Statistics. Vital status was further checked against the US Social Security Death Index and the National Death Index.

Statistical analysis

Data were expressed as means (SD) or medians (interquartile ranges). Normality was assessed by the Kolmogorov–Smirnov test. Chi-square analysis with Fisher's exact test (when appropriate) was used to compare categorical data. Continuous data were compared by using Student's *t*-test or the Mann–Whitney test. The Kaplan–Meier method was used to assess the association between sleep apnoea and occurrence of cardiovascular events based on the overall study population. Mortality curves were compared with the log-rank test. Variables with a significant unadjusted association with cardiovascular events ($P \leq 0.05$) were entered into a Cox regression analysis after forcing the entry of treatment groups as independent variables. Analyses were performed using StatView 5.0.1 (SAS Institute Inc., Cary, NC, USA) and SPSS 19.0 (SPSS Inc., Chicago, IL, USA) software. Statistical significance was defined as $P < 0.05$.

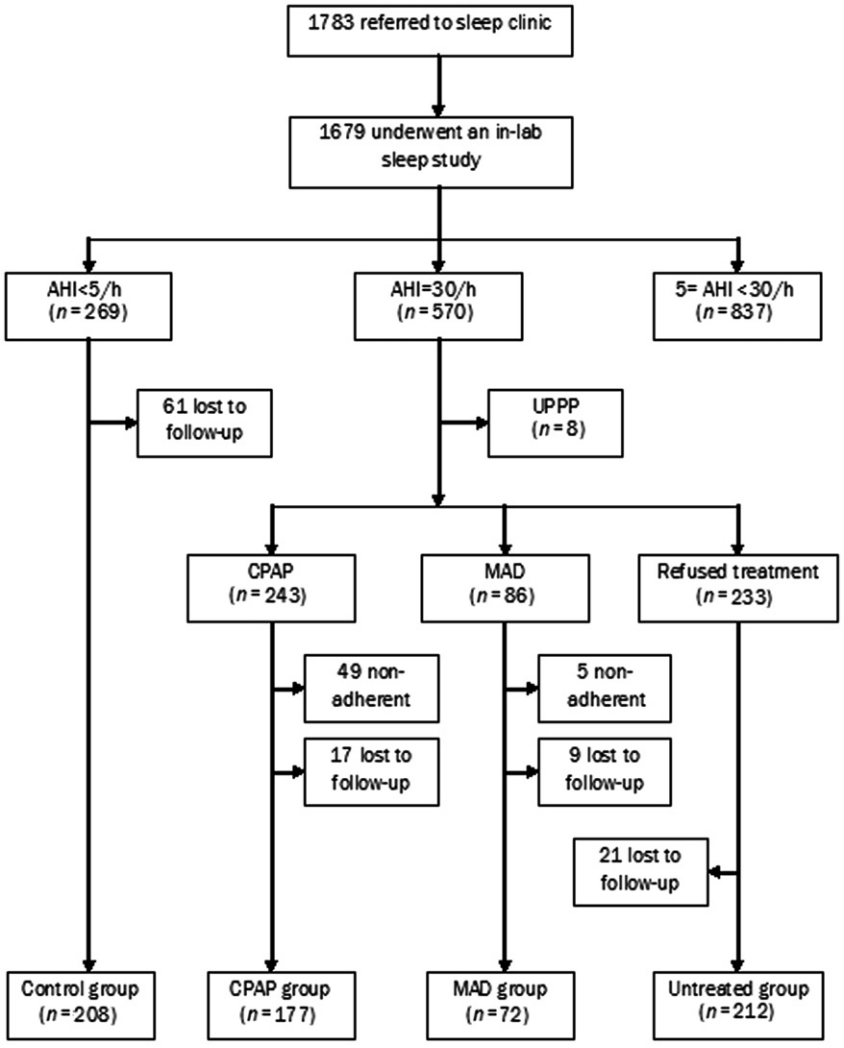

Figure 1 Study flow diagram. AHI, apnoea-hypopnoea index; CPAP, continuous positive airway pressure; MAD, mandibular advancing device.

RESULTS

Between February 2002 and January 2004, 1761 patients were referred to our sleep clinic for evaluation of sleep-disordered breathing. Fifty-eight were previously diagnosed with OSA, and 27 had left ventricular systolic dysfunction with left ventricular ejection fraction < 40%. Of the 1676 who underwent in-lab sleep study, 837 had mild to moderate OSA ($5 \leq$ AHI < 30/h), 570 were severe (AHI ≥ 30/h) and 296 did not meet the diagnostic criteria for OSA (Fig. 1). Out of 570 patients with severe sleep apnoea, eight underwent uvulopalatopharyngoplasty, and 562 received CPAP as initial treatment. After 3 months, 319 could not tolerate CPAP. Eighty-six were fitted with a MAD while 233 were either not a candidate for an oral appliance or refused further therapeutic intervention. During the course of the study, 47 patients with sleep apnoea and 61 without sleep-breathing disorders were lost for follow-up. In addition, 49 of the CPAP-treated group and 5 of the MAD-treated group were non-adherent to therapy and were excluded from the final analysis. The baseline characteristics of patients with and without complete follow-up were no different from the parent group (Table S1 in the online supporting information).

A total of 669 patients were included in the final analysis. These were classified into four study groups (control group without OSA, CPAP-treated group, MAD-treated group and untreated group). Table 1 shows the baseline characteristics of each study group. Patients with OSA were older and more obese, as reflected by the body mass index, than the non-apnoeic controls. As expected, the prevalence of hypertension, diabetes and lipid disorders was higher in those with OSA compared with those without sleep-breathing disorder; however, there was no difference in age, body mass index, AHI or prevalence of cardiovascular risk factors among the OSA groups. The mean optimal CPAP for each of the OSA groups during titration were 10.4 ± 3.1 cm H_2O for CPAP-treated, 10.3 ± 2.9 cm H_2O for MAD-treated and 10.3 ± 2.6 cm H_2O for untreated group. For those who were refitted with a MAD, the residual AHI following MAD titration was significantly higher compared with CPAP titration (16.3 ± 5.1/h vs. 4.5 ± 2.3/h; $P < 0.001$). Median follow-up of the cohort was 79 months (interquartile range 76–88 months). Patients treated with CPAP had a mean adherence of 5.8 ± 1.6 h per night while those treated with MAD had a reported mean adherence of 6.5 ± 1.2 h per night.

Table 1 Baseline characteristics of study population

	Non-apnoeic controls ($n = 208$)	Severe OSA treated with CPAP ($n = 177$)	Severe OSA treated with MAD ($n = 72$)	Untreated severe OSA ($n = 212$)
Age (years)*	46.8 (13.7)	51.6 (12.3)	50.8 (12.7)	50.3 (13.2)
Gender (M/F)	113/95	108/69	41/31	138/74
White race (%)	146 (70)	128 (73)	57 (79)	147 (69)
BMI (kg/m^2)*	32.7 (11.6)	37.0 (9.2)	37.1 (12.2)	36.6 (9.3)
Previous IHD (%)	12 (6)	20 (11)	11 (15)	26 (12)
Previous CVA (%)	0	2 (1)	3 (4)	3 (1)
Hypertension (%)*	79 (38)	101 (57)	37 (51)	116 (55)
Diabetes (%)*	22 (11)	37 (21)	14 (19)	37 (17)
Hyperlipidemia (%)*	51 (25)	69 (39)	24 (33)	73 (34)
Current smoking (%)	73 (35)	66 (37)	27 (38)	81 (38)
Lipid-lowering therapy (%)*	47 (23)	61 (34)	21 (29)	76 (36)
Antiplatelet therapy (%)	45 (22)	48 (27)	22 (31)	63 (29)
Epworth Sleepiness scale	9.6 (5.3)	11.5 (4.9)	10.2 (4.9)	10.4 (6.2)
AHI (events/h)*	2.6 (1.4)	44.8 (9.4)†	44.5 (7.7)‡	43.4 (8.6)§

Data are given as mean (SD) or *n* (%) unless otherwise indicated.

* $P < 0.05$ for comparisons of age, BMI, hypertension, hyperlipidemia, lipid-lowering therapy and AHI across groups.

† $P < 0.05$ for comparisons of severe OSA treated with CPAP and non-apnoeic controls.

‡ $P < 0.05$ for comparisons of severe OSA treated with MAD and non-apnoeic controls.

§ $P < 0.05$ for comparisons of untreated severe OSA and non-apnoeic controls.

AHI, apnoea/hypopnoea index; BMI, body mass index; CPAP, continuous positive airway pressure; CVA, cerebrovascular accident; IHD, ischaemic heart disease; MAD, mandibular advancing device; OSA, obstructive sleep apnoea.

Table 2 All-cause mortality in the study cohort

Causes of death, *n*	Non-apnoeic controls ($n = 208$)	Severe OSA treated with CPAP ($n = 177$)	Severe OSA treated with MAD ($n = 72$)	Untreated severe OSA ($n = 212$)
Cardiovascular	4 (1.9%)	6 (3.4%)	3 (4.2%)	29 (13.7%)
Respiratory failure	0	1 (0.5%)	1 (1.4%)	5 (2.4%)
Infection	1 (0.5%)	2 (1.1%)	0	3 (1.4%)
Cancer	1 (0.5%)	1 (0.5%)	2 (2.8%)	4 (1.9%)
Other	1 (0.5%)	3 (1.7%)	2 (2.8%)	1 (0.5%)

CPAP, continuous positive airway pressure; MAD, mandibular advancing device; OSA, obstructive sleep apnoea.

By the end of the study period, 42 patients (6.2%) had died of cardiovascular diseases and 28 (4.1%) of non-cardiovascular causes (Table 2). Among patients with OSA, 38 died from causes attributed to cardiovascular events (8.2%). The non-apnoeic group had the lowest cardiovascular death rate (0.28 per 100 person-years (95% CI: 0.08–0.71)) followed by the CPAP-treated (0.56 per 100 person-years (95% CI: 0.20–1.23)) and the MAD-treated OSA group (0.61 per 100 person-years (95% CI: 0.13–1.78)), with the highest cardiovascular mortality rate observed in the untreated OSA group (2.1 per 100 person-years (95% CI: 1.37–2.92)) (Table 3). Cardiovascular death was significantly higher in the untreated OSA group than the non-apnoeic group ($P < 0.001$), including death because of myocardial infarction or stroke. Cumulative cardiovascular mortality was also significantly higher in the untreated OSA group compared with CPAP-treated and the MAD-treated group, ($P < 0.001$ and $P = 0.047$, respectively). However, the cumulative cardiovascular mortality in the CPAP-treated and the MAD-treated groups were similar to those of the non-apnoeic controls ($P = 0.21$ and $P = 0.29$, respectively). Similarly, there was no difference in the cumulative cardiovascular mortality between OSA patients treated with CPAP or MAD (hazard ratio 1.08 (95% CI: 0.55–1.74); $P = 0.71$). The Kaplan–Meier plot of the primary endpoint in the overall study population is shown in Figure 2.

Table 4 shows the unadjusted hazard ratios for variables related to cardiovascular mortality. Hypertension, current smoking, previous heart disease and untreated OSA were each associated with cardiovascular mortality in the univariate Cox analysis. In the Cox multivariate regression analysis, untreated severe OSA was a strong predictor of cardiovascular death (hazard ratio 6.53 (95% CI: 2.30–18.54); $P = 0.004$) (Table 5). Patients under CPAP or MAD treatment had an adjusted hazard ratios that did not differ significantly from 1.0 suggesting that these groups have similar cardiovascular mortality rates to non-apnoeic controls.

Table 3 Incidence of cardiovascular events during study follow-up in non-apnoeic controls, CPAP-treated, MAD-treated and untreated severe OSA

	Non-apnoeic controls ($n = 208$)	Severe OSA treated with CPAP ($n = 177$)	Severe OSA treated with MAD ($n = 72$)	Untreated severe OSA ($n = 212$)
Cardiovascular death				
Number of events (M/F)	4 (1/3)	6 (3/3)	3 (2/1)	29 (17/12)
Events per 100 person-years	0.28	0.56‡	0.61†	2.1*

* $P < 0.001$ compared to the non-apnoeic controls.
† $P < 0.05$ compared to untreated severe OSA.
‡ $P < 0.001$ compared to untreated severe OSA.
CPAP, continuous positive airway pressure; F, female; M, male; MAD, mandibular advancing device; OSA, obstructive sleep apnoea.

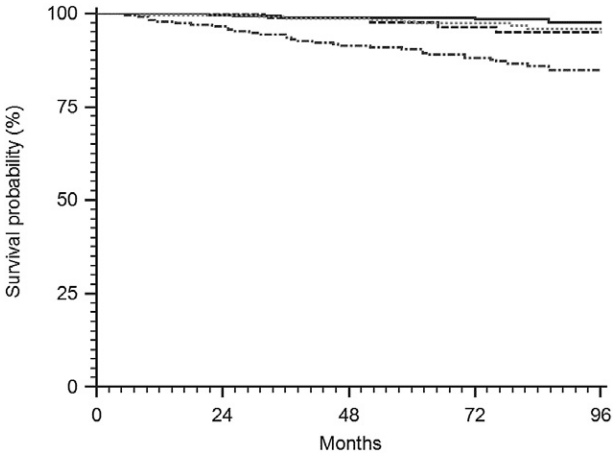

Figure 2 Kaplan–Meier cardiovascular mortality curves for the overall study population. CPAP, continuous positive airway pressure; MAD, mandibular advancing device. ——, control; – – – –, MAD-treated; ·····, CPAP-treated; – · – · –, untreated.

Table 4 Variables associated with cardiovascular death in univariate Cox analysis

Variable	Unadjusted HR (95% CI)	*P*-value
Age	1.04 (0.99–1.07)	0.78
Body mass index	1.01 (0.96–1.03)	0.83
Diabetes	1.41 (0.67–2.93)	0.37
Hypertension	2.27 (1.17–4.31)	0.01
Hyperlipidemia	1.72 (0.94–3.15)	0.08
Current smoking	1.99 (1.08–3.64)	0.03
Previous heart disease	2.98 (1.51–5.92)	0.005
Lipid-lowering agents	0.71 (0.35–1.43)	0.32
CPAP-treated OSA	0.56 (0.28–1.43)	0.21
MAD-treated OSA	0.67 (0.19–1.97)	0.38
Untreated OSA	4.72 (2.46–9.10)	<0.001
Non-apnoeic controls	1.00 (reference)	

CPAP, continuous positive airway pressure; MAD, mandibular advancing device; OSA, obstructive sleep apnoea.

Table 5 Variables associated with cardiovascular death in adjusted multivariate Cox regression analysis

Variable	Adjusted HR (95% CI)	*P*-value
Hypertension	1.65 (0.83–3.26)	0.15
Current smoking	1.99 (1.08–3.67)	0.02
Previous heart disease	2.37 (1.15–4.87)	0.01
CPAP-treated OSA	0.87 (0.16–2.04)	0.39
MAD-treated OSA	0.98 (0.13–2.69)	0.48
Untreated OSA	6.53 (2.30–18.54)	0.004
Non-apnoeic controls	1.00 (reference)	

CI, confidence interval; CPAP, continuous positive airway pressure; HR, hazard ratio; MAD, mandibular advancing device; OSA, obstructive sleep apnoea.

DISCUSSION

Available evidence suggests that adequate treatment of OSA with CPAP results in risk reduction of both fatal and non-fatal cardiovascular events.[5,18–20] However, few long-term data have been published on the incidence of cardiovascular events in patients who have been prescribed MAD. This study supports a beneficial effect of long-term MAD therapy on cardiovascular mortality in patients with OSA, which is independent of age, body mass index, smoking, diabetes, hypertension and previous cardiac diseases.

In accordance with previously published studies, we found that untreated severe OSA is associated with elevated risk of death. The consistency of our findings with other longitudinal studies[21–24] increases confidence in the validity of the role of sleep-disordered breathing in cardiovascular mortality. However, this is the first study to suggest that MAD may reduce mortality from cardiac events. Despite the lower efficacy of MAD compared with CPAP in ameliorating polysomnographic indices, the clinical endpoint of cardiovascular mortality was not different from those who had been treated with CPAP. These results may have been driven partially by the mitigating effects of MAD on cardiovascular risk factors. Comparison studies showed that both CPAP and MAD lowered the morning diastolic blood pressure compared with baseline values in mild to moderate OSA with no significant differences in the reduction in blood pressure produced by these two treatments.[25] In another long-term follow-up study (2.5–4.5 years) of patients with

mild to moderate OSA, a significant improvement in systolic and diastolic blood pressure, and cardiac rhythm was observed at the end of the trial compared with baseline measurement.[26] More compelling is the evidence derived from improvement in endothelial function following treatment with MAD. Using finger plethysmography to measure the response to hyperaemia of the peripheral arterial tone after brachial artery occlusion, Itzhaki *et al*.[27] demonstrated an improvement in endothelial functioning after 3 months of treatment with the modified Herbst mandibular advancement split. Similarly, Trzepizur *et al*.[28] assessed microvascular reactivity in 24 patients with moderate to severe OSA after 2 months of CPAP alternating with MAD treatment. Although MAD was less effective in reducing AHI and nocturnal oxygen desaturations, both interventions resulted in significant improvement in acetylcholine-induced peak cutaneous vascular conductance.

While treatment effects cannot be proven by observational studies, the results of the current investigation add important information with respect to the efficacy of oral appliances following extended therapy. The comparable cardiovascular mortality between CPAP and MAD despite the higher residual AHI in the latter therapy may suggest a threshold above which OSA attributed-cardiovascular complications may arise. In a large cohort of men with sleep-disordered breathing, Marin *et al*.[23] noted that the incidence of cardiovascular events in untreated mild-to-moderate OSA was not statistically different from a population-based healthy men. Only those patients with untreated severe sleep apnoea (AHI > 30) displayed more than twofold increase in fatal cardiovascular events. These results were later duplicated by a larger study demonstrating an increased long-term incidence of non-fatal cardiovascular events in those with AHI $\geq$ 20 who could not tolerate CPAP.[29] Could the reduction of AHI by MAD, albeit incomplete, from a severe OSA to a mild-to-moderate classification abrogate the risk of cardiovascular diseases? Alternatively, it can be hypothesized that the lower efficacy of MAD in reducing sleep-disordered breathing could be compensated by a higher daily rate of use compared with CPAP treatment. Indeed, we have observed in our cohort a higher adherence rate with the use of MAD compared with CPAP. Because the extent to which a treatment alleviates the health risk associated with a disease in clinical practice is not only a function of its efficacy but also of its treatment adherence, it is plausible that the prolonged use might limit the extent of oxidative injury that is thought to promote cardiovascular diseases in OSA.[30]

There are several methodological limitations regarding our study. First, the design of the study introduces an inherent selection bias when comparing patients who are not randomized to selected treatment. To minimize this effect, we used a multivariate regression analysis in order to account for confounding parameters that were considered relevant to the outcome in question. However, we could not rule out other confounders that were not taken into account in the design of the study including the use of cardiac or diabetes prescriptions drugs that may impact cardiovascular mortality. Second, we did not use an objective measure for MAD compliance, and instead relied on recorded self-reports. However, a study[31] using a novel intraoral monitoring device to assess objective adherence found that the average use of the oral appliance was 6.8 h per night, which is similar to the self-reported adherence in our study as well as other studies.[32,33] Third, some of the hazard ratios for known cardiovascular risk factors did not achieve statistical significance in our modelling. We speculate that the concurrent treatment of these conditions may have reduced their effect on the selected mortality. In addition, the design of the study may not have adequate power to attain statistical significance for these parameters. Finally, we have observed a relatively high number of patients who were not willing to pursue further treatment for OSA after a failed CPAP trial. Previous studies have noted similar rates.[5] We speculate that the relatively high rate of non-adherence may be attributed to lack of awareness of the long-term consequences of sleep apnoea at the time these patients presented for treatment. In addition, the technological advances in term of CPAP or oral appliance designs over the last decade may have led to a better acceptance of these devices with time.

In conclusion, this cohort study showed that untreated OSA was associated with increased risk for cardiovascular mortality. Even though oral appliance therapy achieved less satisfactory results in normalizing polysomnographic indices compared with CPAP, the risk of cardiovascular mortality in both treatment groups was comparable. In view of the relatively poor adherence to CPAP therapy, further clinical trials with MAD are needed to confirm our results.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Demographic and clinical characteristics of patients with complete follow-up (C) and those without complete follow-up or non-adherent to treatment (I).