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Mandibular Advancement vs CPAP for Blood Pressure Reduction in Patients with Obstructive Sleep Apnea

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Running title: Mandibular Advancement for Sleep Apnea

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Twitter handle: @CHRLe1212. In patients with moderate-to-severe obstructive sleep apnea (OSA) and hypertension, a mandibular advancement appliance (MAD) is an effective alternative to a continuous positive airway pressure (CPAP) mask to reduce blood pressure.

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ABSTRACT

BACKGROUND Hypertension guidelines recommend diagnosis and treatment of obstructive sleep apnea (OSA) in patients with hypertension. The mandibular advancement device (MAD) is an oral appliance therapy for patients who decline or cannot tolerate CPAP.

OBJECTIVE We compared the relative effectiveness of MAD versus CPAP in reducing 24-hour ambulatory BP.

METHODS In an investigator-initiated, randomized, non-inferiority trial (pre-specified margin 1.5 mmHg), 321 participants, aged over 40, with hypertension and increased cardiovascular risk were recruited at 3 public hospitals for polysomnography. Of these, 220 participants with moderate-to-severe OSA (apnea–hypopnea index (AHI) ≥ 15 events/hour) were randomized to either MAD or CPAP (1:1). The primary outcome was the difference between the 24-hour mean arterial BP at baseline and 6 months.

RESULTS Compared to baseline, the 24-hour mean arterial BP decreased by 2.5 mmHg ($P = 0.003$) at 6 months in the MAD group, whereas no change was observed in the CPAP group ($P = 0.374$). The between-group difference was -1.6 mmHg (95% confidence interval: -3.51 to 0.24, non-inferiority $P < 0.001$). The MAD group demonstrated a larger between-group reduction in all secondary ambulatory BP parameters compared to the CPAP group, with the most pronounced effects observed in the asleep BP parameters. Both the MAD and CPAP improved daytime sleepiness, with the between-group difference similar ($P = 0.384$). There were no between-group differences in cardiovascular biomarkers.

CONCLUSION MAD is non-inferior to CPAP for reducing 24-hour mean arterial BP in participants with hypertension and increased cardiovascular risk.

(word count: 242)

CONDENSED ABSTRACT

In an investigator-initiated, randomized, non-inferiority trial, 220 participants with moderate-to-severe OSA were randomized to either MAD or CPAP. At 6 months, compared to baseline, the MAD group showed a reduction of 2.5 mmHg in 24-hour mean arterial BP ($P = 0.003$), while no change was observed in the CPAP group ($P = 0.374$). The between-group difference in 24-hour mean arterial BP change was -1.6 mmHg (95% CI: -3.51 to 0.24, non-inferiority $P < 0.001$). These findings suggest that MAD could be considered an alternative to CPAP for optimizing blood pressure control in OSA patients with hypertension and high cardiovascular risk.

KEYWORDS: Obstructive sleep apnea, hypertension, non-inferiority trial, mandibular advancement device, continuous positive airway pressure

ABBREVIATIONS AND ACRONYMS

AHI	Apnea-Hypopnea Index
BMI	Body Mass Index
BP	Blood Pressure
CPAP	Continuous Positive Airway Pressure
ESS	Epworth Sleepiness Scale
hsCRP	High-sensitivity C-Reactive Protein
hsTnT	High-sensitivity Troponin T
MAD	Mandibular Advancement Device
NT-proBNP	N-Terminal pro B-type Natriuretic Peptide
OSA	Obstructive Sleep Apnea

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INTRODUCTION

Hypertension is a major risk factor for cardiovascular and cerebrovascular diseases.¹ While pharmacological therapy is the cornerstone of blood pressure (BP) management, obstructive sleep apnea (OSA) is increasingly recognized as an under-diagnosed and modifiable cause of hypertension.² Patients with OSA develop recurrent collapse of the upper airway during sleep, resulting in hypoxemia, sympathetic hyperactivity, and BP surges.³ Hypertension guidelines^{4,5} and scientific statements⁶ recommend screening and treating OSA in patients with hypertension.

Continuous positive airway pressure (CPAP) is recommended as the first-line treatment for OSA and typically involves the application of auto-titrating positive airway pressure via a nasal or oronasal interface to maintain upper airway patency during sleep. However, many patients decline therapy or struggle with adherence,⁷ particularly those without excessive daytime sleepiness.^{8,9}

Therapy with a mandibular advancement device (MAD), an oral appliance that advances the mandible, is a viable alternative to CPAP for patients with OSA.¹⁰⁻¹² There is evidence that MAD improves OSA symptoms and quality of life,^{13,14} and meta-analyses have suggested that MAD and CPAP are similarly effective in reducing BP.¹⁵⁻¹⁷ Nevertheless, these early studies had several limitations, such as small sample sizes (29-108 participants) and included participants with and without hypertension.¹⁸⁻²³ Moreover, most had short treatment periods (1-3 months),¹⁸⁻²² excluded severe OSA,^{18,20,23} or did not specify BP reduction as the primary outcome.^{18,19,21-23}

We addressed these limitations by conducting a randomized clinical trial to compare the effectiveness of MAD versus CPAP in reducing BP in patients with moderate-to-severe OSA and hypertension. Our hypothesis was that MAD would be non-inferior to CPAP in reducing 24-hour mean arterial BP.

METHODS

TRIAL DESIGN. The Cardiosleep Research Program on Obstructive Sleep Apnea, Blood Pressure Control and Maladaptive Myocardial Remodeling—Non-inferiority Trial (CRESCENT) was an investigator-initiated, randomized, open-label, non-inferiority trial (NCT04119999) funded by a publicly competitive research grant from the Ministry of Health in Singapore. The non-inferiority design was justified because of higher acceptance and treatment adherence for the MAD than CPAP, and both therapies being superior to placebo.^{15–17} Trial design and analysis plan details were published previously.²⁴ Manufacturers of the MAD and CPAP had no role in the trial design, data accrual or analysis, or generation of this manuscript. The trial was approved by the institutional review board (The Domain Specific Review Board-C: 2019/00359, approved on August 28, 2019). All participants provided written informed consent.

RECRUITMENT. Recruitment extended from October 1, 2019, to December 5, 2022. We recruited participants through medical record screening, performed by clinical trial coordinators, at three public hospitals in Singapore (National University Hospital, National Heart Centre Singapore, and Ng Teng Fong General Hospital). Since the predominant ethnicity in Singapore is Chinese, we recruited Adults of Chinese ethnicity aged ≥ 40 years with known hypertension, and at least one other factor for high cardiovascular risk were recruited for screening polysomnography.²⁴ The exclusion criteria were ongoing treatment for diagnosed OSA; Cheyne-Stokes breathing or predominantly central sleep apnea; secondary hypertension due to renal, endocrine, or vascular problems; unsuitable anatomy for MAD, life expectancy < 1 year, hypertensive crisis, acute coronary syndromes, or acute heart failure in the past 30 days.²⁴ The trial was summarized in the Central Illustration.

SCREENING POLYSOMNOGRAPHY. The participants underwent in-laboratory, attended polysomnography an average of 13.7 ± 17.5 days after recruitment, and completed

the Epworth Sleepiness Scale (ESS) questionnaire. All polysomnograms were conducted using American Academy of Sleep Medicine (AASM) type I sleep diagnostic software (Embla® RemLogic, Natus Medical Inc., Canada), and scored by a Registered Polysomnographic Technologist-credentialed sleep technician. The primary measure was the apnea-hypopnea index (AHI), scored according to the AASM 2012 Scoring Manual, which was the most updated version for OSA diagnosis when the trial began in 2019.²⁵ OSA was diagnosed on the basis of AHI, quantified as the total number of apneas or hypopneas recorded per hour of sleep. Apnea was defined as a $\geq 90\%$ decrease in airflow from baseline for at least 10 seconds. Hypopnea was defined as a $\geq 30\%$ decrease in airflow from baseline for ≥ 10 seconds, associated with either an oxygen desaturation of $\geq 3\%$ and/or an arousal. The oxygen desaturation index (ODI) was defined as the number of episodes of oxygen desaturation of $\geq 3\%$ per hour of sleep. We defined moderate-to-severe OSA as an AHI ≥ 15 events per hour.

RANDOMIZATION AND INTERVENTIONS. Participants diagnosed with OSA were randomly assigned to treatment by MAD or CPAP in a 1:1 ratio. Randomization was performed using a computer-generated sequence and minimization procedure to balance the group assignment according to age (≥ 60 vs < 60 years old), body mass index (BMI) (≥ 25 vs < 25 kg/m²), and AHI (≥ 30 vs < 30 events per hour). A web-based system was established to ensure the allocation was adequately blinded. Group allocation was concealed until randomization. Blinding post-randomization was not possible. Crossover of the groups was not allowed. The treatment duration was 6 months.

ACCLIMATIZATION PHASE. A 1-month acclimatization phase was included in the design. Participants assigned to the MAD group were provided with a custom-made, removable, two-piece, adjustable MAD device (SomnoDent Flex[®], SomnoMed, Australia), whereas those assigned to the CPAP group were provided with an auto-titrating CPAP

machine (AirSense™ 10, Resmed, Australia). Specialists trained in the respective therapies facilitated the participants with the devices through a combination of face-to-face and telephone sessions. The detailed MAD and CPAP titration protocols are provided in Supplemental Method 1.

Device adherence was determined in the MAD group by an embedded compliance micro-recorder chip (DentiTrac®, Braebon, Canada), and in the CPAP group by a cloud-based telemedicine management platform (AirView™, ResMed Corp, San Diego, CA). The residual AHI in the MAD group was determined by a home-based sleep study using a wrist-worn sleep monitoring device (WatchPAT® 200, Itamar Medical, Israel, 3% hypopnea scoring rule was used), and in the CPAP group by the in-built sensor in the CPAP machine. The prespecified treatment adherence and treatment response definitions are provided in Supplemental Method 2.

OUTCOMES. At baseline and 6-months follow-up, the participants in the MAD and CPAP groups underwent 24-hour ambulatory BP monitoring, an ESS questionnaire survey, and blood tests for cardiovascular biomarkers (high-sensitivity C-reactive protein [hsCRP], N-terminal pro B-type natriuretic peptide [NT-proBNP], and high-sensitivity troponin T [hsTnT]). Ambulatory BP monitoring was performed with readings acquired every 30 minutes using an approved device (Welch Allyn ABPM 7100, Welch Allyn, Skaneateles Falls, New York, USA). The standard operating procedure and patient instruction sheet for the 24-hour ambulatory BP monitoring are provided in Supplemental Method 3. Sleep and wake times were determined from participant log-book entries. The primary outcome was the difference in 24-hour mean arterial BP between baseline and 6-month follow-up. Secondary outcomes included 24-hour awake and asleep systolic and diastolic BP; pulse pressure; nocturnal BP dipping (> 10% decrease in systolic BP during sleep time); percentages of

participants with systolic BP < 130 mmHg and < 120 mmHg, respectively; ESS score; and cardiovascular biomarkers.

NON-INFERIORITY MARGIN AND SAMPLE SIZE CALCULATION. The non-inferiority margin was determined with the two-step fixed-margin approach, in which previous studies comparing the active control with placebo were used to derive a single fixed value for the margin. Based on a previous result that CPAP could lower the 24-hour mean arterial BP by 3.3 mmHg (95% confidence interval [CI]: -5.3 to -1.3 mmHg) with respect to sham CPAP,²⁶ the non-inferiority threshold was set at 1.5 mmHg after rounding up the reported smallest effect of 1.3 mmHg.²⁴ The null hypothesis is that CPAP was more effective than MAD in lowering 24-hour mean arterial BP by at least 1.5 mmHg. To detect the non-inferiority of MAD with respect to CPAP based on a desired statistical power of 90%, a 2.5% type-1 error rate, and 20% attrition rate, a sample size of 220 participants with OSA was determined.²⁷

STATISTICAL ANALYSIS. The sample characteristics of participants randomized to MAD and CPAP were summarized with mean \pm standard deviation (SD), median (IQR: interquartile range), and frequency (%). Exploratory data analyses were carried out with Wilcoxon-Mann-Whitney test and Fisher's Exact test. Change analyses between baseline and 6-month outcomes were ascertained with Wilcoxon signed ranked test and McNemar's test.

Confirmatory analyses (based on the intention-to-treat principle) of the relative reduction in 24-hour mean arterial BP, comparing MAD and CPAP, used analysis of covariance (ANCOVA) estimated with ordinary least squares.²⁸ The hypotheses concerning MAD being non-inferior to CPAP were examined with the 95% CIs, while referencing the above-mentioned non-inferiority threshold (i.e., 1.5 mmHg). MAD was considered non-inferior to CPAP if the upper limit of the 95% CI was less than the predetermined threshold.

Pre-specified subgroup analyses were also conducted with age (> 60 vs ≤ 60 years old), gender (male vs female), BMI (> 25 vs ≤ 25 kg/m²), waist circumference (split by tertiles), AHI (> 30 vs ≤ 30 events per hour), ODI (> 30 vs ≤ 30 events per hour), ESS (> 10 vs ≤ 10), presence of diabetes mellitus, coronary artery disease, number of BP medications and device adherence (split by tertiles). All statistical analyses were performed with Stata MP Version 16.0 (Stata Corp, Texas, USA).

RESULTS

SAMPLE CHARACTERISTICS. Between October 2019 and December 2022, a total of 220 participants (median age 61.0 years, 85.5% [188/220] male) were randomly assigned to MAD or CPAP in a 1:1 allocation (**Figure 1**). In accordance with the Asian cut-off, 44.5% (98/220) of the participants were overweight (BMI 23.0-27.5 kg/m²) and 49.5% (109/220) were obese (BMI > 27.5 kg/m²) (**Table 1**).²⁹ The most prevalent high cardiovascular risk markers were coronary artery disease (60.9%, 134/220) and diabetes mellitus (59.1%, 130/220). Hypertension had been present for over 10 years in 44.1% (97 out of 220) of participants. Baseline ESS and polysomnography findings are shown in **Table 2**. OSA was considered severe in 65.0% (143 out of 220) of the participants.

Six-month follow-up visits were completed by August 2023. A total of 21 participants (MAD: 12 and CPAP: 9) withdrew from the study prematurely. Those withdrawing had generally milder median OSA-related indices than retained participants (Supplemental Table 1) with significantly lower waist circumference (93.5 vs. 97.5 cm; $P = 0.045$), waist/hip ratio (0.94 vs. 0.96; $P = 0.032$), ESS score (7 vs. 8; $P = 0.042$), AHI (31.8 vs. 39.8; $P = 0.039$), ODI (14.1 vs. 28.4; $P = 0.001$), and respiratory disturbance index (31.8 vs. 39.9; $P = 0.040$).

ACCLIMATIZATION PHASE. The acclimatization phase started 55 (IQR: 37–76) days for the MAD group and 27 (IQR: 22–35) days for the CPAP group after

polysomnography. The longer waiting time for the MAD group was mainly due to the manufacturing of the custom-made MADs and international shipping times.

For the MAD group, 82.7% (91/110) participants had valid adherence data. The median duration of MAD usage was 5.5 (IQR: 3.9–6.9) hours per night, and 74.7% (68/91) used the device for ≥ 4 hours per night. In contrast, 94.5% (104/110) of the participants on CPAP had valid adherence data. The median duration of CPAP usage was 5.0 (IQR: 3.3–6.1) hours per night and 70.2% (73/104) used the device for ≥ 4 hours per night. The median residual AHI for the MAD and CPAP groups were 12.6 (IQR: 6.6–20.7) and 2.2 (IQR: 1.1–4.6) events per hour, respectively.

SIX-MONTH DEVICE ADHERENCE AND RESIDUAL AHI. In the MAD group, 89.1% (98/110) of the participants completed the 6-month follow-up, and of these, 86.7% (85/98) had valid adherence data. The median duration of MAD usage during the 6-month treatment period (from first to last day during the 6-month) was 5.5 (IQR: 3.7–6.7) hours per night, with 72.9% (62/85) using the MAD device for ≥ 4 hours per night and 56.5% (48/85) using the MAD device for ≥ 6 hours per night. The residual AHI was 10.8 (IQR: 5.0–18.9) events per hour. In the CPAP group, 91.8% (101/110) of the participants completed the 6-month follow-up and 97.0% (98/101) had valid adherence data. In this group, the median duration of CPAP usage was 5.0 (IQR: 3.0–5.9) hours per night, with 69.4% (68/98) using CPAP for ≥ 4 hours per night and 23.2% (23/99) using CPAP for ≥ 6 hours per night. The residual AHI was 2.0 (IQR: 1.0–3.1) events per hour. More details about device adherence and residual AHI can be found in Supplemental Table 2.

PRIMARY OUTCOME. A total of 98 (89.1%) participants from the MAD group and 101 (91.8%) participants from the CPAP group completed the baseline and 6-month 24-hour ambulatory BP monitoring. The baseline characteristics of the MAD completers and CPAP completers were similar (Supplemental Table 3). For the ambulatory BP monitoring,

the total numbers of BP measurements captured during the 24-hour period were similar between the 2 groups at both the baseline (MAD group: 46 [IQR: 41–48]; CPAP group: 44 [IQR: 40–48], $P = 0.246$) and 6-month (MAD group: 41 [IQR: 36–46], CPAP group: 42 [IQR: 37–46], $P = 0.913$). Details of the BP measures and changes from baseline to 6-month follow-up are shown in **Figure 2** and **Table 3**.

In the MAD group, there was a significant reduction in the 24-hour mean arterial BP from baseline to 6 months (95.6 ± 8.5 to 93.5 ± 8.1 mmHg; $P = 0.003$). The reduction was non-significant in the CPAP group (95.5 ± 8.8 to 95.3 ± 9.8 mmHg; $P = 0.374$). Thus, the between-group difference in 24-hour mean arterial BP was significant (ANCOVA coefficient: 1.6 mmHg; 95% CI: -3.51 to 0.24; non-inferiority $P < 0.001$; superiority $P = 0.086$). Since the 95% CI did not cross the pre-specified noninferiority margin of 1.5 mmHg, MAD was non-inferior to CPAP (**Figure 3**).

In the prespecified subgroup analysis, there was evidence of potential heterogeneity according to age, sex, BMI, ESS, diabetes, and device adherence (**Figure 4**). Note that a total of 21 participants had changes in BP medication during the 6-month treatment period (Supplemental Table 4). After excluding these 21 participants, the between-group difference in 24-hour ambulatory BP remained similar (Supplemental Table 5). Similarly, after excluding the 21 participants who withdrew prematurely (MAD group: 12; CPAP group: 9), the results remained similar (Supplemental Table 6)

SECONDARY AND OTHER OUTCOMES. The MAD group recorded a larger reduction in all the other 24-hour ambulatory BP measures when compared with the CPAP group (**Table 3**). All the results were statistically significant, except for asleep pulse pressure ($P = 0.957$). A more pronounced reduction in the MAD group was observed in asleep mean BP, systolic BP and diastolic BP compared to the corresponding daytime BP (**Table 3**).

The percentage of participants who achieved 24-hour systolic BP < 130 mmHg at baseline and 6-month follow-up did not change in the MAD (69.4% [75/108] vs. 69.4% [68/98], $P = 0.839$) and CPAP group (68.6% [72/105] vs. 66.3% [67/101], $P = 0.999$). The percentage of participants who achieved 24-hour systolic BP < 120 mmHg increased from 32.4% [35/108] at baseline to 43.9% [43/98] ($P = 0.043$) at the 6-month follow-up in the MAD group. The corresponding percentages remained unchanged at 31.4% [33/105] ($P = 0.999$) in the CPAP group. Asleep BP dipping was observed in 16.7% [18/108] and 18.4% [18/98] ($P = 0.999$) of the participants in the MAD group at baseline and 6-month follow-up, respectively. The corresponding percentages in the CPAP group were 28.6% [30/105] and 27.7% [28/101] ($P = 0.999$), respectively.

Both the MAD and CPAP were effective in reducing excessive daytime sleepiness. The percentage of participants in the MAD group with ESS score > 10 (excessive daytime sleepiness) decreased from 26.4% [29/110] at baseline to 11.0% [11/100] at 6-month follow-up ($P = 0.001$). A reduction of participants with ESS score > 10 was also observed in the CPAP group, from 34.5% [38/110] at baseline to 7.0% [7/100] at 6 months ($P < 0.001$). The between-group difference was 12.1% ($P = 0.384$).

There were no significant between-group differences in the change of hsCRP, NT-proBNP, and hsTnT in plasma from baseline to 6-month follow-up (Supplemental Table 7).

The common side effects reported in the MAD group included dry or painful sensations in the mouth, throat, or nose (27.0%, [27/100]), jaw pain (22.0%, [22/100]), teeth discomfort (17.0%, [17/100]), and hypersalivation (10.0%, [10/100]). The CPAP group reported air leakage (48.5%, [48/99]), dryness or pain in the mouth, throat, or nose (44.4%, [44/99]), sleep disturbances (14.1%, [14/99]), blocked or runny nose (14.1%, [14/99]), mask discomfort (11.1%, [11/99]), and facial rash (10.1%, [10/99]).

During the 6-month treatment period, 6.4% (7/110) participants in the MAD group and 9.1% (10/110) participants in the CPAP group experienced unplanned hospitalization ($P = 0.449$). Two participants each were hospitalized for cardiovascular events in the MAD group (hypertension, $n = 1$; heart failure, $n = 1$) and CPAP group (myocardial infarction, $n = 2$). The duration of hospitalization was similar for the MAD group (3.0 days, IQR: 1–5) and the CPAP group (2.5 days, IQR: 2–5) ($P = 0.803$).

DISCUSSION

To the best of our knowledge, the CRESCENT trial is the largest randomized clinical trial on the comparative effectiveness of MAD versus CPAP for BP reduction. All participants had hypertension and a high risk of cardiovascular disease, and two-thirds of the participants had severe OSA. With the median usage of 5.5 hours per night for the MAD group and 5.0 hours for the CPAP group, we found that MAD was non-inferior to CPAP for reducing 24-hour mean arterial BP at 6-month follow-up. This was also true for various parameters, including awake and asleep, systolic and diastolic BPs. The between-group difference in effectiveness favored MAD and was more pronounced for asleep than for awake BPs. Both MAD and CPAP were effective in reducing excessive daytime sleepiness.

The AASM currently recommends MAD for patients with OSA who are intolerant of or do not wish to receive CPAP therapy, without specifying levels of severity.¹⁰ However, most sleep physicians avoid prescribing MAD for severe OSA due to limited evidence on its ability to normalize AHI. Moreover, this recommendation is for patients with OSA who seek treatment at sleep clinics, and it remains uncertain whether patients with hypertension who have OSA diagnosed opportunistically will experience tangible benefits as such patients often do not experience excessive daytime sleepiness. In this regard, the CRESCENT trial demonstrated that MAD is a safe and acceptable therapy that is non-inferior to CPAP for reducing BP. Moreover, the between-group difference (2 mmHg) in systolic BP seen with

MAD is associated with a 10% lower stroke mortality and 7% lower cardiovascular mortality.³⁰ Based upon the totality of the data, we observed there was a trend for superiority of MAD, although this study was not designed to test superiority.

The 2023 European Society of Hypertension guideline recommends that 24-hour ambulatory BP monitoring be used for the assessment of asleep BP.³¹ Compared with office BP measurement, 24-hour ambulatory BP measurement and asleep BP measurement are superior in predicting death and cardiovascular outcomes.³² To that end, it is encouraging that our study showed MAD has greater effectiveness in reducing asleep BP. Further studies are warranted to evaluate the role of MAD in reducing the risk of cardiovascular disease.

Both the CRESCENT and the SAVE (Sleep Apnea and Vascular Endpoint)³³ enrolled a relatively asymptomatic population of Asian participants with established coronary artery disease and/or high cardiovascular risk. CPAP adherence was found to be low among SAVE participants, averaging 3.3 hours per night, while CRESCENT participants exhibited higher adherence, averaging 5.0 hours per night. We hypothesize that this disparity in adherence may be attributed to several factors. The CRESCENT was conducted during the coronavirus disease 2019 pandemic when overseas travel was significantly reduced (elaborated in the 'Limitations'). Singapore, where the CRESCENT was conducted, being a smaller country than Australia, India, and China where the SAVE took place, may have facilitated easier access for CRESCENT participants to research coordinators and sleep physicians for CPAP-related issues compared to their counterparts in the SAVE. Finally, the study duration for CRESCENT (6 months) was shorter than that of SAVE (3.7 years).

LIMITATIONS. There were some limitations to this trial. First, most of the trial was conducted during the coronavirus disease 2019 pandemic, when overseas travel was drastically reduced, and most participants stayed and slept at home. As such, therapy adherence might be higher than if the trial had been conducted during a non-pandemic period.

Second, over two-thirds of the participants did not have excessive daytime sleepiness as recruitment was predominantly from internal medicine and cardiology clinics. Our findings may not be as generalizable to sleep clinic patients in whom a high proportion report symptoms such as sleepiness. Third, the lack of BP reduction in the CPAP group could be because the baseline BP of the study participants was well controlled (125 mmHg) and the average CPAP adherence was 5 hours, which is less than the minimum 6 hours previously proposed for benefits.³⁴ Besides, auto-CPAP was used in the CPAP arm, and there is emerging evidence that fixed pressure CPAP may be superior to auto-CPAP in terms of impact on BP.³⁵ Fourth, the participants were exclusively of Chinese ethnicity, reflecting the predominant ethnicity in Singapore. Although Chinese craniofacial features increase the propensity of developing severe OSA,³⁶ there is no biological reason to think that these results cannot be generalized to Caucasian populations. While further studies on other ethnicities are needed, ethnic Chinese make up approximately 17.3% of the world population, and 5.7 million ethnic Chinese residing in the U.S. Our findings should also be relevant to other East-Asians, including Koreans and Japanese, who share similar craniofacial features with the Chinese. Fifth, the findings may not be generalizable to women as the participants were mainly male.

CONCLUSION

MAD is non-inferior to CPAP for reducing 24-hour mean arterial BP in participants with hypertension and moderate-to-severe OSA. The between-group difference, favoring MAD, was particularly evident in asleep BP, supporting the use of MAD as an effective first line alternative to CPAP for reduction of BP and cardiovascular risk in these patients.

CLINICAL PERSPECTIVES

Competency in Patient Care and Procedural Skills: In patients with moderate-to-severe obstructive sleep apnea (OSA) and hypertension, a mandibular advancement appliance (MAD) is an effective alternative to a continuous positive airway pressure (CPAP) mask to reduce blood pressure.

Translational Outlook: Further studies are warranted to replicate these findings in more diverse cohorts and to assess the impact of MAD on long-term outcomes in patients with OSA.

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Figure Legends**Figure 1. CONSORT Diagram**

The screening was conducted at the general medicine and/or cardiology clinics of the participating hospitals. Once 220 participants were found to have moderate-to-severe obstructive sleep apnea when 306 consented individuals underwent polysomnography, screening and polysomnography were stopped.

Figure 2. Changes in blood pressures from baseline to 6-month.

Changes in mean arterial (MBP, left), systolic (SBP, middle), and diastolic (DBP, right) blood pressures from baseline to 6-month follow up for the MAD group and CPAP group. MAD = mandibular advancement device; CPAP = continuous positive airway pressure. The P-value for noninferiority was reported.

Figure 3. Effect size in comparison with the pre-specified non-inferiority margin.

The non-inferiority of MAD against CPAP is demonstrated because the confidence interval does not exceed the predefined margin of 1.5 mmHg (dotted line). MAD = mandibular advancement device; CPAP = continuous positive airway pressure.

Figure 4. Forest plot of primary outcome by prespecified subgroups.

The widths of the confidence intervals have not been adjusted for multiplicity. Diabetic subjects have a higher baseline blood pressure which was significantly correlated with 6-month blood pressure. The statistically significant result for the diabetes versus non-diabetes subgroup is small in terms of effect size (coefficient: 0.26). Hence it is clinically non-significant. AHI = Apnea Hypopnea Index; BMI = Body Mass Index; BP = Blood Pressure;

CPAP = Continuous Positive Airway Pressure; ESS = Epworth Sleepiness Scale; MAD = Mandibular Advancement Device; ODI = Oxygen Desaturation Index.

CENTRAL ILLUSTRATION. CRESCENT trial

MAD is non-inferior to CPAP for reducing 24-hour mean arterial blood pressure in participants with hypertension and moderate-to-severe obstructive sleep apnea. The between-group difference, favoring MAD, was particularly evident in asleep blood pressure, supporting the use of MAD as an effective alternative to CPAP for blood pressure reduction. MAD = mandibular advancement device; CPAP = continuous positive airway pressure.

Table 1. Baseline Demographic and Clinical Characteristics of the Study Participants		
Variable	MAD (n=110)	CPAP (n=110)
Demographic characteristics		
Age (years), median (IQR)	61.5 (56.0-66.0)	61.0 (55.0-65.0)
Male sex, n (%)	96 (87.3)	92 (83.6)
Height (m), median (IQR)	169.0 (162.0-172.0)	167.5 (162.0-172.0)
Weight (kg), median (IQR)	78.1 (68.6-86.1)	77.4 (67.8-85.9)
BMI (kg/m ²), median (IQR)	27.6 (25.4-30.5)	27.4 (25.2-30.6)
Neck circumference (cm), median (IQR)	39.5 (37.5-42.0)	39.5 (36.5-41.5)
Waist circumference (cm), median (IQR)	97.3 (93.0-103.3)	96.5 (92.2-104.0)
Hip circumference (cm), median (IQR)	101.5 (97.5-106.5)	101.1 (97.0-106.5)
Waist/Hip ratio, median (IQR)	1.0 (0.9-1.0)	1.0 (0.9-1.0)
BMI 23 – < 27.5 (kg/m ²), n (%)	48 (43.6)	50 (45.5)
BMI ≥ 27.5 (kg/m ²), n (%)	56 (50.9)	53 (48.1)
Hypertension duration, n (%)		
<5 years	16 (14.6)	27 (24.6)
5-10 years	17 (15.5)	15 (13.6)
>10 years	52 (47.3)	45 (40.9)
Unknown	25 (22.7)	23 (20.9)
Number of blood pressure medications, n (%)		
1	27 (24.6)	42 (38.2)
2	53 (48.2)	41 (32.3)
3	22 (20.0)	22 (20.0)
≥4	8 (7.3)	5 (4.0)
Cardiovascular risk features, n (%)		
Diabetes mellitus*	65 (59.1)	65 (59.1)
Previous stroke*	8 (7.3)	8 (7.3)
Coronary artery disease*	66 (60.0)	68 (61.8)

Chronic kidney disease*	9 (8.2)	8 (7.3)
Age \geq 75 years*	2 (1.8)	1 (0.9)
Smoker	8 (7.3)	6 (5.5)
Hyperlipidemia	86 (78.2)	86 (78.2)
Atrial fibrillation	3 (2.7)	4 (3.6)
Previous myocardial infarction	32 (29.1)	33 (30.0)
Previous PCI	51 (46.4)	57 (51.8)
Previous CABG	11 (10.0)	12 (10.9)
Medications, n (%)		
Aspirin	59 (53.6)	67 (60.9)
P2Y12 inhibitor	35 (31.8)	24 (21.8)
Beta-blocker	60 (54.6)	61 (55.5)
ACEI/ARB	89 (80.9)	86 (78.2)
Calcium channel blocker	55 (50.0)	45 (40.9)
Diuretic	18 (16.4)	12 (10.9)
Statin	98 (89.1)	93 (84.6)
Ezetimibe	16 (14.6)	16 (14.6)
Anticoagulant	3 (2.7)	2 (1.8)
<p>*Factors of high cardiovascular risk. All the participants had at least one of these factors</p> <p>ACEI: angiotensin-converting-enzyme inhibitors, ARB: angiotensin receptor blockers, BMI: body-mass index, CABG: coronary artery bypass surgery, IQR: interquartile range, PCI: percutaneous coronary intervention</p>		

Table 2. Baseline Epworth Sleepiness Scale and Polysomnography Findings		
Variable	MAD (n=110)	CPAP (n=110)
Daytime sleepiness severity, n (%)		
Non-sleepy, ESS 0-10	81 (73.6)	72 (65.5)
Mildly sleepy, ESS 11-14	17 (15.5)	26 (23.6)
Moderately sleepy, ESS 15-17	7 (6.4)	8 (7.3)
Severely sleepy, ESS 18-24	5 (4.6)	4 (3.6)
AHI, events per hour, median (IQR)	37.5 (23.9-49.9)	39.7 (24.6-54.7)
Patients with AHI		
15 - < 30 events per hour, n (%)	37 (33.6)	39 (35.5)
≥ 30 events per hour, n (%)	73 (66.4)	71 (64.5)
ODI, events per hour, median (IQR)	25.0 (14.4-41.8)	31.5 (16.5-47.7)
Patients with ODI ^a		
< 15 events per hour, n (%)	31 (28.2)	21 (19.1)
15 - < 30 events per hour, n (%)	37 (33.6)	32 (29.1)
≥ 30 events per hour, n (%)	42 (38.2)	57 (51.8)
Mean SpO ₂ (%), median (IQR)	95.0 (93.0-95.0)	94.0 (93.0-95.0)
Minimum SpO ₂ (%), median (IQR)	82.0 (77.0-86.0)	80.5 (74.0-84.0)
RDI, events per hour, median (IQR)	37.5 (24.9-50.2)	40.1 (24.6-54.7)
Patients with RDI		
< 15 events per hour, n (%)	1 (0.9)	0 (0.0)
15 - < 30 events per hour, n (%)	36 (32.7)	39 (35.5)
≥ 30 events per hour, n (%)	73 (66.4)	71 (64.6)
Arousal index, events per hour, median (IQR)	15.2 (6.6-24.2)	15.9 (8.6-24.5)
Patients with arousal index		
< 15 events per hour, n (%)	55 (50.0)	51 (46.4)

15 - < 30 events per hour, n (%)	39 (35.5)	40 (36.4)
≥ 30 events per hour, n (%)	16 (14.6)	19 (17.3)
AHI: Apnea-Hypopnea Index, ESS: Epworth Sleepiness Scale, IQR: interquartile range, ODI: oxygen desaturation index, RDI: respiratory disturbance index, SpO ₂ : saturation of peripheral oxygen ^a Scored using the 3% rule (≥ 3% oxygen desaturation from pre-event baseline)		

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	MAD		CPAP		Difference (95% CI) in BP changes (mmHg)	p value ANOVA
	Baseline (n=108) ^b	6-month (n=98) ^c	Baseline (n=105) ^d	6-month (n=101) ^e		
24-hour, mmHg, median (IQR)						
Mean BP (primary endpoint) ^a	96.0 (90.5-100.5)	93.5 (88.0-99.0) ^f	95.0 (90.0-100.0)	95.0 (88.0-101.0)	-1.64 (-3.51 to 0.24)	<0.001 ^g
Systolic BP	125.0 (117.5-132.0)	123.0 (115.0-133.0) ^f	125.0 (118.0-132.0)	125.0 (116.0-134.0)	-2.12 (-4.55 to 0.31)	0.002
Diastolic BP	80.0 (75.5-86.0)	79.0 (73.0-83.0) ^f	80.0 (74.0-85.0)	79.0 (72.0-85.0)	-1.27 (-2.97 to 0.44)	<0.001
Pulse pressure	44.0 (39.0-49.5)	44.0 (40.0-50.0)	45.0 (40.0-52.0)	46.0 (39.0-52.0)	-0.53 (-1.90 to 0.83)	0.002
Awake, mmHg, median (IQR)						
Mean BP	97.5 (91.0-101.5)	96.0 (90.0-101.0)	97.0 (92.0-104.0)	96.0 (90.0-104.0)	-1.15 (-3.17 to 0.86)	0.005
Systolic BP	126.0 (120.5-134.5)	124.0 (117.0-134.0)	129.0 (119.0-136.0)	127.0 (119.0-136.0)	-1.83 (-4.56 to 0.90)	0.009
Diastolic BP	81.5 (76.5-88.0)	81.0 (75.0-85.0) ^f	81.0 (75.0-88.0)	81.0 (74.0-88.0)	-0.83 (-2.66 to 1.00)	0.007
Pulse pressure	45.0 (40.0-50.5)	44.0 (40.0-50.0)	45.0 (40.0-52.0)	46.0 (40.0-52.0)	-0.61 (-2.33 to 1.11)	0.008
Asleep, mmHg, median (IQR)						
Mean BP	92.0 (85.0-99.0)	90.0 (83.0-96.0) ^f	90.0 (85.0-98.0)	91.0 (84.0-98.0)	-2.43 (-4.97 to 0.11)	0.001
Systolic BP	121.5 (113.0-131.0)	118.0 (110.0-129.0) ^f	121.0 (113.0-129.0)	120.0 (111.0-131.0)	-2.85 (-6.14 to 0.44)	0.005
Diastolic BP	77.0 (71.0-84.0)	75.0 (69.0-81.0) ^f	75.0 (70.0-82.0)	76.0 (70.0-83.0)	-2.26 (-4.59 to 0.06)	0.001
Pulse pressure	44.0 (39.0-48.0)	43.0 (39.0-51.0)	44.0 (39.0-49.0)	45.0 (39.0-50.0)	0.02 (-1.68 to 1.72)	0.957

BP: blood pressure, IQR: interquartile range

^a Mean BP is calculated as one-third of the sum of systolic BP and 2 times of the diastolic BP

^b 2 participants withdrew from the MAD group before baseline evaluation.

^c 12 participants withdrew from the MAD group before ambulatory BP monitoring during 6-month follow up.

^d 5 participants withdrew from the CPAP group before baseline evaluation.

^e 9 participants withdrew from the CPAP before ambulatory BP monitoring during 6-month follow up.

^f Change from baseline to 6-month $p < 0.05$.

^g Statistically significant (< 0.001 , non-inferiority). Statistically insignificant (0.086, superiority)

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Figure 1. CONSORT Diagram

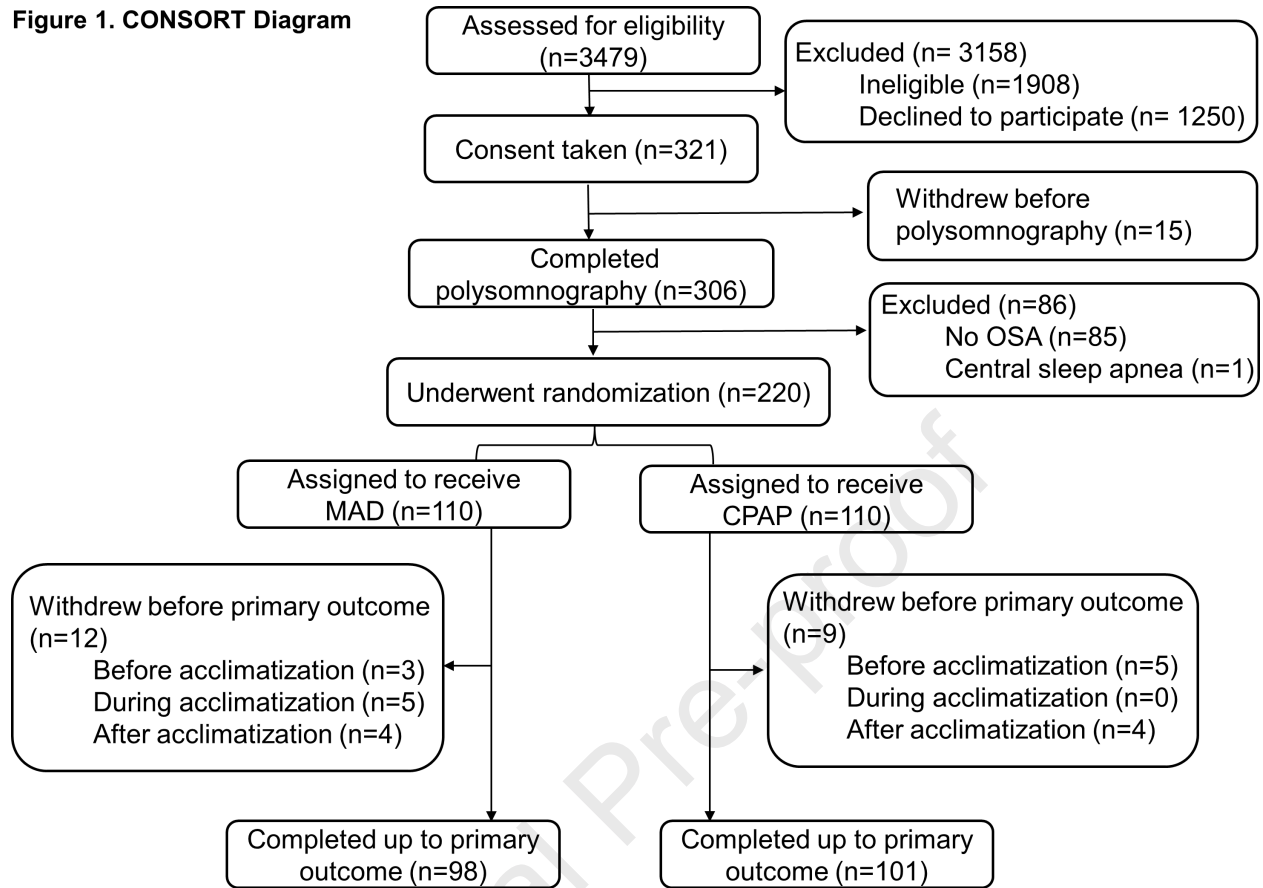
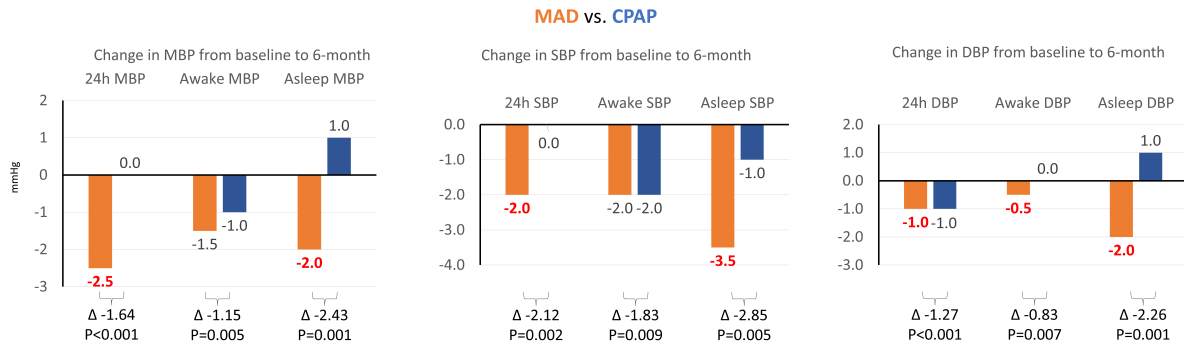
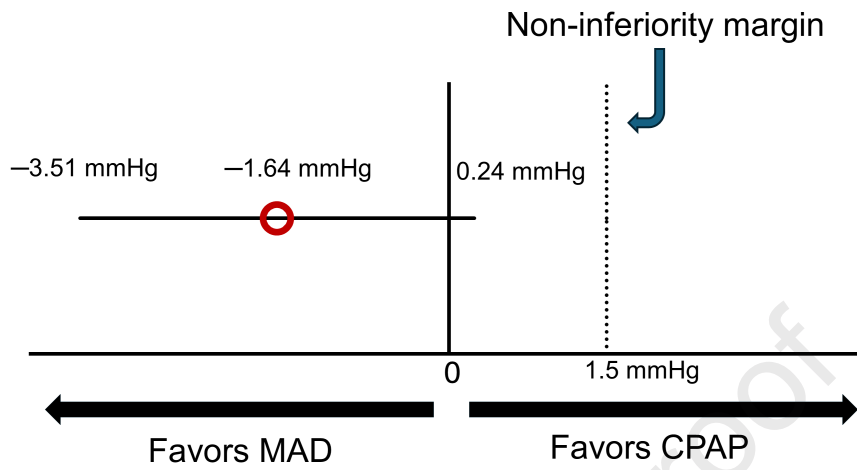


Figure 2. Changes in mean arterial (MBP, left), systolic (SBP, middle), and diastolic (DBP, right) blood pressures from baseline to 6-month follow up for the MAD group and CPAP group.



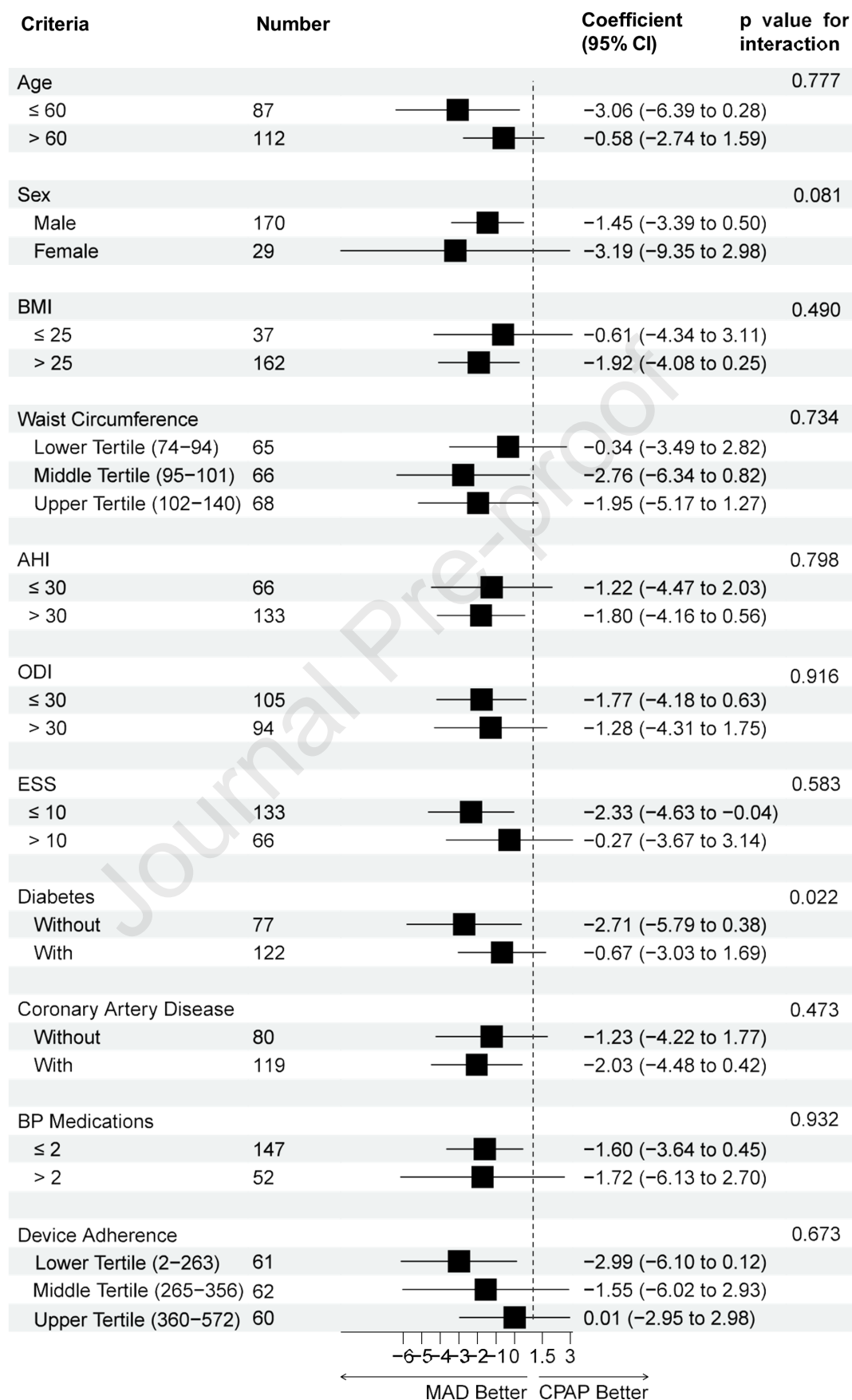
MAD = mandibular advancement device; CPAP = continuous positive airway pressure. The P- value for noninferiority was reported

Figure 3. Effect size of MAD versus CPAP in comparison with the predefined non-inferiority margin

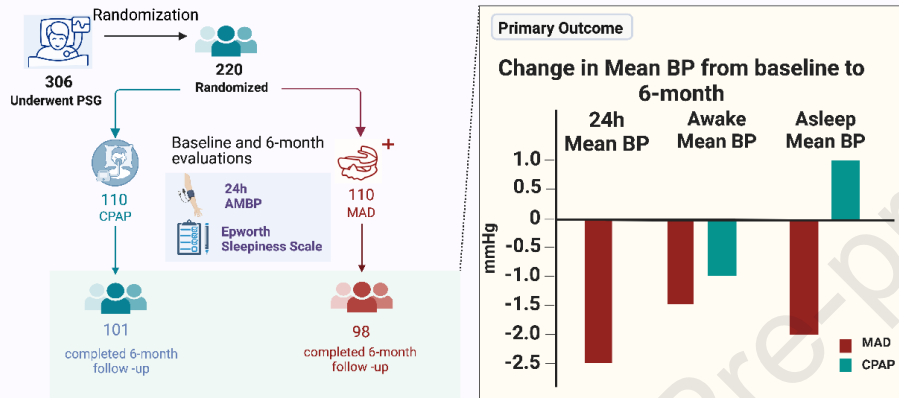


The non-inferiority of MAD against CPAP is demonstrated because the confidence interval does not exceed the predefined margin of 1.5 mmHg (dotted line).¹

Figure 4



CENTRAL ILLUSTRATION: Mandibular Advancement vs CPAP for Blood Pressure Reduction in Patients with Obstructive Sleep Apnea



Central Illustration - approved 3/7/24

Original Investigation

Mandibular Advancement vs CPAP for Blood Pressure Reduction in Patients with Obstructive Sleep Apnea

(Running title: Mandibular Advancement for Sleep Apnea)

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Contents

Supplemental Method 1. MAD and CPAP titration protocol and prespecified device adherence and treatment effects. **Page 3**

Supplemental Method 2. Standard operating procedure for 24-hour ambulatory blood pressure monitoring. **Page 6**

Supplemental Method 3. CRESCENT Trial - 24-hour ambulatory blood pressure monitoring instructions. **Page 7**

Supplemental Table 1. Baseline characteristics of the participants who completed the study versus those who withdrew. **Page 8**

Supplemental Table 2. Device adherence and residual AHI at acclimatization period and 6-month follow-up. **Page 9**

Supplemental Table 3. Baseline characteristics of the participants who completed both the baseline and 6-month ambulatory blood pressure monitoring. **Page 10**

Supplemental Table 4. Medication changes. **Page 11**

Supplemental Table 5. Between-group difference in blood pressure changes from baseline to 6-month in participants without medication change. **Page 12**

Supplemental Table 6. Between-group difference in blood pressure changes from baseline to 6-month follow-up, excluding those who withdrew. **Page 13**

Supplemental Table 7. Between-group difference in cardiovascular biomarkers changes from baseline to 6-month. **Page 14**

Supplemental Method 1. MAD and CPAP Titration Protocol and prespecified device adherence and treatment effects

Device visit 0

CPAP arm (not applicable)

MAD arm

- Dental examination
- Individual 3D dental scan images for manufacture of the device will be taken at a mandibular protrusive bite of 75% of maximum protrusion
-

Device visit 1

- Explanation of sleep study result and importance of OSA control by study team members

CPAP arm

- Nasal examination (anterior rhinoscopy) by an otolaryngologist
- Prescription of nasal spray is offered if nose looks very obstructed or patients complain of frequent nasal blockage
- Resmed Airsense 10 Autoset CPAP is used in the CRESCENT trial
- Fitting of patient with an appropriate mask interface prior to commencing CPAP
 - Nasal mask is recommended by default
 - Full-face mask is recommended for patients who are habitual mouth breathers, have severe nasal blockage, or do not want a mask over the nose alone
- CPAP is configured to auto setting (4cm/H₂O-20cm/H₂O)
- CPAP education including instruction on CPAP machine operation, cleaning and storage by a trained therapist

MAD arm

- SomnoDent Fusion Flex is used in the CRESCENT trial
- Device assembly including the wings and titration key
- Protrusion will be set at 70-75% of maximum protrusion
- A periodontal probe will be used to verify the remaining protrusion distance before maximum protrusion is reached. During the titration procedure, the mandible is gradually positioned in a more anterior position to achieve a maximum therapeutic effect on opening the upper airway
- The number of 90 degree turns is calculated accordingly (patient will be instructed on the number of turns per week until dental visit 2, in order to reach maximum tolerated protrusion during the acclimatization period).
- If the patients develop side effects during the titration, the MAD will be advanced until the maximum comfortable limit of advancement is achieved
- MAD education including instruction on cleaning and storage of the device by a trained therapist

4 weeks acclimatization period (between device visit 1 and visit 2)

- Telephone support (face-to-face if necessary) from a device therapist is available during this acclimatization period

CPAP arm

- CPAP adherence will be reviewed weekly by the trained therapist via AirView, a secure cloud-based patient management system
- If CPAP usage does not reach the pre-defined minimum threshold of 4 hours per night for at least 5 nights in the preceding week, the patient will be contacted by text message and/or phone call to explore any potential issues limiting usage. Side effects will be sorted out and adherence reinforced

MAD arm

- The patients will be contacted once a week by text message and/or phone call to determine the subjective adherence and side effects (especially teeth or temporomandibular joint pain)
- Clinical titration of the MAD to a maximum tolerated advancement
- Home-based portable sleep study using WatchPAT will be performed at the end of the 4-week acclimatization period to document treatment effects

Device visit 2 (beginning of the treatment period)

- Explanation of device adherence report
- Discuss side effects and adherence, offer alternatives if required

Device visit 3 (1 month from visit 2, *optional visit*)

- Review the latest device adherence report
- Follow-up on the device adjustments made during prior device visits, if any
- If there is a significant adjustment/change of the device setting/mask during this visit, or if adherence is poor and patient is deemed to benefit from closer follow-up, the patient will be scheduled for device visit 4

Device visit 4 (2 months from visit 3, *optional visit*)

- Review the latest device adherence report
- Follow-up on the device adjustments made during prior device visits

Device visit 5 (end of 6-month treatment period)

- A new mask (CPAP arm) will be replaced if required
- Assessment of the device adherence and AHI

Device visit 6 (end of 12-month treatment period)

- Return of CPAP machine if the patients decline to continue with the treatment.
- CPAP/MAD will be offered to those who are willing to continue with the treatment
- Assessment of the device adherence and AHI

Treatment Period

Important device-related definitions

Device adherence will be measured based the following pre-defined definitions:

- Number of nights with ≥ 4 hours **divided by** total number of nights: ≥ 0.7 Yes/No
- Total number usage hours **divided by** total number of night _ hrs/night

- Total number usage hour **divided by** total number of night: ≥ 4.0 Yes/No
- Total number usage hour **divided by** total number of night: ≥ 5.0 Yes/No
- Total number usage hour **divided by** total number of night: ≥ 6.0 Yes/No

Device adherence variability will be reported. It is defined as daily variability in device adherence. Various measurements of adherence variability will be used:

- Corrected variability independent of the mean (cVIM)
- Coefficient of variation
- Standard deviation

Treatment response will be measured based on the following pre-defined criteria:

Device treatment effect will be determined at the end of the 4-week acclimitization period. It will be determined by the AirView™ (CPAP arm) and WatchPAT (MAD arm). Treatment response will be measured based on the following pre-defined criteria:

- Final AHI < 5 events per hour Yes/No
- $\geq 50\%$ reduction in AHI Yes/No
- $\geq 20\%$ reduction in AHI + final AHI < 15 events per hour Yes/No

Supplemental Method 2. Standard Operating Procedure for 24hr Ambulatory Blood Pressure Monitoring (ABPM) – CRESCENT

Introduction: Participants in this study will undergo 24-hour Ambulatory Blood Pressure Monitoring (ABPM) using the Welch Allyn ABPM device at three points: baseline, 6 months, and 12 months. This procedure aims to gather comprehensive blood pressure data over an entire day, helping us gain valuable insights into blood pressure patterns.

Equipment:

- We will employ the Welch Allyn 7100 ABPM device, which should be equipped with two fresh AA batteries before each use.
- The monitor will connect to a laptop or desktop computer via a USB port, using a specific cable for this purpose.

Software:

- For data analysis, we will utilize the Welch Allyn CardioPerfect Software module, which will be installed on a designated computer.

Cuff Selection and Placement:

- The non-dominant arm will be designated for monitoring.
- The device will record blood pressure at 30-minute intervals over 24 hours.
- We have four cuff sizes available to accommodate various arm circumferences:
 - Small adult: 20-24 cm
 - Adult: 24-32 cm
 - Adult plus: 32-38 cm
 - Large adult: 38-55 cm

Procedure:

- Position the ABPM monitor on the hip, securing it with the strap either over the shoulder or around the waist.
- Place the appropriate cuff size on the non-dominant arm.
- Press the Start/Stop button to initiate the first blood pressure reading. A successful placement will not display an "error" signal, and the time should be visible on the monitor's display.

Participant Diary:

- Participants will receive an ABPM Participant Diary, urging them to record their bedtime, wake-up time, and any intercurrent naps diligently.

Data Retrieval:

- Upon the participant's return to the clinic, the monitor can be removed if it has been worn for a full 24 hours. If not, we will ask the participant to wait until a 24-hour recording is completed (if possible).
- We will then connect the monitor to the computer using the CardioPerfect software for data retrieval.
- To consider the procedure valid, the report must consist of a minimum of 21 readings over 24 hours. If there are fewer than 21 readings, the test will be deemed invalid, and the participant will be requested to repeat the ABPM for another 24 hours.

Supplemental Method 3. CRESCENT Trial - 24-Hour Blood Pressure Monitoring Instructions

Thank you for participating in the CRESCENT Trial's 24-hour blood pressure monitoring. To ensure accurate results, please adhere to the following guidelines:

- 1. Continuous Wear:** The blood pressure monitor should be worn continuously for the next 24 hours.
- 2. Automated Readings:** The monitor will automatically record your blood pressure every 30 minutes throughout the day and night. Please do not remove or adjust the blood pressure cuff during this period.
- 3. Removal After 24 Hours:** Only remove the blood pressure cuff and switch off the monitoring device after a full 24 hours have passed.
- 4. Minimal Interaction:** Avoid pressing any buttons on the monitoring device, except for the power button when turning it off after 24 hours.
- 5. Proper Cuff Placement:** Keep the blood pressure cuff securely on your arm at all times. Do not remove or adjust it during the monitoring period.
- 6. Tubing Caution:** Be mindful not to kink or twist the tubing, as this could lead to inaccuracies in the readings.
- 7. Normal Activities:** Carry out your regular daily activities as usual (with the exception of showering).
- 8. Error Handling:** If the monitor encounters an error during the first reading, it will automatically attempt a second reading. Please do not intervene; simply keep your arm relaxed to allow for accurate measurements.
- 9. Skin Sensitivity:** Be aware that wearing the cuff for an extended period may cause minor skin irritation or rashes, particularly for those with sensitive skin. Avoid scratching and keep the area dry if this occurs.
- 10. Blood Pressure Diary:** Lastly, remember to diligently fill out your blood pressure diary and return it to us. Your participation is greatly appreciated, and it contributes to the success of our trial.

Thank you for your cooperation and commitment to the CRESCENT Trial. Your contribution is invaluable in advancing medical research.

Supplemental Table 1. Baseline characteristics of the participants who completed versus withdrew from the study

Variable	Complete (n=199)	Withdrew (n=21)	P value
Demographic			
Age (years), median (IQR)	62.0 (56.0-65.0)	58.0 (53.0-64.0)	0.115
Male sex, n (%)	170 (85.4)	18 (85.7)	0.972
Height (m), median (IQR)	168.0 (162.0-172.0)	166.0 (160.0-172.0)	0.841
Weight (kg), median (IQR)	78.1 (68.6-86.1)	75.7 (67.0-81.0)	0.320
BMI (kg/m ²), median (IQR)	27.7 (25.4-30.7)	26.5 (25.2—29.2)	0.293
Neck circumference (cm), median (IQR)	39.5 (37.0-41.7)	39.0 (36.5-40.0)	0.342
Waist circumference (cm), median (IQR)	97.5 (92.5-104.0)	93.5 (90.0-95.0)	0.045
Hip circumference (cm), median (IQR)	101.2 (97.5-106.5)	101.5 (95.9-107.5)	0.450
Waist/Hip ratio, median (IQR)	1.0 (0.9-1.0)	0.9 (0.9-1.0)	0.032
Hypertension duration			
<5 years	37 (18.6)	6 (28.6)	0.025
5-10 years	30 (15.1)	2 (9.5)	
>10 years	93 (46.7)	4 (19.1)	
Unknown	39 (19.6)	9 (42.9)	
Number of blood pressure lowering medication			
1	61 (30.7)	8 (38.1)	0.926
2	86 (43.2)	8 (38.1)	
3	40 (20.1)	4 (19.1)	
≥4	12 (6.0)	1 (4.8)	
Polysomnography findings			
Total sleep time (min), median (IQR)	361.0 (312.0-391.0)	323.0 (271.4-394.5)	0.219
AHI, events per hour, median (IQR)	39.8 (24.6-54.1)	31.8 (22.1-38.3)	0.039
Number (%) of patients with AHI >30 events/hour	133 (66.8)	11 (52.4)	0.185
ODI, events per hour, median (IQR)	28.4 (16.5-46.1)	14.1 (10.8-30.0)	0.001
RDI, events per hour, median (IQR)	39.9 (24.9-54.1)	31.8 (22.1-39.4)	0.040
Arousal index, events per hour, median (IQR)	15.4 (7.8-24.2)	12.1 (7.5-25.9)	0.884
Mean SpO ₂ (%), median (IQR)	94.2 (93.0-95.0)	95.0 (94.0-95.0)	0.251
Minimum SpO ₂ (%), median (IQR)	81.0 (76.0-85.0)	85.0 (78.0-88.0)	0.074
ESS score, median (IQR)	8.0 (4.0-12.0)	7.0 (3.0-9.0)	0.042

BMI: body-mass index, AHI: apnea-hypopnea index, ODI: oxygen desaturation index, RDI: respiratory disturbance index, ESS: Epworth Sleepiness Scale, SpO₂: saturation of peripheral oxygen, IQR: interquartile range

Supplemental Table 2. Device adherence and residual AHI at acclimatization period and 6-month follow-up

Variable	MAD	CPAP
Acclimatization period	(n=91) ^a	(n=104) ^b
Device adherence		
At least 70% of the night used at least 4 hours, n (%)	65 (71.4)	60 (57.7)
Six-month follow-up		
Device adherence	(n=85) ^e	(n=99) ^f
At least 70% of the night used at least 4 hours, n (%)	59 (69.4)	63 (64.3)
Average usage, (minutes), median (IQR)	327.0 (224.0-401.0)	299.0 (182.0-353.0)
Average usage at least 4 hours per night, n (%)	64 (75.3)	68 (68.7)
Average usage at least 5 hours per night, n (%)	57 (67.1)	51 (51.5)
Average usage at least 6 hours per night, n (%)	48 (56.5)	23 (23.2)
Residual AHI	(n=98)	(n=99) ^f
AHI (events per hour), median (IQR)	10.8 (5.0-18.9) ^c	2.0 (1.0-3.1) ^d
AHI <5 (events per hour), n (%)	16 (17.2)	93 (93.9)
≥50% reduction in AHI, n (%)	71 (76.3)	99 (100.0)
≥20% reduction in AHI + final AHI <15, n (%)	62 (66.7)	97 (98.0)

AHI: apnea-hypopnea index, IQR: interquartile range

^a 9 have no dentitrac due to manufacturing problems caused by the COVID-19 pandemic, 2 dentitrac malfunctioned during acclimatization period, 3 withdrew before starting acclimatization, 5 withdrew before end of acclimatization period

^b 1 had no data from the CPAP machine during acclimatization period, 5 withdrew before starting acclimatization

^c Residual AHI is obtained by manually scored the sleep study tracing from home-based portable sleep study using a wrist-worn, WatchPAT device (3% hypopnea scoring criteria)

^d Residual AHI is obtained from CPAP-built in

^e 4 withdrew before 6-month follow up, of which, 1 of the 4 who withdrew returned the MAD device and underwent homebased sleep study before withdrawing, hence we were able to obtain compliance data from the dentitrac and the AHI after 6 months of treatment. 5 dentitrac malfunctioned. 9 have no dentitrac due to manufacturing problems caused by the COVID-19 pandemic

^f 1 had no data from CPAP machine during 6-month follow up, 1 only performed ABPM at 6-month follow up due to work schedule, 4 withdrew before 6-month follow up.

Supplemental Table 3. Baseline characteristics of the participants who completed both the baseline and 6-month ambulatory blood pressure monitoring

Variable	MAD (n=98)	CPAP (n=101)	P value
Demographic			
Age (years), median (IQR)	62.0 (57.0-66.0)	61.0 (55.0-65.0)	0.367
Male sex, n (%)	85 (86.7)	85 (84.2)	0.607
Height (m), median (IQR)	169.0 (162.0-173.0)	167.0 (162.0-172.0)	0.256
Weight (kg), median (IQR)	79.0 (68.6-86.5)	77.8 (68.6-86.1)	0.781
BMI (kg/m ²), median (IQR)	27.7 (25.4-30.5)	27.7 (25.4-30.9)	0.944
Neck circumference (cm), median (IQR)	39.5 (37.3-42.0)	39.5 (37.0-41.5)	0.626
Waist circumference (cm), median (IQR)	97.5 (93.3-103.7)	97.5 (92.5-104.0)	0.767
Hip circumference (cm), median (IQR)	101.0 (97.5-106.0)	101.3 (97.7-106.5)	0.652
Waist/Hip ratio, median (IQR)	1.0 (0.9-1.0)	1.0 (0.9- 1.0)	0.258
Hypertension duration			
<5 years	14 (14.3)	23 (22.8)	0.494
5-10 years	16 (16.3)	14 (13.9)	
>10 years	48 (49.0)	45 (44.6)	
Unknown	20 (20.4)	19 (18.8)	
Number of blood pressure lowering medication			
1	26 (26.5)	36 (35.6)	0.185
2	52 (53.1)	40 (39.6)	
3	16 (16.3)	22 (21.8)	
≥4	4 (4.1)	3 (3.0)	
Polysomnography findings			
Total sleep time (min), median (IQR)	359.0 (302.0-388.0)	364.0 (323.0-394.0)	0.568
AHI, events per hour, median (IQR)	39.1 (24.9-50.4)	40.7 (24.6-56.3)	0.685
Number (%) of patients with AHI >30 events/hour	68 (69.4%)	65 (64.4%)	0.451
ODI, events per hour, median (IQR)	27.1 (16.0-44.6)	32.7 (17.1-48.1)	0.234
RDI, events per hour, median (IQR)	39.3 (25.0-50.8)	40.7 (24.6- 56.3)	0.665
Arousal index, events per hour, median (IQR)	15.4 (6.6-24.2)	15.7 (8.7-23.9)	0.429
Mean SpO ₂ (%), median (IQR)	95.0 (93.0-95.0)	94.0 (93.0-95.0)	0.863
Minimum SpO ₂ (%), median (IQR)	82.0 (77.0-85.0)	80.0 (74.0-84.0)	0.136
ESS score, median (IQR)	8.0 (4.0-11.0)	8.0 (5.0-12.0)	0.492

BMI: body-mass index, AHI: apnea-hypopnea index, ODI: oxygen desaturation index, RDI: respiratory disturbance index, ESS: Epworth Sleepiness Scale, SpO₂: saturation of peripheral oxygen, IQR: interquartile range

Supplemental Table 4. Medication changes

Study number	Type of change	Details of the change
033CSC_010M	increase type	New Amlodipine 2.5 mg once every morning
051CSC_023M	increase dose	Increase in dose of Enalapril from 7.5 mg twice daily to 10 mg twice daily
096CSC_032M	switch type	Switched from Lisinopril 2.5 mg once every morning to Valsartan 40 mg once every morning
136CSC_074M	increase dose	Increased in dose of Amlodipine from 2.5 mg once every morning to 5 mg once every morning
145CSC_051M	increase type	New Telmisartan 40mg once every morning
163CSC_056M	increase type	New Frusemide 20mg once every morning
173CSC_055M	switch type	Switched from Nifedipine 60 mg twice daily to Amlodipine 10 mg once every morning
180CSC_058M	decrease type	Stopped Atenolol 50 mg once every morning
183CSC_062M	increase dose	Increased Amlodipine from 2.5 mg once every morning to 5 mg once every morning
242CSC_081M	increase dose	Increased Carvedilol from 6.25 mg twice daily to 12.5 mg twice daily
251CSC_086M	increase dose	Increased Enalapril 7.5 mg twice daily to 10 mg twice daily
274CSC_095M	switch type + increase dose	Switched from Atenolol 100 mg once every morning to Carvedilol 6.25 mg twice daily, increased Prazosin from 2 mg once every night to 4 mg once every night
311CSC_106M	decrease type	Stopped amlodipine 2.5 mg once every morning
050CSC_023C	increase dose	Increase in dose of Valsartan from 40 mg once every morning to 80 mg once every morning
054CSC_024C	switch type + increase dose	Increase in dose of Valsartan from 40 mg once every night to 160 mg once every morning 80 mg once every night, increase in dose of Bisoprolol from 5 mg once every morning to 10mg once every morning, new Spironolactone 12.5 mg once every morning, reduce Frusemide from 40 mg once every morning to 20 mg once every morning when required
169CSC_061C	increase type	New Spironolactone 25 mg once every morning
210CSC_079C	increase type	New Amlodipine 2.5 mg once every morning
214CSC_077C	decrease type	Stopped Amlodipine 7.5 mg once every morning
226CSC_081C	increase dose	Increased Losartan from 75 mg once every morning to 100 mg once every morning
245CSC_087C	decrease type	Stopped Hydrochlorothiazide
259CSC_093C	increase dose + decrease type	Increased Bisoprolol from 5 mg once every morning to 7.5 mg once every morning, stopped Nifedipine 30 mg once every morning

Study numbers end with M: MAD group; Study numbers end with C: CPAP group

Supplemental Table 5. Between-group difference in blood pressure changes from baseline to 6-month in participants without medication change

	MAD (n=85) ^a		CPAP (n=93) ^a		Difference (95% CI) in BP changes (mm Hg)	p value ANOVA
	Baseline	6-month	Baseline	6-month		
24-hour, mmHg, median (IQR)						
Mean BP	95.0 (89.0-101.0)	93.0 (87.-99.0) ^b	96.0 (90.0-100.0)	94.0 (88.0-101.0)	-1.39 (-3.33 to 0.56)	0.002 ^c
Systolic BP	124.5 (117.0-132.0)	123.0 (115.0-133.0) ^b	126.0 (117.0-133.0)	125.0 (116.0-132.0)	-1.83 (-4.33 to 0.67)	0.005
Diastolic BP	79.5 (75.0-86.0)	78.0 (73.0-84.0) ^b	80.0 (73.0-86.0)	79.0 (72.0-85.0)	-1.07 (-2.87 to 0.72)	0.003
Pulse pressure	44.0 (39.0-49.0)	44.0 (39.0-50.0)	46.0 (40.0-52.0)	45.0 (39.0-51.0)	-0.38 (-1.80 to 1.05)	0.005
Awake, mmHg, median (IQR)						
Mean BP	96.5 (91.0-102.0)	95.0 (90.0-101.0)	98.0 (92.0-104.0)	96.0 (90.0-104.0)	-0.94 (-3.02 to 1.13)	0.021
Systolic BP	125.5 (120.0-135.0)	124.0 (117.0-134.0)	129.0 (119.0-136.0)	127.0 (118.0-136.0)	-1.64 (-4.45 to 1.17)	0.014
Diastolic BP	81.5 (76.0-88.0)	80.0 (75.0-85.0)	82.0 (75.0-88.0)	81.0 (74.0-88.0)	-0.59 (-2.50 to 1.31)	0.016
Pulse pressure	45.0 (39.0-51.0)	44.0 (40.0-50.0)	45.0 (40.0-52.0)	46.0 (40.0-52.0)	-0.62 (-2.44 to 1.20)	0.011
Asleep, mmHg, median (IQR)						
Mean BP	91.0 (85.0-98.0)	90.0 (83.0-97.0) ^b	90.0 (85.0-98.0)	90.0 (84.0-98.0)	-2.40 (-5.15 to 0.35)	0.003
Systolic BP	120.0 (112.0-130.0)	118.0 (109.0-130.0)	120.0 (112.0-129.0)	120.0 (111.0-129.0)	-2.62 (-6.14 to 0.90)	0.011
Diastolic BP	76.0 (71.0-84.0)	75.0 (69.0-81.0) ^b	76.0 (70.0-82.0)	75.0 (69.0-83.0)	-2.34 (-4.87 to 0.20)	0.002
Pulse pressure	43.5 (39.0-48.0)	42.0 (39.0-51.0)	44.0 (39.0-49.0)	45.0 (39.0-49.0)	0.30 (-1.50 to 2.10)	0.906

BP: blood pressure, IQR: interquartile range

^a13 from the MAD group and 8 from the CPAP group have medication changes. Refer to Supplemental Table 3 for the details of the changes.

^bchange from baseline to 6-month p<0.05

^cstatistically significant non-inferiority at 5%

Supplemental Table 6. Between-group difference in blood pressure changes from baseline to 6-month follow-up, excluding those who withdrew

	MAD (n=98) ^b		CPAP (n=101) ^c		Difference (95% CI) in BP changes (mmHg)	p value ANOVA
	Baseline	6-month	Baseline	6-month		
24-hour, mmHg, median (IQR)						
Mean BP (primary endpoint) ^a	96.0 (89.0-101.0)	93.5 (88.0-99.0) ^d	96.0 (90.0-100.0)	95.0 (88.0-101.0)	-1.64 (-3.51 to 0.24)	<0.001 ^e
Systolic BP	125.0 (118.0-132.0)	123.0 (115.0-133.0) ^d	126.0 (118.0-133.0)	125.0 (116.0-134.0)	-2.12 (-4.55 to 0.31)	0.002
Diastolic BP	80.0 (75.0-86.0)	79.0 (73.0-83.0) ^d	80.0 (74.0-86.0)	79.0 (72.0-85.0)	-1.27 (-2.97 to 0.44)	<0.001
Pulse pressure	44.0 (39.0-50.0)	44.0 (40.0-50.0)	45.0 (40.0-52.0)	46.0 (39.0-52.0)	-0.53 (-1.90 to 0.83)	0.002
Awake, mmHg, median (IQR)						
Mean BP	97.0 (91.0-102.0)	96.0 (90.0-101.0)	98.0 (92.0-104.0)	96.0 (90.0-104.0)	-1.15 (-3.17 to 0.86)	0.005
Systolic BP	126.0 (121.0-135.0)	124.0 (117.0-134.0)	129.0 (119.0-136.0)	127.0 (119.0-136.0)	-1.83 (-4.56 to 0.90)	0.009
Diastolic BP	81.0 (76.0-88.0)	81.0 (75.0-85.0) ^d	82.0 (76.0-88.0)	81.0 (74.0-88.0)	-0.83 (-2.66 to 1.00)	0.007
Pulse pressure	45.0 (40.0-51.0)	44.0 (40.0-50.0)	45.0 (40.0-52.0)	46.0 (40.0-52.0)	-0.61 (-2.33 to 1.11)	0.008
Asleep, mmHg, median (IQR)						
Mean BP	92.0 (85.0-99.0)	90.0 (83.0-96.0) ^d	91.0 (85.0-99.0)	91.0 (84.0-98.0)	-2.43 (-4.97 to 0.11)	0.001
Systolic BP	121.5 (113.0-130.0)	118.0 (110.0-129.0) ^d	121.0 (113.0-130.0)	120.0 (111.0-131.0)	-2.85 (-6.14 to 0.44)	0.005
Diastolic BP	76.5 (71.0-84.0)	75.0 (69.0-81.0) ^d	76.0 (70.0-83.0)	76.0 (70.0-83.0)	-2.26 (-4.59 to 0.06)	0.001
Pulse pressure	44.0 (40.0-49.0)	43.0 (39.0-51.0)	44.0 (39.0-49.0)	45.0 (39.0-50.0)	0.02 (-1.68 to 1.72)	0.957

BP: blood pressure, IQR: interquartile range

^a Mean BP is calculated as one-third of the sum of systolic BP and 2 times of the diastolic BP

^b 12 participants withdrew from the MAD group before ABPM during 6-month follow up.

^c 9 participants withdrew from the CPAP before ABPM during 6-month follow up.

^d Change from baseline to 6-month p<0.05.

^e Statistically significant (<0.001, non-inferiority). Statistically insignificant (0.086, superiority)

Supplemental Table 7. Between-group difference in cardiovascular biomarkers changes from baseline to 6-month follow-up

	MAD		CPAP		Difference (95% CI) in biomarkers changes	p value ANOVA
	Baseline (n=108)	6-month (n=99)	Baseline (n=105)	6-month (n=100)		
High-sensitivity CRP, mg/L, median (IQR)	0.9 (0.5-1.8)	0.8 (0.4-1.2) ^a	1.2 (0.5-2.9)	1.0 (0.5-2.6) ^b	0.05 (-0.91 to 1.00)	0.925
NT-pro BNP, pg/ml, median (IQR)	49.3 (20.5-95.4)	44.6 (26.9-115.3)	51.8 (25.7-100.2)	41.2 (21.9 -98.4) ^c	22.07 (-11.60 to 55.75)	0.198
High-sensitivity Troponin T, pg/ml, median (IQR)	7.3 (5.3-10.4)	7.8 (6.0-10.1) ^c	6.8 (5.1-9.1)	7.3 (4.9-10.5)	0.28 (-0.72 to 1.29)	0.577

CRP: C-reactive protein, IQR: interquartile range, NT-pro BNP: N-terminal pro B-type natriuretic peptide

^an=98 as the high-sensitivity CRP result was invalid for one patient

^bn=99 as the high-sensitivity CRP result was invalid for one patient

^cchange from baseline to 6-month, p<0.05