

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



Yi-Hui Ou, BSc (PHARM),^a Juliana Tereza Colpani, DDS, MS,^b Crystal S. Cheong, MBBS,^c Weiqiang Loke, BDS,^b As tar Thant, RPSGT,^a E' Ching Shih, MBBS,^c Frank Lee, BDS,^b Siew-Pang Chan, PhD,^{a,d,e} Ching-Hui Sia, MBBS,^e Chieh-Yang Koo, MBBS,^e Serene Wong, MBBS,^f Aiping Chua, MBBS,^g Chin-Meng Khoo, MBBS,^a William Kong, MBBS, PhD,^{a,e} Calvin W. Chin, MD, PhD,^{h,i} Pipin Kojojojo, MBBS, PhD,^e Philip E. Wong, MBBS,^j Mark Y. Chan, MBBS, PhD,^{a,d,e} A. Mark Richards, MD, PhD,^{a,d,e,k} Peter A. Cistulli, MBBS, PhD,^{l,m} Chi-Hang Lee, MBBS, MD^{a,d,e}

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 continuous positive airway pressure (CPAP).

OBJECTIVES We compared the relative effectiveness of MAD vs CPAP in reducing 24-hour ambulatory blood pressure (BP).

METHODS In an investigator-initiated, randomized, noninferiority trial (prespecified margin 1.5 mm Hg), 321 participants aged ≥ 40 years 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 ≥ 15 events per 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 with baseline, the 24-hour mean arterial BP decreased by 2.5 mm Hg ($P = 0.003$) 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 mm Hg (95% CI: -3.51 to 0.24 , noninferiority $P < 0.001$). The MAD group demonstrated a larger between-group reduction in all secondary ambulatory BP parameters compared with 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.

CONCLUSIONS MAD is noninferior to CPAP for reducing 24-hour mean arterial BP in participants with hypertension and increased cardiovascular risk. (Cardiosleep Research Program on Obstructive Sleep Apnea, Blood Pressure Control and Maladaptive Myocardial Remodeling—Non-inferiority Trial [CRESCENT]; [NCT04119999](https://clinicaltrials.gov/ct2/show/study/NCT04119999)) (J Am Coll Cardiol 2024;83:1760-1772) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



Listen to this manuscript's audio summary by Editor-in-Chief Dr Valentin Fuster on www.jacc.org/journal/jacc.

From the ^aDepartment of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; ^bDepartment of Endodontics, Operative Dentistry and Prosthodontics, Faculty of Dentistry, National University of Singapore, Singapore; ^cDepartment of Otolaryngology-Head & Neck Surgery, National University Hospital, Singapore, Singapore; ^dCardiovascular Research Institute, National University Heart Centre, Singapore, Singapore; ^eDepartment of Cardiology, National University Heart Centre, Singapore, Singapore; ^fDepartment of Medicine, Alexandra Hospital, Singapore; ^gDepartment of Medicine, Ng Teng Fong General Hospital, Singapore; ^hDepartment of Cardiology, National Heart Centre Singapore, Singapore; ⁱCardiovascular ACP, Duke-NUS Medical School, Singapore; ^jDepartment of Medicine, Raffles Hospital, Singapore; ^kChristchurch Heart Institute, University of Otago, Dunedin, New Zealand; ^lSleep Research Group, Charles Perkins Centre and Northern Clinical School, Faculty of Medicine and Health, University of Sydney, Camperdown, New South Wales, Australia; and the ^mDepartment of Respiratory and Sleep Medicine, Royal North Shore Hospital, St Leonards, New South Wales, Australia.

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 underdiagnosed 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.

SEE PAGE 1773

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 vs CPAP in reducing BP in patients with moderate-to-severe OSA and hypertension. Our hypothesis was that MAD would be noninferior to CPAP in reducing 24-hour mean arterial BP.

METHODS

TRIAL DESIGN. CRESCENT (Cardiosleep Research Program on Obstructive Sleep Apnea, Blood Pressure Control and Maladaptive Myocardial Remodeling—Non-inferiority Trial; [NCT04119999](#)) was an investigator-initiated, randomized, open-

label, noninferiority trial 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 article. 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 3 public hospitals in Singapore (National University Hospital, National Heart Centre Singapore, and Ng Teng Fong General Hospital). Because the predominant ethnicity in Singapore is Chinese, we recruited adults of Chinese ethnicity aged ≥ 40 years with known hypertension and at least 1 other factor for high cardiovascular risk 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 is 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) 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

ABBREVIATIONS AND ACRONYMS

AASM = American Academy of Sleep Medicine

AHI = apnea-hypopnea index

BMI = body mass index

BP = blood pressure

CPAP = continuous positive airway pressure

ESS = Epworth Sleepiness Scale

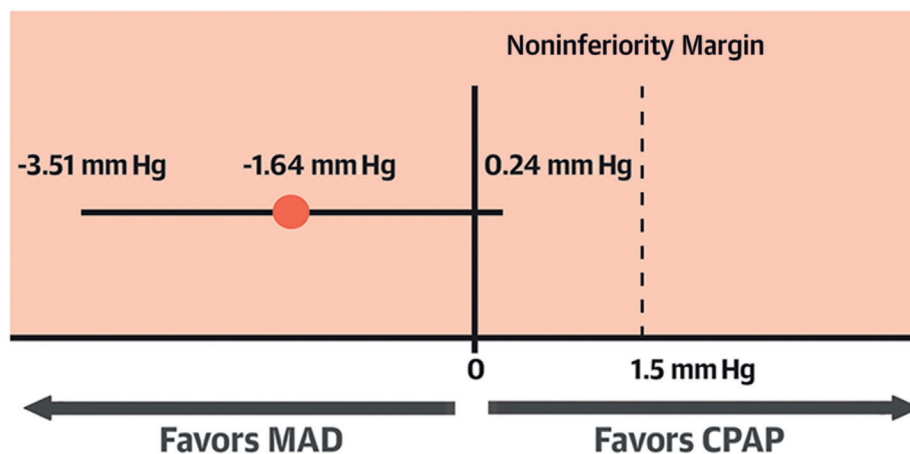
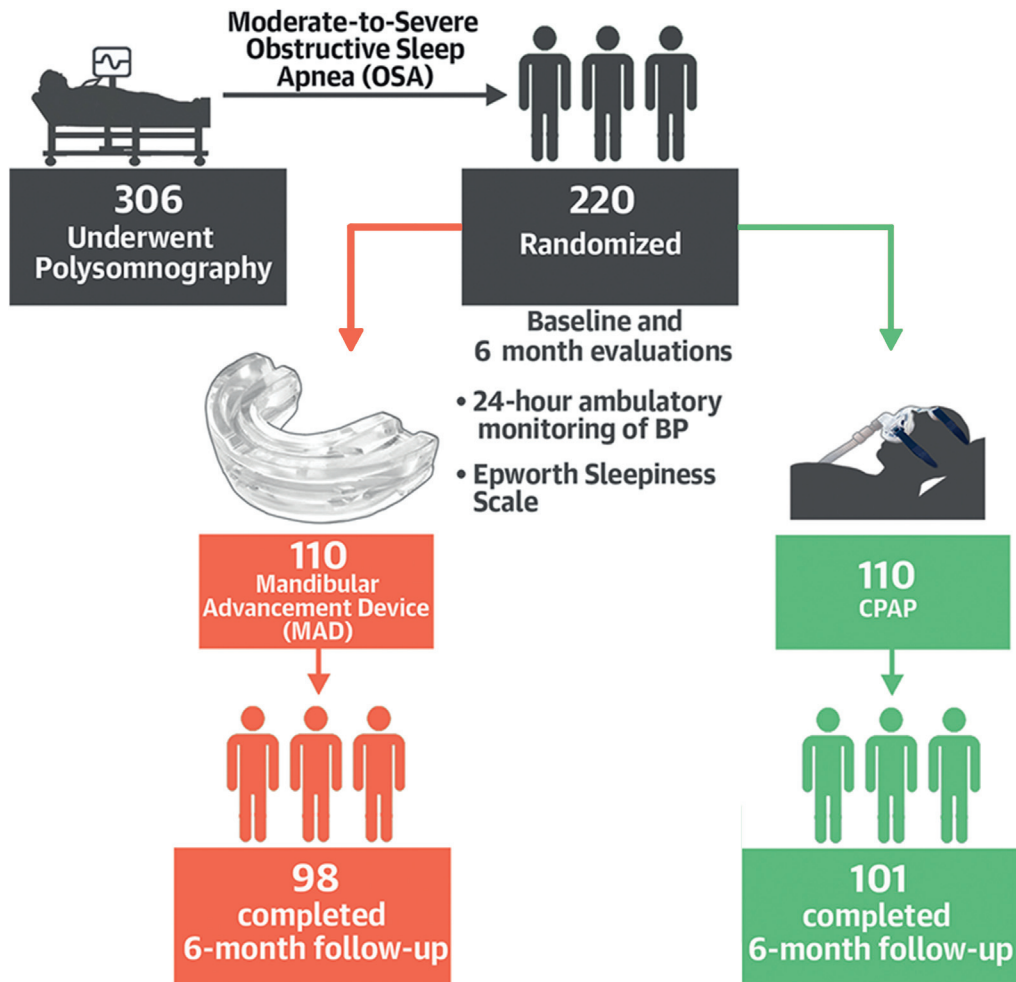
MAD = mandibular advancement device

ODI = oxygen desaturation index

OSA = obstructive sleep apnea

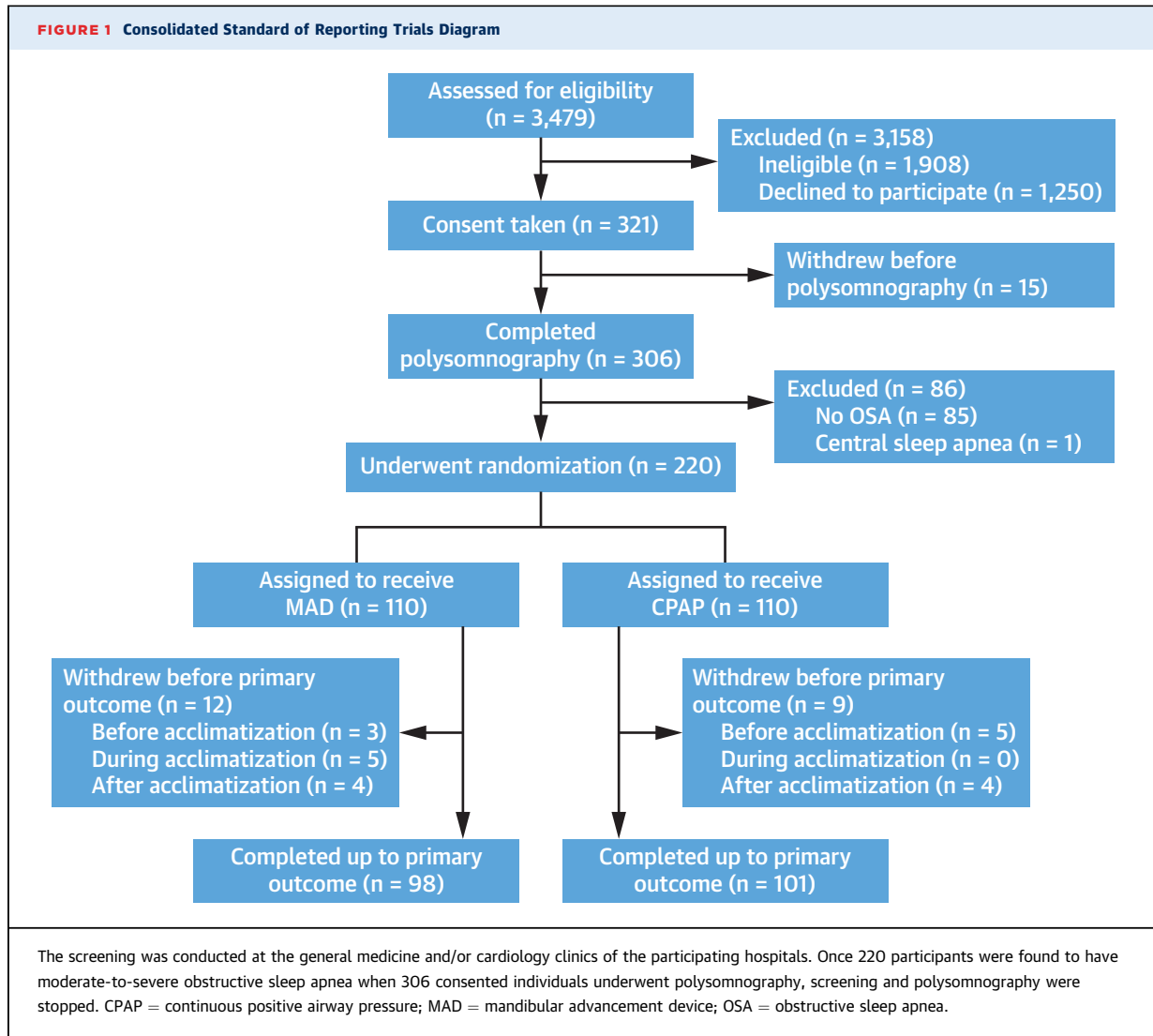
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

CENTRAL ILLUSTRATION Cardiosleep Research Program on Obstructive Sleep Apnea, Blood Pressure Control, and Maladaptive Myocardial Remodeling—Noninferiority Trial



Ou Y-H, et al. J Am Coll Cardiol. 2024;83(18):1760-1772.

MAD is noninferior 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. CPAP = continuous positive airway pressure; MAD = mandibular advancement device.



diagnosed based on the 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), 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, 2-piece, adjustable MAD device (SomnoDent Flex, SomnoMed), whereas those assigned to the CPAP group were provided with an auto-titrating CPAP machine (AirSense 10, Resmed).

TABLE 1 Baseline Demographic and Clinical Characteristics of the Study Participants

	MAD (n = 110)	CPAP (n = 110)
Demographics		
Age, y	61.5 (56.0-66.0)	61.0 (55.0-65.0)
Male	96 (87.3)	92 (83.6)
Height, m	169.0 (162.0-172.0)	167.5 (162.0-172.0)
Weight, kg	78.1 (68.6-86.1)	77.4 (67.8-85.9)
BMI, kg/m ²	27.6 (25.4-30.5)	27.4 (25.2-30.6)
Neck circumference, cm	39.5 (37.5-42.0)	39.5 (36.5-41.5)
Waist circumference, cm	97.3 (93.0-103.3)	96.5 (92.2-104.0)
Hip circumference, cm	101.5 (97.5-106.5)	101.1 (97.0-106.5)
Waist/hip ratio	1.0 (0.9-1.0)	1.0 (0.9-1.0)
BMI 23-<27.5 kg/m ²	48 (43.6)	50 (45.5)
BMI ≥27.5 kg/m ²	56 (50.9)	53 (48.1)
Hypertension duration, y		
<5	16 (14.6)	27 (24.6)
5-10	17 (15.5)	15 (13.6)
>10	52 (47.3)	45 (40.9)
Unknown	25 (22.7)	23 (20.9)
Number of blood pressure medications		
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		
Diabetes mellitus ^a	65 (59.1)	65 (59.1)
Previous stroke ^a	8 (7.3)	8 (7.3)
Coronary artery disease ^a	66 (60.0)	68 (61.8)
Chronic kidney disease ^a	9 (8.2)	8 (7.3)
Age ≥75 y ^a	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		
Aspirin	59 (53.6)	67 (60.9)
P2Y ₁₂ 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)

Values are median (Q1-Q3) or n (%). ^aFactors of high cardiovascular risk. All the participants had at least 1 of these factors.
ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; BMI = body mass index; CABG = coronary artery bypass surgery; CPAP = continuous positive airway pressure; MAD = mandibular advancement device; PCI = percutaneous coronary intervention.

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), and in the CPAP group by a cloud-based telemedicine management platform (AirView, ResMed Corp). 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, 3% hypopnea scoring rule was used), and in the CPAP group by the in-built sensor in the CPAP machine. The pre-specified treatment adherence and treatment response definitions are provided in [Supplemental Method 2](#).

OUTCOMES. At baseline and 6-month 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, N-terminal pro-B-type natriuretic peptide, and high-sensitivity troponin T). Ambulatory BP monitoring was performed with readings acquired every 30 minutes using an approved device (Welch Allyn ABPM 7100, Welch Allyn). 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 mm Hg and <120 mm Hg, respectively, ESS score, and cardiovascular biomarkers.

NONINFERIORITY MARGIN AND SAMPLE SIZE CALCULATION. The noninferiority margin was determined with the 2-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 mm Hg (95% CI: -5.3 to -1.3 mm Hg) with respect to sham CPAP,²⁶ the noninferiority threshold was set at 1.5 mm Hg after rounding up the reported smallest effect of 1.3 mm Hg.²⁴ The null hypothesis is that CPAP was more effective than MAD in lowering 24-hour mean arterial BP by at least 1.5 mm Hg. To detect the noninferiority 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 ± SD, median (Q1-Q3), and frequency (%). Exploratory data analyses were carried out with Wilcoxon-Mann-Whitney test and Fisher exact test. Change analyses between baseline and 6-month outcomes were ascertained with Wilcoxon signed ranked test and McNemar 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 noninferior to CPAP were examined with the 95% CIs, while referencing the previously mentioned noninferiority threshold (ie, 1.5 mm Hg). MAD was considered noninferior to CPAP if the upper limit of the 95% CI was less than the predetermined threshold.

Prespecified subgroup analyses were also conducted with age (>60 vs ≤60 years), 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 or 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).

RESULTS

SAMPLE CHARACTERISTICS. Between October 2019 and December 2022, a total of 220 participants (median age 61.0 years, 85.5% [188 of 220] male) were randomly assigned to MAD or CPAP in a 1:1 allocation (Figure 1). In accordance with the Asian cutoff, 44.5% (98 of 220) of the participants were overweight (BMI 23.0-27.5 kg/m²) and 49.5% (109 of 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 of 220) and diabetes mellitus (59.1%, 130 of 220). Hypertension had been present for more than 10 years in 44.1% (97 of 220) of participants. Baseline ESS and polysomnography findings are shown in Table 2. OSA was considered severe in 65.0% (143 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

TABLE 2 Baseline ESS and Polysomnography Findings

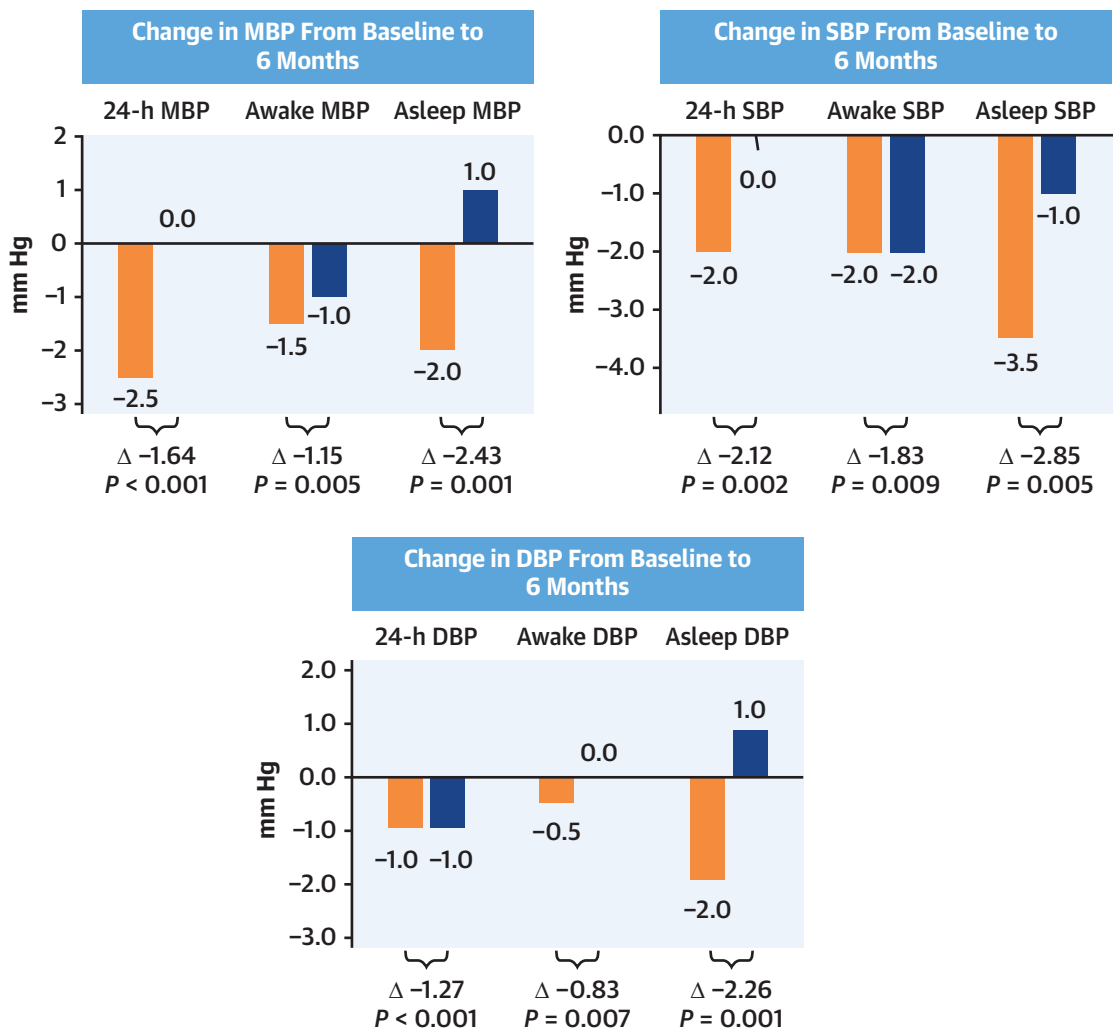
	MAD (n = 110)	CPAP (n = 110)
Daytime sleepiness severity		
Non-sleepy, ESS 0-10	81 (73.6)	72 (65.5)
Mildly sleepy, ESS 11-14	17 (15.5)	26 (23.6)
Moderately sleepy, ESS 15-17	7 (6.4)	8 (7.3)
Severely sleepy, ESS 18-24	5 (4.6)	4 (3.6)
AHI, events per hour	37.5 (23.9-49.9)	39.7 (24.6-54.7)
Patients with AHI		
15 to <30 events per hour	37 (33.6)	39 (35.5)
≥30 events per hour	73 (66.4)	71 (64.5)
ODI, events per hour	25.0 (14.4-41.8)	31.5 (16.5-47.7)
Patients with ODI [‡]		
<15 events per hour	31 (28.2)	21 (19.1)
15 to <30 events per hour	37 (33.6)	32 (29.1)
≥30 events per hour	42 (38.2)	57 (51.8)
Mean SpO ₂ , %	95.0 (93.0-95.0)	94.0 (93.0-95.0)
Minimum SpO ₂ , %	82.0 (77.0-86.0)	80.5 (74.0-84.0)
RDI, events per hour	37.5 (24.9-50.2)	40.1 (24.6-54.7)
Patients with RDI		
<15 events per hour	1 (0.9)	0 (0.0)
15 to <30 events per hour	36 (32.7)	39 (35.5)
≥30 events per hour	73 (66.4)	71 (64.6)
Arousal index, events per hour	15.2 (6.6-24.2)	15.9 (8.6-24.5)
Patients with arousal index		
<15 events per hour	55 (50.0)	51 (46.4)
15 to <30 events per hour	39 (35.5)	40 (36.4)
≥30 events per hour	16 (14.6)	19 (17.3)

Values are n (%) or median (Q1-Q3). [‡]Scored using the 3% rule (≥3% oxygen desaturation from pre-event baseline).
AHI = apnea-hypopnea index; ESS = Epworth Sleepiness Scale; ODI = oxygen desaturation index; RDI = respiratory disturbance index; SpO₂ = saturation of peripheral oxygen; other abbreviations as in Table 1.

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 days (Q1-Q3: 37-76 days) for the MAD group and 27 days (Q1-Q3: 22-35 days) for the CPAP group after polysomnography. The longer waiting time for the MAD group was mainly because of the manufacturing of the custom-made MADs and international shipping times.

For the MAD group, 82.7% (91 of 110) participants had valid adherence data. The median duration of MAD usage was 5.5 hours per night (Q1-Q3: 3.9-6.9 hours per night), and 74.7% (68 of 91) used the device for ≥4 hours per night. In contrast, 94.5% (104 of 110) of the participants on CPAP had valid adherence data. The median duration of CPAP usage was 5.0 hours per night (Q1-Q3: 3.3-6.1 hours per night) and 70.2% (73 of

FIGURE 2 Changes in BPs From Baseline to 6 Months

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

104) used the device for ≥ 4 hours per night. The median residual AHI for the MAD and CPAP groups were 12.6 events per hour (Q1-Q3: 6.6-20.7 events per hour) and 2.2 events per hour (Q1-Q3: 1.1-4.6 events per hour), respectively.

6-MONTH DEVICE ADHERENCE AND RESIDUAL AHI.

In the MAD group, 89.1% (98 of 110) of the participants completed the 6-month follow-up, and of these, 86.7% (85 of 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 period) was 5.5 hours per night (Q1-Q3: 3.7-6.7 hours per night), with 72.9% (62 of 85) using the MAD device for ≥ 4 hours per night and 56.5% (48 of 85) using the MAD device for ≥ 6 hours per night. The residual AHI was 10.8 events per hour (Q1-Q3: 5.0-18.9 events per hour). In the CPAP group, 91.8% (101 of 110) of the participants completed the 6-month follow-up and 97.0% (98 of 101) had valid adherence data. In this group, the median duration of CPAP usage was 5.0 hours per night (Q1-Q3: 3.0-5.9 hours per night), with 69.4% (68 of 98) using CPAP for ≥ 4 hours

TABLE 3 Between-Group Difference in BP Changes From Baseline to 6-Month Follow-Up

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

Values are median (Q1-Q3). ^a2 participants withdrew from the MAD group before baseline evaluation. ^b12 participants withdrew from the MAD group before ambulatory BP monitoring during 6-month follow-up. ^c5 participants withdrew from the CPAP group before baseline evaluation. ^d9 participants withdrew from the CPAP before ambulatory BP monitoring during 6-month follow-up. ^eMean BP is calculated as one-third of the sum of systolic BP and 2 times that of the diastolic BP. ^fChange from baseline to 6-month $P < 0.05$. ^gStatistically significant (<0.001 , noninferiority). Statistically insignificant (0.086, superiority).
BP = blood pressure; other abbreviations as in Table 1.

per night and 23.2% (23 of 99) using CPAP for ≥ 6 hours per night. The residual AHI was 2.0 events per hour (Q1-Q3: 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 baseline (MAD group: 46 [Q1-Q3: 41-48]; CPAP group: 44 [Q1-Q3: 40-48], $P = 0.246$) and 6 months (MAD group: 41 [Q1-Q3: 36-46], CPAP group: 42 [Q1-Q3: 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 mm Hg to 93.5 ± 8.1 mm Hg; $P = 0.003$). The reduction was nonsignificant in the CPAP group (95.5 ± 8.8 mm Hg to 95.3 ± 9.8 mm Hg; $P = 0.374$). Thus, the between-group difference in 24-hour mean arterial BP was significant (ANCOVA

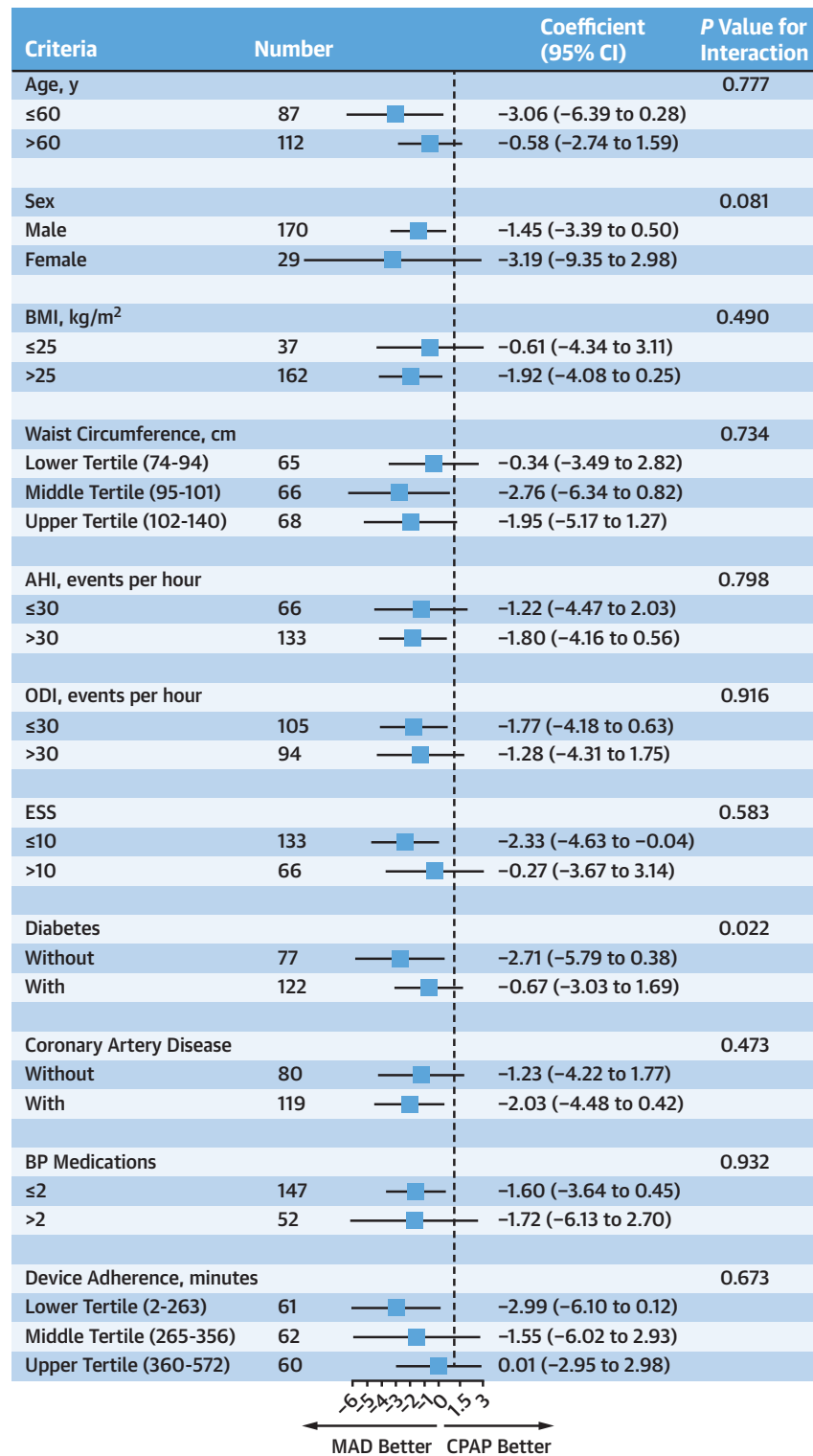
coefficient: 1.6 mm Hg; 95% CI: -3.51 to 0.24; non-inferiority $P < 0.001$; superiority $P = 0.086$). Because the 95% CI did not cross the prespecified non-inferiority margin of 1.5 mm Hg, MAD was noninferior to CPAP (Central Illustration).

In the prespecified subgroup analysis, there was evidence of potential heterogeneity according to age, sex, BMI, ESS, diabetes, and device adherence (Figure 3). 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 with the corresponding daytime BP (Table 3).

The percentage of participants who achieved 24-hour systolic BP <130 mm Hg at baseline and

FIGURE 3 Forest Plot of Primary Outcome by Prespecified Subgroups



The widths of the CIs have not been adjusted for multiplicity. Diabetic subjects have a higher baseline BP, which was significantly correlated with 6-month BP. The statistically significant result for the diabetes vs non-diabetes subgroup is small in terms of effect size (coefficient: 0.26). Hence it is clinically nonsignificant. AHI = apnea-hypopnea index; BMI = body mass index; BP = blood pressure; ESS = Epworth Sleepiness Scale; ODI = oxygen desaturation index; other abbreviations as in Figure 1.

6-month follow-up did not change in the MAD (69.4% [75 of 108] vs 69.4% [68 of 98], $P = 0.839$) and CPAP groups (68.6% [72 of 105] vs 66.3% [67 of 101], $P = 0.999$). The percentage of participants who achieved 24-hour systolic BP <120 mm Hg increased from 32.4% (35 of 108) at baseline to 43.9% (43 of 98) ($P = 0.043$) at the 6-month follow-up in the MAD group. The corresponding percentages remained unchanged at 31.4% (33 of 105) ($P = 0.999$) in the CPAP group. Asleep BP dipping was observed in 16.7% (18 of 108) and 18.4% (18 of 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 of 105) and 27.7% (28 of 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 of 110) at baseline to 11.0% (11 of 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 of 110) at baseline to 7.0% (7 of 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 high-sensitivity C-reactive protein, N-terminal pro-B-type natriuretic peptide, and high-sensitivity troponin T 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 of 100]), jaw pain (22.0% [22 of 100]), teeth discomfort (17.0% [17 of 100]), and hypersalivation (10.0% [10 of 100]). The CPAP group reported air leakage (48.5% [48 of 99]); dryness or pain in the mouth, throat, or nose (44.4% [44 of 99]); sleep disturbances (14.1% [14 of 99]); blocked or runny nose (14.1% [14 of 99]); mask discomfort (11.1% [11 of 99]); and facial rash (10.1% [10 of 99]).

During the 6-month treatment period, 6.4% (7 of 110) of participants in the MAD group and 9.1% (10 of 110) of 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 [Q1-Q3: 1-5 days]) and the CPAP group (2.5 days [Q1-Q3: 2-5 days]) ($P = 0.803$).

DISCUSSION

To the best of our knowledge, the CRESCENT trial is the largest randomized clinical trial on the comparative effectiveness of MAD vs 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 noninferior 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 noninferior to CPAP for reducing BP. Moreover, the between-group difference (2 mm Hg) in systolic BP seen with MAD is associated with a 10% lower stroke mortality and 7% lower cardiovascular mortality.³⁰ Based on 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, whereas 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 with their counterparts in the SAVE. Finally, the study duration for CRESCENT (6 months) was shorter than that of SAVE (3.7 years).

STUDY LIMITATIONS. First, most of the trial was conducted during the COVID-19 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 nonpandemic period. Second, more than 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 mm Hg) 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. Although further studies on other ethnicities are needed, ethnic Chinese make up approximately 17.3% of the world population, and 5.7

million ethnic Chinese reside in the United States. 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.

CONCLUSIONS

MAD is noninferior 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.

ACKNOWLEDGMENTS The CRESCENT trial was supported by the Clinician Scientist Award (CSASI18may-0005) and Collaborative Centre Grant (NMRC/CG2/001b/2021) from the National Medical Research Council, Ministry of Health, Singapore, and the USyd-NUS Partnership Collaboration Award, a joint award from the National University of Singapore and the University of Sydney. The authors are grateful to Miss Venesa Loh and Miss Junping Liu from the National University Hospital for providing administrative support for the CRESCENT trial.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was supported by a Clinician Scientist Award from the National Medical Research Council of Singapore (Grant number: CSASI18may-0001) and the USyd-NUS Partnership Collaboration Award, a joint award from the National University of Singapore and the University of Sydney. Dr Cistulli has an appointment as an endowed Academic Chair at the University of Sydney that was created from ResMed funding (he receives no personal fees, and this relationship is managed by an Oversight Committee of the University); has received research support from ResMed, SomnoMed, Zephyr Sleep Technologies, and Bayer; is a consultant/adviser to Signifier Medical Technologies, SomnoMed, ResMed, and Sunrise Medical; and has a pecuniary interest in SomnoMed related to a previous role in R&D (2004). Dr Lee has received an honorarium from ResMed (2022); and has received a research grant from Boston Scientific Corporation. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Chi-Hang Lee, Department of Cardiology, National University Heart Centre Singapore, 1 E Kent Ridge Road, NUHS Tower Block Level 9, Singapore 119228, Singapore. E-mail: mdclchr@nus.edu.sg. @CHRLee1212.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND

PROCEDURAL SKILLS: In patients with moderate-to-severe OSA and hypertension, an MAD is an effective alternative to a CPAP mask to reduce BP.

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.

REFERENCES

- Roth GA, Mensah GA, Johnson CO, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update from the GBD 2019 Study. *J Am Coll Cardiol*. 2020;76(25):2982–3021. <https://doi.org/10.1016/j.jacc.2020.11.010>
- Brouwers S, Sudano I, Kokubo Y, Sulaica EM. Arterial hypertension. *Lancet*. 2021;398(10296):249–261. [https://doi.org/10.1016/S0140-6736\(21\)00221-X](https://doi.org/10.1016/S0140-6736(21)00221-X)
- Lévy P, Kohler M, McNicholas WT, et al. Obstructive sleep apnoea syndrome. *Nat Rev Dis Primers*. 2015;1:15015. <https://doi.org/10.1038/nrdp.2015.15>
- Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;71(19):e127–e248. <https://doi.org/10.1016/j.jacc.2017.11.006>
- Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39(33):3021–3104. <https://doi.org/10.1093/eurheartj/ehy339>
- Yeghiazarians Y, Jneid H, Tietjens JR, et al. Obstructive sleep apnea and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2021;144(3):e56–e67. <https://doi.org/10.1161/CIR.0000000000000988>
- Patel SR, Bakker JP, Stitt CJ, Aloia MS, Nouraei SM. Age and sex disparities in adherence to CPAP. *Chest*. 2021;159(1):382–389. <https://doi.org/10.1016/j.chest.2020.07.017>
- Jacobsen AR, Eriksen F, Hansen RW, et al. Determinants for adherence to continuous positive airway pressure therapy in obstructive sleep apnea. *PLoS One*. 2017;12(12):e0189614. <https://doi.org/10.1371/journal.pone.0189614>
- Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy. *Proc Am Thorac Soc*. 2008;5(2):173–178. <https://doi.org/10.1513/pats.200708-119MG>
- Ramar K, Dort LC, Katz SG, et al. Clinical practice guideline for the treatment of obstructive sleep apnea and snoring with oral appliance therapy: an update for 2015. *J Clin Sleep Med*. 2015;11(7):773–827. <https://doi.org/10.5664/jcsm.4858>
- Francis CE, Quinnett T. Mandibular advancement devices for OSA: an alternative to CPAP? *Pulm Ther*. 2021;7(1):25–36. <https://doi.org/10.1007/s41030-020-00137-2>
- Ou YH, Tan A, Lee CH. Management of hypertension in obstructive sleep apnea. *Am J Prev Cardiol*. 2023;13:100475. <https://doi.org/10.1016/j.ajpc.2023.100475>
- Almeida FR, Henrich N, Marra C, et al. Patient preferences and experiences of CPAP and oral appliances for the treatment of obstructive sleep apnea: a qualitative analysis. *Sleep Breath*. 2013;17(2):659–666. <https://doi.org/10.1007/s11325-012-0739-6>
- Trzepizur W, Cistulli PA, Glos M, et al. Health outcomes of continuous positive airway pressure versus mandibular advancement device for the treatment of severe obstructive sleep apnea: an individual participant data meta-analysis. *Sleep*. 2021;44(7):zsab015. <https://doi.org/10.1093/sleep/zsab015>
- Bratton DJ, Gaisl T, Wons AM, Kohler M. CPAP vs mandibular advancement devices and blood pressure in patients with obstructive sleep apnea: a systematic review and meta-analysis. *JAMA*. 2015;314(21):2280–2293. <https://doi.org/10.1001/jama.2015.16303>
- de Vries GE, Wijkstra PJ, Houwerzijl EJ, Kerstjens HAM, Hoekema A. Cardiovascular effects of oral appliance therapy in obstructive sleep apnea: a systematic review and meta-analysis. *Sleep Med Rev*. 2018;40:55–68. <https://doi.org/10.1016/j.smrv.2017.10.004>
- Pengo MF, Soranna D, Giontella A, et al. Obstructive sleep apnoea treatment and blood pressure: which phenotypes predict a response? A systematic review and meta-analysis. *Eur Respir J*. 2020;55(5):1901945. <https://doi.org/10.1183/13993003.01945-2019>
- Barnes M, McEvoy RD, Banks S, et al. Efficacy of positive airway pressure and oral appliance in mild to moderate obstructive sleep apnea. *Am J Respir Crit Care Med*. 2004;170(6):656–664. <https://doi.org/10.1164/rccm.200311-1571OC>
- Lam B, Sam K, Mok WYW, et al. Randomised study of three non-surgical treatments in mild to moderate obstructive sleep apnoea. *Thorax*. 2007;62(4):354–359. <https://doi.org/10.1136/thx.2006.063644>
- Phillips CL, Grunstein RR, Darendeliler MA, et al. Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: a randomized controlled trial. *Am J Respir Crit Care Med*. 2013;187(8):879–887. <https://doi.org/10.1164/rccm.201212-2223OC>
- Dal-Fabbro C, Garbuio S, D’Almeida V, Cintra FD, Tufik S, Bittencourt L. Mandibular advancement device and CPAP upon cardiovascular parameters in OSA. *Sleep Breath*. 2014;18(4):749–759. <https://doi.org/10.1007/s11325-014-0937-5>
- Yamamoto U, Nishizaka M, Tsuda H, Tsutsui H, Ando SI. Crossover comparison between CPAP and mandibular advancement device with adherence monitor about the effects on endothelial function, blood pressure and symptoms in patients with obstructive sleep apnea. *Heart Vessels*. 2019;34(10):1692–1702. <https://doi.org/10.1007/s00380-019-01392-3>
- Uniken Venema JAM, Knol-de Vries GE, van Goor H, Westra J, Hoekema A, Wijkstra PJ. Cardiovascular and metabolic effects of a mandibular advancement device and continuous positive airway pressure in moderate obstructive sleep apnea: a randomized controlled trial. *J Clin Sleep Med*. 2022;18(6):1547–1555. <https://doi.org/10.5664/jcsm.9908>
- Ou YH, Colpani JT, Chan SP, et al. Mandibular advancement device versus CPAP in lowering 24-hour blood pressure in patients with obstructive sleep apnoea and hypertension: the CRESCENT trial protocol. *BMJ Open*. 2023;13(5):e072853. <https://doi.org/10.1136/bmjopen-2023-072853>
- Thornton AT, Singh P, Ruehland WR, Rochford PD. AASM criteria for scoring respiratory events: interaction between apnea sensor and hypopnea definition. *Sleep*. 2012;35(3):425–432. <https://doi.org/10.5664/sleep.1710>
- Pepperell JCT, Ramdassingh-Dow S, Crosthwaite N, et al. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. *Lancet*. 2002;359(9302):204–210. [https://doi.org/10.1016/S0140-6736\(02\)07445-7](https://doi.org/10.1016/S0140-6736(02)07445-7)
- Flight L, Julious SA. Practical guide to sample size calculations: non-inferiority and equivalence trials. *Pharm Stat*. 2016;15(1):80–89. <https://doi.org/10.1002/pst.1716>

- 28.** Egbewale BE, Lewis M, Sim J. Bias, precision and statistical power of analysis of covariance in the analysis of randomized trials with baseline imbalance: a simulation study. *BMC Med Res Methodol.* 2014;14(1):49. <https://doi.org/10.1186/1471-2288-14-49>
- 29.** Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet.* 2004;363(9403):157-163. [https://doi.org/10.1016/S0140-6736\(03\)15268-3](https://doi.org/10.1016/S0140-6736(03)15268-3)
- 30.** Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* 2002;360(9349):1903-1913. [https://doi.org/10.1016/S0140-6736\(02\)11911-8](https://doi.org/10.1016/S0140-6736(02)11911-8)
- 31.** Mancía G, Kreutz R, Brunström M, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension Endorsed by the European Renal Association (ERA) and the International Society of Hypertension (ISH). *J Hypertens.* 2023;41(12):1874-2071. <https://doi.org/10.1097/HJH.0000000000003480>
- 32.** Yang WY, Melgarejo JD, Thijs L, et al. Association of office and ambulatory blood pressure with mortality and cardiovascular outcomes. *JAMA.* 2019;322(5):409-420. <https://doi.org/10.1001/jama.2019.9811>
- 33.** McEvoy RD, Antic NA, Heeley E, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med.* 2016;375(10):919-931. <https://doi.org/10.1056/NEJMoa1606599>
- 34.** Weaver TE, Maislin G, Dinges DF, et al. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. *Sleep.* 2007;30(6):711-719. <https://doi.org/10.1093/sleep/30.6.711>
- 35.** Pépin JL, Tamisier R, Baguet JP, et al. Fixed-pressure CPAP versus auto-adjusting CPAP: comparison of efficacy on blood pressure in obstructive sleep apnoea, a randomised clinical trial. *Thorax.* 2016;71(8):726-733. <https://doi.org/10.1136/thoraxjnl-2015-207700>
- 36.** Hnin K, Mukherjee S, Antic NA, et al. The impact of ethnicity on the prevalence and severity of obstructive sleep apnea. *Sleep Med Rev.* 2018;41:78-86. <https://doi.org/10.1016/j.smrv.2018.01.003>
-
- KEY WORDS** continuous positive airway pressure, hypertension, mandibular advancement device, noninferiority trial, obstructive sleep apnea
-
- APPENDIX** For supplemental methods and tables, please see the online version of this paper.