Health Outcomes of CPAP versus Oral Appliance Treatment for Obstructive Sleep Apnea: A Randomised Controlled Trial

Craig L Phillips PhD\textsuperscript{1,2}, Ronald R Grunstein MD\textsuperscript{2,3}, M. Ali Darendeliler PhD\textsuperscript{4}, Anastasia S Mihailidou PhD\textsuperscript{5}, Vasantha K Srinivasan MDSc\textsuperscript{4}, Brendon J Yee MD\textsuperscript{2,3}, Guy B Marks MD\textsuperscript{2,6} and Peter A Cistulli MD\textsuperscript{1,2}

1. Department of Respiratory and Sleep Medicine, Royal North Shore Hospital
2. NHMRC Centre for Integrated Research and Understanding of Sleep (CIRUS), Woolcock Institute of Medical Research, Sydney Medical School, University of Sydney
3. Department of Respiratory and Sleep Medicine, Royal Prince Alfred Hospital
4. Department of Orthodontics, Sydney Dental Hospital and Faculty of Dentistry, University of Sydney
5. Department of Cardiology, Royal North Shore Hospital and Kolling Medical Research Institute, Royal North Shore Hospital and University of Sydney
6. Department of Respiratory Medicine, Liverpool Hospital

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Corresponding Author:
Craig L Phillips
Email: craig.phillips@sydney.edu.au

Contact address:
Department of Respiratory and Sleep Medicine
Royal North Shore Hospital
St Leonards
NSW 2065 Australia

Author Contributions:
PC, RG, AD, GM and CP were responsible for the concept and design of the study. AM, VS, AD and CP were responsible for data acquisition. CP, PC, GM, RG and AM performed the analysis and interpretation of data. CP, PC, GM drafted the manuscript. All authors were responsible for revising of the manuscript for important intellectual content. CP and GM performed all statistical analyses. PC, RG, and AD obtained funding for the study. PC, CP, BY, AM provided administrative, technical and material support for the study. CP and PC supervised the study. CP is the guarantor.

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At a Glance Commentary:

Scientific Knowledge on the Subject:

Continuous Positive Airway Pressure (CPAP) is considered to be the treatment of choice for Obstructive Sleep Apnoea (OSA). Oral appliance (OA) therapy such as the mandibular advancement device (MAD) is a viable alternative with growing use, particularly in patients with milder OSA. Similar improvements in important health outcomes have been independently demonstrated with both treatments. Comparative effectiveness studies that examine multiple important health outcomes with these treatment modalities in patients with the full spectrum of OSA severity are lacking.

What This Study Adds to the Field:

In the short term, health outcomes in patients with moderate to severe OSA were similar after treatment with CPAP and MAD. This was likely explained by the greater
efficacy of CPAP being offset by inferior compliance relative to MAD. These findings strongly challenge current practice parameters recommending MAD treatment be considered only in mild to moderate OSA patients. Long-term comparative effectiveness studies between CPAP and MAD that include objectively measured treatment compliance are needed to better define treatment strategies for patients with OSA.
Abstract

Rationale: Continuous Positive Airway Pressure (CPAP) and Mandibular Advancement Device (MAD) therapy are commonly used to treat Obstructive Sleep Apnea (OSA). Differences in efficacy and compliance of these treatments are likely to influence improvements in health outcomes.

Objectives and Methods: To compare health effects after 1 month of optimal CPAP and MAD therapy in OSA using a randomised crossover design.

Measurements and main results: Cardiovascular (24-hour blood pressure, arterial stiffness), neuro-behavioural (subjective sleepiness, driving simulator performance) and Quality of Life (FOSQ, SF-36) were compared between treatments. Our primary outcome was 24-hour mean arterial pressure (24MAP). 126 patients with moderate-severe OSA (AHI = 25.6 (SD 12.3)) were randomly assigned to a treatment order and 108 completed the trial with both devices. CPAP was more efficacious than MAD in reducing AHI (CPAP AHI=4.5±6.6/hr, MAD AHI=11.1±12.1/hr, p<0.01) but reported compliance was higher on MAD (MAD: 6.50±1.3 hrs/night versus CPAP: 5.20±2.0 hrs/night, p<0.00001). 24MAP was not inferior on treatment with MAD compared to CPAP (CPAP-MAD difference, 0.2mmHg [95%CI -0.7 to 1.1], however overall, neither treatment improved BP. In contrast, sleepiness, driving simulator performance and disease-specific QOL improved on both treatments by similar amounts although MAD was superior to CPAP for improving four general QOL domains.

Conclusions: Important health outcomes were similar after 1 month of optimal MAD and CPAP treatment in patients with moderate-severe OSA. The results may be
explained by greater efficacy of CPAP being offset by inferior compliance relative to MAD, resulting in similar effectiveness.

**Trial Registration:** Australian and New Zealand Clinical Trials Registry at [https://www.anzctr.org.au](https://www.anzctr.org.au), trial number ACTRN12607000289415.
INTRODUCTION

Obstructive sleep apnea (OSA) affects up to 17% of adults\(^1\) and is characterised by disordered breathing during sleep, resulting in sleep fragmentation and intermittent hypoxemia. Patients often suffer excessive daytime sleepiness and many are at increased risk for motor vehicle crashes.\(^2\) Neurocognitive decline\(^3\) and a lower self-reported quality of life (QOL) are also common. In addition, hypertension is highly prevalent and there is an increased incidence of cardiovascular mortality, stroke and heart attack.\(^4\)\(^-\)\(^6\) Hence OSA is a major public health problem, imposing a major financial burden on health systems.\(^7\)\(^,\)\(^8\)

The usual treatment of choice for OSA is nasal continuous positive airway pressure (CPAP).\(^9\) Randomised controlled trials have demonstrated improvements in many health outcomes including subjective sleepiness,\(^10\) QOL,\(^11\) and blood pressure (BP).\(^12\) Evidence also suggests that this treatment may reduce motor vehicle and driving simulator crashes.\(^13\) Long term treatment may also reduce the incidence of cardiovascular events, at least in patients with severe OSA.\(^14\) However, despite these health-related improvements, many patients either reject treatment outright or only partially tolerate it, resulting in significant residual OSA.\(^15\) This limits the clinical effectiveness of this treatment modality.

More recently, oral appliances (OA) have proven to be an effective treatment for OSA, particularly oral appliances such as the mandibular advancement Device (MAD) which reposition the tongue and/or lower jaw to increase the dimensions of the airway lumen. **Whilst the overall effect of these devices on sleep-disordered breathing is inferior to CPAP, their uptake and acceptance as an alternative therapy**
is generally higher.\textsuperscript{11} Similar to CPAP, several randomised controlled trials have reported improvements in BP\textsuperscript{16,17}, sleepiness\textsuperscript{18} and QOL.\textsuperscript{16}

Although a number of randomised trials have also directly compared CPAP with MAD,\textsuperscript{16,19-26} outcomes are often limited to OSA alleviation and this has often been without gold-standard polysomnography.\textsuperscript{20,21} Few studies have assessed more clinically relevant health outcomes and used polysomnography to also assess treatment efficacy. Furthermore, many studies are small\textsuperscript{19-23} or exclude patients with severe OSA,\textsuperscript{16,20,22} limiting the generalisability of the findings. Many studies have also not considered variation in treatment acclimatisation and optimisation periods.\textsuperscript{16,19,21,22} Finally, because of the rapid changes in device development there are no studies that have used state-of-the-art MAD devices that are optimally titrated and applicable to current clinical practice.

In the present study, we aimed to compare the effect of CPAP and MAD treatments on health outcomes across multiple clinically relevant domains including cardiovascular function, sleepiness, driving simulator performance and QOL. We hypothesised that the sub-optimal efficacy with MAD would be counterbalanced by superior compliance relative to CPAP, resulting in similar overall alleviation of OSA. This would in turn result in similar effectiveness of both treatments for health outcomes related to OSA. The results from this study have previously been reported in the form of abstracts.\textsuperscript{27,28}
METHODS

A randomised crossover open label study design was used to compare the health effects of 1 month of optimal treatment of OSA with CPAP versus MAD therapy. Optimal treatment was defined as attaining the highest compliance and best efficacy with each treatment under standard clinical practices.

Sample

The study was conducted at three sleep centres in Sydney, Australia (see online data supplement). Eligibility criteria included patients with newly diagnosed OSA (AHI>10 events/h), aged ≥20 years, >=2 symptoms of OSA (snoring, fragmented sleep, witnessed apneas, or daytime sleepiness), and a willingness to use both treatments. Recruitment was enriched for moderate-severe OSA. Patients were excluded for any of the following reasons: previous OSA treatment or a need for immediate treatment based on clinical judgement, central sleep apnea, a co-existing sleep disorder, regular use of sedatives or narcotics, pre-existing lung or psychiatric disease and any contra-indication for oral appliance therapy (eg periodontal disease or insufficient dentition). Dental eligibility was assessed by an orthodontist at the Sydney Dental Hospital. All study procedures, were approved by the site-specific Institutional Human Research Ethics Committees. Prior to consenting, patients were told they would be compensated for participating in the study by receiving the treatment device recommended by their sleep physician at no cost.

Procedures

All sleep studies were performed using full polysomnography according to standard procedures (see online supplement). Treatment efficacy was established by
polysomnography at the end of each treatment period under intention-to-treat conditions, with device use during the night being under patient control. Patients who met all eligibility criteria were randomised to both the treatment acclimatisation and treatment arm orders. This was to minimise any bias related to treatment preference based upon the order of treatment exposure and resulted in 4 randomised sequences (Figure 1).

The CPAP device used in the trial was the ResMed Autoset S8 (ResMed, Bella Vista, Australia). The Mandibular Advancement Device (MAD) was the Somnodent (SomnoMed Ltd Australia), a custom fitted and titratable two-piece device with proven clinical effectiveness in treating OSA. The procedures for fitting, titration and acclimatisation to each device are described in detail in the online supplement. Briefly, a fixed CPAP pressure was determined using a previously validated auto-titrating method based on the 95th percentile pressure that controlled most of the OSA events. In contrast, MAD was self-titrated by gradually advancing the device until the maximum comfortable limit of mandibular advancement was achieved. During each of the 4-6 weeks acclimatisation with each device, all patients were asked to use their device for as long as they could tolerate it on a nightly basis. Once usage patterns had stabilised, treatment was considered to be optimised.

All outcomes were assessed on three occasions, at baseline prior to treatment acclimatisation and then at the end of each of the 1-month treatment arms. The primary outcome was the difference in 24-hour mean arterial pressure (24MAP) between CPAP and MAD determined from 24-hour ambulatory blood pressure monitoring. Secondary cardiovascular outcomes included other 24 hour ambulatory
blood pressures as well as central blood pressure and arterial stiffness (SphymoCor, AtCor Medical, Ryde, Australia)\(^{33}\). We also assessed neuro-behavioural function and quality of life using the Functional Outcomes of Sleep Questionnaire (FOSQ)\(^{34}\), the Short Form 36 (SF36)\(^{35}\), the Epworth Sleepiness Score (ESS)\(^{36}\) and the AusEd driving simulator (Australasian Sleep Trials Network, Australia)\(^{37}\). Daily diaries were also used to monitor treatment side-effects and compile subjective compliance data. After completing the trial but before knowledge of their results, patients reported their treatment preference (CPAP, MAD, either, or neither). Details of all outcome assessments are available in the online supplement.

**Statistical analysis**

In order to ensure an adequate sample size to assess multiple unrelated outcomes, we powered the study on a blood pressure outcome. \textit{The analysis was designed to establish non-inferiority of MAD compared with CPAP for the primary outcome (24MAP).} A previous study which also did not select patients on the basis of their hypertensive status showed that OSA treatment with therapeutic CPAP lowered 24MAP by 3.3mmHg relative to sham CPAP.\(^{38}\) Therefore, we assumed that we could establish non-inferiority of MAD to CPAP for control of 24MAP with a non-inferiority margin of 1.6mmHg. Based on our own data,\(^{17}\) we estimated a within-subject mean square error of 3.9 for 24MAP. Hence, in order to detect non-inferiority of this outcome with 90\% power, using a non-inferiority margin of 1.6mmHg, a sample size of 108 completers was deemed to be required.

We limited our analyses to the 108 subjects who completed the trial, regardless of compliance with their assigned treatment. In an initial analysis, no acclimatisation or
treatment arm order effects were found (see online data supplement). The primary hypothesis was tested by comparing the upper limit of the 95% confidence interval for the MAD-CPAP difference in 24MAP with the \textit{a priori} non-inferiority margin using the paired t-test. All other outcomes were compared using repeated measures analysis of variance (see online supplement).

Power analysis was performed using PASS software version 11 (NCSS Inc, Kaysville Utah). All other analyses were made using the PASW statistical software version 17 (SPSS Inc., Chicago, IL).

RESULTS

Patient Flow

The patient flow through the study is detailed in figure 1. Amongst the 51 screening failures, 36 patients did not fulfil dental criteria and an additional 6 declined to have the required dental work that would make them eligible for MAD treatment. Only 18 patients (14%) withdrew after randomisation leaving 108 (86%) who completed the study. However, only 2 patients withdrew because of treatment intolerance (1 CPAP and 1 both CPAP and MAD). None of the investigator-initiated withdrawals that were due to adverse or serious adverse events were trial related.

Patient characteristics

Of the 126 randomised patients, 81% were male and a majority (82%) had moderate or severe OSA with AHI≥15/hr (Table 1). Amongst the 108 completers, 18% had mild OSA (AHI=13), 50% had moderate OSA (AHI=22) and 32% had severe OSA (AHI=42). Hence in the overall group 82% had moderate-severe OSA (AHI=26 &
ODI=21 per hour). At baseline, 50% of patients were sleepy based on an Epworth Sleepiness Score (ESS) >10 and 38% of patients were on anti-hypertensive medication.

**Treatment efficacy and preference**

After titration and acclimatisation with each device, the mean (SD) CPAP pressure was 10.5±2.0 cmH2O (range 4-18 cmH2O) whilst the mean mandibular advancement was 8.09±2.6 mm (range 1.1-15 mm). All metrics of sleep disordered breathing on the intention-to-treat polysomnography night improved markedly with both treatments (Figure 2a left panel) although the improvement was greater with CPAP than MAD (Table 2). This was most evident in patients with severe OSA (Figure E1). In total, nearly twice as many patients had complete resolution of their OSA with CPAP compared to MAD (Figure 2 right panel). In contrast, with MAD treatment patients reported longer sleep and higher compliance than with CPAP (Table 2). Higher compliance with MAD was consistently reported in mild, moderate and severe OSA (Figure E2). In patients where both objective and subjective CPAP compliance measures were available, objective compliance was slightly lower (objective: 4.68±2.0 hrs/night, subjective 5.1±2.0 hrs/night, p<0.001). Equivalent objective compliance data were not available for MAD treatment. Treatment preference results showed that 55 patients (51%) preferred MAD, 25 (23.1%) preferred CPAP, 23 (21.3%) preferred either and 5 (4.6%) preferred neither.

**Blood pressure outcomes**

In the entire group, 24-hr ambulatory BP profiles (Figure E3) showed a clear sleep-wake pattern during each treatment with no apparent between treatment differences resulting in MAD being non-inferior to CPAP for control of 24MAP (Mean CPAP-MAD
difference (95% CI): 0.2 (-0.7 to 1.1) mmHg). However, ultimately neither treatment lowered any blood pressure from baseline in the entire group. In contrast, in the sub-group of patients who were initially hypertensive, there were consistent treatment-related 24 hour BP improvements of between 2 and 4 mmHg in all indexes with neither treatment having a superior effect (Figure 3 and Table E1). Central blood pressures measured during pulse wave analysis also remained unchanged in the entire group (Table E2) but there were reductions from baseline in arterial stiffness (aortic augmentation index) of between 1 and 2% with no between treatment differences.

**Neuro-behavioural outcomes**

In contrast to BP, most neuro-behavioural outcomes improved after both treatments (Table 4). In particular, there was no between treatment difference in the improvement to subjective sleepiness (ESS) or in total and subscale measures of disease specific quality of life (FOSQ). However, MAD performed better than CPAP for improving four of eight SF-36 general QOL domains and the overall mental component score. Finally, speed deviation and reaction times to divided attention tasks during driving simulation improved to the same extent with both treatments. Figure 4 shows the ESS scores measured after acclimatisation and treatment washout and after treatment (MAD or CPAP). Washout values were similar to baseline indicating a return to pre-treatment sleepiness levels.

**DISCUSSION**
This is the largest randomised trial comparing the two leading forms of treatment for OSA on a range of unrelated health outcomes. The study has addressed many deficits from previous trials that have examined these treatments in head-to-head comparisons. While CPAP demonstrated superior efficacy in terms of AHI reduction, self-reported compliance with MAD treatment was higher. The resulting effects on clinically important OSA-related health outcomes were either equivalent between treatments or better with MAD. Notably, these outcomes were achieved in the context of moderate to severe OSA. Overall, the comparable impact of both treatments on health outcomes has potential implications for clinical practice and future research.

**Efficacy and Compliance**

In all previous randomised trials that have directly compared CPAP with MAD, both treatments are shown to alleviate OSA but CPAP is consistently superior to MAD, particularly in patients with severe OSA.\(^{16,19-26}\) In contrast, no studies have yet shown that nightly usage of CPAP is superior to MAD. In fact, results either favour MAD\(^{16,22}\) or do not favour either treatment.\(^{20,21,26}\) On this basis, we hypothesised that comparable outcomes between treatments would be achieved because the well-known superior efficacy of CPAP in alleviating OSA would be offset by inferior compliance relative to MAD. Indeed, our efficacy and compliance data and the resultant outcomes support this hypothesis. Finally, we have also confirmed the finding from most studies showing a clear patient preference for MAD therapy\(^{20,21,23,24,27}\). These results are likely to have an important bearing on treatment effectiveness.
Blood Pressure and Arterial Stiffness

In this trial we could only demonstrate clear improvements in BP in patients who were hypertensive at baseline. However no improvements were evident with either treatment in the whole group. In this context, hypertensive status together with sleepiness, OSA severity and treatment compliance have all been proposed to influence BP responses to treatment. Apart from hypertension however, we do not believe that any of these other factors explain the lack of change in BP after treatment since we could not find any correlation between changes in any BP outcome with any of these factors (data not shown). The literature indicates that treatment related improvements in BP are at best relatively small (2-3 mmHg), even in hypertensive patients. It follows that demonstrating any BP improvement will be difficult, particularly if the prevalence of untreated hypertension turns out to be lower than expected, as occurred in our study. However we have demonstrated that both treatments were associated with small reductions in arterial stiffness and neither treatment proved superior. Arterial stiffness has increasingly been shown to improve cardiovascular risk stratification and both uncontrolled and randomised controlled studies have shown improvements after CPAP. Overall our results point to the need for further comparative effectiveness studies which specifically target hypertensive patients.

Neuro-behavioural Function and QOL

Overall, this study has found that improvements with MAD in sleepiness, QOL and driving simulator performance were as good as or better than CPAP. Previous studies that have compared subjective sleepiness and QOL after treatment with oral appliance and CPAP therapies have either favoured CPAP or have shown
similar effects between treatments\textsuperscript{16,23,25,26}. However in the studies that favoured CPAP, non-adjustable oral appliances were used and these may have been inferior to fully adjustable models, as used in our study. We found in the whole group that neither treatment had a superior effect in reducing subjective sleepiness determined from the ESS score. Additional analyses in patients who were sleepy (ESS\textgeq{}10) or who had severe OSA (AHI\textgreater{}30) also indicated a comparable improvement between treatments (data not shown). Furthermore neither treatment was superior for improving disease specific QOL determined from the overall and subscale scores in the Functional Outcomes of Sleep Questionnaire (FOSQ). This is consistent with two other studies.\textsuperscript{16,25} In contrast, our study is the first to show that MAD treatment was superior to CPAP for improving four of eight SF-36 domains. Finally, we have shown in over 100 patients that driving simulator performance improves equally between oral appliance and CPAP therapies. One small study examined driving simulator performance between 9 patients treated with OA and 10 patients treated with CPAP and found a similar result.\textsuperscript{45} Hence the data which suggest that CPAP treatment reduces the risk of motor vehicle crashes may also apply for MAD treatment.\textsuperscript{46} Overall our data support more widespread use of MAD treatment for OSA.

\textbf{Study strengths}

The variations in health outcomes found in previous trials comparing CPAP to MAD are likely due to multiple factors. These include the exclusion in some studies of patients with severe OSA,\textsuperscript{16,20,22} small sample sizes (<50 patients),\textsuperscript{19-23} high dropout rates (>20\%)\textsuperscript{16,20}, non-adjustable oral appliances\textsuperscript{21} and sub-optimal compliance with CPAP therapy (<4hrs).\textsuperscript{16} In addition, the acclimatisation and optimisation periods with each device may have varied from one patient to another but were often
included as part of the treatment period.\textsuperscript{16,19,21,22} Our trial was designed to address many of these deficiencies. In addition, we believe that our choice to power the study using a non-inferiority design with mean blood pressure as the outcome has given us some degree of confidence that we would have the statistical power to examine multiple clinically important health outcomes. We also deliberately enriched our study population with moderate to severe OSA patients including those with associated co-morbid hypertension and sleepiness. Our findings in this context suggest that the clinical role of MAD treatment should be extended beyond the currently accepted mild to moderate OSA range (AASM practice parameters\textsuperscript{47}). Importantly, our protocol design ensured that all patients were fully acclimatised and optimally titrated with both devices over the same timeframe prior to commencing the interventions. Hence every patient had equal opportunity for exposure to both treatments. Furthermore, we randomised the order of acclimatisation and intervention to reduce the risk of compliance being altered by treatment order exposure. In the end we achieved an objective CPAP compliance (4.6 hours) that was comparable or better than previous trials and despite the demanding protocol, our dropout rate was only 15%.

**Study limitations**

There are several limitations that should be considered in relation to our study. Firstly, we acknowledge that the interpretation of our results is limited to patients that are eligible and willing to trial both treatments. In this context we found that 20\% of assessed patients were not eligible for trialling MAD whereas all patients were able to trial CPAP. We also recognise that we had no objective measure of MAD compliance, as this was not available at the time the study was conducted. We have
therefore assumed that the small discrepancy between objective and subjective CPAP compliance would be similar with MAD, making a between treatment comparison of self-reported compliance valid. In fact new research using a novel technology for measuring long term objective MAD compliance\textsuperscript{48} has found no difference between objective and subjective compliance. This may indicate that our MAD-CPAP compliance difference was underestimated making the true night-night residual AHI more equal between treatments. Furthermore, we acknowledge that our measure of treatment efficacy (on-treatment AHI) may be slightly underestimated during polysomnography because there were a small number of patients whose AHI was largely determined without CPAP or MAD treatment. This was despite all patients being strongly encouraged to use treatment on the night of polysomnography. It is also possible that the use of auto CPAP titration followed by fixed pressure treatment may have resulted in sub-optimal efficacy (AHI reduction) and/or compliance. However, comparable improvements in OSA have previously been shown when comparing auto to manual titration\textsuperscript{49} and compliance with auto versus fixed CPAP has been shown to be similar.\textsuperscript{50} In our study, the AHI on CPAP during the end of treatment polysomnography was 4.5 events/hour and overall objective compliance was 4.7 hours. Hence we do not believe that efficacy or compliance was compromised by our approach to CPAP titration or the use of a fixed pressure. In fact we chose to use a fixed pressure because it may be more effective in lowering BP.\textsuperscript{51}

In this study we found that overall neither treatment appeared to improve BP from baseline, which likely relates to the normotensive status of most participants. This then limits the ability to claim true non-inferiority for BP control. Regardless, we
believe our decision to pursue a non-inferiority analysis for BP was well founded. Non-inferiority designs rely on the premise that the active control (in this case CPAP) has superior efficacy to placebo as established in previous trials. Based on meta-analyses of randomised trials, we believed this has been adequately demonstrated, even in trials in which elevated BP was not a specific inclusion criterion which was the case in this study. It could also be argued that our treatment periods were relatively short, limiting the impact on BP. However, studies using similar treatment periods have reported significant treatment effects. Ultimately our cross-over design made the study challenging and time consuming for our patients and extending the treatment periods would have negatively impacted the feasibility of completing such a large study. The finding of a significant treatment effect amongst patients who were hypertensive at baseline is an indication that the treatment period was of sufficient duration. Furthermore, we observed very clear therapeutic effects from each treatment for important neuro-behavioural and QOL outcomes that were either comparable or favoured MAD. Sleepiness, which is arguably the main factor motivating patients to seek OSA treatment, showed clear clinical improvement and deterioration after initiation and withdrawal of either treatment. Finally we cannot claim that the improvements in health outcomes would be sustained in the long term, or indeed whether BP may deteriorate due to partially effective treatment. Further long-term studies with objective assessment of compliance with both devices will clarify how true night-to-night residual OSA impacts on health outcomes.

Conclusions
This short-term study has demonstrated that the health outcomes in patients with moderate to severe OSA were similar after treatment with CPAP and MAD. The results are likely explained by the greater efficacy of CPAP being offset by inferior compliance relative to MAD resulting in a similar “treatment” AHI with each device. These findings strongly challenge current practice parameters that recommend that MAD treatment should only be considered in mild to moderate OSA patients or in those who have failed or refuse CPAP treatment. Our findings provide a strong rationale for a long-term comparative effectiveness study of these two treatment modalities. Such studies will hopefully allow a rigorous evidence-based approach to changing current treatment recommendations.
Additional Contributions:

The authors wish to thank Woolcock Institute staff - Amanda Greenwood and Nancy Nguyen for their invaluable input into the running of this trial and Dr Wei Xuan for statistical advice. We also wish to thank Drs Oyku Dalci and Nour Eldin Taraf from Sydney Dental Hospital and CPAP therapists Dianne Richards, Gislaine Gauthier and Vivienne Jacobs.
REFERENCES


Figure 1. Study Flowchart

177 Patients assessed for eligibility

176 Randomised

51 screen failures
36 – Did not fulfill dental criteria
4 – Dental treatment too expensive
3 – AHI <10
2 – Declined with no reason
2 – Declined after considering dental Tx
1 – Exaggerated gag reflex
1 – Protocol violation
1 – AHI too severe (98/hr)
1 – Recruitment closed

Baseline Assessment

122 Entered Acclimatisation phase

62 Acclimatised to CPAP then MAS
7 Early withdrawals
1 – Time commitments
1 – Not compliant
1 – Personal reasons & time
1 – Unable to tolerate CPAP and wished to withdraw
1 – Serious Adverse Event

55 completed acclimatisation

60 Acclimatised to MAS then CPAP

2 Early withdrawals
1 – Time commitments
1 – Broken tooth & time

58 completed acclimatisation

2 weeks washout

110 Entered Treatment phase

56 completed CPAP first

3 Early withdrawals
1 – Unable to tolerate either device
1 – No perceived treatment benefit
1 – Adverse Event

54 completed MAS first

2 weeks washout

56 completed MAS last

2 Early withdrawals
1 – Personal reasons & time
1 – Not compliant with protocol

56 Completers

52 completed CPAP last

52 Completers

108 Completers
Note: 108 patients completed the trial. Based upon the separate randomisation to the acclimatisation phase and to the treatment phase for each of MAD (M) and CPAP (C), there were 4 randomisation sequences with patient numbers as follows: M/C/M/C=26; M/C/C/M=29; C/M/C/M=27; C/M/M/C=26. SAE = Serious Adverse Event; AE = Adverse Event.
Figure 2: Overall Treatment Response

Left panel: Baseline versus Intention-to-treat AHI for CPAP and MAD

Right panel: Treatment response based on Intention-to-treat AHI for CPAP and MAD

where:

Complete response = AHI reduced to < 5/hr;

Partial response = AHI reduced by > 50% but still > 5/hr

Failure = AHI reduced by < 50%

Note: Intention-to-treat AHI data includes all assessed patients regardless of treatment use on the night
Figure 3: Change from baseline in 24-hour blood pressure variables

Data represent mean differences from baseline (95%CI) on CPAP (closed symbols) and MAD (open symbols) for the 24hour, Wake and Sleep periods.

Top panels: All Completers (n=108)
Bottom panels: Hypertensive Completers (n=45) where baseline hypertension was defined as 24hr SBP >130 and / or 24hr DBP >80 mmHg.
Figure 4: Epworth Sleepiness Score at Baseline, after CPAP or MAD treatment and after acclimatisation and treatment washout periods
## Table 1 Baseline characteristics of all randomised patients

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<th>Mean (SD)</th>
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<td><strong>Number Randomised</strong></td>
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<td>Mild/Moderate/Severe OSA</td>
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<td>Minimum SpO2</td>
<td>82.7 (7.6)</td>
<td>62-93</td>
</tr>
<tr>
<td>Arousal Index (/hr)</td>
<td>34.3 (15.3)</td>
<td>8.1-79.6</td>
</tr>
<tr>
<td>Epworth Sleepiness Score</td>
<td>9.1 (4.2)</td>
<td>1-18</td>
</tr>
<tr>
<td><strong>Office Blood Pressure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>123.7 (14.1)</td>
<td>98-163</td>
</tr>
<tr>
<td>Diastolic</td>
<td>80.6 (9.1)</td>
<td>67-106</td>
</tr>
<tr>
<td><strong>Medication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Hypertensive</td>
<td>48</td>
<td>-</td>
</tr>
<tr>
<td>Anti-Diabetic</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td>Reflux</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>Anti-Depressants</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>Anti-Thrombotic</td>
<td>11</td>
<td>-</td>
</tr>
</tbody>
</table>

Mild OSA = AHI between 5 and 15 events/hour  
Moderate OSA = AHI between 15 and 30 events/hour  
Severe OSA = AHI > 30 events/hour
Table 2: Intention-to-treat polysomnography and self-reported compliance

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD) CPAP</th>
<th>Mean (SD) MAD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysomnography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHI (hr⁻¹)</td>
<td>4.5 (6.6)</td>
<td>11.1 (12.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ODI 3% (hr⁻¹)</td>
<td>6.0 (9.7)</td>
<td>9.0 (11.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Min SpO2 (%)</td>
<td>90.6 (5.0)</td>
<td>87.2 (5.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SpO2 T90 (% TST)</td>
<td>5.8 (16.9)</td>
<td>6.6 (15.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Arousal Index (hr⁻¹)</td>
<td>16.6 (10.6)</td>
<td>19.2 (11.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>11.5 (15.7)</td>
<td>15.3 (21.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>82 (12)</td>
<td>82 (12)</td>
<td>0.9</td>
</tr>
<tr>
<td>Diary Data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subj Compliance (hrs/night)</td>
<td>5.2 (2.0)</td>
<td>6.5 (1.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Subj Sleep (hrs/night)</td>
<td>6.9 (0.9)</td>
<td>7.1 (0.7)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

AHI = Apnea Hypopnea Index; ODI = Oxygen Desaturation Index; Min SpO2 = Minimum Arterial Oxygen Saturation; SpO2T90 = % Total Sleep Time below 90%

Arterial Oxygen Saturation; Compliance (hrs/night) = total hours of use divided by the number of nights with access to treatment

Note: Polysomnography data includes all assessed patients regardless of treatment use on the night
Table 3: Sleepiness, Quality of Life and Driving Simulator Performance (n=108)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>CPAP</th>
<th>MAD</th>
<th>Baseline - CPAP Difference (95% CI)</th>
<th>Baseline - MAD Difference (95% CI)</th>
<th>CPAP - MAD Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleepiness and Quality of Life</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESS</td>
<td>9.1 (0.4)</td>
<td>7.5 (0.4)</td>
<td>7.2 (0.4)</td>
<td>1.6 (1.0 to 2.2)**</td>
<td>1.9 (1.4 to 2.5)**</td>
<td>0.31 (-0.2 to 0.9)</td>
</tr>
<tr>
<td>FOSQ</td>
<td>16.3 (0.2)</td>
<td>17.3 (0.2)</td>
<td>17.3 (0.2)</td>
<td>-1.0 (-1.4 to -0.6)**</td>
<td>-1.0 (-1.4 to -0.6)**</td>
<td>-0.3 (-0.4 to 0.3)</td>
</tr>
<tr>
<td>Activity</td>
<td>3.08 (0.06)</td>
<td>3.3 (0.05)</td>
<td>3.3 (0.05)</td>
<td>-0.21 (-0.31 to -0.12)**</td>
<td>-0.24 (-0.34 to -0.15)**</td>
<td>-0.03 (-0.4 to 0.3)</td>
</tr>
<tr>
<td>Vigilance</td>
<td>3.10 (0.06)</td>
<td>3.32 (0.05)</td>
<td>3.33 (0.06)</td>
<td>-0.21 (-0.30 to -0.13)**</td>
<td>-0.23 (-0.33 to -0.13)**</td>
<td>-0.02 (-0.1 to 0.06)</td>
</tr>
<tr>
<td>Intimacy</td>
<td>3.15 (0.08)</td>
<td>3.35 (0.08)</td>
<td>3.34 (0.08)</td>
<td>-0.20 (-0.35 to -0.05)*</td>
<td>-0.19 (-0.35 to -0.03)*</td>
<td>0 (-0.1 to 0.2)</td>
</tr>
<tr>
<td>Productivity</td>
<td>3.43 (0.04)</td>
<td>3.6 (0.04)</td>
<td>3.6 (0.04)</td>
<td>-0.17 (-0.26 to -0.09)**</td>
<td>-0.19 (-0.27 to -0.11)**</td>
<td>-0.02 (-0.09 to 0.06)</td>
</tr>
<tr>
<td>Social</td>
<td>3.57 (0.05)</td>
<td>3.76 (0.05)</td>
<td>3.73 (0.05)</td>
<td>-0.18 (-0.28 to -0.08)**</td>
<td>-0.15 (-0.26 to -0.05)**</td>
<td>-0.03 (-0.07 to 0.13)</td>
</tr>
<tr>
<td><strong>SF36</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Function</td>
<td>82.3 (1.8)</td>
<td>83.7 (1.9)</td>
<td>84.7 (1.9)</td>
<td>-1.4 (-4.5 to 1.7)</td>
<td>-2.4 (-5.7 to 0.9)</td>
<td>-1.3 (-3.7 to 1.0)</td>
</tr>
<tr>
<td>Role Physical</td>
<td>70.4 (3.4)</td>
<td>81.7 (3.2)</td>
<td>79.9 (2.9)</td>
<td>-11.3 (-17.6 to -5.1)**</td>
<td>-9.5 (-15.2 to -3.7)**</td>
<td>1.9 (-4.6 to 8.3)</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>76.5 (2.2)</td>
<td>76.2 (2.1)</td>
<td>81 (1.9)</td>
<td>0.3 (-4.2 to 4.8)</td>
<td>-4.5 (-8.4 to -0.5)*</td>
<td>-4.8 (-8.7 to -0.9)*</td>
</tr>
<tr>
<td>General Health</td>
<td>63.1 (2.0)</td>
<td>65.7 (1.9)</td>
<td>67.4 (2.0)</td>
<td>-2.6 (-5.5 to 0.3)</td>
<td>-4.3 (-7.0 to -1.6)**</td>
<td>-1.7 (-4.1 to 0.7)</td>
</tr>
<tr>
<td>Vitality</td>
<td>48.9 (2.1)</td>
<td>56.3 (2.2)</td>
<td>60.1 (2.0)</td>
<td>-7.4 (-10.8 to -3.9)**</td>
<td>-11.2 (-14.8 to -7.6)**</td>
<td>-3.8 (-7.7 to -0.02)*</td>
</tr>
<tr>
<td>Social Function</td>
<td>77.6 (2.3)</td>
<td>79.7 (2.2)</td>
<td>84.8 (1.8)</td>
<td>-2.1 (-6.1 to 1.9)</td>
<td>-7.2 (-10.9 to -3.5)**</td>
<td>-5.1 (-8.9 to -1.3)**</td>
</tr>
<tr>
<td>Role Emotional</td>
<td>65.1 (4)</td>
<td>78.8 (3.3)</td>
<td>81.6 (2.9)</td>
<td>-13.7 (-21.7 to -5.7)**</td>
<td>-16.5 (-23.5 to -9.5)**</td>
<td>-2.8 (-8.4 to 2.8)</td>
</tr>
<tr>
<td>Mental Health</td>
<td>71.7 (1.5)</td>
<td>72.6 (1.6)</td>
<td>75.3 (1.5)</td>
<td>-1.0 (-3.5 to 1.6)</td>
<td>-3.6 (-5.9 to -1.3)**</td>
<td>-2.6 (-5.1 to 0.2)*</td>
</tr>
<tr>
<td>Physical Component</td>
<td>68.1 (1.8)</td>
<td>72.6 (1.7)</td>
<td>74.4 (1.6)</td>
<td>-4.4 (-7.0 to -1.9)**</td>
<td>-6.3 (-8.9 to -3.7)**</td>
<td>-2.0 (-4.5 to 0.6)</td>
</tr>
<tr>
<td>Mental Component</td>
<td>71.5 (2.2)</td>
<td>77.1 (2)</td>
<td>80.6 (1.8)</td>
<td>-5.6 (-9.4 to -1.7)**</td>
<td>-9.1 (-12.4 to -5.7)**</td>
<td>-3.5 (-6.7 to -0.3)</td>
</tr>
<tr>
<td><strong>AusEd Driving</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean RT to DAT (sec)</td>
<td>1.05 (0.03)</td>
<td>0.98 (0.03)</td>
<td>0.97 (0.03)</td>
<td>0.07 (0.007 to 0.13)*</td>
<td>0.07 (0.02 to 0.13)*</td>
<td>0.004 (-0.05 to 0.06)</td>
</tr>
<tr>
<td>Lapses</td>
<td>0.16 (0.06)</td>
<td>0.32 (0.15)</td>
<td>0.26 (0.12)</td>
<td>-0.16 (-0.47 to 0.15)</td>
<td>-0.11 (-0.34 to 0.13)</td>
<td>0.06 (-0.06 to 1.8)</td>
</tr>
<tr>
<td>Crashes</td>
<td>0.25 (0.09)</td>
<td>0.22 (0.06)</td>
<td>0.14 (0.04)</td>
<td>0.03 (-0.13 to 0.19)</td>
<td>0.12 (-0.04 to 0.27)</td>
<td>0.1 (-0.04 to 0.24)</td>
</tr>
<tr>
<td>Mean Lane Deviation (cm)</td>
<td>59.1 (2.3)</td>
<td>59.6 (2.3)</td>
<td>58.7 (2.4)</td>
<td>-0.51 (-4.1 to 3.0)</td>
<td>0.4 (-2.9 to 3.7)</td>
<td>1.01 (-1.7 to 3.7)</td>
</tr>
<tr>
<td>Mean Speed Deviation</td>
<td>3.0 (0.26)</td>
<td>2.39 (0.18)</td>
<td>2.45 (0.20)</td>
<td>0.62 (0.31 to 0.93)**</td>
<td>0.56 (0.15 to 0.96)**</td>
<td>-0.04 (-0.31 to 0.22)</td>
</tr>
</tbody>
</table>

RT to DAT = Reaction Time to Divided Attention Task

** p<0.01, * p< 0.05
ONLINE DATA SUPPLEMENT

Comparison of Health Outcomes of CPAP versus Oral Appliance Treatment for Obstructive Sleep Apnea: A Randomised Controlled Trial

Authors: Craig L Phillips
          Ronald R Grunstein
          M. Ali Darendeliler
          Anastasia S Mihailidou
          Vasantha K Srinivasan
          Brendon J Yee
          Guy B Marks
          Peter A Cistulli
METHODS

Design Overview. A randomised crossover open label study design was used to compare the health effects of 1 month of optimal treatment of OSA with CPAP versus MAD therapy. Optimal treatment was defined as attaining the highest compliance and best efficacy with each treatment under standard clinical practices during each 4-6 week acclimatisation period. Recruitment and follow up of patients occurred between June 2007 and December 2010. The trial was registered with the Australian and New Zealand Clinical Trials Registry (ANZCTR) at https://www.anzctr.org.au, trial number ACTRN12607000289415.

Setting and participants. The study was conducted between the Woolcock Institute of Medical Research, Royal North Shore and Royal Prince Alfred hospitals in Sydney, Australia. Patients with newly diagnosed OSA by overnight polysomnography were recruited from these and other affiliated sleep clinics. Selection criteria included adults aged ≥20 years, an apnea-hypopnea index (AHI) >10 /hr of sleep, >=2 symptoms of OSA (snoring, fragmented sleep, witnessed apneas, or daytime sleepiness), and a willingness to use both treatments. Recruitment was enriched for moderate-severe OSA. Patients were excluded for any of the following reasons: previous OSA treatment or a need for immediate treatment based on clinical judgement, central sleep apnea, a co-existing sleep disorder, regular use of sedatives or narcotics, pre-existing lung or psychiatric disease and any contra-indication for oral appliance therapy (eg periodontal disease or insufficient dentition). Dental eligibility was assessed by an orthodontist at the Sydney Dental Hospital. All study procedures, were approved by the site-specific Institutional Human Research Ethics Committees (Sydney Southwest Area Health
Service Protocol X07-0168). Prior to consenting, patients were told they would be compensated for participating in the study by receiving the treatment device recommended by their sleep physician at no cost.

**Randomisation and Interventions.** Patients who met all eligibility criteria were randomised to both the treatment acclimatisation and treatment arm orders. This was to minimise any bias related to treatment preference based upon the order of treatment exposure and resulted in 4 randomised sequences for MAD (M) and CPAP (C) as follows: MCMC, MCCM, CMMC and CMCM. Each sequence was generated by a computer program using random permuted blocks. The acclimatisation periods for each treatment were generally between 4-8 weeks. Treatment periods were for 1 month each.

**CPAP.** The CPAP device used was the ResMed Autoset S8 (ResMed, Bella Vista, Australia). Prior to CPAP acclimatisation, patients were fitted with an appropriate mask interface. All patients received CPAP education including instruction on CPAP machine operation by a trained therapist. The machines were initially set in auto-CPAP mode for home use and patients were asked to return the device after they had reported >4 hours/night usage during sleep. This usually occurred within 1 week. The optimum fixed pressure was then set to the 95th percentile pressure that controlled most of the OSA events, as routinely used in clinical practice. This approach to CPAP titration has been shown to produce similar outcomes to in-laboratory titration.¹ Patients were then asked to use the device each night for as long as they could tolerate it. Both face-to-face and telephone support from a CPAP therapist was available during this acclimatisation period. Pressures were
occasionally altered by 1-2 cmH20 to overcome any residual OSA detected by the device and at the same time, to maximise usage and comfort as well as to minimise mask leak. Once the usage pattern had stabilised, treatment was considered to be optimised and patients were asked to surrender the machine until the CPAP treatment phase of the study.

**MAD.** The mandibular advancement splint (Somnodent, SomnoMed Ltd Australia) is a custom fitted and titratable two-piece device. Individual dental impressions for manufacture of the device were taken at a mandibular protrusive bite of 60% of maximum protrusion. The mechanical operation of this device and its effectiveness in treating OSA, including comparison to placebo, has been reported previously.\(^2^4\) Once fitted with the device, patients underwent acclimatisation during which they incrementally advanced the device until the maximum comfortable limit of advancement was achieved. Patients were asked to use the device each night for as long as they could tolerate it. Both face-to-face and telephone orthodontic support was available during acclimatisation. The advancements were recorded in a diary and the final position was verified by the orthodontist, after which the device was surrendered until the MAD treatment phase of the study.

**Outcomes and Follow-up.** All outcomes were assessed on three occasions, at baseline prior to treatment acclimatisation and then at the end of each of the 1 month treatment arms. Polysomnography (E-Series, Compumedics, Melbourne, Australia, Alice 5, Philips Respironics, Andover, MA, USA or Sandman Elite, Nellcor Puritan Bennett, Pleasanton, CA, USA) and scoring were conducted using standard techniques.\(^5\) Recordings included 4 channels of electroencephalogram (EEG), 2
channels of electro-oculogram (EOG), chin electromyogram (EMG), electrocardiogram (ECG), anterior tibial EMG, nasal pressure, chest and abdomen movements, body position and arterial oxygen saturation (SpO2). Office BP was assessed in duplicate in the seated position after 5-min rest by conventional sphygmomanometry. Twenty-four hour ambulatory BP monitoring was performed using the Spacelabs-90217 monitor. BP was measured at 30-min intervals during the day (06:00-20:00) and every 60-min at night (20:00-06:00). Participants were instructed to undertake their usual daily activity and maintain a diary to note their activity at each recording, and their sleep time. Minimal editing of data and criteria according to the modified Casadei method were used to eliminate artefact. Central BP and arterial stiffness were assessed after 10-min rest in the supine position using pulse wave analysis as previously described (SphymoCor, AtCor Medical, Ryde, Australia). Daytime functioning was measured with a sleep-related QOL questionnaire, the Functional Outcomes of Sleep Questionnaire (FOSQ), a general QOL questionnaire, the Short Form 36 (SF36) and a subjective sleepiness questionnaire, the Epworth Sleepiness Score (ESS). Patients also underwent a computer-based driving simulator performance assessment (AusEd, Australasian Sleep Trials Network, Australia) with a 10-min practice period preceding each 30-min drive. Patients were also asked to complete a daily diary recording details of treatment usage and side-effects. Diaries were used to compile subjective compliance data. Compliance was determined by dividing the total hours of reported use each night by the number of nights with access to treatment. After completing the trial but before knowledge of their results, patients reported their treatment preference (CPAP, MAD, either, or neither).
Statistical analysis

We selected the difference in 24-hour mean arterial pressure (24MAP) between CPAP and MAD as the primary outcome. The analysis was designed to establish non-inferiority of MAD compared with CPAP for this outcome. A previous study showed that OSA treatment with therapeutic CPAP lowered 24MAP by 3.3mmHg relative to sham CPAP. This study did not select patients on the basis of their hypertensive status. Therefore, we assumed that by using similar selection criteria we could establish non-inferiority of MAD to CPAP for control of 24MAP with a non-inferiority margin of 1.6mmHg.

An analysis of variance with the 4 randomised groups was used to establish that no acclimatisation or treatment arm order effects occurred in the 24MAP, ESS, FOSQ or SF36 component responses after MAD and CPAP (all p>0.39). The primary hypothesis was tested by comparing the upper limit of the 95% confidence interval for the MAD-CPAP difference in 24MAP with the a priori non-inferiority margin using the paired t-test. All other health outcomes including subjective sleepiness (ESS), quality of life (FOSQ, SF-36), driving simulator performance and arterial stiffness were assessed with the repeated measures analysis of variance. This approach allowed direct between-treatment comparisons as well as post-hoc comparisons between each treatment and baseline. We limited the analysis to the 108 subjects who completed the trial, regardless of compliance with their assigned treatment. Compared with an intention-to-treat analysis, this was a more conservative approach that would reduce the likelihood of falsely claiming (1) non-inferiority for the primary outcome and (2) no between-treatment differences for other outcomes.
Sample size and study power

In order to ensure an adequate sample size to assess multiple unrelated health outcomes, we powered the study on a blood pressure outcome – 24 hour Mean Arterial Pressure (24MAP). Based on our own data, we estimated a within-subject mean square error of 3.9 for 24MAP. Hence, in order to detect non-inferiority of this outcome with 90% power, using a non-inferiority margin of 1.6mmHg and assuming a true difference between treatment means of 0, a sample size of 108 completers was required. Power analysis was performed using PASS software version 11 (NCSS Inc, Kaysville Utah). All other analyses were made using the PASW statistical software version 17 (SPSS Inc., Chicago, IL).
References for Online Supplement


Table E1: 24hr BP in All (n=108: top panel) and Hypertensive Completers (n=45: bottom panel)

<table>
<thead>
<tr>
<th>Variable BP</th>
<th>Baseline Mean (SE)</th>
<th>CPAP Mean (SE)</th>
<th>MAD Mean (SE)</th>
<th>Mean Baseline - CPAP Difference (95% CI)</th>
<th>Mean Baseline - MAD Difference (95% CI)</th>
<th>Mean CPAP - MAD Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Completers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office SBP (mmHg)</td>
<td>123.7 (1.4)</td>
<td>123.9 (1.3)</td>
<td>123.9 (1.1)</td>
<td>-0.2 (-2.4 to 2.0)</td>
<td>-0.3 (-2.3 to 1.8)</td>
<td>-0.04 (-2.1 to 2.0)</td>
</tr>
<tr>
<td>Office DBP (mmHg)</td>
<td>80.6 (0.9)</td>
<td>79.6 (0.9)</td>
<td>79.7 (0.8)</td>
<td>1.1 (-0.5 to 2.6)</td>
<td>1.0 (-0.4 to 2.4)</td>
<td>0.08 (-1.5 to 1.4)</td>
</tr>
<tr>
<td>24 hr ABPM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>123.9 (1.2)</td>
<td>124.4 (1.0)</td>
<td>123.9 (1.1)</td>
<td>-0.5 (-2.0 to 0.9)</td>
<td>-0.0 (-1.5 to 1.5)</td>
<td>0.5 (-0.7 to 1.8)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>77.3 (0.8)</td>
<td>77.2 (0.7)</td>
<td>77.1 (0.7)</td>
<td>0.1 (-0.9 to 1.1)</td>
<td>0.2 (-0.7 to 1.1)</td>
<td>0.2 (-0.7 to 1.0)</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>92.7 (0.8)</td>
<td>92.7 (0.7)</td>
<td>92.5 (0.7)</td>
<td>0.0 (-1.0 to 1.0)</td>
<td>0.3 (-0.8 to 1.3)</td>
<td>0.2 (-0.7 to 1.1)</td>
</tr>
<tr>
<td>Wake SBP (mmHg)</td>
<td>129.2 (1.1)</td>
<td>130.0 (1.1)</td>
<td>129.4 (1.1)</td>
<td>-0.8 (-2.4 to 0.9)</td>
<td>-0.2 (-1.7 to 1.4)</td>
<td>0.6 (-0.8 to 2.0)</td>
</tr>
<tr>
<td>Wake DBP (mmHg)</td>
<td>81.6 (0.8)</td>
<td>81.4 (0.8)</td>
<td>81.1 (0.8)</td>
<td>0.2 (-0.8 to 1.2)</td>
<td>0.5 (-0.5 to 1.5)</td>
<td>0.3 (-0.6 to 1.2)</td>
</tr>
<tr>
<td>Wake MBP (mmHg)</td>
<td>96.9 (0.8)</td>
<td>97.0 (0.8)</td>
<td>96.5 (0.8)</td>
<td>-0.0 (-1.1 to 1.1)</td>
<td>0.4 (-0.7 to 1.5)</td>
<td>0.4 (-0.5 to 1.1)</td>
</tr>
<tr>
<td>Sleep SBP (mmHg)</td>
<td>112.1 (1.3)</td>
<td>112.0 (1.1)</td>
<td>111.6 (1.2)</td>
<td>0.0 (-1.7 to 1.8)</td>
<td>0.4 (-1.3 to 2.2)</td>
<td>0.4 (-1.3 to 2.1)</td>
</tr>
<tr>
<td>Sleep DBP (mmHg)</td>
<td>68.1 (0.9)</td>
<td>68.1 (0.8)</td>
<td>67.9 (0.8)</td>
<td>0.0 (-1.5 to 1.6)</td>
<td>0.2 (-1.1 to 1.5)</td>
<td>0.2 (-1.1 to 1.5)</td>
</tr>
<tr>
<td>Sleep MBP (mmHg)</td>
<td>83.3 (0.9)</td>
<td>83.3 (0.8)</td>
<td>82.7 (0.9)</td>
<td>0.1 (-1.4 to 1.5)</td>
<td>0.7 (-0.8 to 2.1)</td>
<td>0.6 (-0.7 to 1.9)</td>
</tr>
<tr>
<td><strong>Nocturnal Dipping</strong></td>
<td></td>
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</tr>
<tr>
<td>SBP Dip (%)</td>
<td>13.3 (0.6)</td>
<td>13.7 (0.6)</td>
<td>13.5 (0.6)</td>
<td>-0.4 (-1.7 to 1.0)</td>
<td>-0.2 (-1.5 to 1.2)</td>
<td>0.2 (-1.1 to 1.5)</td>
</tr>
<tr>
<td>DBP Dip (%)</td>
<td>16.6 (0.7)</td>
<td>16.2 (0.8)</td>
<td>16.1 (0.8)</td>
<td>0.4 (-1.4 to 2.2)</td>
<td>0.5 (-1.2 to 2.2)</td>
<td>0.1 (-1.4 to 1.6)</td>
</tr>
<tr>
<td><strong>Hypertensive Completers</strong></td>
<td></td>
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</tr>
<tr>
<td>Office SBP (mmHg)</td>
<td>134.6 (1.9)</td>
<td>132.0 (1.9)</td>
<td>120.9 (1.7)</td>
<td>2.7 (-1.0 to 6.3)</td>
<td>4.7 (-1.4 to 8.0)</td>
<td>2.0 (-1.5 to 5.6)</td>
</tr>
<tr>
<td>Office DBP (mmHg)</td>
<td>87.3 (1.4)</td>
<td>84.5 (1.5)</td>
<td>83.7 (1.2)</td>
<td>2.8 (-0.0 to 5.7)</td>
<td>3.6 (1.3 to 5.9)**</td>
<td>0.8 (-1.8 to 3.4)</td>
</tr>
<tr>
<td>24 hr ABPM</td>
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</tr>
<tr>
<td>SBP (mmHg)</td>
<td>133.9 (1.4)</td>
<td>130.9 (1.3)</td>
<td>131.1 (1.6)</td>
<td>3.0 (0.6 to 5.4)*</td>
<td>2.9 (0.3 to 5.4)*</td>
<td>-0.2 (-2.3 to 2)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>83.6 (1.1)</td>
<td>81.2 (1.1)</td>
<td>81.5 (1.2)</td>
<td>2.4 (0.9 to 3.9)**</td>
<td>2.1 (0.4 to 3.7)*</td>
<td>-0.3 (-1.8 to 1.1)</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>99.8 (0.9)</td>
<td>97.4 (1.0)</td>
<td>97.6 (1.2)</td>
<td>2.5 (0.9 to 4.1)**</td>
<td>2.2 (0.4 to 4.0)*</td>
<td>-0.3 (-1.9 to 1.3)</td>
</tr>
<tr>
<td>Wake SBP (mmHg)</td>
<td>138.9 (1.4)</td>
<td>136.6 (1.4)</td>
<td>134.6 (1.4)</td>
<td>2.3 (-0.5 to 5.1)</td>
<td>2.5 (-0.1 to 5.1)</td>
<td>0.2 (-2.0 to 2.5)</td>
</tr>
<tr>
<td>Wake DBP (mmHg)</td>
<td>87.4 (1.2)</td>
<td>85.2 (1.3)</td>
<td>85.0 (1.3)</td>
<td>2.1 (0.7 to 3.6)**</td>
<td>2.4 (0.8 to 3.9)**</td>
<td>0.2 (-1.1 to 1.5)</td>
</tr>
<tr>
<td>Wake MBP (mmHg)</td>
<td>103.5 (1.0)</td>
<td>101.4 (1.1)</td>
<td>101.2 (1.2)</td>
<td>2.1 (0.4 to 3.7)*</td>
<td>2.4 (0.5 to 4.2)*</td>
<td>0.3 (-1.2 to 1.7)</td>
</tr>
<tr>
<td>Sleep SBP (mmHg)</td>
<td>122.7 (1.7)</td>
<td>118.6 (1.6)</td>
<td>119.2 (1.9)</td>
<td>4.1 (1.7 to 6.5)**</td>
<td>3.4 (0.6 to 6.3)*</td>
<td>-0.7 (-3.5 to 2.2)</td>
</tr>
<tr>
<td>Sleep DBP (mmHg)</td>
<td>75.2 (1.3)</td>
<td>72.1 (1.1)</td>
<td>73.3 (1.3)</td>
<td>3.1 (0.7 to 5.5)*</td>
<td>1.9 (-0.4 to 4.2)</td>
<td>-1.1 (-3.5 to 1.1)</td>
</tr>
<tr>
<td>Sleep MBP (mmHg)</td>
<td>91.1 (1.3)</td>
<td>88.1 (1.1)</td>
<td>88.1 (1.4)</td>
<td>3.0 (0.8 to 5.2)**</td>
<td>3.0 (0.3 to 5.7)*</td>
<td>0.0 (-2.3 to 2.4)</td>
</tr>
<tr>
<td><strong>Nocturnal Dipping</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP Dip (%)</td>
<td>11.6 (0.9)</td>
<td>13.0 (1.1)</td>
<td>12.5 (1.0)</td>
<td>-1.4 (-3.3 to 0.4)</td>
<td>-0.8 (-2.7 to 0.9)</td>
<td>0.6 (-1.4 to 2.5)</td>
</tr>
<tr>
<td>DBP Dip (%)</td>
<td>13.9 (1.1)</td>
<td>15.0 (1.3)</td>
<td>13.6 (1.2)</td>
<td>-1.1 (-3.6 to 1.4)</td>
<td>0.3 (-2.2 to 2.8)</td>
<td>1.4 (-3.6 to 0.8)</td>
</tr>
</tbody>
</table>
** p<0.01, * p< 0.05

Table E2 Pulse Wave Analysis results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>CPAP</th>
<th>MAD</th>
<th>Mean Baseline - CPAP Difference (95% CI)</th>
<th>Mean Baseline - MAD Difference (95% CI)</th>
<th>Mean CPAP - MAD Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSBP (mmHg)</td>
<td>123.4 (1.2)</td>
<td>123.3 (1.2)</td>
<td>124.2 (1.3)</td>
<td>0.1 (-1.9 – 2.1)</td>
<td>-0.9 (-2.8 – 1.1)</td>
<td>-0.9 (-2.7 – 0.8)</td>
</tr>
<tr>
<td>PDBP (mmHg)</td>
<td>77.3 (0.9)</td>
<td>75.9 (0.9)</td>
<td>77.2 (1.0)</td>
<td>1.3 (-0.2 – 2.8)</td>
<td>0.1 (-1.2 – 1.4)</td>
<td>-1.2 (-2.7 – 0.2)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>93.9 (1.0)</td>
<td>92.8 (0.9)</td>
<td>94.0 (1.0)</td>
<td>1.1 (-0.5 – 2.6)</td>
<td>-0.1 (-1.5 – 1.3)</td>
<td>-1.2 (-2.6 – 0.3)</td>
</tr>
<tr>
<td>CSBP (mmHg)</td>
<td>114.1 (1.3)</td>
<td>113.1 (1.2)</td>
<td>114.3 (1.3)</td>
<td>1.0 (-0.8 – 2.9)</td>
<td>-0.2 (-1.9 – 1.5)</td>
<td>-1.2 (-2.9 – 0.4)</td>
</tr>
<tr>
<td>CPP (mmHg)</td>
<td>35.9 (0.9)</td>
<td>36.1 (0.8)</td>
<td>36.2 (0.8)</td>
<td>-0.2 (-1.6 – 1.2)</td>
<td>-0.2 (-1.4 – 0.9)</td>
<td>-0.1 (-1.3 – 1.2)</td>
</tr>
<tr>
<td>Alx (%)</td>
<td>23.6 (1.2)</td>
<td>21.7 (1.2)</td>
<td>22.4 (1.2)</td>
<td>1.8 (0.6 – 3.1) **</td>
<td>1.2 (0.2 – 2.2) *</td>
<td>-0.7 (-1.7 – 0.4)</td>
</tr>
<tr>
<td>Alx&lt;sub&gt;75&lt;/sub&gt; (%)</td>
<td>16.9 (1.2)</td>
<td>15.7 (1.2)</td>
<td>15.8 (1.2)</td>
<td>1.3 (0.1 – 2.4) *</td>
<td>1.1 (0.0 – 2.2) *</td>
<td>-0.2 (-1.2 – 0.9)</td>
</tr>
</tbody>
</table>

** p<0.01 * p<0.05

PSBP = Peripheral SBP
PDBP = Peripheral DBP
MAP = Mean Arterial Pressure
CSBP = Central SBP
CPP = Central Pulse Pressure
Alx = Augmentation Index
Alx<sub>75</sub> = Augmentation Index corrected to a heart rate of 75bpm
AP = Augmentation Pressure
LEGEND FOR ONLINE DATA SUPPLEMENT FIGURES

Figure E1

Intention-to-treat AHI (±SEM) according to baseline OSA severity
Closed symbols = CPAP, Open symbols = MAD. The AHI was lower on CPAP than MAD for patients with mild, moderate and severe OSA at baseline
All p< 0.05 (Wilcoxin Signed Rank Test)

Figure E2

Subjective compliance (±SEM) according to baseline OSA severity where compliance = total hours of reported use over all nights of the treatment period
Closed symbols = CPAP, Open symbols = MAD.
The compliance was lower on CPAP than MAD for patients with mild, moderate and severe OSA at baseline (all p < 0.05)

Figure E3

24-hour blood pressure profiles during CPAP and MAD treatment showing blood pressure dipping during the sleep period. Data are means (SEM)
Figure E1

Intention to Treat AHI (events/hour)

Baseline OSA Severity

Figure E2

Subjective Compliance (hours/night)

Baseline OSA Severity
Figure E3