The prevalence of minimally symptomatic OSA presenting without overt daytime sleepiness among middle-aged adults has been shown to be as high as 30%, making OSA one of the most frequent disorders and, thus, of epidemiologic interest. Prospective epidemiologic studies have implicated OSA syndrome (OSAS) as an independent risk factor for stroke and myocardial ischemia. Multiple biologic factors underpinning the association between OSAS and atherosclerosis have been proposed, including intermittent hypoxia, increased sympathetic activity, and intrathoracic pressure changes, all of which may be associated with endothelial dysfunction.

Endothelial dysfunction and increased arterial stiffness play a central role in the development of atherosclerosis and are associated with conventional cardiovascular risk factors. Therefore, early detection of these measures of cardiovascular risk are of great interest, with the anticipation that an early therapeutic intervention will benefit those patients who are at increased risk for future cardiovascular events.

**Background:** Minimally symptomatic OSA is a highly prevalent disorder, and the effects of CPAP on vascular function in these patients are unknown. This trial aimed to investigate whether CPAP improves vascular function in minimally symptomatic OSA.

**Methods:** In two centers taking part in the MOSAIC (Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular) trial, 253 patients with minimally symptomatic OSA were randomized to 6 months of CPAP or standard care. Two hundred eight patients attended their follow-up visit within the predefined time window and had complete measurements of arterial stiffness (augmentation index [AIx]), and 64 patients had endothelial function measurements by brachial artery flow-mediated dilatation (FMD). Multivariable analyses adjusting for baseline measurements and minimization factors were performed to assess the effect of CPAP treatment on FMD (% dilatation) and AIx (% augmentation) compared with standard care.

**Results:** The mean ± SD baseline oxygen desaturation index and Epworth Sleepiness Score (ESS) of the 208 patients (age 58 ± 7.3 years, 31 women) were 13.7 ± 12.8 events/h and 8.3 ± 4.2, respectively. There was no CPAP treatment effect on arterial stiffness (AIx, −1.4%; 95% CI, −3.6 to +0.9%; \(P = .23\)), but CPAP improved endothelial function (FMD, +2.1%; 95% CI, +1.0 to +3.2%; \(P < .0001\)). CPAP reduced daytime sleepiness (ESS, −2.2; 95% CI, −3.0 to −1.5; \(P < .0001\)) compared with standard care. There was a larger improvement in FMD in patients using CPAP for >4 h/night than those who used it less (\(P = .013\)).

**Conclusions:** CPAP improves endothelial function, but not arterial stiffness, in minimally symptomatic OSA. Thus, minimally symptomatic OSA may be a cardiovascular risk factor.

**Trial registry:** ISRCTN Register; No.: ISRCTN 34164388; URL: http://isrctn.org

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**Abbreviations:** AIx = augmentation index; ESS = Epworth Sleepiness Score; FMD = flow-mediated dilatation; MOSAIC = Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular; ODI = oxygen desaturation index; OSAS = OSA syndrome; OSLER = Oxford Sleep Resistance test
OSA with moderate to severe daytime symptoms has been associated with endothelial dysfunction and increased arterial stiffness, which have been shown to improve after CPAP therapy. Vascular function has been shown to be impaired in patients with minimally symptomatic OSA; there are, however, no data from randomized controlled trials on the effect of CPAP on endothelial dysfunction and arterial stiffness in such patients. These minimally symptomatic patients would normally not receive CPAP therapy, as there is currently conflicting evidence of any symptomatic benefit or a reduction in BP. To investigate the hypothesis that CPAP improves vascular function in patients with minimally symptomatic OSA, we investigated the effects of 6 months of CPAP therapy on endothelial function and arterial stiffness in a subset of patients in the MOSAIC (Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular) randomized controlled trial.

**Materials and Methods**

**Study Design and Patients**

The MOSAIC trial was conducted between May 2006 and February 2010: nine centers from the United Kingdom and one from Canada participated. Patients with minimally symptomatic OSA were randomized to either 6 months of CPAP therapy or standard care. In two centers (Oxford and Taunton), measurements of arterial stiffness were performed. Measurements of endothelial function were performed in Oxford between October 2006 and June 2008. The trial was performed according to the Declaration of Helsinki and was approved by the Oxford research ethics committee (REC No: 05/Q1604/159) and registered (ISRCTN 34164388).

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Patients with possible OSA were usually referred because of severe snoring or witnessed apneas. Patients were eligible for the trial if they were aged between 45 and 75 years, had proven OSA with a severity defined as > 7.5 oxygen desaturations of > 4% per hour (oxygen desaturation index [ODI] > 7.5/h) in the original sleep study, and no history of excessive daytime sleepiness or any other concerning daytime symptoms of OSA that would have justified initiation of CPAP therapy. This decision followed a detailed discussion between physician and patient about the evidence for possible benefits of CPAP vs the potentially lifelong usage of a CPAP device and mask every night.

Patients with ventilatory failure, Cheyne-Stokes breathing, previous exposure to CPAP, BP > 180/110 mm Hg, a current heavy goods vehicle or public service vehicle driver license, a history of any sleep-related accident, or disability precluding informed consent or compliance with the protocol were not eligible for the trial. Written informed consent was obtained from participants.

**Sleep Study, Assessment of Sleepiness, and CPAP**

OSA was diagnosed from a one-night in-hospital respiratory polygraphic sleep study as previously described and validated (e-Appendix 1). The severity of OSA was quantified as the number of oxygen desaturations > 4% per hour of study (ODI). In addition, to ensure consistency across the two centers, an ambulatory overnight pulse oximetry (Pulseox-300i; Konica-Minolta Inc) was performed at baseline and at 6 months, the data from which (ODI4%) were used for statistical analysis.

Subjective sleepiness was assessed using the Epworth Sleepiness Score (ESS). Objective sleepiness was assessed using one sleep resistance challenge (Oxford Sleep Resistance [OSLER] test) administered at the same time of day. Assessments of both subjective and objective sleepiness were performed at baseline and after 6 months.

Patients allocated to CPAP therapy were instructed in the use of an autoadjusting CPAP machine (AutoSet S8; ResMed) by a trained sleep nurse. CPAP usage was downloaded from the machine after 6 months. Those allocated to standard care were advised to continue with their current medication but were not given specific weight reduction or lifestyle advice. The clinical trial staff members, who maintained the CPAP machines and assisted the patients, were not involved in outcome assessments.

**Cardiovascular Risk Score and Arterial Stiffness Assessed by Pulse Wave Analysis**

The Pocock cardiovascular risk score was used at baseline and at 6 months to estimate an individual’s 5-year risk of death from cardiovascular events (e-Appendix 1). Radial artery pulse waveforms were recorded at baseline and after 6 months using a pressure tonometer and designated software to calculate augmentation index (AIx) (an estimate of arterial stiffness) as previously described (e-Appendix 1).

**Endothelial Function Assessed by Flow-Mediated Dilatation**

Flow-mediated dilatation (FMD) measurements were performed by ultrasound according to the method originally described by Celermajer and colleagues (e-Appendix 1). FMD measurements were performed at baseline and at 6 months.

**BP**

Participants measured their BP at home three times per day in triplicate on 7 continuous days with a standard digital automatic monitor (Omron Healthcare, Inc) in the sitting position after a period of rest of 5 min. The average of the 7-day readings was used for analysis. Ambulatory BP was measured in the week prior...
to randomization and in the week prior to the 6-month follow-up visit.

**Randomization**

Allocation to the CPAP or standard care group was achieved by telephoning the Medical Research Council Clinical Trials Unit. The allocation sequence was computer generated and incorporated minimization for OSA severity as assessed by ODI (above or below 20/h), Pocock cardiovascular risk score (above or below 40), and participating center.

**Data Analysis**

All values are presented as means (SD), medians (quartiles), or percentages, as appropriate. Further details on data analysis are given in e-Appendix 1.

**RESULTS**

**Trial Profile, Patient Characteristics, and CPAP Compliance**

Figure 1 shows the trial profile. In the two study centers where vascular function assessments were performed, 253 patients were recruited and were randomized to either CPAP or standard care. Of these, 245 patients had measurements of arterial stiffness, and 64 of those patients had endothelial function assessments.

During the follow-up period, eight patients withdrew; and in 16 patients pulse wave analysis was not possible at either enrollment or 6 months. Twenty-one patients did not attend their follow-up visit within the predefined time window (no earlier than 4 weeks before and no later than 8 weeks after the scheduled follow-up visit). Thus, data on arterial stiffness of 208 patients and data on endothelial function of 64 patients were included in the analysis. These sample sizes give 96% power to detect a minimum clinically relevant difference in AIx of 5% (SD, 9.6)\textsuperscript{12,25} and 81% power to detect a minimum clinically relevant difference of 2% (SD, 2.7) on FMD.\textsuperscript{13,26}

The two treatment arms were similar regarding their baseline characteristics (Table 1), which was also true for the group of patients with data on FMD (data not shown). The median (25th, 75th percentiles) nightly adherence to CPAP was 2.84 (0.35, 5.05) h.

**Pulse Wave Analysis**

Baseline arterial stiffness, assessed by the AIx, was similar in the two treatment arms (Table 2). There was no evidence of an effect on arterial stiffness with 6 months of CPAP therapy compared with standard

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**Table 1—Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CPAP Group (n = 107)</th>
<th>Standard Care Group (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58.4 (7.2)</td>
<td>58.2 (7.5)</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>90 (84.1)</td>
<td>87 (86.1)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>32.6 (5.6)</td>
<td>32.6 (5.4)</td>
</tr>
<tr>
<td>Waist/hip circumference ratio</td>
<td>1.0 (0.1)</td>
<td>1.0 (0.1)</td>
</tr>
<tr>
<td>Neck circumference, cm</td>
<td>43.1 (4.0)</td>
<td>43.5 (3.7)</td>
</tr>
<tr>
<td>Current smoker, No. (%)</td>
<td>9 (8.4)</td>
<td>18 (17.8)</td>
</tr>
<tr>
<td>Ex-smoker, No. (%)</td>
<td>57 (53.3)</td>
<td>48 (47.5)</td>
</tr>
<tr>
<td>Hypertension, No. (%)</td>
<td>86 (80.4)</td>
<td>84 (83.2)</td>
</tr>
<tr>
<td>Diabetes, No. (%)</td>
<td>16 (15.0)</td>
<td>22 (21.8)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.2 (1.3)</td>
<td>5.2 (1.1)</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>5.7 (1.5)</td>
<td>5.9 (1.5)</td>
</tr>
<tr>
<td>Antihypertensive medication, No. (%)</td>
<td>52 (48.6)</td>
<td>51 (50.5)</td>
</tr>
<tr>
<td>Cholesterol-lowering medication, No. (%)</td>
<td>39 (36.5)</td>
<td>33 (32.7)</td>
</tr>
<tr>
<td>Glucose-lowering medication, No. (%)</td>
<td>13 (12.2)</td>
<td>17 (16.8)</td>
</tr>
<tr>
<td>7-d systolic BP, mm Hg</td>
<td>130.0 (11.6)</td>
<td>132.3 (13.5)</td>
</tr>
<tr>
<td>7-d diastolic BP, mm Hg</td>
<td>81.0 (8.2)</td>
<td>82.2 (8.1)</td>
</tr>
<tr>
<td>5-y cardiovascular risk, % (SD)</td>
<td>1.8 (1.4)</td>
<td>2.1 (1.7)</td>
</tr>
<tr>
<td>Oxygen saturation dips &gt; 4% (per h of sleep)</td>
<td>9.5 (3.8-17.2)</td>
<td>10.4 (5.7-16)</td>
</tr>
<tr>
<td>Epworth Sleepiness Score</td>
<td>8.4 (4.1)</td>
<td>8.3 (4.3)</td>
</tr>
<tr>
<td>OSLER subjects falling asleep, No. (%)</td>
<td>43 (40.2)</td>
<td>44 (43.6)</td>
</tr>
</tbody>
</table>

Values are means (SD) or median (25th and 75th percentiles) unless otherwise noted. Cardiovascular risk score estimates the risk of death (in percent) in the next 5 y due to a cardiovascular event. OSLER = Oxford Sleep Resistance test.

\*Defined by medical history.
compared with standard care. The effects of CPAP on BP and cardiovascular risk score in this subgroup were of similar size to the effects observed in the full MOSAIC trial. There was no evidence of a difference between those patients recruited by the Oxford and Taunton centers and reported in this substudy vs those not included.

Subgroup Interaction Testing
There was no evidence of a treatment interaction between those patients recruited by the Oxford and Taunton centers and reported in this substudy vs those not included. Results from the full MOSAIC trial are summarized in the online supplement (e-Tables 1-3).

### Table 2—Changes in Endothelial Function and Arterial Stiffness

<table>
<thead>
<tr>
<th>Measure</th>
<th>CPAP Group (n = 107)</th>
<th>Control Group (n = 101)</th>
<th>Adjusted Treatment Effect (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measure</td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>FMD, %</td>
<td>3.4 (3.4)</td>
<td>4.4 (3.0)</td>
<td>3.4 (2.4)</td>
<td>2.6 (2.3)</td>
</tr>
<tr>
<td>GTN, %</td>
<td>14.5 (5.1)</td>
<td>13.2 (4.9)</td>
<td>13.7 (5.2)</td>
<td>14.2 (5.5)</td>
</tr>
<tr>
<td>AIx, %</td>
<td>27.9 (9.5)</td>
<td>25.2 (9.8)</td>
<td>29.1 (10.8)</td>
<td>27.1 (10.8)</td>
</tr>
</tbody>
</table>

Before and after values are mean (SD). AIx = augmentation index; FMD = flow mediated dilatation (n = 64); GTN = endothelium-independent vasodilatation induced by nitroglycerin (n = 64).

Flow-Mediated Dilatation
Baseline brachial artery diameter was similar in patients in the CPAP and control group, 4.58 (0.92) mm and 4.75 (0.69) mm, respectively. Endothelial function, as assessed by measurement of FMD of the brachial artery, improved significantly after 6 months of CPAP therapy when compared with standard care (Fig 2, Table 2). As would be expected, there was no evidence of a difference in the change in nitroglycerin-induced endothelium-independent vasodilatation between the CPAP and standard care groups (Table 2). The treatment effect was statistically significantly higher in patients using CPAP ≥4 h/night compared with those using it <4 h/night (Fig 4), showing dose dependency.

BP and Cardiovascular Risk Score
There was no statistically significant effect of CPAP on systolic BP (+1.7 mm Hg [95% CI, −0.4 to +3.8 mm Hg]), diastolic BP (+0.5 mm Hg [95% CI, −1.8 to +0.9 mm Hg]), and 5-year calculated cardiovascular risk (+0.1% [95% CI, −0.1 to +0.2%]), compared with standard care. The effects of CPAP on BP and cardiovascular risk score in this subgroup were of similar size to the effects observed in the full MOSAIC trial. There was no evidence of a difference between those patients recruited by the Oxford and Taunton centers and reported in this substudy vs those not included.

Measures of OSA Severity and Sleepiness
ODI decreased in the CPAP arm compared with standard care by an average of 7.9 (95% CI, −10.5 to −5.4) events/h from baseline, and ESS decreased by an average of 2.2 points (95% CI, −3.0 to −1.5). The odds of falling asleep during the OSLER test at 6 months were 48% lower in the CPAP group compared with the standard care group (95% CI, 3% to 72%). The effects of CPAP on ODI and ESS in this subgroup were similar in size to the effects observed in the full MOSAIC trial.

Subgroup Interaction Testing
There was no evidence of a treatment interaction between those patients recruited by the Oxford and Taunton centers and reported in this substudy vs those not included. Results from the full MOSAIC trial are summarized in the online supplement (e-Tables 1-3).
controlled studies on the effects of CPAP on endothelial function in nonsleepy patients with OSA, there are some data from patients with more severe OSA; Ip and coworkers found that FMD improved after 4 weeks of CPAP treatment in a randomized controlled trial including 27 patients with moderate to severe OSA (no data on sleepiness). The magnitude of improvement in FMD in the study by Ip et al. (5.2%) was considerably larger than in our study. A possible explanation for this difference is the different study populations; Ip et al. only included patients with more severe OSA without comorbidities, whereas in our study many patients had cardiovascular or metabolic comorbidities, which are known to impair endothelial function and, thus, potentially mask a beneficial effect of CPAP. Kohler et al. found that 2 weeks of CPAP therapy withdrawal was associated with a statistically significant decrease in FMD of 3.2%.

**Discussion**

This randomized controlled trial found that patients with minimally symptomatic OSA who were treated with CPAP showed an improvement in endothelial function but not in arterial stiffness. The observed improvement in endothelial function suggests that patients with OSA may benefit from CPAP treatment in terms of cardiovascular risk reduction.

In this trial, endothelial function improved after 6 months of CPAP therapy. The observed adjusted difference in FMD change between the CPAP and standard care group was 2.1% (Fig 2); the size of this difference has been shown to be of clinical significance in studies looking at the association between FMD and subsequent cardiovascular events. Importantly, longer nightly usage of CPAP was associated with larger improvements in FMD after 6 months of follow-up. Although there are no further data from randomized controlled studies on the effects of CPAP on endothelial function in nonsleepy patients with OSA, there are some data from patients with more severe OSA; Ip and coworkers found that FMD improved after 4 weeks of CPAP treatment in a randomized controlled trial including 27 patients with moderate to severe OSA (no data on sleepiness). The magnitude of improvement in FMD in the study by Ip et al. (5.2%) was considerably larger than in our study. A possible explanation for this difference is the different study populations; Ip et al. only included patients with more severe OSA without comorbidities, whereas in our study many patients had cardiovascular or metabolic comorbidities, which are known to impair endothelial function and, thus, potentially mask a beneficial effect of CPAP. Kohler et al. found that 2 weeks of CPAP therapy withdrawal was associated with a statistically significant decrease in FMD of 3.2%.

**Figure 3.** Forest plot showing no statistically significant difference in the treatment effect on augmentation index in patients using CPAP < 4 h/night compared with those using it ≥ 4 h/night. The dashed line represents the overall treatment effect.

**Figure 4.** Forest plot showing a statistically significant difference in the treatment effect on FMD of the brachial artery in patients using CPAP < 4 h/night compared with those using it ≥ 4 h/night. The dashed line represents the overall treatment effect. See Figure 1 legend for expansion of abbreviation.
in a randomized, placebo-controlled trial including 41 patients with moderate to severe OSAS (original ESS, 14.6 ± 3.2). These findings are corroborated by Cross et al., who found that 6 weeks of CPAP therapy improved endothelial function (assessed by forearm venous occlusion plethysmography) in a trial including 27 subjects with severe OSAS (ESS > 10).

AIx, a measure of central arterial stiffness and pressure wave reflection, independently predicts cardiovascular events in high-risk populations. The findings of a case-control study suggest that arterial stiffness is elevated in patients with minimally symptomatic OSA. However, in the current trial there was no evidence of an effect of CPAP reducing arterial stiffness in such patients. The 95% CI of the difference in change in AIx between the two groups was −3.6 to +0.9%; thus, we have excluded a decrease in AIx in the CPAP group of > 3.6%, which is within the range of the minimally expected and clinically meaningful difference. Although there are no other data from randomized controlled studies on arterial stiffness in nonsleepy OSA, the findings of randomized controlled trials in patients with moderate to severe symptomatic OSAS suggest that CPAP may have a positive effect on arterial stiffness. An explanation for the lack of effect in the current study may be that we studied a population of patients with milder OSA. In addition, our study population had a higher age and higher proportion of patients with cardiovascular comorbidities than those of previous studies, both of which are well known to increase arterial stiffness and, thus, may have masked any positive effect of CPAP.

In theory, the relatively low median compliance with CPAP in our trial (2.8 h per night) may be an additional explanation for the lack of a therapeutic effect on arterial stiffness. In the study by Barbé et al., only patients with hypertensive and nonhypertensive were included, whereas patients with and without hypertension were included in the current trial, thus, reducing the chances of finding a beneficial treatment effect of CPAP on AIx.

Any subgroup analysis is prone to unintended selection bias, and this may also apply to a nested substudy. However, as there was no evidence of a treatment interaction on the outcomes of the MOSAIC trial between those patients recruited by the Oxford and Taunton centers and reported in this substudy vs those not included, we are confident that this substudy is representative of the whole MOSAIC study population. The lack of a sham intervention might have introduced a confounder related to subjective outcomes, such as ESS. Finally, although the size of improvement in FMD with CPAP observed in the current study has been shown to be of clinical relevance in other patient cohorts, this has not been proven in patients with OSA.

In conclusion, this substudy of the MOSAIC trial has shown that in patients with minimally symptomatic OSA, endothelial function improves with 6 months of CPAP therapy. Although CPAP therapy was not associated with a significant beneficial effect on arterial stiffness, BP, and cardiovascular risk score, the findings suggest that patients with minimally symptomatic OSA may benefit from CPAP therapy in terms of vascular function improvement. However, whether such an improvement in endothelial function ultimately results in a reduced number of cardiovascular events in these patients remains to be proven.

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Author contributions: Prof Kohler takes responsibility for the integrity of the work. Prof Kohler contributed to study design, acquisition of data, data analysis and interpretation, drafting of the manuscript, and approval of the final version.

Ms Craig contributed to acquisition of data, drafting of the manuscript, revision of the manuscript for intellectual content, and approval of the final version.

Dr Pepperell contributed to acquisition of data, drafting of the manuscript, revision of the manuscript for intellectual content, and approval of the final version.

Dr Nicolò contributed to acquisition of data, drafting of the manuscript, revision of the manuscript for intellectual content, and approval of the final version.

Mr Bratton contributed to data analysis and interpretation, drafting of the manuscript, revision of the manuscript for intellectual content, and approval of the final version.

Mr Butterfield contributed to acquisition of data, data analysis and interpretation, drafting of the manuscript, and approval of the final version.

Dr Lenders contributed to acquisition of data, data analysis and interpretation, drafting of the manuscript, and approval of the final version.

Dr Dicrandell contributed to acquisition of data, data analysis and interpretation, drafting of the manuscript, and approval of the final version.
Mr Nunn: contributed to data analysis and interpretation, drafting of the manuscript, revision of the manuscript for intellectual content, and approval of the final version.

Dr Leeson: contributed to acquisition of data, drafting of the manuscript, revision of the manuscript for intellectual content, and approval of the final version.

Dr Stradling: contributed to study design, data analysis and interpretation, drafting of the manuscript, revision of the manuscript for intellectual content, and approval of the final version.

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Role of sponsors: The sponsors had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Additional information: The e-Appendix and e-Tables can be found in the “Supplemental Materials” area of the online article.

REFERENCES


