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ECG risk markers for atrial fibrillation and sudden cardiac death in minimally symptomatic obstructive sleep apnoea: the MOSAIC randomised trial

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ABSTRACT

Objective: Obstructive sleep apnoea (OSA), atrial fibrillation (AF) and sudden cardiac death (SCD) may occur concomitantly, and are of considerable epidemiological interest, potentially leading to morbidity and mortality. Effective treatment of OSA with continuous positive airway pressure (CPAP) could prevent progression and/or recurrence of AF and factors leading to SCD. Recently, a randomised controlled trial showed a statistically and clinically significant prolongation of measures of cardiac repolarisation after CPAP withdrawal in symptomatic patients with moderate to severe OSA. Whether or not CPAP therapy improves ECG risk markers of AF and SCD in patients with minimally symptomatic OSA as well, is unknown.

Methods: 3 centres taking part in the MOSAIC (Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular) trial randomisd 303 patients with minimally symptomatic OSA to receive either CPAP or standard care for 6 months. Treatment effects of CPAP on P-wave duration, P-wave dispersion, QT interval, QT dispersion, Tpeak-to-Tend (TpTe) and TpTe/QT ratio were analysed.

Results: Participants were primarily men (83%). Mean age was 57.8 (7.2) and mean ODI (Oxygen Desaturation Index) at baseline was 13.1/h (12.3). Full 12-lead ECG data was available in 250 patients. Mean (SD) baseline intervals of P-wave duration, P-wave dispersion, QT_c interval, QT dispersion, TpTe and TpTe/QT ratio in ms were 87.4 (8.3), 42.3 (11.9), 397.8 (22.7), 43.1 (16.7), 73.5 (13.7) and 0.19 (0.0), respectively. No treatment effect of CPAP on risk markers for AF and SCD was found.

Conclusions: There seems to be no effect of CPAP on ECG measures of arrhythmia risk in patients with minimally symptomatic OSA.

Trial registration number: ISRCTN34164388; Post-results.

Strengths and limitations of this study

- This is the first randomised controlled trial evaluating the effect of continuous positive airway pressure (CPAP) on ECG risk markers for atrial fibrillation and sudden cardiac death in minimally symptomatic obstructive sleep apnoea (OSA).
- The Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular (MOSAIC) randomised trial was a rigorously planned and performed study aimed at giving clinicians a better foundation for treatment decision in the many patients with OSA lacking overt daytime sleepiness. However, the presented analysis was not the primary objective of the MOSAIC trial.
- Adherence to CPAP is usually an issue in patients with minimally symptomatic OSA.

INTRODUCTION

Up to 30% of middle-aged adults are affected by minimally symptomatic obstructive sleep apnoea (OSA).[1] These patients do not have overt daytime sleepiness and may have little motivation for continuous positive airway pressure (CPAP) therapy, the most effective treatment for OSA. Symptomatic OSA is an established independent risk factor for arterial hypertension[2] and has been linked to atrial fibrillation (AF)[3] and to sudden cardiac death (SCD).[4] OSA, AF and SCD may occur concomitantly and are of considerable epidemiological interest, potentially leading to morbidity and mortality. Effective treatment with CPAP might prevent progression and/or recurrence of AF and factors leading to SCD. While there is good evidence for this relationship in symptomatic patients with moderate to severe OSA, no data is available from randomised controlled trials (RCTs) on this association in patients with minimally symptomatic OSA.

OSA is associated with electrical and mechanical atrial remodelling.[5] OSA severity has been shown to be significantly associated with prolonged signal-averaged P-wave duration (SAPWD) and CPAP therapy is believed

to be able to reverse atrial remodelling, as it significantly reduced SAPWD[6] and P-wave dispersion (Pd)[7] in patients with moderate-to-severe OSA.

In patients with moderate to severe symptomatic OSA, 2 weeks of CPAP withdrawal led to significant lengthening of QTc and Tpeak-to-Tend (TpTe) intervals in a randomised trial by Rossi *et al*.[8]

It is unclear if there are similar effects of CPAP in patients with minimally symptomatic OSA to guide therapeutic decisions. To answer this question, we investigated the hypothesis that CPAP improves ECG risk markers of AF and SCD in patients with minimally symptomatic OSA and analysed ECG data from a subset of patients in the Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular (MOSAIC) RCT.

METHODS

Study design

Nine centres from the UK and one from Canada participated in the MOSAIC trial, which was conducted between May 2006 and February 2010. In three centres (Oxford, Taunton and Reading), 12-lead ECG measurements were obtained at baseline and at 6 months. The trial was performed according to the Declaration of Helsinki, and was registered (ISRCTN34164388).

Study participants

Patients with minimally symptomatic OSA, who were usually referred due to witnessed apnoeas or severe snoring, were randomised to either 6 months of CPAP therapy or standard care (SC). Eligibility criteria were as follows: age between 45 and 75 years, proven OSA on the diagnostic sleep study defined as >7.5 oxygen desaturations of >4% per hour (Oxygen Desaturation Index (ODI) >7.5/h) in the baseline sleep study, and no history of excessive daytime sleepiness or daytime symptoms of OSA that would have warranted CPAP therapy initiation. Patients were not eligible for inclusion if they had been previously diagnosed with ventilatory failure, Cheyne-Stokes breathing, or blood pressure >180/110 mm Hg. Patients with previous exposure to CPAP, 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 also excluded. Cardiovascular disease was not an exclusion criterion. All randomised patients gave written informed consent.

Sleep study

Diagnosis of OSA was made after a one-night, in-hospital, respiratory polygraphy as standard in the participating centres. The severity of OSA was quantified as the number of oxygen desaturations >4% per hour of study (ODI). Subjective daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS).[9] Objective sleepiness was assessed using one Oxford Sleep Resistance test administered at the same time of the day (Stowood Scientific Instruments Oxford, UK), which evaluates the ability to stay awake for 40 min in a quiet, darkened room. For consistency purposes across the three centres, a second ambulatory pulse-oximetry recording (Konica-Minolta Inc, Osaka, Japan) was performed at baseline and at 6 months in all eligible patients, and used as the trial ODI values. Patients were then informed in detail about possible pros and cons of CPAP. Patients with an ESS above the conventional upper normal limit (9) were included, if suitable for patients.

Randomisation

Parallel randomisation was performed by telephoning the Medical Research Council Clinical Trials Unit. The computer-generated allocation sequence with 1:1 ratio incorporated minimisation for OSA severity, as assessed by ODI (above or below 20/h), Pocock cardiovascular risk score[10] (above or below 40), and participating centre.

Continuous positive airway pressure

Patients allocated to CPAP were instructed in the use of an auto-adjusting CPAP machine (Autoset S8, ResMed, Abingdon, UK) by trained staff who were not involved in outcome assessments or data analysis. After 6 months, CPAP usage was downloaded from the machine.

Standard care

Patients randomised to SC were instructed to continue their current medication. No specific advice regarding diet and lifestyle was given.

ECG

All patients were instructed to abstain from caffeine, alcohol or tobacco at baseline and at 6 months follow-up. Participants rested for 5 min in the supine position before measurements, and room temperature and lighting were kept constant. Standard commercially available 12-lead ECG devices were used in all centres. Paper-speed was set at 25 mm/s and amplitude at 10 mm/s. All measurements of ECG intervals were performed using a dedicated ECG analysis calipre software (DatInf Measure 2.1d, DatInf GmbH, Tübingen, Germany) offline by the same investigator (CS), who was not aware of the randomisation sequence or other patient-specific data. The means of all available consecutive heart cycles (three in the majority of cases) were used in all 12 leads for computation of ECG markers. The ECG indices were defined as follows: P wave: the onset of the P wave was defined as the point of first detectable upward or downward slope from the isoelectric line for positive or negative waveforms, respectively. Return to the isoelectric line was considered as the end of the P wave. Pmax/Pmin was defined as the longest/shortest mean value of consecutive heart cycles in any of the 12 leads. Pd was defined as the difference between Pmax and Pmin. The PQ interval was defined as the

point from the beginning of the P wave to the first part of the QRS complex. The QT interval was defined as the time from the onset of the QRS complex to the cutting point of the tangent to the downward slope of the T wave and the isoelectric line. QTmax/QTmin was defined as the longest/shortest mean value of consecutive heart cycles in any of the 12 leads. QT dispersion was defined as the difference between QTmax and QTmin. The TpTe interval was defined as the time from the peak of the T wave to the cutting point of the tangent to the downward slope of the T wave and the isoelectric line. TpTe/QT ratio was used as a measure of dispersion of repolarisation,[11] and calculated as mean TpTe divided by mean QT (from all leads). QT and TpTe intervals were corrected for heart rate using Bazett's formula.[12]

Data analysis

Endpoints were the absolute changes in P wave dispersion, QT dispersion, heart rate, Pmean, Pmax, Pmin, QTmean, QT_cmean, QTmax, QTmin, $TpTe_c$ and TpTe/QT ratio over follow-up. In subgroup analyses, we compared the effects of using CPAP >4 or ≤4 h/night against control on each outcome, and the effect of CPAP in patients with ODI >20 vs <20 at baseline. The effect of CPAP on QT_c and $TpTe_c$ intervals was compared between patients with QTc intervals ≥ or <430 ms at baseline and with $TpTe_c$ intervals ≥ or <90 ms at baseline.

Values are presented as mean (SD) unless otherwise stated. Statistical analysis was performed with STATA V.13 for Windows (STATA Corporation, College Station, Texas, USA). Treatment effects were estimated using multiple linear regression adjusting for allocation group, the minimisation variables, and the baseline value of the corresponding outcome. The effect of CPAP in different subgroups was assessed by adding a treatment-by-subgroup interaction term to each model. All analyses were performed using the intention-to-treat principle and a two-sided p value of <0.05 was considered to be statistically significant.

RESULTS

Trial profile and patient characteristics

Figure 1 shows the trial profile; 391 patients were initially randomised in the 10 participating centres of the MOSAIC trial. In the three centres (Oxford, Reading, Taunton) in which 12-lead ECGs measurements were performed, 303 patients were randomised. Of these, five patients were lost to follow-up, three withdrew and one patient died. In 21 patients, no analysable ECG data at baseline were available, mostly due to AF (5 patients in

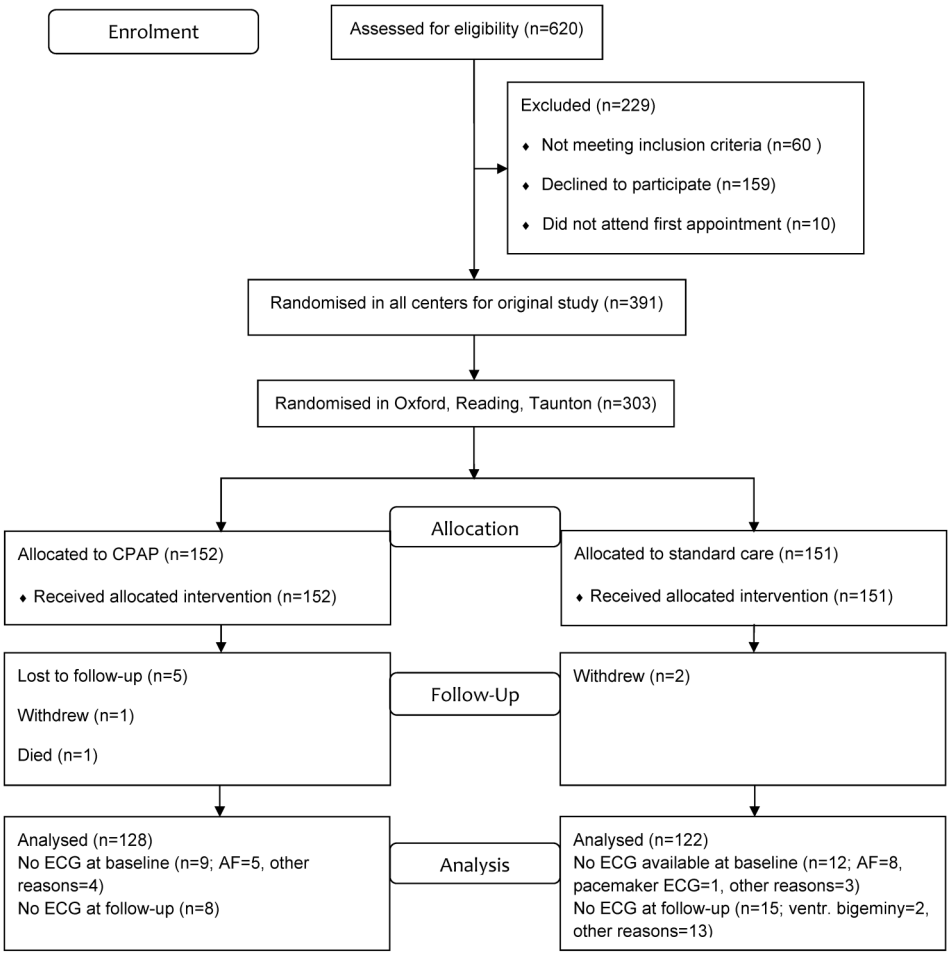

Figure 1 Study flow.

CPAP group, 8 patients in SC group). In 23 patients no analysable ECG data at follow-up were available due to several reasons; 2 of them in the SC group had ventricular bigeminy. No other arrhythmias were recorded. Thus, data from 250 patients were available for analysis. Baseline patient characteristics were similar between treatment groups (table 1). Data on the main outcomes in MOSAIC are published elsewhere.[13] There was no evidence of any significant differences in our subset of patients when compared with the original study in the treatment effects from CPAP on either ODI or ESS.[13] Median (IQR) CPAP usage was 2.7 h/night (0.5, 4.9); 36 patients (28%) in the CPAP group did not use their CPAP device at all.

Baseline analysis

There was no correlation between OSA severity (ODI) and any of the analysed ECG risk markers at baseline.

Effect of CPAP on ECG risk markers for AF and SCD

Table 2 shows ECG interval times at baseline and at follow-up. There were no relevant differences between the two groups at baseline. No treatment effect of CPAP on ECG risk markers for AF and SCD was found when compared with SC.

Table 1 Baseline characteristics

	Standard care	NCPAP
N	151	152
Age (years)	57.5 (7.4)	58.0 (7.1)
Males, n (%)	127 (84.1)	123 (80.9)
Body mass index (kg/m^2)	32.6 (5.6)	32.0 (5.4)
Waist/hip circumference ratio	1.0 (0.1)	1.0 (0.1)
Never smoked, n (%)	57 (37.7)	55 (36.2)
Ex-smoker, n (%)	70 (46.6)	82 (53.9)
Current smoker, n (%)	24 (15.9)	15 (9.9)
ODI (median, IQR)	9.1 (4.6, 15.2)	9.9 (3.9, 17.4)
Epworth sleepiness scale	8.4 (4.1)	8.5 (4.3)
Osler min (median, IQR)	35 (22, 35)	35 (27, 35)
Diabetes mellitus, n (%)	32 (21.2)	19 (12.5)
Angina pectoris, n (%)	16 (10.6)	7 (4.6)
Myocardial infarction, n (%)	12 (7.9)	8 (5.3)
Atrial fibrillation, n (%)	8 (5.3)	5 (3.3)
Arterial hypertension, n (%)	67 (44.4)	65 (42.8)
Antihypertensive medication, n (%)	69 (45.7)	61 (40.1)
Cholesterol-lowering medication, n (%)	44 (29.1)	45 (29.6)
Glucose-lowering medication, n (%)	23 (15.2)	15 (9.9)
Diuretics, n (%)	29 (19.2)	26 (17.1)
Potassium (mmol/L)	4.0 (0.4)	4.0 (0.4)

Values are mean (SD) unless otherwise stated.
NCPAP, Nasal Continuous Positive Airway Pressure; ODI, Oxygen Desaturation Index; OSLER, Oxford Sleep Resistance test.

Subgroup analyses

Treatment effects in patients who used their CPAP for at least 4 h/night did not differ from those in patients using their CPAP device for <4 h/night. There were no differences in CPAP treatment effects on ECG markers in patients with an ODI at baseline >20/h versus those with an ODI ≤20/h. Moreover, patients with QT_c intervals at baseline ≥430 ms (15 in CPAP group, 5 in control group) did not significantly differ in terms of CPAP treatment effect on QT_c at follow-up from patients with QTc intervals at baseline ≤430 ms, and the same was true in patients having a $TpTe_c$ interval at baseline greater than 90 ms (13 in CPAP group, 18 in control group).

DISCUSSION

This is the first RCT providing data on the effect of CPAP on ECG risk markers for AF and SCD in patients with minimally symptomatic OSA. We found no treatment effect of CPAP on any of the evaluated ECG risk markers.

The MOSAIC randomised trial, from which these data were derived, was a rigorously planned and performed study aimed at giving clinicians a better evidence base for treatment decisions in the many patients with OSA lacking overt daytime sleepiness. Although a previous study showed adverse effects of CPAP withdrawal on heart rhythm in symptomatic patients with moderate to severe OSA,[8] no data from randomised trials in minimally symptomatic OSA patients have yet been available.

Effect of CPAP on ECG risk markers for AF

A prolonged P wave on the surface ECG represents intra-atrial conduction slowing, while an increase in P wave dispersion indicates heterogeneous intra-atrial and interatrial conduction, providing a substrate that favours re-entry mechanisms. These variables have been shown to represent independent predictors for new onset AF as well as for relapse of AF after catheter ablation.[14 15] In a large retrospective cohort analysis, P wave dispersion >80 ms and Pmax >120 ms, were associated with HRs for developing AF of 1.95 and 1.9, respectively.[14] The prevalence of OSA among patients with AF is reported to be as high as 32%[16] to 56%.[17] These high prevalence rates must be considered carefully due to different study populations and designs. Nevertheless, clinicians should be aware of the potentially negative effects of OSA on treatment success of AF. This might be especially important for those patients undergoing catheter ablation of AF given recent findings of a meta-analysis by Qureshi *et al*,[18] who found a 44% lower risk of AF recurrence in patients with OSA who used CPAP versus those who did not.

Table 2 CPAP treatment effects on ECG risk markers for atrial fibrillation and sudden cardiac death

	Standard care			CPAP				
Outcome	N	Baseline mean (SD)	Follow-up mean (SD)	N	Baseline mean (SD)	Follow-up mean (SD)	Treatment effect (95% CI)	P Value
Heart rate	122	65.4 (11.2)	64.7 (12.6)	128	65.1 (10.5)	64.0 (10.2)	−0.4 (−2.4 to 1.7)	0.71
P wave max	119	106.6 (9.9)	106.8 (10.7)	126	108.3 (11.2)	108.1 (12.4)	0.0 (−2.4 to 2.5)	0.98
P wave mean	119	87.1 (8.0)	86.1 (8.2)	126	87.6 (8.6)	87.6 (10.0)	0.9 (−0.8 to 2.6)	0.32
P wave dispersion	119	41.9 (12.0)	43.4 (12.0)	126	42.6 (11.8)	43.3 (12.8)	−0.4 (−3.4 to 2.7)	0.82
QTmax	118	400.3 (30.4)	402.4 (33.6)	126	406.3 (34.6)	408.8 (35.1)	1.5 (−4.3 to 7.3)	0.61
QTmean	118	382.1 (28.7)	384.4 (30.6)	126	387.5 (31.4)	389.8 (30.4)	0.9 (−3.9 to 5.7)	0.72
QT_cmean*	118	395.1 (20.2)	395.3 (21.0)	126	400.3 (24.6)	399.8 (25.6)	0.9 (−3.5 to 5.4)	0.68
QT dispersion	118	41.5 (15.4)	41.0 (17.1)	126	44.6 (17.8)	43.7 (16.8)	1.8 (−2.3 to 5.8)	0.39
PQ	114	155.9 (24.1)	154.3 (23.6)	125	156.3 (26.9)	157.5 (26.6)	2.4 (−2.1 to 7.0)	0.30
TpTe/QT	122	0.2 (0.0)	0.2 (0.0)	128	0.2 (0.0)	0.2 (0.0)	0.0 (−0.0 to 0.0)	0.89
$TpTe_c$*	122	76.2 (13.5)	75.1 (11.4)	128	76.0 (14.4)	75.5 (13.2)	0.2 (−2.6 to 2.9)	0.92

Values are mean (SD). 95% CI of the difference between groups in change from baseline.
*Corrected for heart rate.
CPAP, continuous positive airway pressure.

In the current study, the 95% CI for the treatment effect of CPAP on P wave dispersion excludes a reduction >3.4 ms. Therefore, our results do not support CPAP treatment in minimally symptomatic OSA patients in terms of risk reduction for progression and/or recurrence of AF. Moreover, we have previously found no evidence that 6 months of CPAP has an effect on left atrial area as assessed by echocardiography in a subset of MOSAIC patients.[19] Thus, CPAP appears to have no electrical and structural impact on the atria in patients with minimally symptomatic OSA. For further analysis, we compared whether there was a statistically significant different CPAP treatment effect on atrial ECG risk markers in those patients, having had an initial ODI >20/h when compared with those with an ODI <20/h. However, no such group interaction was found.

Effect of CPAP on ECG risk markers for SCD

The QT interval is primarily a measure of ventricular repolarisation, although it includes the QRS interval and, hence, ventricular depolarisation too. An inherited, as well as acquired, QT prolongation is often used as a marker for risk assessment of SCD.[20] Prolongation of the TpTe interval, a measure of cardiac transmural dispersion of repolarisation, of the QT dispersion as a marker of general repolarisation abnormality, and of the TpTe/QT ratio, a measure of disproportional prolongation of global dispersion relative to the QT interval aimed at minimising effects of varying heart rates, are as well linked to an increased risk of SCD through enhanced susceptibility to early and late afterdepolarisations.[21 22] The Rotterdam QT project showed that a QTc interval of more than 440 ms was associated with a 2.3 times higher risk for SCD when compared with a QTc ≤440 ms (95% CI 1.4 to 3.9).[23]

There is growing evidence of a role for OSA in the occurrence of SCD. In a large longitudinal study, OSA has been proposed as a novel risk factor for SCD.[4] In that study, nocturnal hypoxaemia and the apnoea hypopnea index (AHI) strongly predicted SCD independent of well-established risk factors. While the general population is least likely to die from sudden death from cardiac causes during the sleeping hours, in patients with OSA, sudden death from cardiac causes peaked during the sleeping hours.[24]

In the current study, there was no difference in CPAP treatment effect on QT_c between patients with an ODI ≥20/h when compared with patients with an ODI <20/h. Recently, a RCT evaluating the effect of CPAP on measures of cardiac repolarisation in symptomatic patients with moderate to severe OSA showed a statistically and clinically significant prolongation of QT_c and $TpTe_c$ after 2 weeks of CPAP withdrawal.[8] In the latter study, baseline QT_c and $TpTe_c$ intervals were higher than in our study (416.1 vs 397.8 and 114.7 vs 76.1 ms, respectively), and this might be due to the fact that more severe patients with OSA were included. In those patients, a 2-week withdrawal of CPAP led to an increase of the QT_c interval of 21.4 ms, 95% CI 11.3 to 31.6 ms, and the increase in the length of the QT_c interval was positively correlated with the change in the severity of sleep disordered breathing (AHI) (r=0.60, 95% CI 0.36 to 0.77, p<0.001). Conversely, in the current study, the 95% CI for the treatment effect of CPAP on QT_c excludes a reduction greater than 3.5 ms, which probably does not represent a clinically significant effect. It could be argued that in our patient sample, due to low intervals of cardiac repolarisation at baseline, no further reduction through the use of CPAP could be achieved. However, we did not find larger effects of CPAP treatment in patients with QT_c intervals at baseline greater than 430 ms, or $TpTe_c$ intervals at baseline greater than 90 ms.

Limitations

This study has some limitations. First, the presented analysis was not the primary objective of the MOSAIC trial,

thus, our interpretations must be regarded as hypothesis-generating rather than fully robust. Second, high intraobserver and interobserver variability is usually found when measuring ECG intervals. However, all measurements were made offline by the same experienced investigator, who was blinded to treatment allocation and other patient data at the time of analysis. Third, adherence to CPAP is usually an issue in patients with minimally symptomatic OSA. Patients often feel no obvious benefit from therapy, while discomfort using the device can negate any potential benefit. Median usage in the current study was 2.7 h/night. However, subgroup analyses revealed no difference in CPAP treatment effect on any ECG risk marker in the more compliant participants who used their CPAP device more than 4 h/night.

Conclusions

This is the first RCT providing data to evaluate the effect of CPAP on ECG risk markers for AF and SCD in patients with minimally symptomatic OSA. We found no evidence of a treatment effect of CPAP on any of the investigated ECG risk markers.

Based on our results, there seems to be no justification for CPAP treatment in patients with minimally symptomatic OSA in an attempt to reduce arrhythmia risk.

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Competing interests JRS reports personal fees from ResMed UK, outside the submitted work. MK reports grants from University of Zürich during the conduct of the study.

Patient consent Obtained.

Ethics approval Oxford research ethics committee (RECNo: 05/Q1604/159).

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