Effect of continuous positive airway pressure therapy on recurrence of atrial fibrillation after pulmonary vein isolation in patients with obstructive sleep apnea: A randomized controlled trial @

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BACKGROUND Obstructive sleep apnea (OSA) is associated with atrial fibrillation (AF). Whether treatment with continuous positive airway pressure (CPAP) reduces AF recurrence after catheter ablation with pulmonary vein isolation (PVI) is unknown.

OBJECTIVE The purpose of this study was to assess the effect of CPAP treatment on the recurrence and burden of AF after PVI in patients with OSA.

METHODS We randomized patients with paroxysmal AF and an apnea-hypopnea index (AHI) ≥15 events/hour to treatment with CPAP or standard care. Heart rhythm was monitored by an implantable loop recorder. AF recurrence after PVI was defined as any episode of AF lasting >2 minutes after a 3-month blanking period.

RESULTS PVI was performed in 83 patients. Thirty-seven patients were randomized to CPAP treatment and 46 patients to standard care. The AHI was reduced from 26.7 ± 14 events/hour to 1.7 ±

1.3 events/hour at follow-up in the CPAP group ($P = .001$). A total of 57% of patients in both the CPAP group and the standard care group had at least 1 episode of AF 3–12 months after PVI (P for difference $= 1$). AF burden after ablation was reduced in both groups, with no between-group difference ($P = .69$).

CONCLUSION In patients with paroxysmal AF and OSA, treatment with CPAP did not further reduce the risk of AF recurrence after ablation. PVI considerably reduced the burden of AF in OSA patients, without any difference between groups.

KEYWORDS Atrial fibrillation; Continuous positive airway pressure treatment; Implantable loop recorder; Obstructive sleep apnea; Pulmonary vein isolation; Respiratory polygraphy

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https://doi.org/10.1016/j.hrthm.2022.06.016

Introduction

Atrial fibrillation (AF) affects 2%–4% of adults. It reduces quality of life (QoL) and is associated with an increased risk of heart failure, stroke, and mortality. Antiarrhythmic drugs have moderate efficacy and possible bothersome side effects. Catheter ablation with pulmonary vein isolation (PVI) has been increasingly used in the past 2 decades to reduce AF symptoms and reduce the need for antiarrhythmic drugs.[1,2]

AF and obstructive sleep apnea (OSA) frequently coexist, and the presence and severity of OSA are independently associated with the burden of AF.[3] It has been suggested that treatment of OSA with continuous positive airway pressure (CPAP) may reduce the frequency and duration of AF.[4,5] Furthermore, observational studies have shown increased prevalence of AF in patients with OSA and reduced recurrence with CPAP use.[6,7] However, the effect of CPAP on the burden of AF before and after PVI in patients with OSA has not been examined in a controlled setting.

In this randomized controlled trial, we aimed to assess the effect of treatment with CPAP on the burden and recurrence of AF after PVI in patients with OSA. We used implantable loop recorders (ILRs) to monitor heart rhythm. We also evaluated the effect of CPAP on QoL after PVI.

Methods

Study design

We conducted a randomized, controlled, open-label, parallel-group trial—the Atrial fibrillation, Apnea and Airway Pressure (A3) study—at 2 cardiology centers in Norway: Oslo University Hospital, Rikshospitalet, and St. Olav's University Hospital in Trondheim. Patients were followed for 5 months before PVI (phase 1) and 12 months after PVI (phase 2).

Patients

Patients aged 18–75 years with symptomatic, documented paroxysmal AF were eligible for the A3 trial if they had moderate to severe OSA, defined by an apnea-hypopnea index (AHI) ≥15 events/hour on the respiratory polygraph test. Exclusion criteria included previously diagnosed OSA, unstable coronary disease, transitory ischemic attack, stroke, structural heart disease, left ventricular systolic dysfunction (ejection fraction <45%), severe obesity (body mass index >40 kg/m^2), severe excessive daytime sleepiness (Epworth sleepiness scale score ≥15), or present use of amiodarone. Eligible patients underwent a 1-week tolerance test with CPAP. Patients adherent to CPAP treatment (using CPAP ≥4 hours per night) were included in the study and randomized (1:1) to CPAP treatment or standard care, 4 weeks after the implant of an ILR (Reveal Linq™; Medtronic, Inc., Minneapolis, MN). Patients who remained eligible for PVI after the first phase of the trial entered Phase 2. Patients who were no longer eligible for PVI were excluded from the second phase of the trial. Rhythm data were collected during the 5-month period before PVI and for 12 months after PVI (Figure 1). For comparison, we also included a reference group comprising patients with paroxysmal AF, without
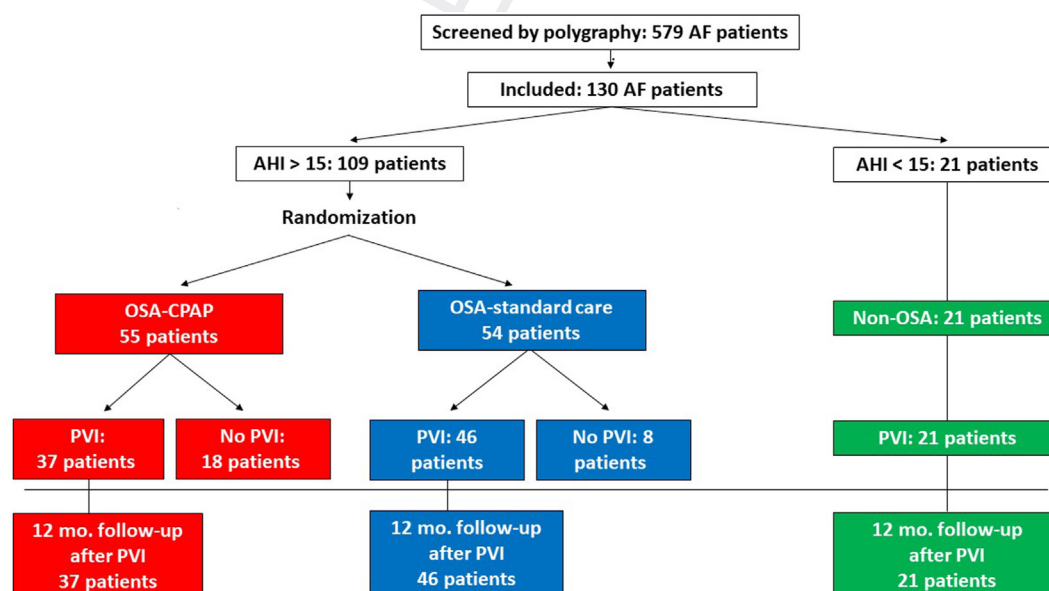
Figure 1   Flowchart of patient selection and intervention groups. Patients with known paroxysmal atrial fibrillation (AF) were screened for obstructive sleep apnea (OSA), defined as apnea-hypopnea index (AHI) ≥15 events/hour. After a tolerance test with continuous positive airway pressure (CPAP), 109 patients were randomized to treatment with CPAP or to standard care (55 to CPAP treatment and 54 to standard care). Of these 109 patients, 18 were excluded from the CPAP group and 8 were excluded from the standard care group before pulmonary vein isolation (PVI) (see text for details). Eighty-three patients proceeded to PVI: 37 in the CPAP group and 46 in the standard care group. All patients who underwent PVI were followed for 12 months after ablation. For comparison, a group of patients without OSA (n = 21) served as extra references.

OSA or with mild OSA (AHI 0 to ≤15 events/hours), who were referred for PVI.

All patients provided written informed consent. The study was approved by the Norwegian South-East Regional Ethics Committee (REK ID: 2015/436) and conducted in compliance with the Declaration of Helsinki. The results are reported in accordance with the guidelines outlined in the Consolidated Standards of Reporting Trials (CONSORT) statement. The trial is registered at ClinicalTrials.gov (NCT02727192).

Assessments

Clinical visits were performed at 1 day before PVI and at 3, 6, and 12 months after PVI (Supplemental Figure 1).

All patients underwent a respiratory polygraph test at home, performed over 2 consecutive nights before the CPAP run-in period. Analyses of the polygraphy tests were performed by the same sleep specialist (BØ), who was blinded to treatment allocation. Recordings were analyzed as recommended by the 2012 American Academy of Sleep Medicine Version 2.0.[8]

The ILR used standard settings to detect AF by analyzing the irregularity and incoherence of R-R intervals and P waves across 2-minute intervals. The device calculated the absolute time in AF and the burden of AF defined as the percentage of time in AF. All ILR recordings were analyzed at Oslo University Hospital. The electrocardiographic strips from each episode interpreted as arrhythmia by the device were reviewed by the first author. A senior electrophysiologist was consulted if there was any doubt about the interpretation.

Questionnaires

Self-reported QoL was assessed with the Atrial Fibrillation Severity Scale (AFSS), the 36-Item Short Form Health Survey (SF-36), the Epworth sleepiness scale, and the European Heart Rhythm Association (EHRA) symptom classification for AF scale. These forms were completed before PVI and 6 and 12 months after PVI. The AFSS is a validated 18-item questionnaire that measures the severity of arrhythmia-related symptoms, with 1 part concerning AF frequency, duration, and severity contributing to a total AF burden score (range 3–30) and another part obtaining AF symptoms score (range 0–35). SF-36 is a questionnaire that consists of 8 vitality subscale measures that can be compressed into 2 summary measures: the physical component summary score and the mental component summary score. The Epworth sleepiness scale is an 8-situation questionnaire that measures the tendency to become sleepy. The EHRA score is a 4-item scale for the classification of AF-related symptoms.

Interventions

In patients who were randomized to CPAP therapy (AirSense 10 Autoset, ResMed), we selected the auto set mode for CPAP pressure (between 3 and 15 cm H_2O) during tolerance testing. Data were downloaded from the CPAP software (Rescan®, ResMed) to estimate the residual AHI.

Treatment

PVI was performed using conscious sedation (midazolam and fentanyl). Five experienced operators performed all the procedures. PVI was achieved with cryoballoon ablation (28-mm Arctic Front Advance cryoballoon catheter and Achieve pulmonary vein catheter; Medtronic Inc.) or radiofrequency (RF) ablation (CARTO 3 system with Thermo-Cool SmartTouch ablation catheter and 12- or 22-polar Lasso pulmonary vein catheter; Johnson & Johnson). Antiarrhythmic drugs were routinely used for 6−8 weeks after PVI. Ablation was considered a failure if antiarrhythmic drugs had to be continued beyond, or reinstituted after, the blanking period.

Primary endpoint

The primary endpoint was freedom from recurrence of AF or organized atrial tachyarrhythmia as assessed by ILR after an initial 3-month blanking period. The recurrence of AF was defined as any episode of at least 2 minutes of AF within 3–12 months after PVI.

Secondary endpoints

Secondary endpoints were the total burden of AF during follow-up and the effect of CPAP on QoL, including sleep quality after PVI.

All adverse events were monitored throughout the study period. We defined a serious adverse event as any untoward medical occurrence that caused death, could be life-threatening, or required hospitalization.

Sample size and statistical analysis

Observational studies have suggested that CPAP treatment of OSA may reduce the AF recurrence rate by 25%–50%,[7,9] which is considered a clinically meaningful reduction. We expected AF to recur in 70% of the patients in the standard care group. To prove a 50% reduction of AF recurrence in the CPAP group with a power of 80% and a significance level of 5%, we would need 28 patients in each group, or 56 in total. We included 109 patients to allow for dropouts. To supplement the logistic regression analysis of the primary endpoint, we performed a Bayesian *post hoc* analysis to assess the posterior probability of a clinically relevant 50% reduction and the probability of any reduction in the odds of recurrence of AF by using CPAP for OSA after PVI given the present data.

Continuous variables are given as mean ± SD for normally distributed data or as median (interquartile range) otherwise. The primary endpoint was compared across groups using the Pearson χ^2 test. Kaplan–Meier curves were constructed to visualize the time to AF recurrence in the 2 treatment groups and in the control patients without OSA. Qualitative variables are were expressed as number (percentage). We calculated the odds ratio (OR) and 95% confidence interval (CI) for AF recurrence using univariable and multivariable logistic regression analysis. Repeated measurements of continuous variables were compared by

Table 1   Baseline characteristics of OSA study participants

Characteristic	Total (n = 83)	OSA-CPAP (n = 37)	OSA-standard care (n = 46)	P value
Baseline				
Age (y)	62 ± 8	62 ± 8	62 ± 7	.22
Male	65 (78)	28 (76)	43 (80)	.63
BMI (kg/m^2)	29.5 ± 4.0	30.0 ± 3.9	29.9 ± 4.1	.22
CHA$_2$DS$_2$–VASc score	1.2 ± 1.0	1.2 ± 1.0	1.3 ± 1.0	.94
EHRA score	2.6 ± 0.8	2.6 ± 0.9	2.5 ± 0.8	.29
Hemoglobin (g/dL)	14.7 ± 1.1	14.8 ± 1.3	14.7 ± 0.9	.75
Creatinine (μmol/L)	80.7 ± 14.5	77.5 ± 13.1	81.4 ± 16.7	.19
Pro–BNP (ng/L)	89 (50–150)	94 (50–140)	88 (50–170)	.14
Medical history				
Time in AF before PVI (y)	5 (3–11)	6 (2–11)	5 (3–11)	.77
Hypertension	32 (38)	14 (38)	18 (39)	.93
Diabetes mellitus	4 (6)	3 (8)	1 (4)	.50
Myocardial infarction	1.9 ± 0.25	2.0 ± 2.3	2.0 ± 0.2	.30
Stroke/transient ischemic attack	4 (5)	3 (8)	1 (2)	.30
Echocardiography				
Left ventricular ejection fraction (%)	57.1 ± 4.3	56.7 ± 3.6	57.1 ± 4.5	.87
LA area (cm^2)	24.8 ± 4.6	25.2 ± 4.0	24.5 ± 4.9	.88
Sleep history				
Epworth total score	5.9 ± 3.0	5.6 ± 2.9	5.7 ± 2.8	.39
Apnea-hypopnea index*	21 (17–32)	21.7 (18–32)	21 (17–35)	.92
Oxygen desaturation index*	22 (17–32)	23 (17–32)	20 (17–33)	.60
Medication				
Beta-blocker	49 (51)	21 (57)	28 (61)	.71
Calcium channel blocker	5 (6)	1 (3)	4 (9)	.38
Flecainide	24 (29)	10 (27)	14 (30)	.74
PVI cryoballoon	54 (65)	20 (54)	34 (74)	.68

Values are given as mean ± SD, n (%), or median (interquartile range) unless otherwise indicated.

AF = atrial fibrillation; BMI = body mass index; CPAP = continuous positive airway pressure; EHRA = European Heart Rhythm Association symptom classification for atrial fibrillation; LA area = traced left atrial area (2-dimensional 4-chamber view); OSA = obstructive sleep apnea; Pro-BNP = pro–brain natriuretic peptide; PVI = pulmonary vein isolation.

independent *t* tests, 1-way analysis of variance, or the Mann-Whitney *U* test, as appropriate. Categorical variables were compared using the χ^2 or Fisher exact test, as appropriate.

Comparisons within each study patient before and after PVI were analyzed using paired *t* tests or the paired Wilcoxon signed-rank test.

Table 2   Primary and secondary endpoints

Outcome	OSA-CPAP (n = 37)		OSA-standard care (n = 46)		OSA-CPAP vs OSA-standard care (odds ratio)	P value (OSA-CPAP vs OSA-standard care)
	Before PVI	12-mo follow-up	Before PVI	12-mo follow-up		
Primary endpoint— recurrence		21 (57)		27 (57)	1.0 (0.42–2.4)	1
Secondary endpoints						
Total AF burden (%)	2.8 (0.9–9.7)	0 (0–0.3)*	1.6 (0.2–6.3)	0 (0–0.3)*		.21
Time in AF (minutes per month)	29 (0–228)	2 (0–101)*	31 (0–338)	1.4 (0–111)*		.72
AFSS total burden score	15 ± 4	11 ± 5*	15 ± 4	10 ± 3.9*		.11
AFSS symptom score	13 (6–16)	6 (3–11)*	10 (7–15)	5 (1–8)*		.68
SF-36 physical component summary score	85 (70–95)	93 (83–99)	85 (80–95)	95 (85–95)		.74
SF36 mental component summary score	84 (76–92)	88 (77–96)	84 (72–92)	88 (80–92)*		.07

Primary endpoints are given as n (%) and odds ratio by logistic regression. Secondary endpoints are given as median (interquartile range) and mean ± SD. *P* values for secondary endpoints refer to a comparison of delta values (net change for each patient within the 2 groups) compared by Mann-Whitney tests for the difference in change between the OSA-CPAP group and the OSA-standard care group.

AF = atrial fibrillation; AFSS = Atrial Fibrillation Severity Scale; CPAP = continuous positive airway pressure; OSA = obstructive sleep apnea; PVI = pulmonary vein isolation; SF-36 = 36-Item Short Form Health Survey.

*Significant *P* value difference from preablation and 12-month follow-up within each group.
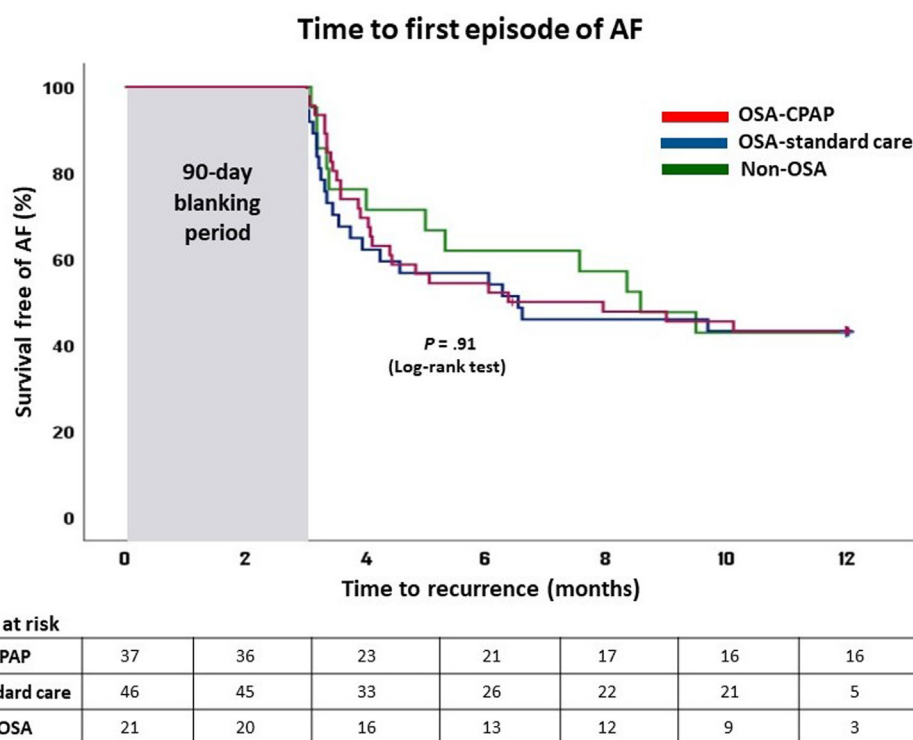
Figure 2   Kaplan-Meier plot showing time to first atrial fibrillation (AF) recurrence lasting ≥120 seconds between 91 and 365 days after pulmonary vein isolation. There was no difference in the risk of recurrence between patients with obstructive sleep apnea (OSA) assigned to continuous positive airway pressure (CPAP) (*red*) and patients with OSA assigned to standard care (*blue*) (log-rank test; $P = .82$). The P value for the log rank test for comparison of all 3 groups including the recurrence rate of patients without OSA (*green*) was .91.

Results
Study population
Patient inclusion and follow-up are shown in Figure 1. Between January 21, 2016, and February 28, 2019, we screened 579 patients with paroxysmal AF who had undergone respiratory polygraphy at home. Forty-two percent were diagnosed with moderate to severe OSA. One hundred fifty eight patients were willing to undergo the CPAP tolerance test. After the exclusion of 49 patients who did not comply with CPAP treatment, we randomized 109 patients to CPAP treatment or standard care in phase 1 of the study. Of these 109 patients, 26 did not proceed to PVI for the following reasons. Twenty-one patients were referred without an initial intention of ablation, and the patients themselves were not motivated for such treatment. One patient withdrew his consent to participate in the study. Four patients were excluded by the investigators because they no longer had an indication for PVI: the first patient developed chronic AF, the second patient was ablated for atrioventricular nodal reentrant tachycardia and thereafter had no detectable AF, the third patient no longer had detectable AF after correction of hyperthyroidism, and the fourth patient had no detectable AF without any specific explanation. Therefore, phase 2 comprised 83 patients, 37 in the CPAP group and 46 in the standard care group. The results of the patients who participated in phase 2 of the trial are presented here. We compare their results to those of a reference group comprising 21 patients with AHI 0–15 (non-OSA group).

The study groups were well balanced. Baseline characteristics, medical history, echocardiographic findings, and drug treatment at inclusion are summarized for the OSA groups in Table 1. Some baseline variables, including the ablation method, were unevenly distributed between the groups. These variables did not influence the effect of CPAP on the primary endpoint (all interaction term $P >.05$; individual models not shown but available on request).

Effect of CPAP treatment on AHI
In the CPAP treatment group, AHI decreased from 26.7 ± 14.7 events/hour at inclusion to 2.2 ± 1.7 events/hour before PVI and 1.7 ± 1.3 events/hour at follow-up ($P <.001$). Overall mean time of CPAP use among patients in the OSA CPAP group was 3.9 ± 1.5 hours/night before PVI and 4.3 ± 1.9 hours/night after PVI.

A total of 60% of patients randomized to CPAP treatment had CPAP usage ≥4 hours/night before PVI. Mean duration of adherence to CPAP therapy in this group was 5.7 ± 1.4 hours/night.

Ablation procedure
Cryoballoon PVI was performed in 54% of the patients (n = 20) in the OSA-CPAP group, 74% of the patients (n = 34) in the OSA-standard care group, and 81% (n = 17) in the non-OSA reference group. The remaining patients underwent RF ablation.
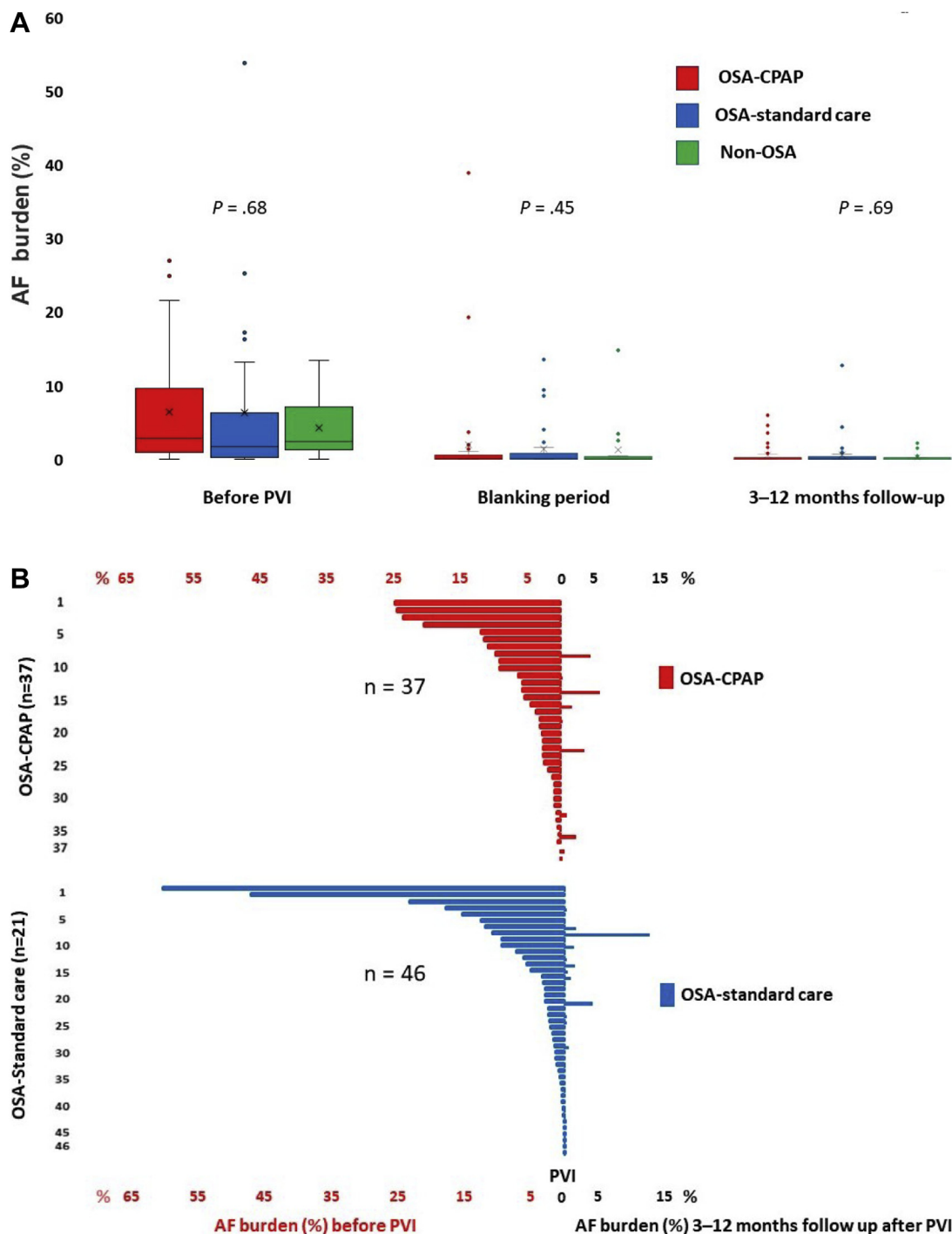
Figure 3   **A:** Atrial fibrillation (AF) burden shown as box-and-whisker plots expressed as the percentage of time in AF per month during 5 months before pulmonary vein isolation (PVI), during the blanking period (0–3 months after PVI), and 3–12 months after PVI. Outliers are shown at the top of the boxplot as individual points. **B, C:** Individual study data for 5 months before PVI **(left)** and 3–12 months after PVI **(right)**. **Top:** Obstructive sleep apnea (OSA)-continuous positive airway pressure (CPAP) group. **Middle:** OSA-standard care group. **Bottom:** Patients without OSA (non-OSA) reference group. *Horizontal axis* is artificially truncated at 65% to the left (before PVI) and 15% to the right (after PVI). Each individual bar represents an individual patient.

Effect of CPAP on AF recurrence and AF burden

AF recurrence rates were 57% in the OSA-CPAP group and 57% in the OSA-standard care group (OR 1.0; 95% CI 0.4–2.4; $P = 1$) (Table 2). The non-OSA group had the same recurrence rate as the OSA patients (57%). Freedom from AF for the 3 groups is shown in Figure 2. The posterior probability of the

existence of any favorable effect of the intervention given the present data was 49.5%. However, the posterior probability of the existence of a clinically relevant 50% reduction in the recurrence of AF by using CPAP for OSA after PVI was only 1.6%.

The method used for PVI was not associated with the primary outcome (univariable OR 0.97; 95% CI 0.4–2.3;
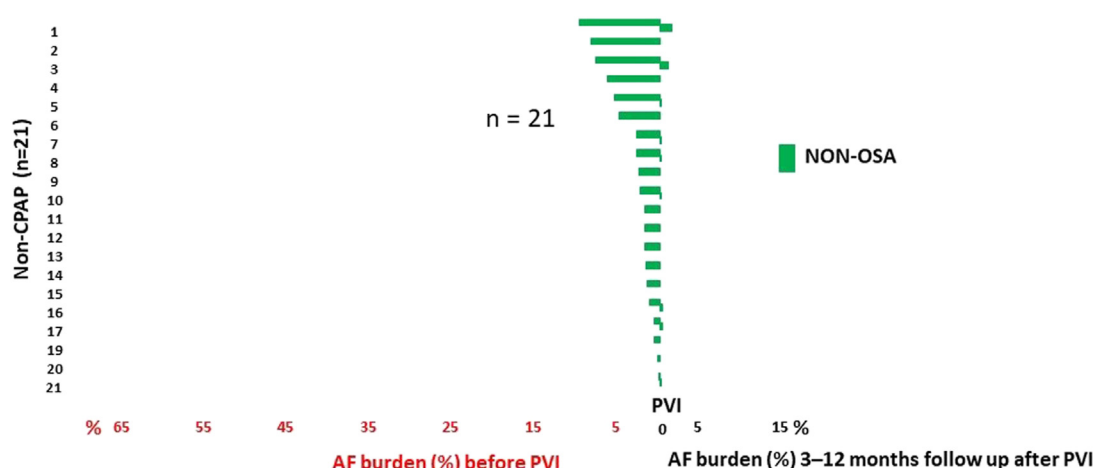
Figure 3   (*continued*).

$P = .84$). The method of PVI also did not interact with the effect of CPAP on the primary endpoint (P for interaction term = 1). Drug treatments at PVI and at 12-month follow-up for the OSA groups and the non-OSA group are given in Supplemental Table 1. Antiarrhythmic drugs did not influence the effect of CPAP treatment (P for interaction term = .76).

In the OSA-CPAP group, the burden of AF fell from 2.8% (0.9%–9.7%) to 0% (0%–0.3%), whereas in the OSA-standard care group, the burden of AF fell from 1.6% (0.2%–6.3%) to 0% (0%–0.3%) (Figures 3A and 3B). There was no between-group difference of change in AF burden (%) from before PVI to follow up ($P = .21$) (Table 2). Patients without OSA had a similar AF burden of 2.4% (1.3%–7.1%) before PVI and reduction after PVI as the OSA patients (Figures 3A and 3C).

QoL

PVI resulted in a significant improvement in AFSS QoL total burden score and symptom score, but there was no significant difference between the OSA-CPAP and OSA-standard care groups (Table 2 and Figure 4). QoL as assessed by the SF-36 physical component summary score and the mental component summary score remained stable after PVI, with no difference between the groups (Table 2). The groups also did not differ in Epworth total score or EHRA scores (Table 1).

Adverse events

One patient in the OSA-standard care group had a pericardial tamponade during the PVI procedure. One patient in the non-OSA group had an incomplete PVI because the procedure was prematurely stopped due to a hypertensive crisis. One patient in the OSA-CPAP group experienced a cerebral ischemic event at 3 months after PVI while still being treated with anticoagulants.

Discussion
Main findings

In this study, treatment with CPAP did not reduce the recurrence rate of AF after PVI and did not reduce the burden of AF beyond PVI and standard care. CPAP was an effective treatment of respiratory obstructive events but did not improve QoL beyond standard care. These results extend previous findings from the A3-study,[10] which showed no difference in the burden of AF in patients treated with CPAP without PVI. Our findings suggest that CPAP treatment in patients with AHI ≥15 has no additive effect on PVI outcomes. Our results are in concordance with a recent study by Caples et al[11] showing no effect of CPAP therapy in preventing AF recurrence within 1 year of cardioversion compared to a non-OSA group.

The current findings contrast, however, with those of some observational studies. Naruse et al[6] and Fein et al[7] reported reduction of AF recurrence and AF burden in OSA patients undergoing CPAP treatment. These studies were not randomized, included a small number of patients, and did not use continuous rhythm monitoring.

In a meta-analysis of 5 observational studies, Li et al[12] found that AF patients with OSA had a greater risk of AF recurrence after PVI than patients without OSA. Li et al found a similar risk for AF recurrence in CPAP users and patients without OSA, which is in accordance with our findings, but those studies did not use continuous cardiac monitoring (ie, ILR).

Over 12 months of follow-up, we found 43% of patients completely free of AF recurrence across the 3 groups, all monitored by ILR, and even those patients with recurrence had a clinically significant reduction of total AF burden. Duytschaever et al[13] reported excellent results after PVI with RF ablation using the CLOSE protocol, with an 85% success rate for single-procedure freedom from any atrial tachyarrhythmia during the first year monitored by ILR. We had a slightly lower success rate, which may be explained in part by the presence of OSA in our randomized patients.
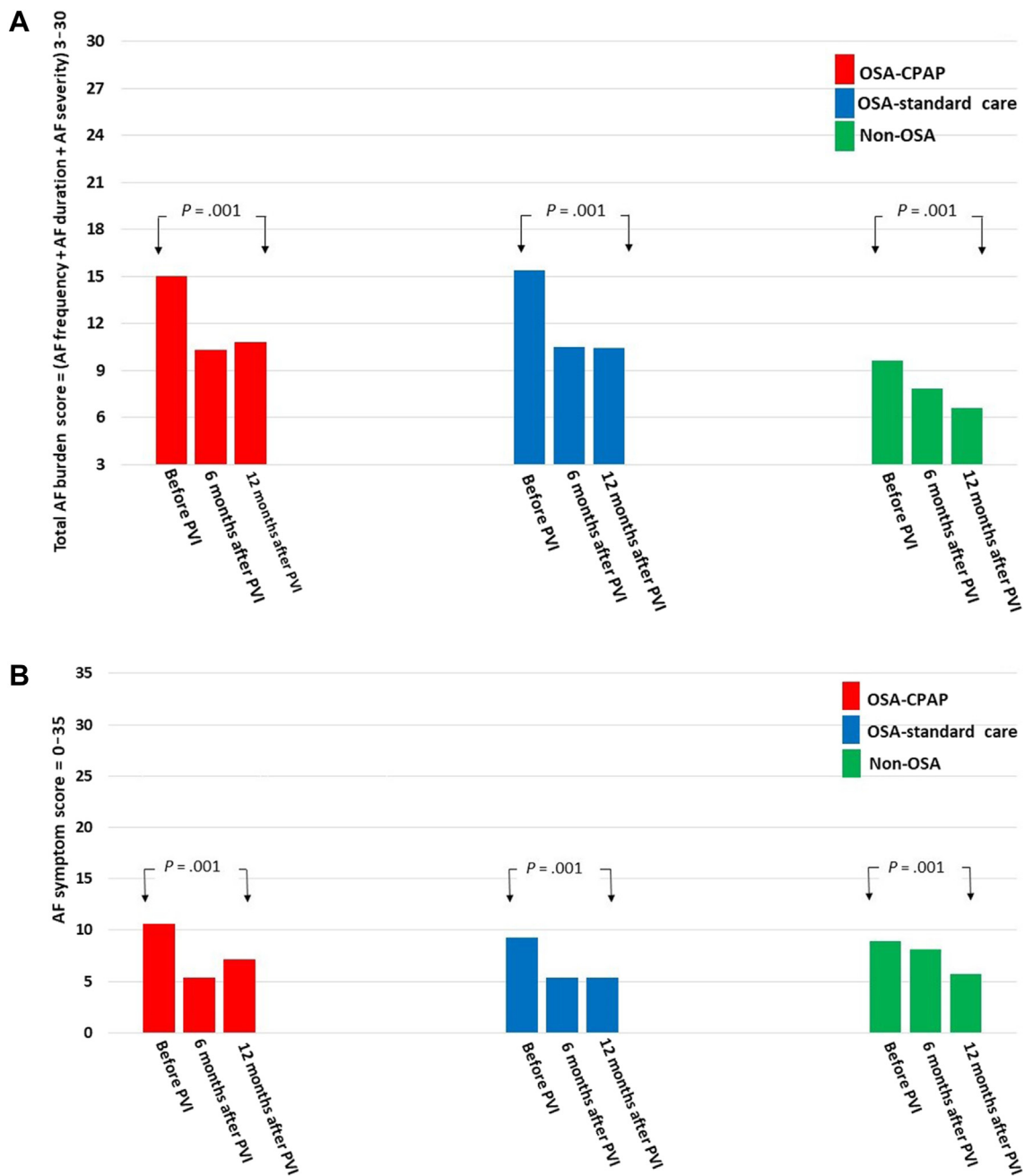
Figure 4　Quality of life as assessed by the Atrial Fibrillation Severity Scale questionnaire in patients with obstructive sleep apnea (OSA) randomized to continuous positive airway pressure (CPAP) or standard care before ablation and 6 and 12 months after ablation. The non-OSA group is included as a reference group. **A:** Total burden score (atrial fibrillation [AF] frequency + AF duration + AF severity; scores 3–30). Higher scores represent greater severity of AF disease burden. **B:** AF symptom scores (0–35), indicating how patients were affected by specific AF-related symptoms. PVI = pulmonary vein isolation.

Our patients received at mixture of RF ablation using the CLOSE protocol or cryoballoon ablation.

Study limitations

Despite a randomized design, a homogeneous study population, the use of CPAP during the run-in period to reduce dropouts, and the continuous monitoring of AF burden using a loop recorder, our study has some limitations. The CPAP group and the standard care group ended up slightly skewed because of the exclusion of more patients randomized to the CPAP group who did not proceed to PVI. Furthermore, our study design was unblinded and open label except for the analysis of sleep mapping, which was blinded. However, any bias related to the lack of blinding would be expected to favor the active treatment group, particularly regarding QoL scores.

The use of cryoballoon and RF ablation in different proportions in the treatment groups might add another level of potential bias, but earlier studies have not shown significant differences between the 2 different ablation strategies on the recurrence rate of AF.[14,15]

We anticipated high recurrence rates of AF in patients with OSA and powered the trial for a 50% effect of the intervention. These assumptions justified a limited number of participants but left us with insufficient statistical power to detect more subtle effects of the intervention. However, the supplementary Bayesian analysis indicated that the probability of a substantial effect size is low.

There were few serious adverse events in our study. Although these events were unlikely to be related to CPAP treatment, such events should be considered in future studies. Our study population consisted of white North-Europeans, mostly men (80%), which may limit the generalizability of our results.

Conclusion
Treatment with CPAP effectively reduced AHI in patients with paroxysmal AF and OSA but did not further reduce the recurrence rate of AF or the time in AF after PVI. PVI is an effective treatment in patients with OSA for reducing AF recurrence and time in AF, as well as QoL symptom scores.

Acknowledgments
We acknowledge the time, commitment, and contributions from our patients in this study. We also express our gratitude to Professor Dr. Paul Dorian from the University of Toronto, Canada, for allowing us to use the AFSS questionnaire.

Appendix
Supplementary data
Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2022.06.016.

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