JACC: CLINICAL ELECTROPHYSIOLOGY
VOL. 1, NO. 1-2, 2015

ISSN 2405-500X/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jacep.2015.02.014

Effect of Obstructive Sleep Apnea Treatment on Atrial Fibrillation Recurrence

A Meta-Analysis

Ashish Shukla, MD, MPH, Anthony Aizer, MD, MSc, Douglas Holmes, MD, Steven Fowler, MD, David S. Park, MD, PhD, Scott Bernstein, MD, Neil Bernstein, MD, Larry Chinitz, MD

ABSTRACT

OBJECTIVES This study aimed to evaluate the cumulative effect of treatment of obstructive sleep apnea (OSA) with continuous positive airway pressure (CPAP) on atrial fibrillation (AF) recurrence.

BACKGROUND OSA is a known predictor for onset and recurrence of AF. The effect of treatment with CPAP on AF recurrence has been evaluated in small studies with varied outcomes.

METHODS We searched MEDLINE, EMBASE, CINAHL, Google Scholar, Cochrane Database of Systematic Reviews, and Cochrane Trials Register for relevant studies. Evaluation of AF recurrence in CPAP users and nonusers in patients with OSA was the primary outcome evaluated in this study. The secondary outcome was evaluation of AF recurrence in CPAP users and nonusers after pulmonary vein isolation (PVI).

RESULTS Seven prospective cohort studies with a total of 1,087 patients met the inclusion criteria. Across all patient groups, the use of CPAP was associated with a significant reduction in AF recurrence (relative risk: 0.58, 95% confidence interval: 0.51 to 0.67; heterogeneity chi-square $p = 0.91$, $I^2 = 0\%$). The beneficial effect of CPAP use was statistically significant in both groups of patients: those who underwent catheter ablation with PVI and those who did not undergo ablation and were managed medically. No other study covariates had any significant association with these outcomes of AF reduction.

CONCLUSIONS The use of CPAP is associated with significant reduction in recurrence of AF in patients with OSA. This effect remains consistent and similar across patient populations irrespective of whether they undergo PVI.
(J Am Coll Cardiol EP 2015;1-2:41–51) © 2015 by the American College of Cardiology Foundation.

Antiarrhythmic drugs and catheter ablation with pulmonary vein isolation (PVI) comprise the mainstay of therapies available to maintain sinus rhythm in patients with atrial fibrillation (AF). Despite being efficacious in the general population, select groups of patients remain resistant to these therapies and continue to have recurrent AF (1,2). Patient comorbidities, such as increasing age, hypertension, obesity, and diabetes mellitus, are known risk factors that are associated both with development of new-onset AF and its recurrence (3). Aggressive treatment of any of these reversible factors with the goal to reduce the future burden of AF has been promoted; however, there remains a paucity of data to support this hypothesis (4).

Obstructive sleep apnea (OSA) is one such known risk factor that is associated both with new-onset AF and also with its recurrence after catheter ablation (5,6). The effect of continuous positive airway pressure (CPAP) use with the goal of reduction in AF recurrence has been evaluated in a few studies with a suggestion of favorable outcomes. However, these studies are often a single-center experience, with small patient populations and divergent results. Consequently, there remains a significant need to comprehensively evaluate the available data to

From the Leon H. Charney Division of Cardiology, New York University Langone Medical Center, New York, New York, USA. Dr. Chinitz has received fellowship grants from Biotronik, Medtronic, and Boston Scientific; and has served as a consultant to St. Jude Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received December 15, 2014; revised manuscript received February 10, 2015, accepted February 12, 2015.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CI = confidence interval

CPAP = continuous positive airway pressure

OSA = obstructive sleep apnea

PVI = pulmonary vein isolation

RR = relative risk

develop a consensus on the effect of CPAP use and evaluate any effect on AF recurrence. Toward this end, we performed a meta-analysis of the available published data to evaluate the effects of the use of CPAP therapy in patients with OSA on AF recurrence.

The prevalence of AF and its associated global impact on health care is expected to rise dramatically in the coming decade. Despite small, albeit significant, improvements in currently-available treatment modalities, there remains a pressing need to evaluate alternative therapies to control AF. Thus, if the use of CPAP has any potential additive or supplementary benefit to control the progression of AF, this is likely to have large-scale effects on this disease entity and its associated patient morbidity and mortality.

METHODS

SEARCH OF THE PUBLISHED DATA. Two independent reviewers (A.S., A.A.) searched MEDLINE, EMBASE, CINAHL, Google Scholar, Cochrane Database of Systematic Reviews, and Cochrane Trials Register. The search was restricted to studies in human subjects published in scientific journals from 1966 to June 2014. The search terms used were "atrial fibrillation," "recurrence," "obstructive sleep apnea," "continuous positive airway pressure," and "pulmonary vein isolation." The reference list of the retrieved studies, review papers, and other meta-analysis relevant to the topic were evaluated to find other potentially-eligible studies. Data from unpublished studies that were available as abstracts were not considered in this analysis.

STUDY SELECTION. Inclusion criteria for a retrieved study to be included in the current analysis were: 1) controlled study, either of an observational type or a randomized controlled trial (RCT); 2) study subjects to include patients with diagnosed OSA; 3) study to have evaluated effect of CPAP therapy on AF recurrence; 4) patients with OSA and symptomatic AF referred for index ablation procedure (PVI); 5) outcome reported clinically in terms of AF recurrence; and 6) study duration of more than 6 months. Exclusion criteria were: 1) no data provided for comparison amongst CPAP users and nonusers; and 2) no report of AF recurrence.

Comparison of AF recurrence in CPAP users and nonusers in patients with OSA was the primary outcome evaluated in this study. The secondary outcome was evaluation of AF recurrence in CPAP users and nonusers after PVI.

DATA ABSTRACTION AND QUALITY ASSESSMENT. The review process was carried out on the basis of the MOOSE (Meta-analysis Of Observational Studies in Epidemiology) group guidelines (7). The reviewers independently assessed the eligibility of each study for inclusion. Any discrepancy in the inclusion or exclusion of a study or data retrieved was resolved by discussion with a third senior reviewer. The data recorded from the included studies were as follows: year of publication, geographic area for patient population, inclusion and exclusion criteria, baseline characteristics of patients, study duration, any PVI performed, and AF recurrence at study endpoint in 2 groups. The quality of each included study was evaluated using the Newcastle-Ottawa scale (8).

STATISTICAL ANALYSIS. All statistical analysis was performed using Stata software version 10.0 (StataCorp, College Station, Texas) and Comprehensive Meta-analysis statistical software version 2.2.064 (Biostat Inc., Englewood, New Jersey). Categorical variables were reported as number and percent, whereas continuous variables were presented as mean ± SD. AF recurrence in each study group was pooled across all studies and analyzed using a point estimate for each study weighted by inverse of the variance ($1/SE^2$). The average effects for the outcomes and their 95% confidence intervals (CIs) were obtained using the Der Simonian and Laird random effects model and reported as relative risk (RR). Effect of heterogeneity across studies was assessed using Cochrane Q (chi-square) statistics and I^2 statistics (9). Using the chi-square statistic, a p value <0.1 was considered significant for heterogeneity and with I^2 statistics, 0% to 40% was considered unimportant, 41% to 60% moderate, 61% to 90% substantial, and 91% to 100% considerable heterogeneity. Publication bias was assessed visually with a funnel plot and further evaluated with the weighted regression test of Eggers (p value for significant asymmetry <0.1). Any effect of bias was further evaluated with fail-safe N models of Rosenthal (10) and Orwin (11).

A subgroup analysis was performed to evaluate the influence of CPAP use on AF recurrence in patients that did or did not undergo PVI. A sensitivity analysis was performed to ascertain whether the summary estimate of the effect was significantly affected by a single study. Toward this end, pooled estimates were recalculated, using a random-effects model, by excluding one study at a time.

Univariate meta-regression analyses were performed to evaluate patient and study covariates as

predictors of AF recurrence. The estimated between-study variance (τ^2) was calculated using an estimate on the basis of restricted maximal likelihood, by estimating parameter variances using the quadratic variance factor (12), and testing Ho: $b_j = 0$ using a t-distribution with $m - k - 1$ degrees of freedom. The p value was considered significant at <0.05.

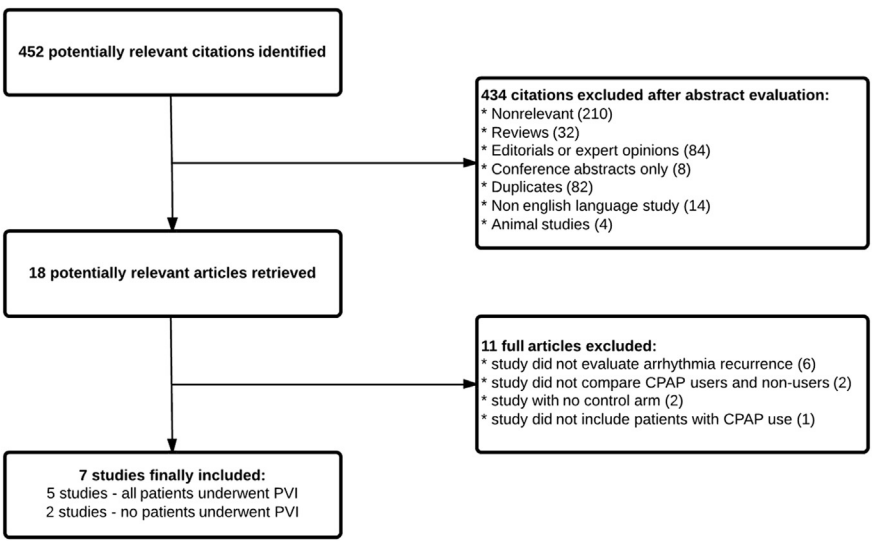
RESULTS

STUDY SELECTION. The search of the published data yielded a total of 452 citations, of which 445 were excluded (**Figure 1**). Seven studies with a prospective cohort design met the pre-specified inclusion and exclusion criteria (13-19). In 5 of these studies, the patients underwent catheter ablation of AF with PVI, and the risk for AF recurrence was compared between CPAP users and nonusers (PVI group) (14,15,17-19). In 2 studies, patients were managed medically, including the use of antiarrhythmic drugs, and AF recurrence was compared among CPAP users and nonusers (non-PVI group) (13,16). One of these studies enrolled patients that underwent cavo-tricuspid isthmus ablation for atrial flutter, and this study was included in the non-PVI group by consensus (16).

STUDY CHARACTERISTICS AND QUALITY. **Table 1** summarizes the characteristics of the 7 studies included in the analysis. Of the 7 studies, 5 were performed in the United States and 1 each in Spain and Japan. The patient population in the included studies ranged from 32 to 640, with a median of 62 patients. The median duration of follow-up was 12 months (range: 7 to 42 months). All studies enrolled patients with documented AF, except one in which 46% of the patients had documented AF at baseline (16). Patients in all studies were diagnosed with OSA on the basis of polysomnography. In all but 2 studies (Naruse et al. [18] and Bazan et al. [16]), diagnosis of OSA and consequent use of CPAP was initiated before enrollment into the respective studies. Additional polysomnography criteria used for diagnosis was detailed in 5 of these studies (15-19). Adherence to use of CPAP was documented on the basis of patient report on follow-up visits in all studies except in the study by Naruse et al. (18). In this study, a modem connected to the CPAP facilitated the downloading of information to a central computer that yielded individual objective adherence data (**Table 2**). Quality of all included studies was high on the basis of Newcastle Ottawa scale (**Table 3**).

Electrocardiographic documentation of AF remained the mainstay for evaluation of AF recurrence. In all but 2 studies, recurrent atrial tachyarrhythmia during the study period was also considered as a primary endpoint (14,16,18). The median blanking period post-ablation was 10 weeks (range 2 to 12 weeks). In 4 of 5 studies, the number of ablation procedures that an enrolled patient underwent was

FIGURE 1 Flow Diagram to Depict the Selection Process of Studies Included in the Meta-Analysis



CPAP = continuous positive airway pressure; PVI = pulmonary vein isolation.

TABLE 1 Summary of the Characteristics of the Included Studies

First Author (Ref. #)	Year Published	Study Design	Geographical Area	Enrollment of Patients	AF Type at Enrollment	Mean Age, Yrs		Male		BMI, kg/m^2		Total Patients In 2 Groups		Patients With AF Recurrence		Study Duration, Months	NOS Study Quality Score
						CPAP +	CPAP −	CPAP +	CPAP −	CPAP +	CPAP −	CPAP +	CPAP −	CPAP +	CPAP −		
Kanagala et al. (13)	2003	Prospective cohort study	United States	Patients with AF/AFl referred for cardioversion	NA	66 ± 12	65 ± 10	9 (82)	21 (81)	42 ± 15	36 ± 8	12	27	5	22	12	8
Jongnarangsin et al. (14)*	2008	Prospective cohort study	United States	OSA patients identified from 324 consecutive patients undergoing AF ablation	P = 23 (72); C = 9 (28)	59 ± 7	59 ± 7	NA	NA	NA	NA	18	14	9	10	7	7
Patel et al. (15)	2010	Prospective cohort study	United States	Patients with OSA identified from 3,000 consecutive patients undergoing AF ablation	P = 258 (40); NP = 382 (60)	49 ± 8	53 ± 12	224 (71)	251 (77)	30 ± 3	31 ± 2	315	325	105	178	32	7
Bazan et al. (16)	2013	Prospective cohort study	Spain	Patients with AFl undergoing CTI ablation screened for OSA	P = 26 (46)	66 ± 11†	64 ± 10†	23 (85)	21 (72)	33.7 ± 8†	30.8 ± 6†	27	29	8	13	12	6
Fein et al. (17)	2013	Prospective cohort study	United States	Patients with OSA and symptomatic AF referred for AF ablation	Ps = 17 (57)*	56.8 ± 4	NA	23 (77)	NA	28.77 ± 0.45	NA	32	30	9	19	12	8
Naruse et al. (18)	2013	Prospective cohort study	Japan	OSA patients identified from 249 consecutive patients that underwent AF ablation	P = 82 (54)‡	60 ± 9*‡	60 ± 9*‡	NA‡	NA‡	NA‡	NA‡	82	34	25	18	18.8	7
Neilan et al. (19)	2013	Prospective cohort study	United States	OSA patients identified from consecutive patients that underwent AF ablation	P = 51 (36), Ps = 91 (64), PAFA = 30 (21)	57 ± 10†	57 ± 10†	115 (81)*	115 (81)*	32.5 ± 6*	32.5 ± 6*	71	71	25	48	42	8

Values are n (%) or mean ± SD, unless otherwise indicated. *No clear data is available for the 2 groups of CPAP users and nonusers. †Patient data presented for the group with known prior history of AF in addition to AFl. ‡Of the total 153 patients enrolled in study (data on 153 patients also included those who did not have OSA, evaluated in this study).

AF = atrial fibrillation; AFl = atrial flutter; BMI = body mass index; C = chronic; CPAP = continuous positive airway pressure; CTI = cavotricuspid isthmus; HTN = hypertension; NA = not available; NOS = Newcastle Ottawa scale; NP = nonparoxysmal; OSA = obstructive sleep apnea; P = paroxysmal; PAFA = prior atrial fibrillation ablation; Ps = persistent.

TABLE 2 Key Features Related to Obstructive Sleep Apnea and Arrhythmia Management in Individual Studies

First Author (Ref. #)	Description of OSA Diagnosis	OSA Diagnostic Criteria	CPAP Adherence	Ablation Strategy	Medical Therapy	Means of AF Recurrence Evaluation
Kanagala et al. (13)	Polysomnography in all patients before inclusion in study	Not described	Self-reported use of CPAP use obtained via questionnaire through the mail, hospital records, and follow-up phone interviews	No ablation performed	All OSA patients*: A: 5 (13%); Pp: 10 (26%); S: 4 (10%); BB: 11 (28%); DHP: 5 (13%); nDHP: 9 (23%); D: 10 (26%)	Either clinical evaluation by a physician or ECG
Jongnarangsin et al. (14)	OSA diagnosed via polysomnography before ablation	Not described	Not documented	PVI + CAFE in cases of persistence of AF despite PVI	Patients free from AAD therapy during study period	12-lead ECG at clinic visits, event monitor, evaluation upon symptoms of arrhythmia
Patel et al. (15)	Polysomnography before PVI	AHI > 15/h and >80% of all apnea/hypopnea events had to be obstructive	Patient-reported adherence at office visits	Paroxysmal: PVI + posterior wall isolation + empirical isolation of the superior vena cava Nonparoxysmal AF: PVI + posterior wall ablation until coronary sinus + left septum + right- and left-sided defragmentation	PVI + OSA + CPAP = 44 of 315 (14%) PVI + OSA - CPAP = 97 of 325 (30%)	Event monitor/Holter monitor
Bazan et al. (16)	Patients underwent polysomnography after CTI ablation	AHI ≥5, severe OSA with AHI ≥30	Patient reported adherence of >4 h/night	No ablation performed	All OSA patients AAD*: 16/ of 56 (29%)	12-lead ECG, Holter monitor
Fein et al. (17)	Polysomnography before AF ablation	AHI >15/h and ≥80% events had to be obstructive	Patient self-reported	PVI + left atrial ablation lines (roof line, mitral isthmus line, and/or posterior left atrial line) ± ablation of extra-PV atrial triggers were performed in patients with inducible sustained AF or atrial tachyarrhythmia	All patients placed on AAD (class Ic and sotalol) after PVI discontinued 3–6 months later with no arrhythmia recurrence. No clear data on AAD therapy in both CPAP + and − groups available	12-lead ECG on clinic visits + transtelephonic monitoring
Naruse et al. (18)	Polysomnography 1 week after AF ablation	AHI >15/h and ≥50% events had to be obstructive	Objective data obtained with a modem connected to the CPAP device, which downloaded the data to a central computer to yield objective adherence data in hours per night	Paroxysmal AF: PVI ± linear ablation of the left atrial roof and/or superior vena cava isolation in case of AF recurrence with pacing or isoproterenol infusion. Persistence AF: PVI + linear ablation of the left atrial roof, superior vena cava isolation ± CAFÉ ablation	Patients with AF recurrence during the blanking period treated temporarily with class I, II, III, and/or IV AADs and stopped if arrhythmia disappeared after temporary treatment. No clear data on AAD therapy in both CPAP + and - group available	12-lead ECG documentation
Neilan et al. (19)	OSA diagnosed before PVI with polysomnography	AASM criteria	Patient self-reported on telephone interviews	Paroxysmal AF: PVI. Persistent AF: PVI + linear ablations to create conduction block across the LA roof, and along the region between the lateral mitral annulus and left inferior pulmonary vein + CAFE ablation	Class I + class III AAD: OSA + CPAP: 50 of 71 (70.4%) OSA - CPAP: 52 of 71 (73.2%)	ECG or prolonged cardiac monitoring

*Data not available separately for CPAP and non-CPAP population.

A = amiodarone; AAD = antiarrhythmic drugs; AASM = American Academy of Sleep Medicine; AF = atrial fibrillation; AHI = apnea hypopnea index; BB = beta adrenergic blockers; CAFÉ = complex fractionated atrial electrograms; CTI = cavotricuspid isthmus; D = digoxin; DHP = dihydropyridines; ECG = electrocardiogram; nDHP = nondihydropyridines; Pp = propafenone; Pc = procainamide; PVI = pulmonary vein isolation; S = sotalol; other abbreviations as in Table 1.

TABLE 3 Evaluation of Study Quality on The Basis of Newcastle Ottawa Scale

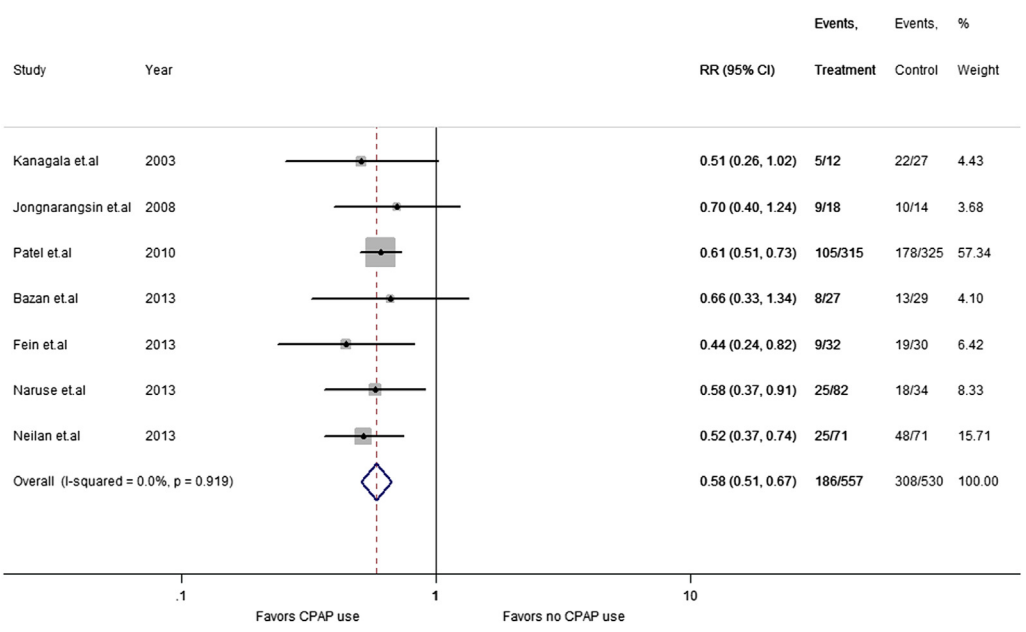
	Selection				Comparability	Outcome				
First Author (Ref. #)	Representativeness	Selection of the Nonexposed Cohorts	Ascertainment	Endpoint Not Present at Start	Comparability (Confounding)	Assessment of Outcome	Follow-Up Duration	Adequacy of Follow-Up	Total	Quality
Fein et al. (17)	*	*	*	*	*	*	*	*	8	High
Patel et al. (15)	*	*	*	*	0	*	*	*	7	High
Naruse et al. (18)	*	*	*	*	0	*	*	*	7	High
Neilan et al. (19)	*	*	*	*	*	*	*	*	8	High
Kanagala et al. (13)	*	*	*	*	*	*	*	*	8	High
Bazan et al. (16)	0	*	*	*	0	*	*	*	6	High
Jongnarangsin et al. (14)	*	*	*	*	0	*	*	*	7	High

*Criteria met.

one (13,14,17,18). In 1 study, repeat ablation was offered upon AF recurrence, but details about the repeat ablation procedures was not available (17).

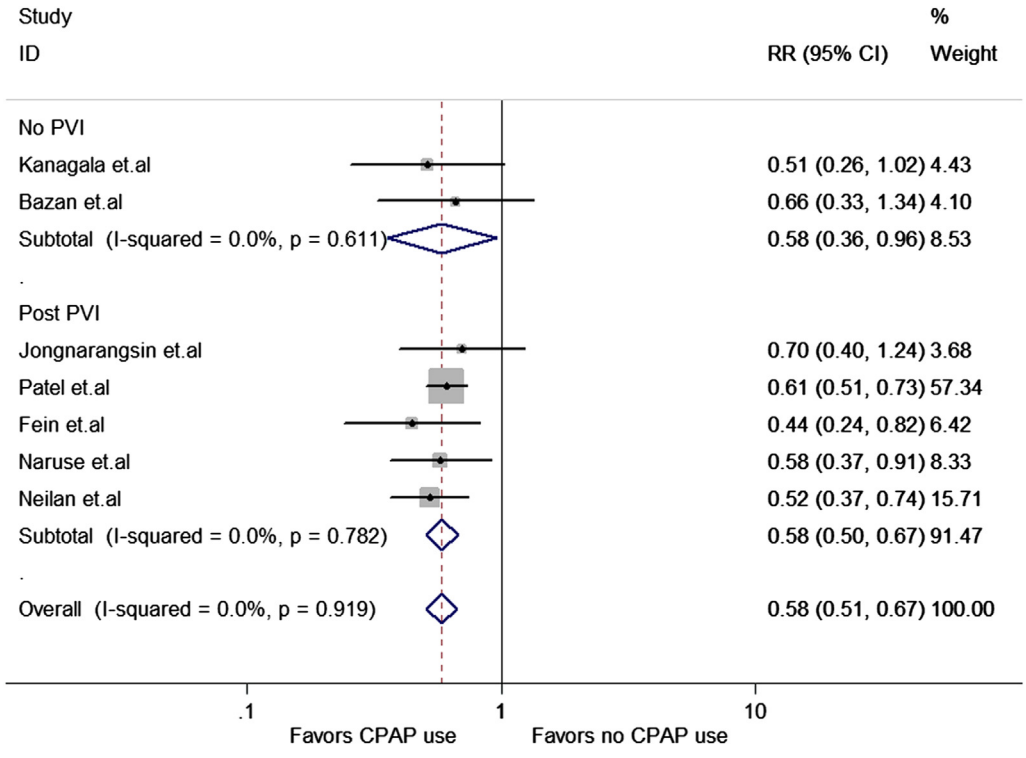
OUTCOME ANALYSIS. Across 7 studies with a total study population of 1,087, users of CPAP had a significant reduction in AF recurrence rate compared with nonusers (n = 186 of 557 [33.3%] vs. 308 of 530 [58.1%]; RR: 0.58; 95% CI: 0.51 to 0.67; $p < 0.001$; p value for chi-square heterogeneity 0.91, and $I^2 = 0\%$) (Figure 2). In the subgroup analysis from 5 studies in which patients underwent PVI, users of CPAP were found to have a lower risk of AF recurrence in comparison with nonusers (n = 173 of 518 [33.3%] vs. 273 of 474 [57.6%]; RR: 0.58; 95% CI: 0.50 to 0.67; $p < 0.001$; p value for chi-square heterogeneity 0.72, and $I^2 = 0\%$). In 2 studies in which patients did not undergo catheter ablation of AF, CPAP users also had a lower risk of AF recurrence in comparison with nonusers (n = 13 of 39 [33.3%] vs. 35 of 56 [62.5%]; RR: 0.58; 95% CI: 0.36 to 0.96; p = 0.03; p value for chi-square heterogeneity 0.6, and $I^2 = 0\%$) (Figure 3).

FIGURE 2 Forest Plot to Compare AF Recurrence in Users Versus Nonusers of CPAP In Patients With OSA



The forest plot exhibits effect size of each included study **(solid box)** with 95% confidence interval (CI) **(black lines through solid squares)**. The **diamond (and broken vertical line)** at the bottom represents pooled summary estimate with its CI given by its width. AF = atrial fibrillation; CPAP = continuous positive airway pressure; OSA = obstructive sleep apnea; RR = relative risk ratio.

FIGURE 3 AF Recurrence in Users Versus Nonusers of CPAP in 2 Groups of Patients With OSA: PVI and Non-PVI Groups



PVI = pulmonary vein isolation; other abbreviations as in Figure 2.

Visual inspection of the funnel plot for AF recurrence in all 7 studies showed no evidence of publication bias that might affect the results (Figure 4). A "small study effect" was excluded by Egger's test of intercept ($p = 0.207$). Rosenthal's fail-safe N indicated that 79 null studies would be needed to bring the p value of the effect to >0.05. Orwin's fail-safe N value was estimated to be 180, suggesting that >180 studies with a mean RR of 1.0 would need to be added to the analysis to make the cumulative effect trivial (defined as a RR of 0.98). (Because the search of the published data in the present analysis revealed only 7 studies, it seems improbable for the current search strategy to have missed such a large number of studies.)

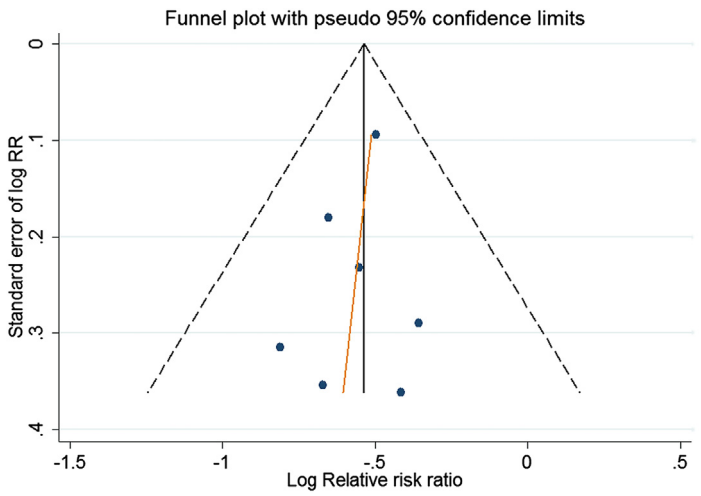
SENSITIVITY ANALYSIS. The results of the sensitivity analysis revealed that no single study dominated an effect upon the pooled outcomes. The RR reduction in AF across studies by excluding studies 1 at a time was homogenous, with a range from 0.55 to 0.59. Exclusion of the study by Patel et al. (15), which included the largest number of patients ($n = 640$), revealed a pooled RR reduction of 0.55 (95% CI: 0.44 to 0.66) (Figure 5) (14).

META-REGRESSION ANALYSIS. The following covariates were considered: study duration, patient age, male sex, body mass index, hypertension, diabetes mellitus, coronary artery disease, left atrial dimension, antiarrhythmic drug use, percent of patients with nonparoxysmal AF, and left ventricular ejection fraction. Upon univariate analysis, none of these covariates showed any significant association with arrhythmia recurrence (Table 4).

DISCUSSION

This pooled analysis of systematically-selected studies presents robust evidence that use of CPAP in patients with OSA is associated with a significant reduction in recurrence of AF. The effect size remains consistent and similar across patient groups irrespective of whether or not the patients underwent PVI or were medically managed. Lack of any significant association between patient and study covariates (known to affect arrhythmia outcomes) and AF recurrence suggests that CPAP use may be primarily responsible for these results and that these findings are not due to a chance effect. These study findings

FIGURE 4 Begg's Funnel Plot of Studies According to Logarithmic RR of AF Recurrence in CPAP Users



Abbreviations as in Figure 2.

TABLE 4 Meta Regression Analysis to Evaluate Influence of Patient or Study Variable on AF Recurrence

	Regression Coefficient	p Value
Study duration	0.001	0.874
Patient age	−0.008	0.558
Male	−0.011	0.46
BMI	−0.001	0.96
Diabetes mellitus	−0.006	0.6
AAD	−0.003	0.34
Persistent AF	−0.01	0.54
Hypertension	−0.006	0.5
CAD	0.003	0.85
LVEF	−0.007	0.61
LAD	−0.01	0.48

CAD = coronary artery disease; LAD = left atrial dimension; LVEF = left ventricular ejection fraction; other abbreviations as in Tables 1 and 2.

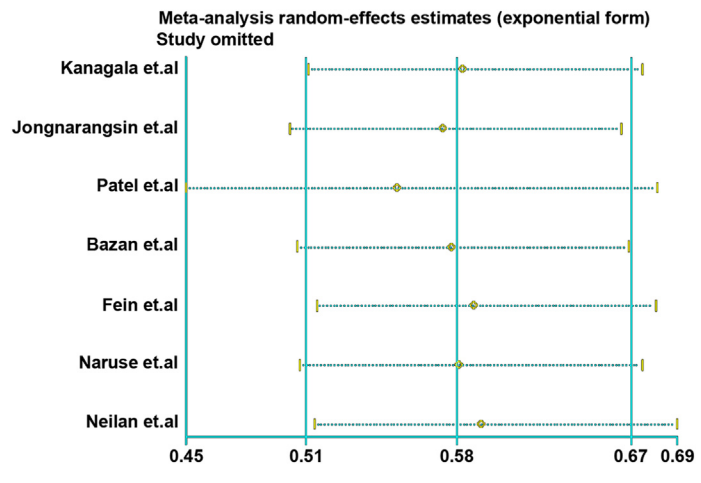
are important as they provide the most conclusive evidence available and give the clinician an additional means to reduce AF recurrence in patients with OSA.

Several mechanisms are proposed by which OSA increases the risk of AF. These include wide fluctuations in intrathoracic blood pressure during apneic episodes, leading to left atrial stretch via pressure and volume overload and alteration of sympathetic tone (20,21). Additionally, there are intermittent periods of hypoxemia and hypercapnia that lead to atrial remodeling with regions of fibrosis (22). These have been corroborated with reports of significant structural changes in the atria with increased atrial size, extensive areas of low voltage (suggesting loss of atrial myocytes with concomitant areas of increased fibrosis), and areas of dissociation in conduction on electrophysiology studies in patients with OSA (23).

In addition to an established relationship between OSA and new-onset AF, there is increasing evidence to support the influence of OSA on recurrence of AF following catheter ablation (6,24). On the basis of data from meta-analyses, patients with OSA can have 25% to 31% increased risk for AF recurrence after catheter ablation in comparison with patients with no sleep apnea (5,25). CPAP is currently the mainstay of available therapy for adults with OSA (26,27). Evidence from meta-analyses of randomized trials suggest that CPAP use reduces the frequency of respiratory events during sleep, decreases daytime sleepiness, and improves quality of life (28). Additionally, its use has been reported to be associated with reduced left ventricular afterload and heart rate during sleep in patients with OSA and congestive heart failure (29). Lowering of blood pressure and alleviation of bradyarrhythmias are other known effects of CPAP use (30).

The results of the present study present the highest strength of evidence currently available for the association between CPAP use and reduced AF recurrence. In these results, the use of CPAP was consistently associated with a significant reduction in AF recurrence across all of the included studies. Despite a large variation in the number of patients included in the analysis (range 32 to 640 patients), the magnitude in AF reduction appears to be uniform across the studies (RR: range 0.44 to 0.70). A sensitivity analysis further confirmed that there was no single-study effect, and the net relative risk reduction

FIGURE 5 Sensitivity Analysis to Evaluate Single-Study Effect on Outcomes



in AF recurrence upon exclusion of studies one by one remained unchanged from the pooled data. Also, although studies conducted in the United States dominated in this analysis, there were 2 studies outside of this geographic distribution with a similar relative risk reduction in AF (16,18). The aforementioned facts indicate the strength of these data.

The physical discomfort associated with CPAP use is one of the key factors associated with its poor adherence in patients (31). Thus, it becomes important to elucidate the mechanisms by which CPAP use may curb the proarrhythmic factors, as this could potentially pave the way for development of novel treatment algorithms for OSA. The results of the subgroup analysis in the current study indicate that the RR reduction in AF recurrence with CPAP use is similar across patient groups irrespective of whether they are managed medically or with PVI. This is a salient finding, because it suggests the presence of alternate proarrhythmic mechanisms that are controlled with CPAP use and that these may remain unchecked with the conventional treatment strategies for AF. These findings concur with results of other electrophysiology studies that reported a significantly large number of nonpulmonary vein triggers for AF in patients with OSA (15,32). They concluded that the presence of such nonpulmonary vein triggers increased the need for a repeat ablation procedure, necessitating ablation of these non-PVI triggers, and they further indicated that PVI by itself would have led to only limited success in these patient populations. In another study by Fein et al. (17) the arrhythmia-free survival rate in CPAP users with OSA was similar to that of patients without OSA (71.9% vs. 66.7%) (17). In this study, PVI offered little benefit toward AF reduction in patients with OSA who were noncompliant with CPAP use. These data collectively suggest that non-PVI triggers are significant mechanisms for AF recurrence and that, unless OSA is effectively treated in patients, neither medical management nor the current invasive treatment approach will have the expected effect in reduction of AF recurrence.

STUDY LIMITATIONS. This paper is subject to the limitations common to any other meta-analysis. There is a risk of bias included in the individual studies due to their observational study design. The high study quality of the included studies along with consistent outcomes, however, suggest that any potential for bias in these results is likely to be small. Next, the number of patients enrolled in most of the included studies is small. Although a meta-analysis attempts to overcome this limitation by mathematically constructing a summary estimate, small numbers of included patients does increase the potential for alpha error in the results. Also, there is a risk for publication bias in any meta-analysis; however this was nonsignificant in these results. A possibility for limited power and a type II error does exist, but this was negated by the high fail-safe number. Next, adherence to CPAP was mostly on the basis of patient self-report, raising concern for overestimation of its use and possible underestimation of the beneficial effects of CPAP. Additionally, meta-regression analyses are limited because they are based upon the prevalence of a variable in the study and not upon the raw patient data. The results of these analyses are, thus, to be interpreted with caution, should be utilized as hypothesis generating, and must be confirmed in future RCTs.

FUTURE DIRECTIONS. In patients with AF, OSA should be suspected and evaluated as a significant comorbidity when clinically warranted. On the basis of the reported prevalence of OSA of up to 49% in patients with AF, OSA may remain undiagnosed across these patients (24,33,34). These findings, along with the beneficial effect of CPAP in such patients noted in the current study, advocate for a need to suspect and actively screen for OSA in patients with AF.

These study results foster the need for adequately-controlled prospective intervention studies to quantify the efficacy of CPAP use in these patients. The ongoing prospective observational study, Reveal XT-SA, is likely to yield definitive evidence for incidence of new-onset AF in patients with OSA and the effect of CPAP use. In addition, however, a randomized study to evaluate the effect of CPAP use in patients with diagnosed AF is warranted. Given that the use of CPAP in patients with OSA can now be a significant third treatment option, its characterization via an appropriately-designed RCT would be ideal. Nevertheless, until these data become available, given the known positive effects of CPAP on multiple other end organs and its innocuous adverse effects, its use needs to be strongly advocated in patients with OSA with the intention of AF reduction.

Current AF guidelines recognize that OSA is one of the risk factors for development of AF and that its presence reduces success with ablation (35,36). However, there is no recommendation to screen patients for and treat OSA. Given the 42% relative risk reduction seen in the present study, which may now evolve to be a third major treatment option (in addition to medical therapy and ablation), revision of the current AF guidelines may be in order.

CONCLUSIONS

The use of CPAP is associated with a 42% relative risk reduction in AF recurrence in patients with OSA. This reduction of AF recurrence appears to be independent of medical or catheter ablation therapy and is consistent across patient groups with OSA. These results advocate for active screening for undiagnosed OSA in patients with AF when OSA is clinically suspected. The use of CPAP offers to be the third potential treatment option for AF (in addition to medical therapy and PVI), and although results from RCTs may be warranted to understand the true extent of its efficacy, its use and adherence needs to be promoted aggressively in these patient groups.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Larry Chinitz, Leon H. Charney Division of Cardiology, NYU Langone Medical Center, 560 First Avenue TH576, New York, New York 10016, USA. E-mail: larry.chinitz@nyumc.org.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Recurrence of AF despite medical therapy or catheter ablation remains a significant problem in select patient groups. OSA in patients is a known predictor for AF recurrence. The results of this study show that use of CPAP in patients with OSA is associated with a significant reduction in AF recurrence. This effect could be independent of either medical therapy or catheter ablation and has the potential to become the third major treatment pathway for AF reduction in patients with OSA.

TRANSLATIONAL OUTLOOK: A randomized controlled trial designed to evaluate the effect of CPAP use and its effect on AF recurrence is warranted to further delineate the mechanisms by which CPAP use is efficacious in patients with OSA.

REFERENCES

1. Wilber DJ, Pappone C, Neuzil P, et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. JAMA 2010;303:333–40.

2. Jais P, Cauchemez B, Macle L, et al. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. Circulation 2008;118:2498–505.

3. Berruezo A, Tamborero D, Mont L, et al. Preprocedural predictors of atrial fibrillation recurrence after circumferential pulmonary vein ablation. Eur Heart J 2007;28:836–41.

4. Shukla A, Curtis AB. Avoiding permanent atrial fibrillation: treatment approaches to prevent disease progression. Vasc Health Risk Manag 2014;10:1–12.

5. Ng CY, Liu T, Shehata M, Stevens S, Chugh SS, Wang X. Meta-analysis of obstructive sleep apnea as predictor of atrial fibrillation recurrence after catheter ablation. Am J Cardiol 2011;108:47–51.

6. Gami AS, Pressman G, Caples SM, et al. Association of atrial fibrillation and obstructive sleep apnea. Circulation 2004;110:364–7.

7. Stroup DF, Berlin JA, Morton SC, et al., Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA 2000;283:2008–12.

8. Wells GA, O'Connell SD, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed June 4, 2014.

9. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.

10. Rosenthal R. The "File drawer problem" and tolerance for null results. Psychol Bull 1979;86:638–41.

11. Orwin R. A fail-safe N for effect size in meta-analysis. J Educ Stat 1983;8:157–9.

12. Knapp G, Hartung J. Improved tests for a random effects meta-regression with a single covariate. Stat Med 2003;22:2693–710.

13. Kanagala R, Murali NS, Friedman PA, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. Circulation 2003;107:2589–94.

14. Jongnarangsin K, Chugh A, Good E, et al. Body mass index, obstructive sleep apnea, and outcomes of catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol 2008;19:668–72.

15. Patel D, Mohanty P, Di Biase L, et al. Safety and efficacy of pulmonary vein antral isolation in patients with obstructive sleep apnea: the impact of continuous positive airway pressure. Circ Arrhythm Electrophysiol 2010;3:445–51.

16. Bazan V, Grau N, Valles E, et al. Obstructive sleep apnea in patients with typical atrial flutter: prevalence and impact on arrhythmia control outcome. Chest 2013;143:1277–83.

17. Fein AS, Shvilkin A, Shah D, et al. Treatment of obstructive sleep apnea reduces the risk of atrial fibrillation recurrence after catheter ablation. J Am Coll Cardiol 2013;62:300–5.

18. Naruse Y, Tada H, Satoh M, et al. Concomitant obstructive sleep apnea increases the recurrence of atrial fibrillation following radiofrequency catheter ablation of atrial fibrillation: clinical impact of continuous positive airway pressure therapy. Heart Rhythm 2013;10:331–7.

19. Neilan TG, Farhad H, Dodson JA, et al. Effect of sleep apnea and continuous positive airway pressure on cardiac structure and recurrence of atrial fibrillation. J Am Heart Assoc 2013;2:e000421.

20. Fusetti M, Fioretti AB, Valenti M, Masedu F, Lauriello M, Pagliarella M. Cardiovascular and metabolic comorbidities in patients with obstructive sleep apnoea syndrome. Acta Otorhinolaryngol Ital 2012;32:320–5.

21. Camen G, Clarenbach CF, Stowhas AC, et al. The effects of simulated obstructive apnea and hypopnea on arrhythmic potential in healthy subjects. Eur J Appl Physiol 2013;113:489–96.

22. Otto ME, Belohlavek M, Romero-Corral A, et al. Comparison of cardiac structural and functional changes in obese otherwise healthy adults with versus without obstructive sleep apnea. Am J Cardiol 2007;99:1298–302.

23. Dimitri H, Ng M, Brooks AG, et al. Atrial remodeling in obstructive sleep apnea: implications for atrial fibrillation. Heart Rhythm 2012;9:321–7.

24. Gami AS, Hodge DO, Herges RM, et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. J Am Coll Cardiol 2007;49:565–71.

25. Li L, Wang ZW, Li J, et al. Efficacy of catheter ablation of atrial fibrillation in patients with obstructive sleep apnoea with and without continuous positive airway pressure treatment: a meta-analysis of observational studies. Europace 2014;16:1309–14.

26. Epstein LJ, Kristo D, Strollo PJ Jr., et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med 2009;5:263–76.

27. Gottlieb DJ, Punjabi NM, Mehra R, et al. CPAP versus oxygen in obstructive sleep apnea. N Engl J Med 2014;370:2276–85.

28. Patel SR, White DP, Malhotra A, Stanchina ML, Ayas NT. Continuous positive airway pressure therapy for treating sleepiness in a diverse population with obstructive sleep apnea: results of a meta-analysis. Arch Intern Med 2003;163:565–71.

29. Tkacova R, Rankin F, Fitzgerald FS, Floras JS, Bradley TD. Effects of continuous positive airway pressure on obstructive sleep apnea and left ventricular afterload in patients with heart failure. Circulation 1998;98:2269–75.

30. Koehler U, Fus E, Grimm W, et al. Heart block in patients with obstructive sleep apnoea: pathogenetic factors and effects of treatment. Eur Respir J 1998;11:434–9.

31. Engleman HM, Wild MR. Improving CPAP use by patients with the sleep apnoea/hypopnoea syndrome (SAHS). Sleep Med Rev 2003;7:81–99.

32. Mohanty S, Mohanty P, Di Biase L, et al. Long-term outcome of catheter ablation in atrial fibrillation patients with coexistent metabolic syndrome and obstructive sleep apnea: impact of repeat procedures versus lifestyle changes. J Cardiovasc Electrophysiol 2014;25:930–8.

33. Fuhrman C, Fleury B, Nguyen XL, Delmas MC. Symptoms of sleep apnea syndrome: high prevalence and underdiagnosis in the French population. Sleep Med 2012;13:852–8.

34. Hiestand DM, Britz P, Goldman M, Phillips B. Prevalence of symptoms and risk of sleep apnea in the US population: results from the National Sleep Foundation Sleep in America 2005 poll. Chest 2006;130:780–6.

35. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014;64:e1–76.

36. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010;31:2369–429.

KEY WORDS **atrial fibrillation, continuous positive airway pressure, obstructive sleep apnea, recurrence**