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Sleep apnea screening instrument evaluation and novel model development and validation in the paroxysmal atrial fibrillation population

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ABSTRACT

Standard sleep apnea (SA) screening instruments perform suboptimally in the atrial fibrillation (AF) population. We evaluated and optimized common OSA screening tools in the AF population. Participants of the Sleep Apnea and Atrial Fibrillation Biomarkers and Electrophysiologic Atrial Triggers (SAFEBEAT, NCT02576587) age (±5 years)-, sex-, body mass index (BMI ± 5 kg/m^2)-matched case control study (n = 150 each group) completed concurrent questionnaires and overnight polysomnography. Models based on STOP, STOP-BANG, Berlin, NoSAS and Epworth Sleepiness Scale and also models with STOP-BANG predictors with resting heart rate or left atrial volume were constructed. "Best subset" analysis was used to select a predictor subset for evaluation. We assessed test performance for two outcome thresholds: apnea-hypopnea index (AHI) $\geq$ 5 and AHI $\geq$ 15. Paroxysmal AF participants were: 61.3 ± 12.1 years, BMI = 31.2 ± 6.6 kg/m^2 with median AHI = 11.8(IQR: 3.8, 24.5); 65 (43.3%) with AHI $\geq$ 15. Only STOP and STOP-BANG did not perform worse in AF relative to controls. For AHI $\geq$ 15, STOP-BANG (AUC 0.71, 95%CI:0.55–0.85) did not perform as well as NABS – a composite of neck circumference, age, and BMI as continuous variables and snoring (AUC 0.88, 95%CI:0.76–0.96). Optimal model for AHI $\geq$ 15 was NABS (sensitivity = 45%, specificity = 97%). For AHI $\geq$ 5, NABS was also the best performing (AUC 0.82, 95%CI:0.68–0.92, sensitivity = 78%, specificity = 67%). We identify a novel, short-item SA screening instrument for use in paroxysmal AF, i.e. NABS, with improved discriminative ability compared to commonly-used instruments. Further validation studies are needed to assess utility in other AF subtypes.

Trial registration: clinicaltrials.gov NCT02576587.

1. Introduction

Atrial fibrillation (AF), the most common chronic arrhythmia, is associated with substantial morbidity and healthcare expense [1]. AF prevalence is projected to increase 2.5-fold by 2050 [2]. Sleep apnea (SA) is highly prevalent in those with AF, occurring in 21–81% of individuals with AF [3]. Untreated SA is associated with poor outcomes following pharmacologic and/or procedural management of AF [4–8]. Studies suggest that SA therapy leads to improved outcomes after AF ablation, cardioversion, and medical management [4,5,9]. Improving SA identification in the AF population, particularly in those with paroxysmal AF (PAF) who have the highest chance of benefiting from pharmacologic or interventional interventions to control AF, could improve outcomes.

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Unfortunately, SA screening instruments derived from and validated in the peri-operative and general medicine populations do not perform well in patients with cardiac disease, particularly in those with atrial AF [10,11]. Patients with AF tend not to show the pathognomonic signs of SA – snoring and daytime sleepiness – and other symptoms such as fatigue and nocturnal dyspnea can be multifactorial (e.g. attributable to underlying cardiac condition or medication side effects), non-specific, and underreported [12–14].

We have completed an individually matched case-control study focused on individuals with paroxysmal AF in which we evaluated the performance characteristics of common SA screening tools and used biologically plausible and relevant cardiac physiologic and structural data in an effort to develop an SA screening instrument optimized for the AF population. We hypothesized that (1) typical SA screening tools have worse performance characteristics in patients with AF vs. those without, (2) AF patient screening can be improved using a subset of variables used in common screening instruments, and (3) adding physiologic measures from echocardiography improves SA screening tool performance.

2. Materials and methods

2.1. Participants and study design

The Sleep Apnea and Atrial Fibrillation Biomarkers and Electrophysiologic Atrial Triggers trial (SAFEBEAT, n = 300), a case-control study, recruited participants from March 2012 to March 2017 (Fig. 1). Adults with PAF diagnosis – defined as recurrent AF episodes self-terminating within 7 days [15] – were recruited from outpatient cardiology clinics at two academic tertiary centers. Participants were matched 1:1 to controls based on sex, race, age (±5 years), and body mass index (BMI ± 5 kg/m^2) to address important biologic confounding influences with impact on both AF and SA development. Exclusion criteria included AF with rapid rate (≥120 beats per minute), post-operative AF, anti-arrhythmic medication with no further clinical AF, prior cardiac ablation or successful cardioversion, implanted cardioverter-defibrillator, significant valvular disease, atrial septal defect, infiltrative or restrictive cardiomyopathy, heart failure, sick sinus syndrome, end-stage renal failure, concurrent treatment for sleep disordered breathing, severe chronic insomnia or circadian rhythm disorder, self-reported sleep duration < 4 h, supplemental oxygen use, unstable medical conditions, immunodeficiencies, non-skin cancer, alcohol or drug abuse, pregnancy, and compromised competence or inability to provide informed consent. The most common screening failures in cases were distance too far to travel (1374), AF ablation/cardioversion/atrial septal defect (1285), cardiomyopathy/pacemaker/ICD (795), and other medical condition (735). The most common screening failures for controls were other medical condition (474), no notes (381), cancer (201), and no established physician/no show to appointment (192). Among eligible candidates, the most common reasons for non-participation were passive refusal (67.2%), not interested in research (20.7%), and too busy (4.5%). Sleep studies were conducted in the Clinical Research Units of University Hospitals of Cleveland or Cleveland Clinic. The University Hospitals Case Medical Center IRB and Cleveland Clinic IRB each approved this study, and informed consent was obtained for all participants.

2.2. Sleep studies

Each participant attended overnight full polysomnography using the Compumedics E-system (Abbottsford, AU) that included C_3/A_2 and C_4/A_1 electroencephalograms, bilateral electrooculograms, a bipolar submental electromyogram, snore sensor, thoracic and abdominal respiratory inductance plethysmography, airflow, pulse oximetry, lead I EKG (250 Hz), body position, and bilateral leg electromyography. Research staff who performed the study were centrally trained and used standardized protocols.

Sleep studies were scored by one of two certified polysomnologists blinded to clinical data [16,17]. Interscorer reliability was greater than 95% for all PSG measures. Arousals were defined as an abrupt shift in electroencephalogram frequency lasting at least 3 s and starting after at least 10 continuous seconds of sleep [18]. In REM sleep, arousals additionally required a simultaneous increase in chin electromyography amplitude.

All events were scored according to the American Sleep Disorders Association criteria [16,17]. Apnea was defined as 10 or more seconds of complete or near complete airflow cessation [16]. Apneas were classified as obstructive if there was maintained respiratory effort and central if there was a complete cessation in respiratory effort. Hypopneas were scored if a minimum 50% reduction in breathing amplitude compared to baseline breathing for at least 10 s accompanied by either arousal or a 3% or greater arterial desaturation [16]. Severity of SA was determined by the apnea-hypopnea index (AHI) which was calculated as the total number of apneas and hypopneas per hour of sleep [19]. Central sleep apnea (CSA) was defined as a central apnea index of ≥5.

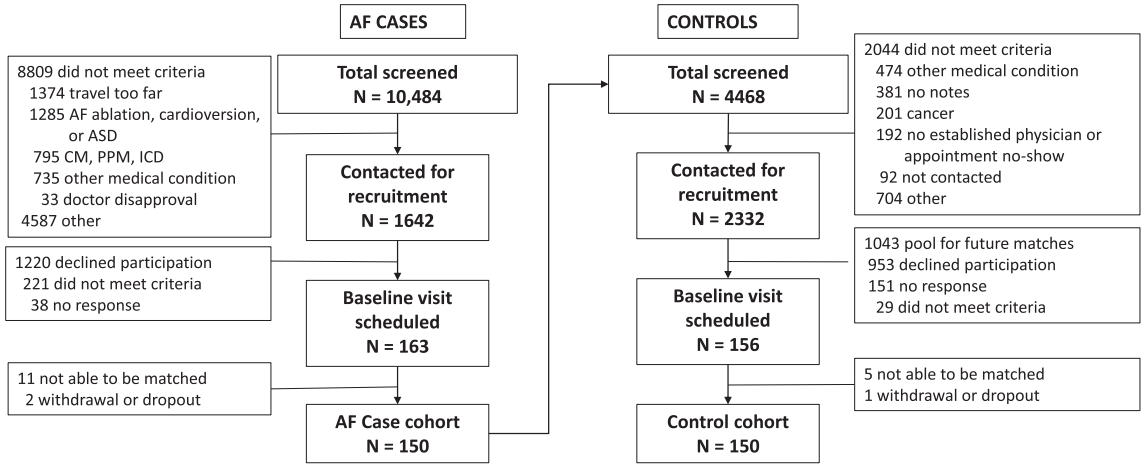

Fig. 1. Study flow: recruitment, attrition, and retention.

2.3. Other measures

Height and weight measured at the baseline visit were used to compute the BMI. All participants completed sleep questionnaires via paper and pen at the baseline visit directly after signing the consent and before participation in the sleep study. In addition, the average of three heart rate readings from each participant measured while sitting at rest during the baseline exam was used in analyses. Echocardiography was performed for research purposes on the morning after the sleep study. Left atrial volume was measured via 2-dimensional Doppler echocardiography. Echocardiography was conducted by a senior sonographer with the participant in the left later decubitus position. Agitated saline was used to enhance imaging. Images were measured in a blinded fashion on 3 representative beats and averaged.

The Epworth sleepiness scale measures propensity to fall asleep in a series of situations and includes 8 items assessed on a 4 point Likert scale (0 = no chance of dozing to 3 = high chance of dozing). The score ranges from 0 to 24 with values < 11 considered normal and higher scores indicating more sleepiness. Epworth sleepiness score has high internal consistency (Cronbach alpha = 0.88) [20,21].

STOP-BANG questionnaire, developed to identify obstructive sleep apnea (OSA), has been validated in surgical populations and studies in the primary care setting show similar predictive performance [22]. The STOP-BANG questionnaire score is calculated by summation of positive responses to the following factors: Snoring, Tiredness, Observed apneas, Elevated pressure (or history of hypertension), BMI > 35 kg/m^2, age > 50, Neck circumference > 40 cm, and male Gender [23].The total score can range from 0 to 8 and a score of $\geq$ 3 is consistent with high pretest probability for OSA. The STOP-BANG questionnaire has a high sensitivity (88%) but moderate specificity (53%) for OSA [24].

The STOP questionnaire is a subset of the STOP-BANG questionnaire that sums each positive response to 4 variables: Snoring, Tiredness, Observed apneas, and Elevated pressure (hypertension history) [25]. A STOP score of at least 2 is considered a positive screening test. STOP has a higher specificity compared to STOP-BANG for moderate-to-severe OSA (53.3% vs. 43.0%, respectively) [25].

The Berlin questionnaire evaluates three domains (10 total questions) to identify OSA in the general population – snoring severity and witnessed apneas, daytime sleepiness, and hypertension/obesity [26]. If 2 of the 3 domains have a positive score, the screen is positive for sleep disordered breathing. At an AHI of $\geq$ 5, sensitivity and specificity of the Berlin questionnaire was 80% and 46%, respectively [24].

NoSAS is geared toward finding those with AHI $\geq$ 20. This screening test incorporates Neck circumference $\geq$ 40 cm (4 points), Obesity (BMI 25 to < 30 = 3 points, BMI $\geq$ 30 = 5 points), Snoring (2 points), Age > 55 years (4 points), and male Sex (2 points) for a total score between 0 and 17 [27]. Scores of 8 or more considered a positive screen [27]. The NoSAS performs similarly to the STOP-BANG and Berlin screening questionnaires [27,28]. The NoSAS tool has a moderate sensitivity and specificity at a threshold of AHI $\geq$ 15 (60.3% and 79.9%, respectively) and AHI $\geq$ 20 (69.4% and 78.2%, respectively) [27].

2.4. Statistical analyses

Participant characteristics were summarized as mean ± standard deviation (SD), median [interquartile range, IQR], or n (%). PAF and control groups were compared using Pearson chi-square tests for categorical variables, pooled *t*-test for normally distributed continuous variables, and Wilcoxon Mann Whitney rank sum test for continuous variables with skewed distributions.

We assumed all data was missing at random. There were no missing values in the Berlin, STOP-BANG, STOP, NoSAS total scores, 1 missing ESS, and only 2 missing in the variables that constructed the STOP-BANG score (for continuous models). Because of the overlap of questions in the 5 scores, only the ESS, STOP-BANG, and Berlin questionnaires required answers to compute all 5 scores. By combining the survey administration and sleep study into one study visit, we attempted to decrease participant burden, which may have improved response rates. We used cases with complete data for the variables under examination.

A general overview of the study starts with evaluation of common SA screening instruments in the AF and non-AF cohorts (Fig. 2). Then, the best performing of the current SA screening instruments in the AF group was evaluated to identify if a subset of those variables would perform comparably or better than the overall screening to find a model with fewer predictors. Lastly, we then tested the addition of physiologic variables – left atrial size and heart rate – on screening performance.

2.4.1. Screening tool performance in AF cases and controls

The entire dataset (no separation into training and validation datasets) was used to evaluate performance characteristics of commonly-used SA screening instruments. Separate prediction models were created for AF and control participants using logistic regression on the entire dataset of each group. AHI $\geq$ 15 and AHI $\geq$ 5 served as the dependent variable and the following were independent variables: STOP-BANG score (possible values 0–8) [23,29] and NoSAS (possible values 0–17) [27,28], Berlin questionnaire (possible values 0–3 positive categories [26,30,31], Epworth Sleepiness Scale (possible values 0–24) [20,21]. Area under the curve (AUC) of receiver operating characteristic (ROC) was used as a measure of performance.

2.4.2. Optimizing prediction models for people with AF

To improve SA screening in AF, the AF cohort was randomly split into training (n = 100) and validation (n = 50) datasets. Based on putative SA physiology as a potential AF-exacerbating factor, heart rate and left atrial volume were added individually to models as biologic markers of altered physiologic and cardiac structural substrate. STOP-BANG was used as the base model because it has the best performance in the AF cohort in the present study when evaluating current screening instruments. Best subsets were used to identify a subset of STOP-BANG predictors for evaluation and 5-fold cross-validation was used to select the best-performing best-subset model [32]. Focusing on a smaller number of predictors was chosen because a model with fewer predictors but comparable performance may have improved clinical applicability.

2.4.3. Predictive utility of physiologic variables for sleep apnea screening in AF

Performance characteristics – mean squared error – were evaluated in the validation subset (n = 50) for the following linear models of AHI: STOP-BANG, STOP-BANG with average heart rate, STOP-BANG with left atrial volume, NABS (**N**eck circumference, **A**ge, **B**MI, and **S**noring) with continuous predictors where applicable, NABS with average heart rate, and NABS with left atrial volume. Heart rate and left atrial volume were chosen prior to analysis because of putative association between SA and worse control of AF leading to a larger left atrial volume and higher heart rate. No model updating was performed since the validation and training datasets populations were not expected to have systematic differences.

SA diagnosis was examined at two thresholds based on clinical cutoffs: (1) AHI $\geq$ 15 and (2) AHI $\geq$ 5 using logistic regression. Area under the curve (AUC) of receiver operating characteristic (ROC),

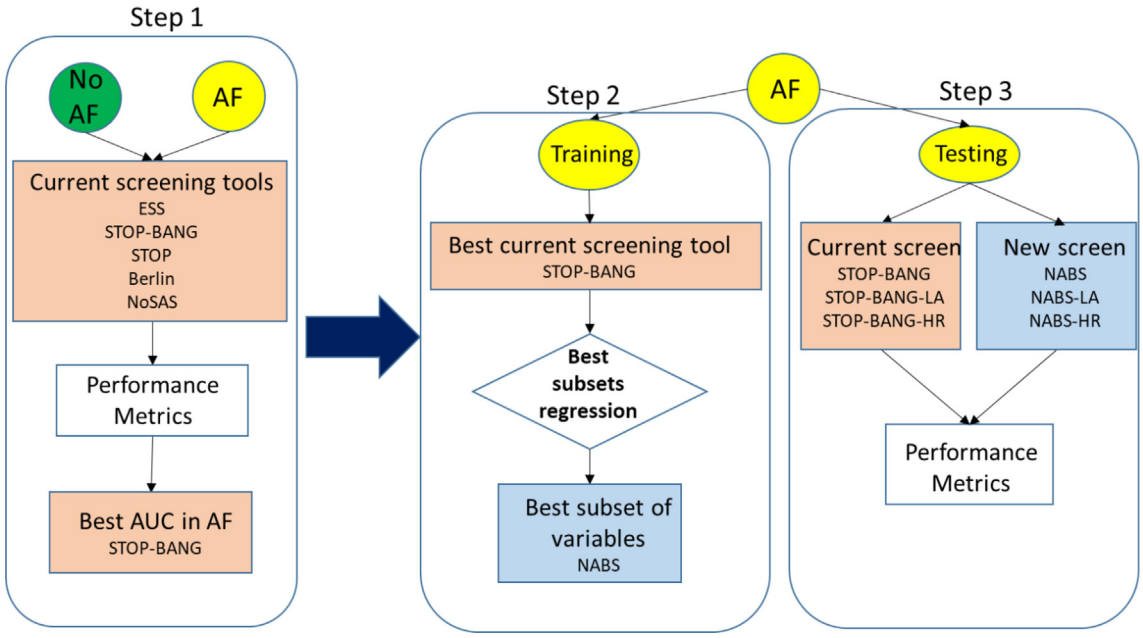

Fig. 2. Statistical methods. Step 1 – evaluate the currently available sleep apnea screening tests in atrial fibrillation and non-atrial fibrillation groups and compare performance metrics. Find the best-performing test according to AUSC in the AF group. Step 2. Split atrial fibrillation group into testing and training. Perform best subsets regression on the training subset to find a better screening test for those with atrial fibrillation. Step 3. Evaluate performance metrics in the new and current best-in-atrial-fibrillation screening test. Evaluate performance metrics if heart rate or left atrial volume are added to the model.

sensitivity, specificity, positive predictive value, negative predictive value were examined to evaluate logistic model performance. Bootstrapping was used to estimate 95% confidence intervals for performance characteristics in the validation dataset and test for significant AUC difference between instruments. Hypotheses of association were evaluated using a two-sided significance level of $\alpha = 0.05$. All analyses were conducted using R software version 3.4.3 (R Core Development Team, Vienna, Austria) [33].

3. Results

3.1. Study population

Table 1 reports the baseline characteristics of the cohort. The 300 participants in the overall cohort were 61.4 ± 11.9 years old and 83.6% Caucasian with a BMI of 31.4 ± 6.7 kg/m^2 and AHI of 11.8 (IQR 3.8 – 24.5). In the PAF group (n = 150), 69 (46.0%) had an AHI $\geq$ 15 and 104 (69.3%) had an AHI $\geq$ 5. The age, sex, race, and BMI-matched control group (n = 150), had similar prevalence of SA when defined both by AHI $\geq$ 15 (43.3%) and AHI $\geq$ 5 (68.0%). Participants in the AF group had a lower heart rate and larger left atrial volume and were more likely to have been prescribed beta-blockers and calcium channel blockers. Comorbidities were evenly balanced across groups.

3.2. Established screening tool performance in AF cases and controls

Screening tools were evaluated using the whole cohort (i.e., not split into training and validation datasets) to understand performance of current tools in patients with and without AF. All except the STOP and STOP-BANG screening instruments performed worse based on AUC in the PAF group compared to controls (Table 2, **Supplementary Fig. S1**). At a threshold of AHI $\geq$ 15, the STOP-BANG instrument performed best overall in PAF participants (AUC = 0.75, 95% CI: 0.68–0.85), while the NoSAS had the best overall performance in controls (AUC = 0.79, 95% CI: 0.72–0.86). The Epworth Sleepiness Scale performed no better than chance in both groups. Overall, performance of common screening instruments was significantly less robust in both AF and controls compared to reported screening tool characteristics [21,23,27–30].

3.3. Optimizing prediction models in AF cases

The AF cohort was split into training and validation datasets. All measures reported are based on performance in the validation dataset. A continuous model utilizing neck circumference, age, BMI, and snoring (NABS) had the lowest prediction error of the best subset models and is specified below for AHI $\geq$ 15 (see also **Supplement** for further description):

Log odds (SA) = −12.6645 + 0.1380 (BMI) + 0.0664 (Age) + 0.0876 (Neck Circumference) + 0.6613 (Snoring)

In the validation dataset, NABS predictors performed better than STOP-BANG at both the AHI $\geq$ 15 (NABS AUC = 0.88, 95% CI: 0.76–0.96 vs. STOP-BANG AUC = 0.81, 95% CI: 0.64–0.91) and AHI $\geq$ 5 (NABS AUC = 0.82, 95% CI: 0.68–0.92 vs. STOP-BANG AUC = 0.73, 95% CI: 0.55–0.87) thresholds (Table 3, **Supplementary Figs. S2 and S3**). The NABS AUC significantly improved upon STOP-BANG performance for AHI $\geq$ 5 (p = 0.04) but not AHI $\geq$ 15 (p = 0.10).

3.4. Predictive utility of physiologic variables for sleep apnea screening in AF cases

There was a decrement in screening prediction in the validation dataset with addition of heart rate or left atrial volume in all models (Table 3, **Supplementary Figs. S2 and S3**).

4. Discussion

In this matched case-control study, SA was common in both people with PAF and their matched controls. Standard SA screening performed poorly in AF. Performance measures were substantially improved for both the AHI $\geq$ 15 and AHI $\geq$ 5 models in the AF group with use of the NABS model. We considered SA more likely

Table 1
Baseline characteristics†

Characteristic	n	Overall (n = 300)	PAF (n = 150)	Control (n = 150)	p-value
Age (years)	300	61.42 ± 11.91	61.28 ± 12.11	61.55 ± 11.75	0.84
Non-white race	299	49 (16.4%)	24 (16.0%)	25 (16.8%)	0.98
Male gender	300	190 (63.3%)	95 (63.3%)	95 (63.3%)	>0.99
BMI (kg/m^2)	300	31.38 ± 6.68	31.20 ± 6.62	31.57 ± 6.76	0.63
Heart rate (bpm)	299	66.87 ± 10.46	64.99 ± 10.19	68.76 ± 10.41	0.002
Apnea-hypopnea index	300	11.80 [3.77, 24.50]	10.60 [3.62, 23.38]	12.70 [3.90, 24.50]	0.33
AHI ≥ 15	300	134 (44.7%)	65 (43.3%)	69 (46.0%)	0.73
AHI ≥ 5	300	206 (68.7%)	102 (68.0%)	104 (69.3%)	0.90
Central sleep apnea†	300	16 (7.8%)	7 (6.9%)	9 (8.7%)	0.83
Neck circumference (cm)	299	39.3 ± 4.5	39.2 ± 4.3	39.4 ± 4.8	0.77
Epworth sleepiness score	299	7.9 ± 4.3	7.5 ± 4.3	8.3 ± 4.3	0.12
STOP-BANG score	300	3.4 ± 1.4	3.5 ± 1.4	3.4 ± 1.5	0.91
STOP score	300	1.9 ± 1.0	1.9 ± 1.0	1.9 ± 1.0	0.58
NoSAS score	300	10.9 ± 4.1	10.8 ± 4.1	11.0 ± 4.0	0.64
Berlin categories positive	300	1.6 ± 0.8	1.6 ± 0.8	1.6 ± 0.9	>0.99
Left atrial volume	284	59.9 [46.9, 75.0]	64.2 [48.9, 77.4]	56.2 [45.1, 70.0]	0.006
Ever smoker	300	159 (53.0%)	81 (54.0%)	78 (52.0%)	0.82
Days per week alcohol consumed	300	1.8 ± 2.0	1.7 ± 2.0	1.9 ± 2.1	0.21
Largest number alcoholic drinks consumed	300	1.2 ± 1.0	1.1 ± 1.0	1.2 ± 1.0	0.36
Comorbidities					
Asthma	293	39 (13.3%)	19 (13.0%)	20 (13.6%)	>0.99
COPD	293	23 (8.0%)	13 (8.8%)	10 (7.1%)	0.75
Myocardial infarction	293	25 (8.5%)	9 (6.0%)	16 (11.1%)	0.18
Hypertension	292	166 (56.8%)	87 (60.0%)	79 (53.7%)	0.34
Hypercholesterolemia	292	177 (61.0%)	86 (60.1%)	91 (61.9%)	0.85
Stroke	298	7 (2.3%)	5 (3.3%)	2 (1.4%)	0.46
Medication use					
Beta-blocker	300	120 (40.0%)	85 (56.7%)	35 (23.3%)	<0.001
Calcium channel blocker	300	28 (9.3%)	20 (13.3%)	8 (5.3%)	0.03
Antihypertensives	300	156 (52.9%)	80 (54.4%)	76 (51.4%)	0.68
Antilipidemics	300	140 (47.9%)	65 (44.8%)	75 (51.0%)	0.35
Antidiabetic	300	36 (12.2%)	17 (11.5%)	19 (12.9%)	0.84

AHI = apnea-hypopnea index; BMI = body mass index; bpm = beats per minute; COPD = chronic obstructive pulmonary disease; NoSAS = 5-item screening score assessing neck circumference, body mass index, snoring, age, and male gender; PAF = paroxysmal atrial fibrillation; SMD = standardized mean difference; STOP = 4-item screening with 1 point each for snoring, tired, observed apnea, and hypertension; STOP-BANG = 8 item screening with 1 point for each item for snoring, tired, observed apnea, hypertension, BMI > 35 kg/m^2, age > 50 years, neck circumference > 40 cm, and male gender.
†Statistics presented as Mean ± SD, Median [2th percentile, 75th percentile], or N(%).

Table 2
Performance characteristics of common OSA screening measures for AHI ≥ 15 in atrial fibrillation and matched controls (n = 150 for both AF and control groups).

OSA screening tool	Sensitivity†	Specificity†	PPV†	NPV†	AUC
Atrial fibrillation cohort					
ESS†	25 (15–37)	74 (63–83)	42 (26–59)	56 (47–66)	0.50 (0.42–0.60)
STOP-BANG	89 (79–96)	42 (32–54)	54 (44–64)	84 (69–93)	0.75 (0.66–0.86)
STOP	74 (61–84)	44 (33–55)	50 (40–60)	69 (54–80)	0.65 (0.56–0.73)
Berlin	72 (60–83)	58 (46–68)	57 (45–67)	73 (61–83)	0.64 (0.52–0.75)
NoSAS	91 (81–97)	38 (27–49)	53 (43–62)	84 (69–94)	0.74 (0.67–0.80)
Control cohort					
ESS	32 (21, 44)	81 (71, 89)	59 (42, 75)	58 (48, 67)	0.57 (0.49–0.68)
STOP-BANG	93 (84, 98)	42 (31, 53)	58 (48, 67)	87 (73, 96)	0.75 (0.69–0.83)
STOP	77 (65, 86)	48 (37, 60)	56 (45, 66)	71 (57, 82)	0.62 (0.53–0.71)
Berlin	75 (64, 85)	62 (50, 72)	63 (51, 73)	75 (63, 84)	0.70 (0.63–0.80)
NoSAS	97 (90, 100)	41 (30, 52)	58 (49, 67)	94 (81, 99)	0.79 (0.72–0.86)

†percent, 95% confidence interval; sensitivity, specificity, PPV, NPV were calculated from the following cutoffs for positive screen: ESS ≥ 11, STOP ≥ 2, STOP-BANG ≥ 3 Berlin ≥ 2 areas positive, NoSAS ≥ 8.
AUC = area under the curve of receiver operating characteristic curve; ESS = Epworth Sleepiness Score; NPV = negative predictive value; PPV = positive predictive value; STOP = 4 point scale on snoring; daytime fatigue; observed apneas; and hypertension; STOP-BANG = 8 binary questions on snoring; daytime fatigue; observed apneas; hypertension; BMI; age; neck circumference; and gender.

Table 3
Performance characteristics of novel models in the validation paroxysmal atrial fibrillation cohort (n = 50) for AHI ≥ 15 and AHI ≥ 5.

Model	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (95%CI)
AHI ≥ 15					
STOP-BANG†	70 (46, 88)	77 (58, 90)	67 (43, 85)	79 (60, 92)	0.81 (0.64, 0.91)
STOP-BANG HR†	45 (23, 68)	80 (61, 92)	60 (32, 84)	69 (51, 83)	0.74 (0.59, 0.86)
STOP-BANG LA†	55 (32, 77)	89 (71, 98)	79 (49, 95)	73 (54, 87)	0.79 (0.63, 0.9)
NABS	65 (41, 85)	93 (78, 99)	87 (60, 98)	80 (63, 92)	0.88 (0.76, 0.96)
NABS-HR	70 (46, 88)	83 (65, 94)	74 (49, 91)	81 (63, 93)	0.85 (0.73, 0.93)
NABS-LA	60 (36, 81)	89 (71, 98)	74 (49, 91)	81 (63, 93)	0.84 (0.69, 0.93)
AHI ≥ 5					
STOP-BANG	97 (84, 100)	6 (0, 27)	65 (49, 78)	50 (1, 99)	0.73 (0.55, 0.87)
STOP-BANG HR	84 (67, 95)	11 (1, 35)	63 (47, 77)	29 (4, 71)	0.64 (0.49, 0.8)
STOP-BANG LA	94 (79, 99)	27 (8, 55)	73 (57, 86)	67 (22, 96)	0.64 (0.5, 0.81)
NABS	97 (84, 100)	44 (22, 69)	76 (60, 88)	89 (52, 100)	0.82 (0.68, 0.92)
NABS-HR	94 (79, 99)	28 (10, 53)	70 (54, 83)	71 (29, 96)	0.77 (0.62, 0.88)
NABS-LA	97 (84, 100)	27 (8, 55)	74 (49, 91)	81 (63, 93)	0.79 (0.61, 0.89)

† STOP-BANG model predictor values were re-estimated using training dataset.
AUC = area under the receiver operating characteristic curve; NABS = continuous variables for neck circumference; age; body mass index; and snoring; NABS-HR = NABS score with continuous variable for heart rate; NABS-LA = NABS with continuous variables for left atrial volume; NPV = negative predictive value; PPV = positive predictive value; STOP-BANG = an OSA screening instrument of 8 dichotomous questions; STOP-BANG HR = STOP-BANG score with added continuous variable for heart rate; STOP-BANG LA = STOP-BANG score with continuous variable for left atrial volume.

in those with poor AF control as evidenced by higher heart rate and left atrial volume since previous studies suggest untreated SA can aggravate AF pharmacologic control and progression.[9,34] However, addition of variables associated with AF rate control and cardiac structure – i.e. heart rate and left atrial volume – did not improve performance. Utility of heart rate was perhaps not apparent due to AV-nodal blockade medication usage in AF as evidenced by decreased heart rate in those with AF compared to controls. Left atrial volume can be affected by several disorders (e.g., AF, heart failure, coronary artery disease) and may, therefore, not be sufficiently specific to improve screening performance.

The NABS model - a simplified, short-item screening instrument consisting of neck circumference, age, BMI, and snoring – improved screening accuracy for SA over existing questionnaires. Reduced screening tool performance in the AF population may be a problem of the feature set rather than poorly calibrated parameter estimates of the variable set in the current screening tools. Age and BMI are well-known risk factors for SA and AF. SA prevalence steadily increases with age [35,36]. Even modest improvements in weight decrease the AHI [37]. Neck circumference and snoring are oft-used clinical surrogates for a collapsible upper airway. Breathing disturbances are further exacerbated by rostral fluid shifts throughout the night leading to neck edema as occurs in cardiac disease [38]. Sex does not seem to be a substantial predictor of SA in the AF population, which is unanticipated. It is possible that the pathophysiology of AF and SA share common factors. NoSAS, which has not been tested in the AF or high SA-prevalence populations, is similar to the NABS instrument developed in our current work, but additionally includes sex [27,28]. However, NoSAS performs worse in this PAF cohort than the NABS, which indicates that including sex does not improve, but rather worsens, model performance. It is possible that in other populations inclusion of sex would improve screening tool performance. Therefore, validation studies in other AF cohorts are needed to evaluate the NABS screening tool.

This study highlights the need to evaluate SA screening tools in various clinical populations and improve SA screening methods in those with cardiovascular disease. Previous work has identified a lack of "classic" symptoms including sleepiness and snoring in those with cardiovascular disease [39–42]. Our findings of worse SA screening tool performance in the AF group compared to controls is consistent with previous findings [3,43]. Once an SA screening tool with adequate performance measures is validated, it would presumably be incorporated into practice. Given that 20–80% of those with AF have SA and SA portends worse AF control [44], integration into clinical practice may be operationalized by using electronic medical record systems. Within the electronic medical system, screening tools can be incorporated to be automatically calculated as long as the input variables are available. To aid in SA diagnosis and reduce provider burden, this tool may be integrated into decision/knowledge support systems in the electronic medical record. This integration would assist with identification of high SA risk and even offer appropriate next steps (i.e., referral to a sleep medicine clinic for testing) for the provider to order if they see fit. This type of implementation may be particularly effective in primary care and cardiology clinics.

Several study strengths and limitations are worth noting. This current study specifically systematically enrolled individuals with PAF and matched controls, which allows for evaluation of current SA screening tools in these two populations. Furthermore, data included in several common SA screening questionnaires were collected, enabling us to simultaneously test several screening strategies. Cardiac structure and function were evaluated by echocardiography allowing assessment of SA-related anatomic remodeling impact in AF. There are also several limitations. Only those with PAF were enrolled and, therefore, may not be generalizable to persistent, longstanding persistent, or permanent forms of AF. Participants were clinically stable with well-controlled heart rates secondary to beta-blocker and calcium channel blocker use, which may belie the utility of heart rate. The limited sample size

may preclude a more granular assessment of potentially important predictors of SA in this population. The control group, while without AF, had a high proportion of underlying cardiovascular risk or disease and may not be reflective of the primary care population. Despite this, standard SA screening instruments did not perform as well in those with PAF compared to the control group.

Current SA screening instruments have suboptimal performance in people with AF. Using a model with fewer continuous variables derived from the STOP-BANG screening improved SA screening in patients with PAF. Study findings should be broadened by examining a population with a spectrum of AF subtypes, i.e. persistent, longstanding persistent, and permanent AF. External validation of this novel screening tool in larger cohorts is necessary before implementation in clinical practice. Future work may be more globally relevant if machine learning algorithms are applied to populations not well characterized by standard SA screening tools (e.g., heart failure, stroke) to integrate novel combinations and multiple patient characteristics or endophenotypes (e.g., physiologic variables, demographics, anthropometry) to improve accuracy of SA screening.

5. Conclusions

Commonly used screening instruments for SA (e.g., Berlin and STOP-BANG) perform suboptimally in the PAF population. An abbreviated screening, NABS, including neck circumference, age, BMI, and snoring improves on the performance of standard SA screening tools in AF participants.

CRediT authorship contribution statement

Anna M. May: Formal analysis, Resources, Funding acquisition, Visualization. **Lu Wang:** Formal analysis. **Deborah H. Kwon:** Validation. **David R. Van Wagoner:** Methodology, Investigation, Resources. **Mina K. Chung:** Validation. **Jarrod E. Dalton:** Validation, Supervision. **Reena Mehra:** Conceptualization, Methodology, Investigation, Project administration, Funding acquisition, Supervision.

Declaration of Competing Interest

AM consulted for Jazz Pharmaceuticals. RM received funds from the American Board of Medicine Sleep Medicine Exam test writing committee and royalties from UpToDate.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2020.100624.

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