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ORIGINAL RESEARCH

# Association Between Sleep Apnea Treatment and Health Care Resource Use in Patients With Atrial Fibrillation

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**BACKGROUND:** Obstructive sleep apnea (OSA) contributes to the generation, recurrence, and perpetuation of atrial fibrillation, and it is associated with worse outcomes. Little is known about the economic impact of OSA therapy in atrial fibrillation. This retrospective cohort study assessed the impact of positive airway pressure (PAP) therapy adherence on health care resource use and costs in patients with OSA and atrial fibrillation.

**METHODS AND RESULTS:** Insurance claims data for  $\geq 1$  year before sleep testing and 2 years after device setup were linked with objective PAP therapy use data. PAP adherence was defined from an extension of the US Medicare 90-day definition. Inverse probability of treatment weighting was used to create covariate-balanced PAP adherence groups to mitigate confounding. Of 5867 patients (32% women; mean age, 62.7 years), 41% were adherent, 38% were intermediate, and 21% were nonadherent. Mean $\pm$ SD number of all-cause emergency department visits (0.61 $\pm$ 1.21 versus 0.77 $\pm$ 1.55 [ $P=0.023$ ] versus 0.95 $\pm$ 1.90 [ $P<0.001$ ]), all-cause hospitalizations (0.19 $\pm$ 0.69 versus 0.24 $\pm$ 0.72 [ $P=0.002$ ] versus 0.34 $\pm$ 1.16 [ $P<0.001$ ]), and cardiac-related hospitalizations (0.06 $\pm$ 0.26 versus 0.09 $\pm$ 0.41 [ $P=0.023$ ] versus 0.10 $\pm$ 0.44 [ $P=0.004$ ]) were significantly lower in adherent versus intermediate and nonadherent patients, as were all-cause inpatient costs (\$2200 $\pm$ \$8054 versus \$3274 $\pm$ \$12 065 [ $P=0.002$ ] versus \$4483 $\pm$ \$16 499 [ $P<0.001$ ]). All-cause emergency department costs were significantly lower in adherent and intermediate versus nonadherent patients (\$499 $\pm$ \$1229 and \$563 $\pm$ \$1292 versus \$691 $\pm$ \$1652 [ $P<0.001$  and  $P=0.002$ ], respectively).

**CONCLUSIONS:** These data suggest clinical and economic benefits of PAP therapy in patients with concomitant OSA and atrial fibrillation. This supports the value of diagnosing and managing OSA and highlights the need for strategies to enhance PAP adherence in this population.

**Key Words:** adherence ■ atrial fibrillation ■ health care resource use ■ obstructive sleep apnea ■ positive airway pressure

Obstructive sleep apnea (OSA) is a common chronic condition, with a recent study estimating a prevalence of nearly 1 billion adults aged 30 to 69 years around the world.<sup>1,2</sup> In the United States, moderate-to-severe OSA is estimated to affect 14.5% of the general population, although most people with OSA are undiagnosed.<sup>3</sup> OSA is particularly common

in patients with cardiovascular disease.<sup>4</sup> An estimated 32% to 63% of patients with atrial fibrillation (AF) also have OSA, and undiagnosed OSA is highly prevalent in patients hospitalized with AF.<sup>5-7</sup>

Although OSA is common, it has variable overt symptoms, which limits the accuracy and sensitivity of screening questionnaires for identifying OSA in

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## CLINICAL PERSPECTIVE

### What Is New?

- Adherence to positive airway pressure therapy for patients with obstructive sleep apnea and atrial fibrillation was associated with significantly lower numbers of emergency department visits and all-cause hospitalizations (and associated costs), compared with nonadherence or intermediate levels of adherence.

### What Are the Clinical Implications?

- Strategies to detect and treat obstructive sleep apnea in patients with atrial fibrillation are warranted.

## Nonstandard Abbreviations and Acronyms

|             |  |
|-------------|--|
| <b>CMS</b>  | Centers for Medicare & Medicaid Services   |
| <b>HCRU</b> | health care resource use                   |
| <b>IPTW</b> | inverse probability of treatment weighting |
| <b>PAP</b>  | positive airway pressure                   |
| <b>SMD</b>  | standardized mean difference               |

patients with AF.<sup>5</sup> In this patient group, OSA has been associated with major cardiovascular and neurologic events, and it is a major predictor of thromboembolic events.<sup>8</sup> In the ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation), patients with AF who also had OSA were at higher risk of hospitalization during follow-up than those without OSA.<sup>9</sup>

OSA and AF share several risk factors, and studies suggest that OSA may play a causal role in the generation and perpetuation of AF via several mechanisms.<sup>10–12</sup> These mechanisms may be short-term, with individual obstructive respiratory events during sleep triggering arrhythmia.<sup>13</sup> Alternatively, long-term exposure to OSA may contribute to a vulnerability of the atrial substrate by fibrosis and structural remodeling, thus lowering the threshold for atrial arrhythmic events and contributing to chronic and progressive AF.<sup>14</sup>

Numerous observational studies and several meta-analyses suggest that OSA increases the risk of recurrent AF after cardioversion and catheter ablation procedures,<sup>15,16</sup> a risk that appears to be mitigated by effective treatment of OSA with positive airway pressure (PAP).<sup>17,18</sup> However, the question of whether treating OSA can reduce the burden of AF is unclear because of a lack of robust evidence from randomized controlled trials. Only 2 small randomized controlled trials have assessed the impact of PAP treatment for OSA in isolation on AF burden, and neither demonstrated a

reduction in AF recurrence.<sup>19,20</sup> Furthermore, evidence for the impact of effective OSA treatment on AF burden outside the setting of ablation is scarce.<sup>9,21</sup> However, some randomized studies have used strict inclusion/exclusion criteria, enrolling only highly selected patients, which limits generalizability. Therefore, there is a need for observational studies and real-world evidence with greater generalizability to the clinical practice setting. As PAP requires consistent use to be effective, it is also possible that some benefits may only become apparent over time. Therefore, the aim of this study was to estimate the population level association between long-term PAP therapy adherence and health care outcomes and costs in patients with AF and OSA in a real-world setting. We hypothesized that patients who adhered to PAP therapy would demonstrate better outcomes than those who did not.

## METHODS

### Data Source

This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.<sup>22</sup> This retrospective observational analysis was conducted using deidentified payer-sourced administrative medical and pharmacy claims data from >100 US commercial, Medicare Advantage, and Medicaid health plans (Inovalon Insights LLC, Bowling, MD), linked with patient PAP use data from cloud-connected devices (via AirView™; ResMed Corp, San Diego, CA). Claims information included details about health care encounters, prescription fills, and diagnosis and procedure codes. Objective PAP data collected in AirView™ include treatment use, clinical therapy metrics, and residual respiratory events.<sup>23–25</sup> Data were linked through a tokenized process, and the resulting database underwent Health Insurance Portability and Accountability Act expert determination to ensure compliance with patient privacy. The study was reviewed by Advarra Institutional Review Board (reference: Pro0004005) and deemed to be exempt from oversight. Because of the retrospective nature of this study, informed consent from participants was not required. The methods (eg, program code) that support the findings of this study are available from the corresponding author on reasonable request.

### Selection Criteria

The target population was patients with AF who were newly diagnosed with OSA and treated with PAP therapy. Patients were eligible for inclusion if they had a new OSA diagnosis within 60 days of a sleep test, received PAP therapy using an AirSense™ 10 device, and had at least 1 year of claims data before sleep test,

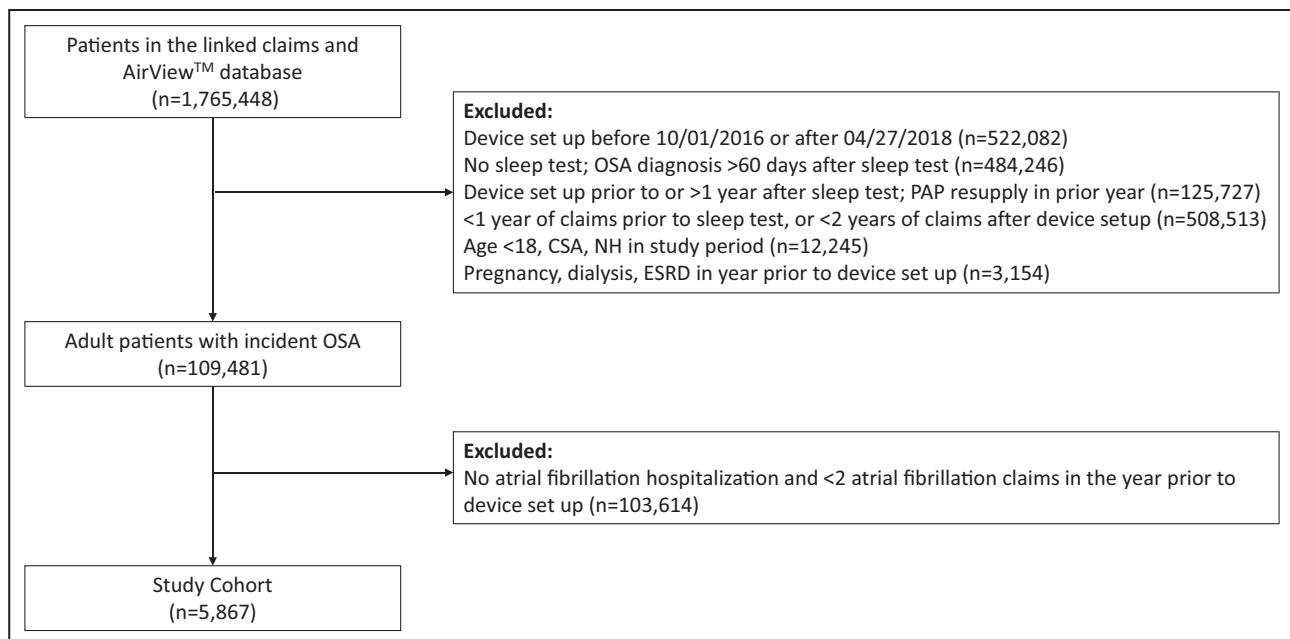
and 2 years of claims data after device setup. This time frame was selected to allow for assessment of comorbidities and health care resource use (HCRU) before initiation of PAP, and to ensure that all patients had 2 years of follow up to assess outcomes. Because the *International Classification of Diseases, Ninth Revision (ICD-9)* codes did not differentiate between types of AF, device setup date had to be between October 1, 2016, and April 27, 2018, to allow for the use of *International Classification of Diseases, Tenth Revision (ICD-10)*, codes throughout the entire study time frame. Eligible patients with AF before device setup were identified on the basis of the presence of at least 2 claims with an *ICD-10* diagnosis of AF (I48.0, I48.1x, I48.2x, or I48.91) or at least 1 hospitalization with an AF code. Patients were excluded if claims in the year before device setup had evidence of PAP resupply, or if they had diagnoses of pregnancy (O00.x–O9A.x), dialysis (Z99.2), or end-stage renal disease (N18.6). Patients who were aged <18 years or those with diagnoses of central sleep apnea (G47.31 or G47.37) or nocturnal hypoventilation (G47.36) at any point during the study period were also excluded (Figure). Receipt of an AirSense™ 10 device was gleaned from device data; all other selection criteria were based on information from claims data.

## Variables of Interest

Outcomes of interest were the numbers of all-cause hospitalizations, emergency department and physician visits, and costs (US\$) in the first and second years

after PAP initiation, to assess the long-term effects of PAP therapy. Costs were based on proxy financials provided by Inovalon Insights LLC, from its proprietary Proxy Financials algorithm, based on the Centers for Medicare & Medicaid Services (CMS) Medicare prospective payment system fee schedules.<sup>26,27</sup> The following cost categories were examined: all-cause inpatient, all-cause outpatient, all-cause emergency department, and total costs (both inclusive and exclusive of OSA-related costs). In the year before PAP device setup, OSA-related costs were those for a sleep test, whereas in the years after device setup, OSA-related costs were those for equipment and supplies (eg, masks and hoses). Secondary outcomes of cardiac- and AF-related hospitalizations and emergency department visits were also examined. Cardiac-related encounters were those with a circulatory system major diagnostic category code and a cardiac primary *ICD-10* diagnosis code (I02–I52), whereas AF-related encounters were those where AF or atrial flutter (*ICD-10*: I48.3x) was the associated primary diagnosis code. Atrial flutter was included for completeness in identifying AF-related encounters, because of the similarities between the conditions and the possibility of an encounter mistakenly listing a primary diagnosis code of atrial flutter instead of AF. All outcomes were defined using claims data.

The primary predictor of interest was long-term adherence to PAP therapy, objectively defined directly from device data. Adherence to PAP therapy in the 2 years after device setup was defined on the basis



**Figure.** Cohort selection criteria.

CSA indicates central sleep apnea; ESRD, end-stage renal disease; NH, nocturnal hypoventilation; OSA, obstructive sleep apnea; and PAP, positive airway pressure.

of an extension of the CMS criteria for 90-day compliance, as previously described.<sup>28–31</sup> CMS considers a patient compliant if he/she has PAP device use of  $\geq 4$  hours/night for  $\geq 70\%$  of nights in a 30-day period within a 90-day window. Those who met these criteria in all 8, 1 to 7, or 0 of the follow-up quarters were defined as being adherent, intermediate, and nonadherent to PAP therapy, respectively.

Covariates included demographics (age at setup, sex, payer, and body mass index), comorbidities (hyperlipidemia, hypertension, gastroesophageal reflux disease, type 2 diabetes, cerebrovascular disease, cancer, anxiety, depression, psychotic disorders, other mood disorders, asthma, chronic obstructive pulmonary disease, pneumonia, coronary artery disease, heart failure, and other arrhythmia, defined on the basis of codes in the claims in the prior year) (Table S1), type of AF, CHA<sub>2</sub>DS<sub>2</sub>-VASc (congestive heart failure, hypertension, age  $\geq 75$  years, clinical history of diabetes, prior stroke/transient ischemic attack/thromboembolism, vascular disease, age 65–74 years, sex [female category]) score,<sup>32</sup> AF medication (antiarrhythmics [class IC and class III], atrioventricular nodal blocking agents [ $\beta$ -blockers, calcium channel blockers, and digoxin], and oral anticoagulants), and prior year hospitalization and number of emergency department visits. Prior year HCRU was included as covariate to account for regression to the mean and the correlation between baseline values and changes at follow-up.<sup>33,34</sup> For patients being treated with oral anticoagulants ( $\geq 1$  prescription fill within 180–360 days before PAP setup), medication adherence was defined as a proportion of days covered  $\geq 80\%$  and was used as a proxy for healthy behaviors, to control for a potential healthy user bias. All covariates were defined from claims data.

## Statistical Analysis

All analyses were conducted using R statistical software, version 4.0.3.<sup>35</sup> The primary objective of the analysis was to assess differences in posttreatment trajectory for patients, based on PAP adherence. We sought to understand whether patients who adhered to PAP therapy had better outcomes over time than they otherwise would have if they had not been adherent to PAP. Baseline covariates were compared between adherence groups using the Kruskal-Wallis test for continuous variables and the  $\chi^2$  test for categorical variables. Multinomial logistic regression was used to determine independent predictors of nonadherence or intermediate adherence to PAP therapy, compared with adherence, using all covariates. Covariates with a  $P \geq 0.1$  for both comparisons were removed from the final model.

Propensity scores estimating the likelihood of being in each adherence group, based on baseline

characteristics and prior year HCRU, were calculated using the PSweight package in R.<sup>36</sup> To mitigate the effects of confounding, inverse probability of treatment weighting (IPTW) was applied to the cohort, and those with extreme weights were trimmed ( $n=19$ ). Patients were trimmed if their propensity score for being in any adherence group was smaller than 0.067, based on a multinomial extension of the Crump trimming method for  $>2$  treatment groups.<sup>37</sup> IPTW weights the cohort so that the distribution of covariates is balanced across adherence groups, mirroring the distribution in the overall cohort.<sup>38</sup> This allows for direct comparison of outcomes after device setup, while accounting for measured differences across groups before PAP device setup, including prior year HCRU. IPTW analysis yields an estimation of the average treatment effect, which can be interpreted as the effect we would expect to see if the entire cohort had been adherent, compared with intermediate or nonadherent. Covariates that are balanced at baseline after IPTW are unlikely to drive differences in outcomes. The quality of balance was assessed using the standardized mean difference (SMD), where an SMD value of  $<0.1$  indicates good balance. Pairwise differences in resource use during the first and second years after PAP setup were assessed using weighted Wilcoxon rank-sum tests, with the survey package in R.<sup>39</sup>

A sensitivity analysis was conducted in the subset of patients who were either adherent or nonadherent using propensity score matching. First, a logistic regression model based on risk of not adhering to PAP therapy was developed using baseline covariates. Model coefficients were used to calculate a propensity score that was used in greedy matching. In addition, exact matching was performed on the following variables: age group, sex, payer, CHA<sub>2</sub>DS<sub>2</sub>-VASc score ( $\leq 2$ , 3, or  $\geq 4$ ), prior year all-cause hospitalization (yes or no), and number of prior year emergency department visits (0, 1, 2, 3–4, or  $\geq 5$ ). An additional sensitivity analysis was conducted to examine the changes over time in significant outcomes from the main analysis, excluding prior year HCRU from the covariates used for IPTW. Trajectories from the year before PAP initiation to the first and second years after PAP initiation were compared across adherence groups by examining the interaction between time and adherence. All comparative analyses of outcomes were conducted in cohorts that had been adjusted for differences at baseline (either through IPTW or propensity score matching).

## RESULTS

### Study Population

There were 5867 patients included in the analysis (32% women; mean age, 62.7 years), of whom 41% were



adherent, 38% were intermediately adherent, and 21% were nonadherent (Table 1). Other comorbidities were common, particularly hypertension (85.1%) and hyperlipidemia (71.9%). Paroxysmal AF was present in 43.8% of patients, and 37.5% had a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 4$  (Table 1). Medication prescription information was available for 4621 patients (78.8%). Of these, 73.8% were using atrioventricular nodal blockers, 55.0% were using oral anticoagulants, and 29.9% were using antiarrhythmic drug therapy (Table 1).

Adherent patients were significantly more likely to be older, have commercial insurance, and have fewer comorbid conditions (Table 1). For those receiving oral anticoagulants, there was a significant positive association between medication adherence and PAP adherence (Table 1). Approximately 24% of intermediate patients reached CMS compliance in 1 of the 8 quarters evaluated, and 15% were compliant in 7 of the 8 quarters. The remaining 61% of patients with intermediate adherence were relatively evenly distributed between achieving compliance in 2 to 6 of the 8 quarters.

### Risk Factors for Nonadherence to PAP Therapy

Prominent independent risk factors for being intermediate or nonadherent to PAP therapy included younger age, Medicaid insurance, coronary artery disease, depression, and emergency department visits in the year before PAP initiation. Patients with hypertension, type 2 diabetes, heart failure, or chronic obstructive pulmonary disease were significantly more likely to be nonadherent to PAP therapy and tended to be more likely to have intermediate adherence. Patients with obesity were significantly more likely to be adherent to PAP therapy. Compared with those who were adherent to oral anticoagulants, those who were not adherent to oral anticoagulants were significantly more likely to be nonadherent to PAP (Table 2). After adjusting for all covariates, there was no significant association between adherence and sex, cerebrovascular disease, other arrhythmia, asthma, pneumonia, psychotic disorders, anxiety, other mood disorders, gastroesophageal reflux disease, cancer, type of AF, or CHA<sub>2</sub>DS<sub>2</sub>-VASc score.

### Inverse Probability of Treatment Weighting

After applying IPTW, the 3 adherence groups were well balanced on all baseline characteristics, including prior year HCRU (absolute value of all SMDs  $< 0.1$ ) (Table 3).<sup>40</sup> This indicates that, after weighting, adherence groups looked similar at baseline in terms of all measured variables.

The mean $\pm$ SD number of all-cause emergency department visits in the first year of PAP use was significantly lower in the adherent group (0.61 $\pm$ 1.21)

compared with both the intermediate group (0.77 $\pm$ 1.55;  $P=0.023$ ) and the nonadherent group (0.95 $\pm$ 1.90;  $P<0.001$ ); this was also the case for annual all-cause hospitalizations (0.19 $\pm$ 0.69 versus 0.24 $\pm$ 0.72 [ $P=0.002$ ] versus 0.34 $\pm$ 1.16 [ $P<0.001$ ]). This finding corresponds to 36% lower rate of all-cause emergency department visits (rate ratio [RR], 0.64 [95% CI, 0.59–0.69]) and a 44% lower rate of all-cause hospitalization (RR, 0.56 [95% CI, 0.49–0.64]) in adherent versus nonadherent patients during the first year. Adherent patients also had fewer cardiac-related emergency department visits than nonadherent patients (0.11 $\pm$ 0.41 versus 0.14 $\pm$ 0.52 [ $P=0.057$ ]) and significantly fewer cardiac-related hospitalizations (0.06 $\pm$ 0.26 versus 0.10 $\pm$ 0.44 [ $P=0.004$ ]). AF-related events were rare in the years after PAP initiation, and small numbers precluded analysis and interpretation of these numbers.

All-cause inpatient costs were significantly lower for adherent patients (\$2200 $\pm$ \$8054) compared with intermediate (\$3274 $\pm$ \$12 065;  $P=0.002$ ) and nonadherent patients (\$4483 $\pm$ \$16 499;  $P<0.001$ ). All-cause emergency department costs were significantly lower in adherent versus nonadherent patients (\$499 $\pm$ \$1229 versus \$691 $\pm$ \$1652;  $P<0.001$ ). Patients with intermediate adherence also had significantly lower emergency department costs compared with nonadherent patients (\$563 $\pm$ \$1292;  $P=0.002$ ). When costs related to OSA equipment were excluded, total costs were significantly lower for adherent versus nonadherent patients (\$9171 $\pm$ \$12 219 versus \$11 890 $\pm$ \$19 888;  $P=0.004$ ) (Table 4).

Results in the second year of PAP use were similar, with adherent patients having significantly fewer all-cause hospitalizations compared with nonadherent patients (0.19 $\pm$ 0.58 versus 0.26 $\pm$ 0.79;  $P=0.049$ ), corresponding to a 27% reduction in the risk of hospitalization (RR, 0.73 [95% CI, 0.63–0.84]). Adherent patients also had significantly fewer all-cause emergency department visits than intermediate and nonadherent patients (0.58 $\pm$ 1.18 versus 0.74 $\pm$ 1.51 [ $P<0.001$ ] versus 0.93 $\pm$ 1.76 [ $P<0.001$ ]), corresponding to a 38% risk reduction (RR, 0.62 [95% CI, 0.58–0.67]). The number of cardiac-related encounters was significantly lower for adherent versus nonadherent patients (0.06 $\pm$ 0.28 versus 0.08 $\pm$ 0.36 [ $P=0.011$ ] for cardiac-related hospitalizations; 0.08 $\pm$ 0.33 versus 0.14 $\pm$ 0.49 [ $P=0.005$ ] for cardiac-related emergency department visits).

Adherent versus nonadherent patients had significantly lower all-cause inpatient hospitalization costs (\$2321 $\pm$ \$9353 versus \$3980 $\pm$ \$18 991;  $P=0.049$ ) and all-cause emergency department costs (\$427 $\pm$ \$984 versus \$667 $\pm$ \$1394;  $P<0.001$ ). Total costs (excluding OSA equipment) were significantly lower for adherent patients (\$8224 $\pm$ \$12984) than for intermediate (\$9426 $\pm$ \$15 990;  $P=0.012$ ) or nonadherent (\$10 289 $\pm$ \$21 803;  $P=0.021$ ) patients (Table 4).

**Table 1. Unadjusted Baseline Characteristics of the Study Population, Overall and by Adherence Group**

| Variable                      | Overall (n=5867) | Adherent (n=2400) | Intermediate (n=2231) | Nonadherent (n=1236) | P value* |
|-------------------------------|------------------|-------------------|-----------------------|----------------------|----------|
| Demographics                  |                  |                   |                       |                      |          |
| Female sex, n (%)             | 1878 (32.0)      | 731 (30.5)        | 734 (32.9)            | 413 (33.4)           | 0.101    |
| Age, mean±SD, y               | 62.7±11.2        | 63.0±10.6         | 62.7±11.2             | 61.9±12.2            | 0.023    |
| Age group, n (%)              |                  |                   |                       |                      | <0.001   |
| 18–54y                        | 1272 (21.7)      | 458 (19.1)        | 489 (21.9)            | 325 (26.3)           |          |
| 55–69y                        | 2947 (50.2)      | 1272 (53.0)       | 1089 (48.8)           | 586 (47.4)           |          |
| ≥70y                          | 1648 (28.1)      | 670 (27.9)        | 653 (29.3)            | 325 (26.3)           |          |
| Payer, n (%)                  |                  |                   |                       |                      | <0.001   |
| Commercial                    | 3759 (64.1)      | 1639 (68.3)       | 1402 (62.8)           | 718 (58.1)           |          |
| Medicaid                      | 513 (8.7)        | 108 (4.5)         | 209 (9.4)             | 196 (15.9)           |          |
| Medicare Advantage            | 1595 (27.2)      | 653 (27.2)        | 620 (27.8)            | 322 (26.1)           |          |
| Baseline AHI, mean±SD†        | 22.7±16.1        | 25.6±18.1         | 21.6±14.8             | 19.9±14.1            |          |
| Sleep test, n (%)             |                  |                   |                       |                      | 0.43     |
| HSAT                          | 1974 (33.7)      | 790 (32.9)        | 770 (34.5)            | 414 (33.5)           |          |
| Polysomnography               | 3792 (64.6)      | 1571 (65.5)       | 1416 (63.5)           | 805 (65.1)           |          |
| HSAT and polysomnography      | 101 (1.7)        | 39 (1.6)          | 45 (2.0)              | 17 (1.4)             |          |
| Obesity, n (%)                |                  |                   |                       |                      | 0.1      |
| Morbidly obese                | 1824 (31.1)      | 764 (31.8)        | 663 (29.7)            | 397 (32.1)           |          |
| Obese                         | 1861 (31.7)      | 784 (32.7)        | 708 (31.7)            | 369 (29.9)           |          |
| No listed obesity             | 2182 (37.2)      | 852 (35.5)        | 860 (38.6)            | 470 (38.0)           |          |
| Comorbidities                 |                  |                   |                       |                      |          |
| No. per patient, mean±SD‡     | 2.9±2.1          | 2.6±2.0           | 3.0±2.2               | 3.4±2.3              | <0.001   |
| Cardiac conditions, n (%)     |                  |                   |                       |                      |          |
| Coronary artery disease       | 2316 (39.5)      | 845 (35.2)        | 909 (40.7)            | 562 (45.5)           | <0.001   |
| Heart failure                 | 1742 (29.7)      | 614 (25.6)        | 670 (30.0)            | 458 (37.1)           | <0.001   |
| Cerebrovascular disease       | 835 (14.2)       | 280 (11.7)        | 344 (15.4)            | 211 (17.1)           | <0.001   |
| Other arrhythmia              | 2184 (37.2)      | 881 (36.7)        | 821 (36.8)            | 482 (39.0)           | 0.34     |
| Atrial flutter                | 359 (6.1)        | 169 (7.0)         | 109 (4.9)             | 81 (6.6)             | 0.007    |
| Respiratory conditions, n (%) |                  |                   |                       |                      |          |
| Asthma                        | 958 (16.3)       | 349 (14.5)        | 368 (16.5)            | 241 (19.5)           | <0.001   |
| COPD                          | 1122 (19.1)      | 362 (15.1)        | 439 (19.7)            | 321 (26.0)           | <0.001   |
| Pneumonia                     | 578 (9.9)        | 207 (8.6)         | 223 (10.0)            | 148 (12.0)           | 0.006    |
| Affective conditions, n (%)   |                  |                   |                       |                      |          |
| Psychotic disorders           | 109 (1.9)        | 30 (1.3)          | 43 (1.9)              | 36 (2.9)             | 0.002    |
| Other mood disorders          | 324 (5.5)        | 114 (4.8)         | 136 (6.1)             | 74 (6.0)             | 0.10     |
| Depression                    | 1031 (17.6)      | 334 (13.9)        | 429 (19.2)            | 268 (21.7)           | <0.001   |
| Anxiety                       | 1149 (19.6)      | 392 (16.3)        | 468 (21.0)            | 289 (23.4)           | <0.001   |
| Other conditions, n (%)       |                  |                   |                       |                      |          |
| Type 2 diabetes               | 1962 (33.4)      | 719 (30.0)        | 748 (33.5)            | 495 (40.1)           | <0.001   |
| Hypertension                  | 4990 (85.1)      | 1996 (83.2)       | 1899 (85.1)           | 1095 (88.6)          | <0.001   |
| Hyperlipidemia                | 4217 (71.9)      | 1719 (71.6)       | 1590 (71.3)           | 908 (73.5)           | 0.36     |
| GERD                          | 1873 (31.9)      | 718 (29.9)        | 725 (32.5)            | 430 (34.8)           | 0.009    |
| Cancer                        | 714 (12.2)       | 288 (12.0)        | 282 (12.6)            | 144 (11.7)           | 0.66     |
| No other comorbidity‡         | 592 (10.1)       | 287 (12.0)        | 216 (9.7)             | 89 (7.2)             | <0.001   |
| AF variables                  |                  |                   |                       |                      |          |
| Type of AF, n (%)             |                  |                   |                       |                      | 0.002    |
| Permanent                     | 1572 (26.8)      | 606 (25.3)        | 601 (26.9)            | 365 (29.5)           |          |

(Continued)

**Table 1. Continued**

| Variable  | Overall (n=5867) | Adherent (n=2400) | Intermediate (n=2231) | Nonadherent (n=1236) | P value* |
|---|------------------|-------------------|-----------------------|----------------------|----------|
| Persistent  | 996 (17.0)       | 449 (18.7)        | 346 (15.5)            | 201 (16.3)           |          |
| Paroxysmal  | 2572 (43.8)      | 1077 (44.9)       | 985 (44.2)            | 510 (41.3)           |          |
| Unspecified   | 727 (12.4)       | 268 (11.2)        | 299 (13.4)            | 160 (12.9)           |          |
| CHA <sub>2</sub> DS <sub>2</sub> -VASc score, mean±SD     | 3.0±1.8          | 2.8±1.8           | 3.1±1.8               | 3.3±1.9              | <0.001   |
| CHA <sub>2</sub> DS <sub>2</sub> -VASc score range, n (%) |                  |                   |                       |                      | <0.001   |
| ≤2  | 2532 (43.2)      | 1136 (47.3)       | 939 (42.1)            | 457 (37.0)           |          |
| 3   | 1138 (19.4)      | 485 (20.2)        | 413 (18.5)            | 240 (19.4)           |          |
| ≥4  | 2197 (37.5)      | 779 (32.5)        | 879 (39.4)            | 539 (43.6)           |          |
| Medication combinations, n (%)§                           |                  |                   |                       |                      | 0.54     |
| ANB+AA+OA   | 851 (18.4)       | 352 (18.9)        | 320 (18.2)            | 179 (18.0)           |          |
| ANB+AA  | 304 (6.6)        | 135 (7.2)         | 102 (5.8)             | 67 (6.7)             |          |
| ANB+OA  | 1334 (28.9)      | 526 (28.2)        | 517 (29.4)            | 291 (29.2)           |          |
| AA+OA   | 145 (3.1)        | 67 (3.6)          | 43 (2.4)              | 35 (3.5)             |          |
| AA  | 83 (1.8)         | 35 (1.9)          | 34 (1.9)              | 14 (1.4)             |          |
| ANB   | 921 (19.9)       | 364 (19.5)        | 350 (19.9)            | 207 (20.8)           |          |
| OA  | 213 (4.6)        | 78 (4.2)          | 93 (5.3)              | 42 (4.2)             |          |
| No medication   | 770 (16.7)       | 308 (16.5)        | 300 (17.1)            | 162 (16.3)           |          |
| On AA <sup>§</sup>  | 1383 (29.9)      | 589 (31.6)        | 499 (28.4)            | 295 (29.6)           | 0.10     |
| On ANB <sup>§</sup>                                       | 3410 (73.8)      | 1377 (73.8)       | 1289 (73.3)           | 744 (74.6)           | 0.74     |
| On OA <sup>§</sup>  | 2543 (55.0)      | 1023 (54.9)       | 973 (55.3)            | 547 (54.9)           | 0.95     |
| No medication <sup>§</sup>                                | 770 (16.7)       | 308 (16.5)        | 300 (17.1)            | 162 (16.3)           | 0.84     |
| No prescription data                                      | 1246 (21.2)      | 535 (22.3)        | 472 (21.2)            | 239 (19.3)           | 0.12     |
| Adherence to OA, n (%)                                    |                  |                   |                       |                      | 0.022    |
| Adherent to OA  | 1053 (69.3)      | 417 (72.8)        | 428 (68.8)            | 208 (64.0)           |          |
| Not adherent to OA  | 467 (30.7)       | 156 (27.2)        | 194 (31.2)            | 117 (36.0)           |          |
| Prior year HCRU, mean±SD                                  |                  |                   |                       |                      |          |
| Physician visits  | 12.69±9.49       | 11.45±8.17        | 12.99±9.89            | 14.56±10.73          | <0.001   |
| All-cause emergency department visits                     | 1.12±2.00        | 0.88±1.61         | 1.12±2.00             | 1.57±2.53            | <0.001   |
| All-cause hospitalizations                                | 0.43±0.90        | 0.36±0.79         | 0.42±0.89             | 0.59±1.10            | <0.001   |
| Cardiac-related emergency department visits               | 0.32±0.67        | 0.30±0.60         | 0.28±0.66             | 0.40±0.79            | <0.001   |
| Cardiac-related hospitalizations                          | 0.22±0.53        | 0.19±0.47         | 0.20±0.52             | 0.30±0.64            | <0.001   |
| Costs, \$US   |                  |                   |                       |                      |          |
| Total (including sleep test)                              | 14273±17642      | 13269±16777       | 13709±15757           | 17242±21721          | <0.001   |
| Total (excluding sleep test)                              | 13295±17580      | 12293±16701       | 12719±15698           | 16281±21670          | <0.001   |
| All-cause inpatient                                       | 5472±14569       | 4839±14095        | 4906±12234            | 7722±18589           | <0.001   |
| All-cause outpatient                                      | 3906±6351        | 3928±6274         | 3852±6345             | 3958±6513            | 0.94     |
| All-cause emergency department                            | 849±1809         | 685±1481          | 868±2005              | 1136±1972            | <0.001   |

Values are mean±SD or number (percentage) of patients. AA indicates antiarrhythmic medication; AF, atrial fibrillation; AHI, apnea-hypopnea index; ANB, atrioventricular nodal blocking agent; CHA<sub>2</sub>DS<sub>2</sub>-VASc, congestive heart failure, hypertension, age, diabetes, prior stroke, sex, vascular disease score; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; HCRU, health care resource use; HSAT, home sleep apnea test; and OA, oral anticoagulant.

\*P values based on Kruskal-Wallis tests for continuous variables and  $\chi^2$  tests for categorical variables.

†For patients with a ResMed ApneaLink Air home sleep test (n=408 total; 155 adherent; 153 intermediate; 100 nonadherent).

‡Does not include hyperlipidemia, hypertension, or obesity.

§For patients with medication data available.

||For patients with ≥1 filled prescription for OA within 180 to 360 days before device setup.



**Table 2. Independent Predictors of Intermediate Adherence or Nonadherence, Compared With Adherence**

| Variable                | Adjusted odds ratio (95% CI)* |                          |
|-------------------------|-------------------------------|--------------------------|
|                         | Nonadherent vs adherent       | Intermediate vs adherent |
| Demographics            |                               |                          |
| Age group, y            |                               |                          |
| 18–54                   | 1.0 (Reference)               | 1.0 (Reference)          |
| 55–69                   | 0.60 (0.50–0.73)              | 0.76 (0.65–0.90)         |
| ≥70                     | 0.51 (0.39–0.66)              | 0.77 (0.62–0.96)         |
| Payer                   |                               |                          |
| Commercial              | 1.0 (Reference)               | 1.0 (Reference)          |
| Medicaid                | 2.59 (1.97–3.41)              | 1.83 (1.41–2.37)         |
| Medicare Advantage      | 1.08 (0.87–1.35)              | 1.00 (0.83–1.19)         |
| Obesity                 |                               |                          |
| No listed obesity       | 1.0 (Reference)               | 1.0 (Reference)          |
| Morbidly obese          | 0.60 (0.50–0.72)              | 0.73 (0.62–0.85)         |
| Obese                   | 0.75 (0.63–0.89)              | 0.86 (0.74–0.99)         |
| Cardiac conditions      |                               |                          |
| Coronary artery disease | 1.22 (1.04–1.43)              | 1.18 (1.03–1.35)         |
| Heart failure           | 1.30 (1.10–1.54)              | 1.11 (0.96–1.29)         |
| Respiratory conditions  |                               |                          |
| COPD                    | 1.39 (1.14–1.68)              | 1.17 (0.99–1.38)         |
| Affective conditions    |                               |                          |
| Depression              | 1.26 (1.04–1.52)              | 1.31 (1.11–1.54)         |
| Other conditions        |                               |                          |
| Type 2 diabetes         | 1.33 (1.13–1.56)              | 1.12 (0.97–1.28)         |
| Hypertension            | 1.38 (1.10–1.73)              | 1.12 (0.94–1.33)         |
| Hyperlipidemia          | 0.90 (0.76–1.07)              | 0.88 (0.77–1.02)         |
| AF variables            |                               |                          |
| Medication combinations |                               |                          |
| No medication           | 1.0 (Reference)               | 1.0 (Reference)          |
| ANB+AA+OA               | 0.87 (0.65–1.18)              | 0.79 (0.62–1.02)         |
| ANB+AA                  | 0.91 (0.64–1.31)              | 0.77 (0.56–1.04)         |
| ANB+OA                  | 1.03 (0.78–1.36)              | 0.88 (0.70–1.11)         |
| AA+OA                   | 1.10 (0.68–1.80)              | 0.58 (0.37–0.90)         |
| AA                      | 0.89 (0.46–1.72)              | 1.06 (0.64–1.75)         |
| ANB                     | 1.09 (0.84–1.43)              | 0.99 (0.80–1.23)         |

(Continued)

**Table 2. Continued**

| Variable                                     | Adjusted odds ratio (95% CI)* |                          |
|--|-------------------------------|--------------------------|
|  | Nonadherent vs adherent       | Intermediate vs adherent |
| OA   | 1.15 (0.74–1.81)              | 1.10 (0.77–1.58)         |
| No prescription data                         | 1.02 (0.85–1.22)              | 0.87 (0.76–1.01)         |
| Adherence to OA                              |                               |                          |
| Adherent to OA                               | 1.0 (Reference)               | 1.0 (Reference)          |
| Not adherent to OA                           | 1.39 (1.03–1.89)              | 1.18 (0.91–1.52)         |
| Not on OA                                    | 1.04 (0.81–1.32)              | 0.79 (0.65–0.97)         |
| No prescription data                         | 1.02 (0.85–1.22)              | 0.87 (0.76–1.01)         |
| Prior year HCRU                              |                               |                          |
| At least 1 all-cause hospitalization         | 1.17 (0.99–1.38)              | 0.97 (0.84–1.12)         |
| No. of all-cause emergency department visits |                               |                          |
| 0  | 1 (Reference)                 | 1.0 (Reference)          |
| 1  | 1.17 (0.98–1.39)              | 1.02 (0.89–1.18)         |
| 2  | 1.22 (0.96–1.53)              | 1.00 (0.82–1.21)         |
| 3–4  | 1.55 (1.18–2.02)              | 1.10 (0.86–1.40)         |
| 5–6  | 2.29 (1.35–3.89)              | 1.33 (0.79–2.23)         |
| ≥7   | 3.06 (1.66–5.65)              | 2.22 (1.22–4.02)         |

AA indicates antiarrhythmic medication; AF, atrial fibrillation; ANB, atrioventricular nodal blocking agent; COPD, chronic obstructive pulmonary disease; HCRU, health care resource use; and OA, oral anticoagulant.

\*Adjusted for all variables listed; other covariates removed from final model if  $P \geq 0.1$  for all levels of both comparisons.

### Sensitivity Analyses: Propensity Score Matching and Pre-Post Interaction Analysis

Because of substantial imbalance in the number of Medicaid enrollees across adherence groups, the sensitivity analysis comparing the clearly adherent and nonadherent groups was limited to patients with commercial or Medicare Advantage insurance. After matching, most covariates were well balanced between groups ( $SMD < 0.1$ ), although some minor imbalances remained for a few variables ( $0.1 \leq SMD \leq 0.2$ ) (Table S2). Results were similar to the IPTW analysis, with adherent patients having significantly fewer all-cause and cardiac-related emergency department visits and hospitalizations, and significantly lower all-cause inpatient and emergency department costs in both time frames. Excluding OSA equipment, total costs were significantly lower for adherent versus nonadherent patients (Table S3). Results from the pre-post interaction analysis showed similar trends as seen in the main analysis. Adherent patients had significantly

**Table 3. Baseline Covariates, by Adherence Group, After IPTW**

| Variable                      | Adherence         |                       |                      | SMD*                  |                      |                          |
|-------------------------------|-------------------|-----------------------|----------------------|-----------------------|----------------------|--------------------------|
|                               | Adherent (n=2398) | Intermediate (n=2223) | Nonadherent (n=1227) | Adherent-intermediate | Adherent-nonadherent | Intermediate-nonadherent |
| Demographics                  |                   |                       |                      |                       |                      |                          |
| Female sex, n (%)             | 774 (32.3)        | 711 (32.0)            | 389 (31.7)           | 0.01                  | 0.01                 | 0.01                     |
| Age, mean±SD, y               | 62.8±11.1         | 62.6±11.0             | 62.7±11.8            | 0.02                  | 0.01                 | -0.01                    |
| Age group, n (%)              |                   |                       |                      | 0.01                  | 0.01                 | 0.00                     |
| 18–54y                        | 522 (21.8)        | 479 (21.5)            | 263 (21.4)           |                       |                      |                          |
| 55–69y                        | 1199 (50.0)       | 1119 (50.4)           | 620 (50.6)           |                       |                      |                          |
| ≥70y                          | 677 (28.2)        | 625 (28.1)            | 344 (28.0)           |                       |                      |                          |
| Payer, n (%)                  |                   |                       |                      | 0.02                  | 0.01                 | 0.01                     |
| Commercial                    | 1540 (64.2)       | 1429 (64.3)           | 787 (64.2)           |                       |                      |                          |
| Medicaid                      | 212 (8.9)         | 187 (8.4)             | 106 (8.7)            |                       |                      |                          |
| Medicare Advantage            | 646 (26.9)        | 607 (27.3)            | 334 (27.2)           |                       |                      |                          |
| Sleep test, n (%)             |                   |                       |                      | 0.09                  | 0.10                 | 0.06                     |
| HSAT                          | 750 (31.3)        | 776 (34.9)            | 443 (36.1)           |                       |                      |                          |
| Polysomnography               | 1611 (67.2)       | 1403 (63.1)           | 768 (62.6)           |                       |                      |                          |
| Both                          | 38 (1.6)          | 44 (2.0)              | 15 (1.3)             |                       |                      |                          |
| Obesity, n (%)                |                   |                       |                      | 0.02                  | 0.02                 | 0.00                     |
| Morbidly obese                | 763 (31.8)        | 689 (31.0)            | 379 (30.9)           |                       |                      |                          |
| Obese                         | 756 (31.5)        | 703 (31.6)            | 390 (31.8)           |                       |                      |                          |
| No listed obesity             | 880 (36.7)        | 831 (37.4)            | 458 (37.3)           |                       |                      |                          |
| Comorbidities                 |                   |                       |                      |                       |                      |                          |
| No. per patient, mean±SD†     | 3.0±2.2           | 2.9±2.1               | 3.0±2.1              | 0.03                  | 0.01                 | -0.02                    |
| Cardiac conditions, n (%)     |                   |                       |                      |                       |                      |                          |
| Coronary artery disease       | 945 (39.4)        | 873 (39.3)            | 489 (39.9)           | 0.00                  | -0.01                | -0.01                    |
| Heart failure                 | 722 (30.1)        | 654 (29.4)            | 364 (29.6)           | 0.02                  | 0.01                 | -0.01                    |
| Cerebrovascular disease       | 341 (14.2)        | 315 (14.2)            | 177 (14.5)           | 0.00                  | -0.01                | -0.01                    |
| Other arrhythmia              | 892 (37.2)        | 824 (37.1)            | 451 (36.7)           | 0.00                  | 0.01                 | 0.01                     |
| Atrial flutter                | 165 (6.9)         | 111 (5.0)             | 79 (6.5)             | 0.08                  | 0.02                 | -0.06                    |
| Respiratory conditions, n (%) |                   |                       |                      |                       |                      |                          |
| Asthma                        | 398 (16.6)        | 359 (16.1)            | 199 (16.3)           | 0.01                  | 0.01                 | 0.00                     |
| COPD                          | 456 (19.0)        | 420 (18.9)            | 232 (18.9)           | 0.00                  | 0.00                 | 0.00                     |
| Pneumonia                     | 246 (10.3)        | 215 (9.7)             | 122 (10.0)           | 0.02                  | 0.01                 | -0.01                    |
| Affective disorders, n (%)    |                   |                       |                      |                       |                      |                          |
| Psychotic disorders           | 45 (1.9)          | 40 (1.8)              | 23 (1.9)             | 0.01                  | 0.00                 | -0.01                    |
| Other mood disorders          | 131 (5.5)         | 121 (5.5)             | 65 (5.3)             | 0.00                  | 0.01                 | 0.01                     |
| Depression                    | 429 (17.9)        | 383 (17.2)            | 220 (18.0)           | 0.02                  | 0.00                 | -0.02                    |
| Anxiety                       | 481 (20.1)        | 434 (19.5)            | 242 (19.7)           | 0.01                  | 0.01                 | 0.00                     |
| Other conditions, n (%)       |                   |                       |                      |                       |                      |                          |
| Type 2 diabetes               | 810 (33.8)        | 743 (33.4)            | 413 (33.7)           | 0.01                  | 0.00                 | -0.01                    |
| Hypertension                  | 2039 (85.0)       | 1891 (85.1)           | 1037 (84.5)          | 0.00                  | 0.01                 | 0.02                     |
| Hyperlipidemia                | 1727 (72.0)       | 1597 (71.8)           | 888 (72.4)           | 0.00                  | -0.01                | -0.01                    |
| GERD                          | 766 (31.9)        | 702 (31.6)            | 388 (31.6)           | 0.01                  | 0.01                 | 0.00                     |
| Cancer                        | 297 (12.4)        | 270 (12.1)            | 158 (12.8)           | 0.01                  | -0.01                | -0.02                    |
| No other comorbidity†         | 249 (10.4)        | 228 (10.3)            | 123 (10.0)           | 0.00                  | 0.01                 | 0.01                     |
| AF variables                  |                   |                       |                      |                       |                      |                          |
| Type of AF, n (%)             |                   |                       |                      | 0.01                  | 0.01                 | 0.02                     |
| Permanent                     | 649 (27.1)        | 598 (26.9)            | 327 (26.7)           |                       |                      |                          |

(Continued)

**Table 3. Continued**

| Variable  | Adherence         |                       |                      | SMD*                  |                      |                          |
|---|-------------------|-----------------------|----------------------|-----------------------|----------------------|--------------------------|
|   | Adherent (n=2398) | Intermediate (n=2223) | Nonadherent (n=1227) | Adherent-intermediate | Adherent-nonadherent | Intermediate-nonadherent |
| Persistent  | 405 (16.9)        | 377 (17.0)            | 206 (16.8)           |                       |                      |                          |
| Paroxysmal  | 1055 (44.0)       | 973 (43.8)            | 548 (44.7)           |                       |                      |                          |
| Unspecified   | 289 (12.0)        | 275 (12.4)            | 145 (11.8)           |                       |                      |                          |
| CHA <sub>2</sub> DS <sub>2</sub> -VASC score, mean±SD     | 3.1±1.9           | 3.0±1.8               | 3.1±1.9              | 0.02                  | 0.00                 | -0.02                    |
| CHA <sub>2</sub> DS <sub>2</sub> -VASC score range, n (%) |                   |                       |                      | 0.01                  | 0.01                 | 0.01                     |
| ≤2  | 1033 (43.1)       | 964 (43.4)            | 532 (43.3)           |                       |                      |                          |
| 3   | 466 (19.4)        | 434 (19.5)            | 235 (19.2)           |                       |                      |                          |
| ≥4  | 899 (37.5)        | 825 (37.1)            | 460 (37.5)           |                       |                      |                          |
| Medication combinations, n (%)‡                           |                   |                       |                      | 0.02                  | 0.01                 | 0.02                     |
| ANB+AA+OA   | 346 (18.3)        | 322 (18.4)            | 175 (18.2)           |                       |                      |                          |
| ANB+AA  | 129 (6.9)         | 113 (6.5)             | 65 (6.7)             |                       |                      |                          |
| ANB+OA  | 549 (29.1)        | 506 (28.9)            | 278 (28.9)           |                       |                      |                          |
| AA+OA   | 59 (3.2)          | 55 (3.1)              | 30 (3.1)             |                       |                      |                          |
| AA  | 35 (1.8)          | 31 (1.8)              | 19 (2.0)             |                       |                      |                          |
| ANB   | 372 (19.7)        | 348 (19.9)            | 189 (19.7)           |                       |                      |                          |
| OA  | 86 (4.6)          | 81 (4.6)              | 44 (4.6)             |                       |                      |                          |
| No medication   | 310 (16.4)        | 294 (16.8)            | 162 (16.8)           |                       |                      |                          |
| On AA†  | 570 (30.2)        | 522 (29.8)            | 288 (30.0)           | 0.01                  | 0.00                 | 0.00                     |
| On ANB‡   | 1396 (74.0)       | 1289 (73.7)           | 707 (73.6)           | 0.01                  | 0.01                 | 0.00                     |
| On OA†  | 1040 (55.1)       | 964 (55.1)            | 527 (54.8)           | 0.00                  | 0.01                 | 0.01                     |
| No medication‡  | 310 (16.4)        | 294 (16.8)            | 162 (16.8)           | -0.01                 | -0.01                | 0.00                     |
| No prescription data                                      | 511 (21.3)        | 473 (21.3)            | 266 (21.7)           | 0.00                  | -0.01                | -0.01                    |
| Adherence to OA, n (%)§                                   |                   |                       |                      | 0.01                  | 0.02                 | 0.01                     |
| Adherent to OA  | 433 (70.0)        | 397 (69.3)            | 218 (69.0)           |                       |                      |                          |
| Not adherent to OA  | 186 (30.0)        | 176 (30.7)            | 98 (31.0)            |                       |                      |                          |
| Prior year HCRU, mean±SD                                  |                   |                       |                      |                       |                      |                          |
| Physician visits  | 12.23±9.11        | 12.73±9.67            | 13.41±9.79           | -0.05                 | -0.12                | -0.07                    |
| All-cause emergency department visits                     | 1.05±1.54         | 1.07±1.70             | 1.07±1.71            | -0.01                 | -0.01                | 0.00                     |
| All-cause hospitalizations                                | 0.43±0.86         | 0.42±0.84             | 0.41±0.82            | 0.01                  | 0.02                 | 0.01                     |
| Cardiac-related emergency department visits               | 0.33±0.63         | 0.28±0.63             | 0.31±0.64            | 0.07                  | 0.03                 | -0.03                    |
| Cardiac-related hospitalizations                          | 0.21±0.49         | 0.20±0.51             | 0.22±0.51            | 0.00                  | -0.03                | -0.04                    |
| Costs, \$US   |                   |                       |                      |                       |                      |                          |
| Total (including OSA equipment)                           | 14 944±19 700     | 13 506±15 053         | 14 031±16 596        | 0.08                  | 0.05                 | -0.03                    |
| Total (excluding OSA equipment)                           | 13 949±19 624     | 12 523±14 985         | 13 092±16 544        | 0.08                  | 0.05                 | -0.04                    |
| All-cause inpatient                                       | 6013±17 002       | 4879±11 648           | 5159±13 423          | 0.08                  | 0.06                 | -0.02                    |
| All-cause outpatient                                      | 4125±6700         | 3792±6242             | 3788±6405            | 0.05                  | 0.05                 | 0.00                     |
| All-cause emergency department                            | 794±1396          | 818±1702              | 807±1452             | -0.02                 | -0.01                | 0.01                     |

Values are mean±SD or number (percentage) of patients. AA indicates antiarrhythmic medication; AF, atrial fibrillation; ANB, atrioventricular nodal blocking agent; CHA<sub>2</sub>DS<sub>2</sub>-VASC, congestive heart failure, hypertension, age, diabetes, prior stroke, sex, vascular disease score; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; HCRU, health care resource use; HSAT, home sleep apnea test; IPTW, inverse probability of treatment weighting; OA, oral anticoagulant; OSA, obstructive sleep apnea; and SMD, standardized mean difference.

\*Pairwise SMDs.

†Does not include hyperlipidemia, hypertension, or obesity.

‡For patients with medication data available.

§For patients with ≥1 filled prescription for OA within 180 to 360 days before device setup.

greater reductions in all-cause emergency department visits and all-cause hospitalizations in the first year. Although not statistically significant, results for all-cause emergency department visits and all-cause hospitalizations continued to be in the same direction in the second year. Reductions in total costs (both inclusive and exclusive of OSA equipment) and inpatient costs were significantly greater for the adherent group compared with the nonadherent group in the first and second years after PAP initiation. Although not statistically significant, reductions in emergency department costs tended to be greater for adherent patients compared with nonadherent patients (Table 5).

## DISCUSSION

This retrospective study analyzed the impact of PAP adherence on outcomes in 5867 patients with AF and newly diagnosed OSA in nationwide US clinical practice. Results from the IPTW analysis indicate that, on average, patients who were adherent to PAP had better outcomes than they otherwise would have if they did not adhere to PAP. Adherence to PAP was associated with significantly fewer all-cause and cardiac-related emergency department visits and hospitalizations. When costs for OSA treatment were excluded, HCRU costs were significantly lower for patients who were adherent to PAP therapy compared with those who were not. Patients who did not meet the criteria for full adherence over 2 years of PAP therapy but had at least 1 quarter where compliance criteria were achieved (intermediate group) also had lower HCRU and associated costs than nonadherent patients. These findings provide evidence for the positive impact of PAP treatment on real-world outcomes.

Our study linked objective PAP device data with nationwide administrative claims data, facilitating greater understanding of actual PAP use and health care system interactions. These unique data highlight the importance of effectively treating OSA in patients with AF. A recent retrospective analysis of patients with OSA and comorbid cardiovascular disease reported a reduction of health care costs in patients treated with and adherent to PAP therapy.<sup>41</sup> In that analysis, durable medical equipment claims were used to categorize adherence to PAP therapy based on a Medicare fee-for-service 5% data set. Differences in costs were primarily attributed to fewer outpatient expenses.

In our study, adherence to PAP therapy was based on the CMS compliance definition, adapted to be applied across 8 quarters. Patients were defined as being adherent to PAP if they met CMS compliance criteria in all 8 quarters and as nonadherent if they did not meet these criteria in any of the 8 quarters; the remainder of the population was classified as having intermediate adherence. Although this may be a conservative

approach, our results were robust across several sensitivity analyses, including an IPTW approach to account for potential confounding.

The characteristics of our sample were consistent with previously published data from registries focused on patients with AF and comorbid OSA. For example, the proportion of participants with hypertension or hyperlipidemia was similar to those in the nationwide ORBIT-AF.<sup>9</sup> In addition, the proportion of female patients, mean age, rates of hypertension, hyperlipidemia, diabetes, chronic obstructive pulmonary disease and heart failure, and the CHA<sub>2</sub>DS<sub>2</sub>-VASc score were similar to those reported by Dalgaard et al.<sup>8</sup>

Our study augments the published literature by demonstrating an association between adherence to PAP therapy based on objective use data and a reduction in the number of all-cause and cardiac-related hospitalizations and emergency department visits. A previous analysis by Holmqvist et al did not identify any significant difference in hospitalizations for patients with AF who were versus were not on PAP therapy; however, they did not account for adherence to treatment.<sup>9</sup> Also, although Dalgaard and colleagues compared rates of major cardiovascular and neurologic events in patients with AF with or without OSA, they did not assess the impact of treating OSA on these outcomes.<sup>8</sup>

Our results also provide insight into the health care burden of patients with AF and OSA. Previous studies have reported a negative impact of OSA on AF treatment outcomes.<sup>16,42-44</sup> An area for future research is the impact of PAP adherence on the effectiveness of treatments for AF, including pharmacologic therapy, direct current cardioversion, and ablation. A recent randomized controlled trial enrolling 25 patients determined the impact of OSA treatment on AF recurrence after cardioversion but did not find any significant difference between PAP therapy and usual care.<sup>19</sup> Using a large data set with objective PAP therapy use data may provide important insights into this research question that might not be detected in small prospective analyses or retrospective analyses of claims-only data.

Although our study has several strengths, it is important to note some limitations, many of which are common to observational research. First, our study is retrospective, and we had to use statistical methods to control for differences in baseline characteristics of the comparison groups (specifically IPTW and propensity-score matching). For example, nonadherent patients had a high burden of comorbidities as well as higher HCRU and costs in the year before PAP setup. Our previous work has shown that comorbidities are a predictor of PAP termination.<sup>45</sup> To mitigate potential confounding of these factors, IPTW and propensity score matching were applied to produce groups that were well balanced at baseline,

**Table 4. HCRU in the First and Second Years of PAP Use, by Adherence Group: IPTW**

| Variable                                       | Adherent<br>(n=2398) | Intermediate<br>(n=2223) | Nonadherent<br>(n=1227) | P value*                  |                          |                              |
|--|----------------------|--------------------------|-------------------------|---------------------------|--------------------------|------------------------------|
|  |                      |                          |                         | Adherent-<br>intermediate | Adherent-<br>nonadherent | Intermediate-<br>nonadherent |
| Year 1 HCRU, mean±SD                           |                      |                          |                         |                           |                          |                              |
| Physician visits, n                            | 12.63±9.83           | 13.29±9.91               | 12.99±10.24             | 0.018                     | 0.91                     | 0.08                         |
| All-cause emergency department visits, n       | 0.61±1.21            | 0.77±1.55                | 0.95±1.90               | 0.023                     | <0.001                   | <0.001                       |
| All-cause hospitalizations, n                  | 0.19±0.69            | 0.24±0.72                | 0.34±1.16               | 0.002                     | <0.001                   | 0.002                        |
| Cardiac-related emergency department visits, n | 0.11±0.41            | 0.13±0.49                | 0.14±0.52               | 0.41                      | 0.06                     | 0.21                         |
| Cardiac-related hospitalizations               | 0.06±0.26            | 0.09±0.41                | 0.10±0.44               | 0.023                     | 0.004                    | 0.33                         |
| Costs, \$US                                    |                      |                          |                         |                           |                          |                              |
| Total (including OSA equipment)                | 10482±12288          | 11774±16962              | 12664±19904             | 0.58                      | 0.97                     | 0.66                         |
| Total (excluding OSA equipment)                | 9171±12219           | 10641±16941              | 11890±19888             | 0.10                      | 0.004                    | 0.13                         |
| All-cause inpatient                            | 2200±8054            | 3274±12065               | 4483±16499              | 0.002                     | <0.001                   | 0.002                        |
| All-cause outpatient                           | 3579±6831            | 3793±7603                | 3630±7102               | 0.08                      | 0.37                     | 0.022                        |
| All-cause emergency department                 | 499±1229             | 563±1292                 | 691±1652                | 0.06                      | <0.001                   | 0.002                        |
| Year 2 HCRU, mean±SD                           |                      |                          |                         |                           |                          |                              |
| Physician visits                               | 11.06±9.07           | 11.75±10.12              | 11.31±9.32              | 0.30                      | 0.84                     | 0.49                         |
| All-cause emergency department visits          | 0.58±1.18            | 0.74±1.51                | 0.93±1.76               | <0.001                    | <0.001                   | 0.004                        |
| All-cause hospitalizations                     | 0.19±0.58            | 0.21±0.76                | 0.26±0.79               | 0.82                      | 0.049                    | 0.06                         |
| Cardiac-related emergency department visits    | 0.08±0.33            | 0.10±0.42                | 0.14±0.49               | 0.44                      | 0.005                    | 0.025                        |
| Cardiac-related hospitalizations               | 0.06±0.28            | 0.07±0.40                | 0.08±0.36               | 0.59                      | 0.011                    | 0.034                        |
| Costs, \$US                                    |                      |                          |                         |                           |                          |                              |
| Total (including OSA equipment)                | 8755±13032           | 9744±16023               | 10370±21814             | 0.40                      | 0.59                     | 0.24                         |
| Total (excluding OSA equipment)                | 8224±12984           | 9426±15990               | 10289±21803             | 0.012                     | 0.021                    | 0.78                         |
| All-cause inpatient                            | 2321±9353            | 2846±12049               | 3980±18991              | 0.72                      | 0.049                    | 0.08                         |
| All-cause outpatient                           | 2671±5545            | 3223±7644                | 2715±5674               | 0.005                     | 0.41                     | 0.003                        |
| All-cause emergency department                 | 427±984              | 556±1375                 | 667±1394                | <0.001                    | <0.001                   | 0.015                        |

Values are mean±SD. HCRU indicates health care resource use; IPTW, inverse probability of treatment weighting; OSA, obstructive sleep apnea; and PAP, positive airway pressure.

\*P values based on weighted Wilcoxon rank-sum test.

indicating that measured confounders were well controlled and are unlikely to explain differences in HCRU. However, it is possible that there is residual unmeasured confounding that could have impacted the study. Furthermore, a healthy user effect (the notion that those who were adherent to PAP therapy were more likely to engage in other healthy behaviors) is an important source of potential bias.<sup>46</sup> To account for this possibility, we included adherence to oral anticoagulants as a covariate to serve as a proxy for healthy behaviors. Although there was a positive relationship between adherence to oral anticoagulants and

adherence to PAP therapy, groups were well balanced on medication adherence after matching and IPTW. Therefore, we believe that it is unlikely that reductions in HCRU and costs can be fully explained by a healthy user effect. Nevertheless, because of the nature of our data set, we are unable to account for additional important patient factors that may influence health, such as healthy habits, laboratory test results, socioeconomic status, and patient-reported outcomes and motivations. Additionally, because this study relied on billing claims to define variables, information on polysomnographic results or measures of disease severity



**Table 5. Change in HCRU From the Year Before to the First and Second Years of PAP Use, by Adherence Group: Pre-Post Interaction Analysis**

| Variable                                     | Adherent<br>(n=2399) | Intermediate<br>(n=2231) | Nonadherent<br>(n=1236) | P value*                  |                          |                              |
|--|----------------------|--------------------------|-------------------------|---------------------------|--------------------------|------------------------------|
|  |                      |                          |                         | Adherent-<br>intermediate | Adherent-<br>nonadherent | Intermediate-<br>nonadherent |
| Change in HCRU (year 1-year before), mean±SD |                      |                          |                         |                           |                          |                              |
| All-cause emergency department visits        | -0.39±1.40           | -0.31±1.80               | -0.21±1.84              | 0.14                      | 0.003                    | 0.09                         |
| All-cause hospitalizations                   | -0.23±0.86           | -0.17±0.91               | -0.11±1.24              | 0.05                      | 0.005                    | 0.13                         |
| Cardiac-related emergency department visits  | -0.20±0.70           | -0.16±0.73               | -0.20±0.78              | 0.07                      | 0.80                     | 0.20                         |
| Cardiac-related hospitalizations             | -0.15±0.49           | -0.11±0.57               | -0.14±0.65              | 0.018                     | 0.70                     | 0.15                         |
| Costs, \$US                                  |                      |                          |                         |                           |                          |                              |
| Total (including OSA equipment)              | -4420±21 305         | -1747±19 143             | -1839±22 352            | 0.001                     | 0.004                    | 0.90                         |
| Total (excluding OSA equipment)              | -4730±21 265         | -1896±19 152             | -1679±22 306            | <0.001                    | <0.001                   | 0.77                         |
| All-cause inpatient                          | -3866±18 081         | -1553±15 116             | -1206±19 376            | 0.001                     | 0.001                    | 0.57                         |
| All-cause emergency department               | -260±1500            | -267±1928                | -171±1804               | 0.89                      | 0.14                     | 0.13                         |
| Change in HCRU (year 2-year before), mean±SD |                      |                          |                         |                           |                          |                              |
| All-cause emergency department visits        | -0.37±1.65           | -0.33±1.88               | -0.25±1.93              | 0.59                      | 0.10                     | 0.19                         |
| All-cause hospitalizations                   | -0.23±0.87           | -0.20±0.92               | -0.19±1.00              | 0.28                      | 0.16                     | 0.62                         |
| Cardiac-related emergency department visits  | -0.22±0.71           | -0.18±0.72               | -0.20±0.78              | 0.11                      | 0.45                     | 0.53                         |
| Cardiac-related hospitalizations             | -0.15±0.52           | -0.13±0.56               | -0.16±0.60              | 0.28                      | 0.58                     | 0.15                         |
| Costs, \$US                                  |                      |                          |                         |                           |                          |                              |
| Total (including OSA equipment)              | -6054±21 853         | -3698±18 572             | -4162±24 283            | 0.002                     | 0.036                    | 0.53                         |
| Total (excluding OSA equipment)              | -5587±21 835         | -3035±18 559             | -3307±24 267            | <0.001                    | 0.012                    | 0.71                         |
| All-cause inpatient                          | -3736±18 425         | -1924±14 747             | -1690±21 041            | 0.007                     | 0.010                    | 0.71                         |
| All-cause emergency department               | -254±1906            | -272±2042                | -215±1705               | 0.82                      | 0.64                     | 0.37                         |

IPW applied to the cohort, excluding prior year HCRU variables in calculating the propensity score, to compare changes over time across adherence groups. Values are mean±SD. HCRU indicates health care resource use; OSA, obstructive sleep apnea; and PAP, positive airway pressure.

\*General estimating equation models were run to compare the changes in outcomes over time (from the year before to years 1 and 2 after PAP initiation) by adherence groups (outcome=adherence+year+adherence×year). P values are derived from the interaction term in the model.

were not available. Baseline apnea-hypopnea index was only available for a small subset of patients (7%) who received an ApneaLink Air™ home sleep apnea test and was therefore not included in any adjusted analyses. Our data set incorporated patients with commercial, Medicaid, and Medicare Advantage insurance, but none of the patients included in the analysis had Medicare fee for service, which may limit the generalizability of the findings. Using a claims-based approach, we also were unable to fully explore the impact of PAP therapy adherence on AF-related HCRU because of the small number of events present, precluding further analysis. Last, we acknowledge that

our study design does not allow for causal conclusions. Additional studies are needed to provide more definitive data, such as multicenter randomized controlled trials, causal inference-designed observational studies, and hybrid studies. Some of these designs may be logistically challenging to conduct with sample sizes as large as the current study.

In conclusion, using a linked data set of objective PAP therapy use data and administrative claims data, this real-world study showed that adherence to PAP therapy was associated with lower HCRU and associated costs. In particular, patients with AF and OSA who were adherent to PAP had fewer hospitalizations

and emergency department visits than those who had intermediate adherence or were nonadherent. These findings highlight the importance of diagnosing and treating OSA in patients with AF.

## APPENDIX

### medXcloud Group

The medXcloud group is an academic-industry collaboration involving employees and consultants of ResMed and global academic thought leaders in the fields of sleep and respiratory medicine. The medXcloud investigators include authors Kimberly L. Sterling, Jean-Louis Pépin, Adam V. Benjafield, Atul Malhotra, and Peter A. Cistulli, as well as Carlos M. Nunez, Meredith Barrett (ResMed Science Center, San Diego, CA), and Jeff Armitstead (ResMed Science Centre, Sydney, Australia).

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### Supplemental Material

Tables S1–S3.

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