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ORIGINAL RESEARCH

Positive Airway Pressure Adherence and Health Care Resource Utilization in Patients With Obstructive Sleep Apnea and Heart Failure With Reduced Ejection Fraction

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BACKGROUND: Obstructive sleep apnea (OSA) is a common comorbidity in patients with heart failure, although current evidence is equivocal regarding the potential benefits of treating OSA with positive airway pressure (PAP) therapy in patients with heart failure. This study assessed the impact of adherence to PAP therapy on health care resource utilization in patients with OSA and heart failure with reduced ejection fraction.

METHODS AND RESULTS: Administrative insurance claims data linked with objective PAP therapy use data from patients with OSA and heart failure with reduced ejection fraction were used to determine associations between PAP adherence and a composite outcome of hospitalizations and emergency room visits. One-year PAP adherence was based on an adapted US Medicare definition. Propensity score methods were used to create groups with similar characteristics across PAP adherence levels. The study cohort included 3182 patients (69.9% male, mean age 59.7 years); 39% were considered adherent to PAP therapy (29% intermediate adherent, 31% nonadherent). One year after PAP initiation, adherent patients had fewer composite visits than matched nonadherent patients, driven by a 24% reduction in emergency room visits for adherent patients. Composite visit costs were lower in adherent versus nonadherent patients ($3500 versus $5879, P=0.031), although total health care costs were not statistically different ($13 028 versus $14 729, P=0.889).

CONCLUSIONS: PAP therapy adherence in patients with OSA with heart failure with reduced ejection fraction was associated with a reduction in health care resource utilization. This suggests that greater emphasis should be placed on diagnosing and effectively treating OSA with PAP in patients with heart failure with reduced ejection fraction.

Key Words: health care resource utilization ■ heart failure ■ obstructive sleep apnea ■ positive airway pressure adherence

The prevalence of heart failure is high and rising due to the aging of the population and improved survival from acute coronary events.[1–3] However, despite considerable pharmacological treatment advances in heart failure, there is general agreement that new therapeutic approaches are desirable.[4] Sleep-disordered breathing is common in patients with heart failure,[5–8] although the impact of therapy remains unclear. The main types of sleep-disordered breathing are obstructive sleep apnea (OSA) and central sleep apnea, depending on the underlying pathophysiology, and treatment approaches for these conditions can vary depending on the characteristics of the patient.

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CLINICAL PERSPECTIVE

What Is New?

- Adherence to positive airway pressure therapy for obstructive sleep apnea in patients with heart failure with reduced ejection fraction is associated with a lower risk of the composite end point of hospitalizations and visits to the emergency room and may also result in potential savings for the health care system.

What Are the Clinical Implications?

- Screening for sleep apnea in patients with heart failure may be warranted, and strategies to optimize adherence to positive airway pressure in these patients are likely beneficial.

Nonstandard Abbreviations and Acronyms

CMS	Centers for Medicare and Medicaid Services
PAP	positive airway pressure

Randomized controlled trials investigating the impact of sleep-disordered breathing therapy in patients with heart failure have had mixed results. Although the SERVE-HF (Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure) study showed higher rates of all-cause and cardiovascular mortality in patients randomized to adaptive servo-ventilation, the population in this study had stable systolic heart failure (heart failure with reduced ejection fraction [HFrEF]) and central sleep apnea.[9] In patients with OSA, Kaneko et al and Mansfield et al showed that patients had some improvement in left ventricular ejection fraction after treatment with continuous positive airway pressure therapy, but the studies were small, of short duration, and the hemodynamic data were somewhat mixed.[10,11] Javaheri et al reported an observational study from Medicare claims suggesting that treatment of sleep-disordered breathing in patients with heart failure resulted in better outcomes compared with untreated patients.[12] These data provide indirect evidence that treatment of sleep-disordered breathing in heart failure may be beneficial.[12] The ADVENT-HF (Adaptive Servo Ventilation on Survival and Hospital Admissions in Heart Failure) study investigating the treatment of sleep-disordered breathing in stable HFrEF patients with adaptive servo-ventilation was recently terminated, but the results are not yet available.[13] Thus, existing data are equivocal regarding the potential benefits of treating sleep-disordered breathing in heart failure. While administrative insurance claims data provide a valuable resource for determining benefits of sleep-disordered breathing therapy, further research is clearly needed.

This study was designed to test the hypothesis that adherence to continuous positive airway pressure or automatically titrating PAP, collectively referred to as positive airway pressure (PAP) therapy, in patients with HFrEF and comorbid OSA is associated with reduced health care resource utilization and costs using administrative insurance claims data linked with objective PAP use data.

METHODS

Data Source

We conducted a retrospective observational study of patients with HFrEF who received a new diagnosis of OSA between September 2014 and April 2019. De-identified payer-sourced ("closed") administrative claims data containing >100 geographically dispersed health plans across the United States (licensed from Inovalon Insights LLC, Bowing, MD) were linked with objective PAP use data (AirView; ResMed Corp, San Diego, CA). The databases were linked through a tokenization process and the resulting linked database underwent a third-party expert determination to ensure compliance with the Health Insurance Portability and Accountability Act. The study design was reviewed by an Institutional Review Board (Advarra, Ref number Pro0004005) and deemed 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 upon reasonable request.

Study Cohort

The study cohort consisted of adults (age ≥18 years) who completed a sleep test (Healthcare Common Procedure Coding System 95808, 95810, 95811, G0398-G0400) where an OSA diagnosis (*International Classification of Diseases, Tenth Revision, Clinical Modification* [*ICD-10-CM*] G47.33, *International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] 327.23) was assigned within 60 days. Patients had to have received an AirSense10 continuous positive airway pressure or automatically titrating positive airway pressure device (ResMed Corp, San Diego, CA) with at least 1 year of claims data before the first sleep test and 1 year of claims data after PAP device setup. HFrEF was identified by the presence of at least 2 health care encounter claims with a diagnosis of systolic heart failure (*ICD-10-CM* I50.2, *ICD-9-CM* 428.2*) or at least 1

hospitalization with a primary diagnosis of systolic heart failure in the year before device setup. Patients were excluded if claims in the year before device setup included any of the following: use of adaptive servo-ventilation or a bilevel PAP device; PAP resupply; a diagnosis of diastolic heart failure, combined systolic and diastolic heart failure, central sleep apnea, nocturnal hypoventilation, pregnancy, or end-stage renal disease; or dialysis use. A subgroup of patients was identified based on the presence of ischemic (*ICD-10-CM* I25.5, *ICD-9-CM* 414.8) or dilated (*ICD-10-CM* I42.0, *ICD-9-CM* 425.4) cardiomyopathy diagnosis in the year before PAP device setup.

PAP Adherence

PAP use was objectively measured by the PAP device for each night it was used over the first year. For reimbursement purposes, the US Centers for Medicare and Medicaid Services (CMS) considers a patient compliant with therapy if the PAP device is used at least 4 hours per night on 70% of nights during a consecutive 30-day period in the first 90 days of therapy. Three levels of adherence were evaluated in this analysis: (1) adherent patients who met CMS criteria for all 4 consecutive 90-day timeframes (quarters) within the first year; (2) nonadherent patients who did not meet CMS criteria in any of the 4 quarters; and (3) intermediate adherent patients who met CMS criteria in at least 1 but no more than 3 quarters.

Outcomes

The primary outcome was health care resource use defined by the occurrence of a composite outcome of all-cause hospitalizations and emergency room visits. Additionally, all-cause hospitalizations, emergency room visits, and cardiovascular hospitalizations were assessed individually. Individual events and costs were examined in addition to composite events and total costs in order to identify the specific utilization types where PAP adherence had the greatest effect. Cardiovascular hospitalizations were defined as a hospitalization that had 1 of the following cardiovascular diseases as the primary diagnosis: myocardial infarction; stroke; heart failure; acute coronary syndrome; arrhythmia; cardiomyopathy; or hypertension. Proxy costs for all resource use were provided by Inovalon Insights LLC based on their proprietary Proxy Financials algorithm. The algorithm is based on CMS Medicare prospective payment fee schedules.

Covariates

To account for potential differences at baseline, the following covariates were included: (1) demographics (age, sex, payer, and obesity); (2) comorbidities based on *ICD-9-CM* and *ICD-10-CM* diagnosis codes in the year before the first sleep test (hyperlipidemia, hypertension, gastroesophageal reflux disease, type 2 diabetes, cancer, cerebrovascular disease, atrial fibrillation, coronary artery disease, other arrhythmia, pulmonary hypertension, psychotic disorders, depression, anxiety, other mood disorders, chronic obstructive pulmonary disease, asthma, and pneumonia); (3) adherence to β-blocker medication; (4) presence of an implanted cardiac device; (5) cardiomyopathy type; and (6) prior year health care resource use (all-cause hospitalizations and emergency room visits).

Pharmacy claims data were used to identify prescription fills of heart failure medications in accordance with current guidelines,[14] including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, mineralocorticoid receptor antagonists, angiotensin receptor neprilysin inhibitors, diuretics, sodium-glucose cotransporter-2 inhibitors, digoxin, and vasodilators. Adherence to β-blocker medication was used as a proxy to assess the effects of healthy user behavior. With a prescription exposure window of 181 to 360 days before starting PAP therapy, patients who filled a prescription for β-blockers were labeled as "on β-blockers." Patients with a proportion of days covered of at least 80% were labeled as "adherent to β-blockers." Patients who were "on β-blockers" but with a proportion of days covered of <80% were labeled as "not adherent to β-blockers."

Statistical Analysis

Statistical analyses were performed using R statistical software version 4.0.3, Matching R package, and PSWeight R package.[15–17] Baseline demographics and covariates were assessed using descriptive statistics. To control for potential confounding, a risk score for each patient was defined based on all covariates. Model coefficients for covariates were scaled to create a single risk score for each patient. Risk-adjusted generalized linear models with a logit link were built to determine the association between PAP adherence and predicted mean number of composite visits, and with all-cause hospitalizations, emergency room visits, and cardiovascular hospitalizations individually, using the adherent and nonadherent patients. Model goodness of fit was assessed by McFadden's grouped Log-likelihood R-squared (LL-R^2) and 90th percentile predicted range. From models that showed a statistically significant difference between adherent and nonadherent groups, the number needed to treat was calculated as 1/absolute risk reduction for the overall cohort. Number needed to treat represents the number of patients that would need to be adherent to PAP therapy to avoid 1 additional event.

A hybrid propensity score matching approach was used to ensure appropriate balance in baseline characteristics between the PAP adherent and nonadherent subgroups when assessing the impact of adherence

on health care resource utilization and costs. 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 on the following variables was performed: age group, sex, payer type, presence of atrial fibrillation, prior year all-cause hospitalizations, and prior year emergency room visits. Balance across groups was assessed using standardized mean difference, with 0<|standardized mean difference|<0.1 indicating good balance. Differences in health care resource use between matched samples after PAP setup were assessed using Wilcoxon signed-rank tests.

Finally, to supplement the findings from propensity score matching and to include a comparison with the intermediate PAP adherence group, inverse probability treatment weighting analyses were conducted. Weights were calculated from propensity scores and applied to create a weighted pseudo-population that mirrored the distribution of the overall cohort and was balanced across groups. This approach allowed for comparison of more than 2 treatment groups, while leveraging the full sample size. Pairwise comparisons of mean health care visits between adherent, intermediate adherent, and nonadherent patients were conducted.

RESULTS

Baseline Characteristics

We identified 3182 patients with OSA with comorbid HFrEF (69.9% male, mean age 59.7 years), of whom 63.2% (n=2011) met CMS compliance criteria in the first 90-day quarter (Table 1). In addition to OSA and HFrEF, 99.7% of the cohort had at least 1 other comorbid condition; the mean number of comorbidities was 5.6 (Table 1). The proportion of patients who were hospitalized in the pre-PAP period was high (43%), with the majority of hospitalizations occurring in the quarter before starting PAP therapy. Baseline characteristics by PAP adherence group are provided in Table S1.

Forty percent of the cohort (n=1268) had identifiable ischemic (19%) or dilated (21%) cardiomyopathy. Patients with ischemic cardiomyopathy were older, had a higher comorbidity burden, and were more commonly insured by Medicare Advantage, while the subgroup with dilated cardiomyopathy were more likely to be female and have morbid obesity (Table S2).

Health care resource use was high in the year before PAP therapy across all types of visits and all adherence groups (Table 1).

PAP Adherence

During the first year of therapy, 39% of patients (n=1252) were considered adherent to PAP therapy, 29% (n=935) had intermediate adherence, and 31% (n=995) were nonadherent. Mean PAP use for each adherence group is listed in Tables 2 and 3. PAP use was consistently higher in the adherent group (Table 2, Table 3). Adherence in the intermediate group was 81% in the first quarter, then consistently decreased over the remaining 3 quarters (adherence rates of 46%, 30%, and 21%, respectively).

Unadjusted comparisons between patients with ischemic and dilated cardiomyopathy showed no difference in objective measurements of PAP adherence (Table S3).

Covariates that were significant predictors of not adhering to PAP included Medicaid or Medicare Advantage insurance (compared with commercial insurance) and the presence of hypertension, coronary artery disease, or pneumonia. Significant predictors of adhering to PAP included older age (>55 years), presence of atrial fibrillation, and being adherent to β-blocker medication. However, after propensity score matching, adherent and nonadherent patient cohorts were well balanced (Table 1). Additionally, after inverse probability treatment weighting, differences between groups were further minimized, and patients in all PAP adherence groups were well balanced (all standardized mean difference <0.1) (Table S3).

Risk-Adjusted Outcomes

The risk-adjusted model for mean number of 1-year composite visits fit well (LL-R^2 of 83%) and showed a statistically significant difference across the risk range between PAP adherent and nonadherent patients (P=0.019) (Figure 1). The number needed to treat (from nonadherent to adherent) to avoid a hospitalization or emergency room visit was 1.5 (P<0.001). The risk-adjusted model for mean number of 1-year emergency room visits also fit well (LL-R^2 of 79%) and showed a statistically significant difference across the risk range of patients (P=0.008). The number needed to treat to avoid an emergency room visit was 1.8 (P<0.001). The model fit for mean number of 1-year all-cause hospitalizations was satisfactory (LL-R^2 of 73%) and did not show a statistically significant difference between PAP adherent and nonadherent patients (P=0.130). The risk-adjusted model for number of 1-year cardiovascular hospitalizations fit poorly (LL-R^2 of 48%), and number of events was low (26% of patients had at least 1 in the year prior, and only 9% in year 1).

Association Between PAP Adherence and Health Care Resource Utilization/Costs

After propensity score matching, 738 adherent and 738 nonadherent patients remained in the cohort (Table 1). The matched cohort was similar to the overall unadjusted cohort in terms of baseline characteristics,

Table 1. Cohort Characteristics, Overall and for Matched Cohort

	Overall (n=3182)	Matched cohort			
		Adherent (n=738)	Nonadherent (n=738)	SMD	95% CI
Female, n (%)	959 (30.1)	205 (27.8)	205 (27.8)	0.00	−0.10, 0.10
Age, y	59.7±11.2	59.4±10.8	59.0±11.5	0.04	−0.07, 0.14
Payer				0.00	−0.10, 0.10
Commercial	1793 (56.3)	441 (59.8)	441 (59.8)		
Medicaid	646 (20.3)	131 (17.8)	131 (17.8)		
Medicare Advantage	743 (23.4)	166 (22.5)	166 (22.5)		
Obesity				0.11	0.01–0.21
Morbidly obese	1242 (39.0)	287 (38.9)	270 (36.6)		
Obese	924 (29.0)	223 (30.2)	226 (30.6)		
Overweight	188 (5.9)	51 (6.9)	45 (6.1)		
Healthy weight	37 (1.2)	10 (1.4)	5 (0.7)		
Not categorized	791 (24.9)	167 (22.6)	192 (26.0)		
Comorbid conditions					
Number	5.6±2.3	5.4±2.2	5.6±2.3	−0.06	−0.16, 0.04
Comorbidity, n (%)					
Hypertension	2927 (92.0)	685 (92.8)	682 (92.4)	0.02	−0.09, 0.12
Pulmonary hypertension	499 (15.7)	99 (13.4)	125 (16.9)	−0.10	−0.20, 0.00
Atrial fibrillation	1335 (42.0)	291 (39.4)	291 (39.4)	0.00	−0.10, 0.10
Atrial flutter	119 (3.7)	32 (4.3)	24 (3.3)	0.06	−0.05, 0.16
Other arrhythmia	1256 (39.5)	276 (37.4)	270 (36.6)	0.02	−0.09, 0.12
Coronary artery disease	2083 (65.5)	478 (64.8)	499 (67.6)	−0.06	−0.16, 0.04
Cerebrovascular disease	490 (15.4)	107 (14.5)	120 (16.3)	−0.05	−0.15, 0.05
Asthma	636 (20.0)	152 (20.6)	147 (19.9)	0.02	−0.09, 0.12
COPD	984 (30.9)	204 (27.6)	233 (31.6)	−0.09	−0.19, 0.02
Pneumonia	528 (16.6)	110 (14.9)	125 (16.9)	−0.06	−0.16, 0.05
Psychotic disorders	114 (3.6)	20 (2.7)	25 (3.4)	−0.04	−0.14, 0.06
Other mood disorders	183 (5.8)	35 (4.7)	47 (6.4)	−0.07	−0.17, 0.03
Depression	712 (22.4)	146 (19.8)	156 (21.1)	−0.03	−0.14, 0.07
Anxiety	633 (19.9)	132 (17.9)	159 (21.5)	−0.09	−0.19, 0.01
Type 2 diabetes	1548 (48.6)	367 (49.7)	352 (47.7)	0.04	−0.06, 0.14
Hyperlipidemia	2453 (77.1)	574 (77.8)	557 (75.5)	0.05	−0.05, 0.16
GERD	976 (30.7)	211 (28.6)	212 (28.7)	0.00	−0.11, 0.10
Cancer	356 (11.2)	81 (11.0)	72 (9.8)	0.04	−0.06, 0.14
Heart failure variables, n (%)					
Implanted cardiac device	868 (27.3)	195 (26.4)	185 (25.1)	0.03	−0.07, 0.13
Cardiomyopathy type				0.04	−0.06, 0.14
Ischemic	603 (19.0)	145 (19.6)	138 (18.7)		
Dilated	665 (20.9)	143 (19.4)	154 (20.9)		
Heart failure medications*					
ACEI	1197 (45.6)	272 (45.6)	280 (47.0)	−0.03	−0.14, 0.09
ARB	672 (25.6)	159 (26.7)	150 (25.2)	0.03	−0.08, 0.15
ARNI	161 (6.1)	23 (3.9)	37 (6.2)	−0.11	−0.22, 0.01
β-blocker	2102 (80.1)	478 (80.2)	484 (81.2)	−0.03	−0.14, 0.09
MRA	800 (30.5)	179 (30.0)	166 (27.9)	0.05	−0.07, 0.16
Diuretic	1704 (64.9)	377 (63.3)	394 (66.1)	−0.06	−0.17, 0.05

(*Continued*)

Table 1. Continued

	Overall (n=3182)	Matched cohort			
		Adherent (n=738)	Nonadherent (n=738)	SMD	95% CI
Vasodilator	207 (7.9)	46 (7.7)	53 (8.9)	−0.04	−0.16, 0.07
SGLT2 inhibitor	46 (1.8)	11 (1.5)	9 (1.5)	0.03	−0.09, 0.14
Digoxin	239 (9.1)	50 (8.4)	62 (10.4)	−0.07	−0.18, 0.04
Has Rx data, no heart failure Rx	295 (11.2)	66 (11.1)	52 (8.7)	0.08	−0.03, 0.19
No Rx data	558 (17.5)	142 (19.2)	142 (19.2)	0.00	−0.10, 0.10
Adherent to β-blocker[†]				0.15	−0.01, 0.30
Yes	988 (69.3)	231 (72.6)	208 (65.8)		
No	437 (30.7)	87 (27.4)	108 (34.2)		
Prior year health care visits, n (%)					
Composite	2277 (71.6)	509 (68.9)	509 (68.9)	0.00	−0.10, 0.10
Emergency room	1650 (51.9)	352 (47.7)	352 (47.7)	0.00	−0.10, 0.10
All-cause hospitalization	1368 (43.0)	313 (42.4)	313 (42.4)	0.00	−0.10, 0.10
Cardiovascular hospitalization	830 (26.1)	213 (28.9)	179 (24.3)	0.10	0.00, 0.21
Prior year health care visits, n per patient					
Composite	1.71±2.11	1.42±1.59	1.47±1.75	−0.03	−0.13, 0.07
Emergency room	1.10±1.76	0.84±1.29	0.88±1.45	−0.03	−0.13, 0.07
All-cause hospitalization	0.61±0.89	0.57±0.82	0.58±0.81	−0.01	−0.11, 0.09
Cardiovascular hospitalization	0.31±0.58	0.33±0.57	0.29±0.56	0.07	−0.03, 0.17

Values are mean±SD or number of patients (%). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; MRA, mineralocorticoid receptor antagonist; Rx, prescription; SGLT2, sodium-glucose cotransporter-2; and SMD, standardized mean difference.

*Medication percentages (other than "No Rx data") are based on patients with Rx data.

†Adherence to β-blocker percentages are based on those who filled a prescription for β-blocker medication in the 181 to 360 days before starting positive airway pressure therapy.

with the exception of mean number of emergency room visits in the year prior, where the matched cohort had fewer. Patients adherent to PAP therapy had fewer composite visits in the year after starting PAP compared with nonadherent patients; this difference was driven by a 24% reduction in emergency room visits for adherent patients (Figure 2). The mean number of emergency room visits after 1 year of PAP therapy was significantly lower for adherent patients compared with nonadherent patients (Table 2). The mean number of all-cause hospitalizations and mean number of cardiovascular hospitalizations after 1 year of PAP therapy did not differ significantly between matched adherent and nonadherent patients (Table 2). Costs for composite visits after 1 year were lower in adherent patients compared with nonadherent patients ($3500 versus $5879, *P*=0.031), although between-group differences in total costs were not statistically different.

Results were similar in the inverse probability treatment weighting analyses. PAP-adherent patients showed significantly fewer composite and emergency room visits in the year after starting PAP therapy compared with nonadherent patients and those with intermediate adherence (Table 3). There were no statistically significant differences between intermediate and nonadherent patients for any outcome. In addition, adherent patients had lower health care costs than intermediate and nonadherent patients for composite visits after 1 year of PAP therapy ($4526 versus $6258 and $6473; *P*=0.004 and 0.002, respectively) although again, differences in total costs were not statistically different.

Unadjusted comparisons between patients with ischemic versus dilated cardiomyopathy showed reductions in mean number of composite hospitalizations and emergency room visits with no major differences between the 2 groups (Table S4).

β-Blocker Adherence as Healthy User Effect Proxy

For patients taking β-blockers, 69.3% were categorized as adherent to the medication and 30.7% were nonadherent. Patients who were adherent to PAP were more often adherent to β-blockers (73.6%, compared with 70.6% and 63.2% of intermediate and

Table 2. Mean Number of Health Care Resource Use Visits and Positive Airway Pressure Therapy Use in Matched Cohort

	Overall (n=3182)	Matched cohort		
		Adherent (n=738)	Nonadherent (n=738)	*P* value
Year 1, n per patient				
Composite	1.24±2.25	0.92±1.59	1.15±1.83	0.006
Emergency room	0.89±1.81	0.64±1.26	0.81±1.43	0.005
All-cause hospitalization	0.35±0.90	0.28±0.71	0.34±0.91	0.140
Cardiovascular hospitalization	0.12±0.48	0.09±0.37	0.11±0.44	0.409
PAP use				
PAP h/d	3.6±2.9	6.6±1.5	0.4±0.6	<0.001
PAP d/wk	4.0±2.6	6.6±0.5	0.9±1.1	<0.001
PAP h/use/d	5.2±2.2	7.0±1.3	2.9±1.6	<0.001

Values are mean±SD. PAP indicates positive airway pressure.

nonadherent patients, respectively), showing that those adherent to β-blockers were more frequently adherent to PAP therapy and those not adherent to β-blockers were more frequently not adherent to PAP. Adherence to β-blockers was included as a covariate in the risk-adjusted models and the propensity score model and was not a significant independent predictor for any health care resource use outcome or the risk of not adhering to PAP therapy. Adherence to β-blockers was well balanced at baseline in both propensity score matching and inverse probability treatment weighting analyses.

DISCUSSION

The main findings of this real-world data analysis were as follows. First, in patients with OSA and HFrEF, 1 year of PAP therapy adherence was associated with a lower risk of the composite outcome of all-cause hospitalizations and emergency room visits. In addition, the composite hospitalization and emergency room visit costs were lower in adherent versus nonadherent patients. Although the total cost was not significantly different, this observation is likely due to the higher cost of PAP equipment and supplies incurred by adherent patients compared with nonadherent patients ($1334 versus $802; *P*<0.001). Second, we saw high hospitalization rates in the year before starting PAP therapy for the patients with HFrEF in our cohort, likely due to the severity of underlying comorbidities. These data raise the possibility of an opportunity for sleep assessment that could be initiated following hospitalizations to reduce future complications.[18] Third, although there was a positive association between β-blocker adherence (as a proxy for a healthy user effect) and PAP adherence, β-blocker adherence was controlled for in the propensity-matched analyses; thus we do not believe that our findings are primarily driven by this effect. Fourth, different statistical approaches, including propensity-score matched analyses and inverse probability treatment weighting analyses, generated consistent findings suggestive of a benefit of PAP therapy for OSA in patients with HFrEF. Additionally, the inverse probability treatment weighting analyses showed that patients defined as intermediately adherent to PAP had outcomes similar to those who were nonadherent, highlighting the importance of high levels of PAP use.[19,20]

The results of this observational study, linking a national administrative insurance claims database and objectively measured PAP adherence, highlight the importance of treating OSA in patients with HFrEF. Of note, the patients studied were clinically diagnosed with OSA, suggesting they may be more symptomatic than patients who may be identified through widespread screening. These patients with clinical OSA might be more likely to benefit from OSA treatment compared with those who are relatively asymptomatic.[21] Additionally, both adherent and nonadherent patients saw a decrease in number of health care visits in year 1 compared with baseline. It is possible that because patients were selected based on utilization in the prior year, this result is due to regression to the mean, although it could also suggest a potential impact of even minimal PAP use in this population, consistent with previous research in OSA.[22–24]

There are a number of possible mechanisms underlying the complications of OSA in heart failure. Although OSA and central sleep apnea have some distinctive manifestations, they frequently co-exist (particularly in heart failure), and many patients will manifest features of both types of sleep disordered-breathing.[25] Intermittent desaturation with re-oxygenation can lead to oxidative stress and potentially worsen underlying cardiovascular dysfunction.[26,27] In addition, sympathetic activation and catecholamine surges can occur with obstructive apneas and arousal from sleep, which could worsen the underlying neuroendocrine activation that is thought to be deleterious in heart

Table 3. Mean Number of Health Care Resource Use Visits and Positive Airway Pressure Use in the Inverse Probability Treatment Weighted Cohort

	Adherence level			*P* value		
	Adherent (n=1252)	Intermediate (n=935)	Nonadherent (n=995)	A-N	A-I	I-N
Year 1, n per patient						
Composite	1.00±1.73	1.30±2.09	1.37±2.56	<0.001	0.001	0.721
Emergency room	0.71±1.38	0.91±1.65	1.00±2.06	<0.001	0.002	0.447
All-cause hospitalization	0.29±0.77	0.38±0.93	0.37±0.99	0.129	0.049	0.651
Cardiovascular hospitalization	0.10±0.43	0.12±0.47	0.12±0.47	0.173	0.167	0.953
PAP use						
PAP h/d	6.6±1.5	2.8±1.4	0.4±0.6	<0.001	<0.001	<0.001
PAP d/wk	6.6±0.5	3.8±1.7	0.9±1.1	<0.001	<0.001	<0.001
PAP h/use/d	7.1±1.4	5.4±1.3	2.9±1.6	<0.001	<0.001	<0.001

Values are mean±SD. A indicates adherent; I, intermediate adherence; N, nonadherent; and PAP, positive airway pressure.

failure.[28,29] Inflammatory pathways may be activated by hypoxemia and sleep disturbance, which might also be important in mediating cardiometabolic dysfunction.[30] Intrathoracic pressure swings are particularly common with OSA; these fluctuations can increase left ventricular transmural pressure and thus, by the Law of Laplace, can increase ventricular afterload.[31] Of note, atrial fibrillation can be particularly problematic in chronic heart failure and may well be triggered by OSA or obesity via mechanical, neurohumoral, and inflammatory pathways.[32–34] In theory, PAP therapy should attenuate sleep disordered-breathing in adherent patients and thus the deleterious effects of hypoxemia, negative intrathoracic pressure, and recurrent arousals from sleep should be mitigated.[35–37] Interestingly, our findings did not differ for patients with ischemic versus dilated cardiomyopathy, suggesting reduced left ventricular ejection fraction per se is mechanistically important.

Strengths and Limitations

Our study has many strengths, including a large heterogeneous population of patients with HFrEF, real-world design, robust statistical methods, and a focus on clinically important outcomes. However, the following limitations should be considered. First, we did not conduct a randomized clinical trial and thus our findings are observational. Nonetheless, large-scale randomized trials in this context are challenging to undertake[38]; thus, our findings are clinically relevant and supportive of further

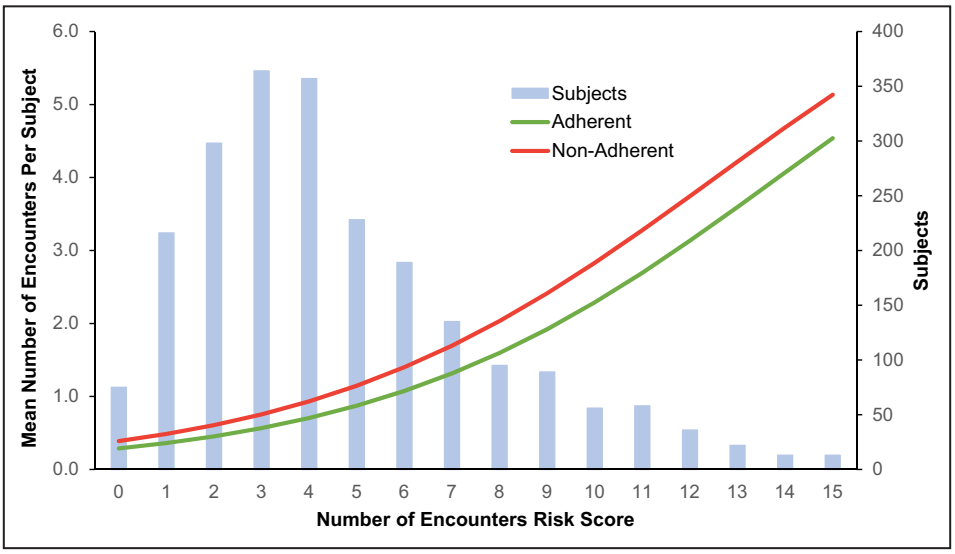

Figure 1. Effect of positive airway pressure adherence on mean number of composite hospitalizations and emergency room visits.

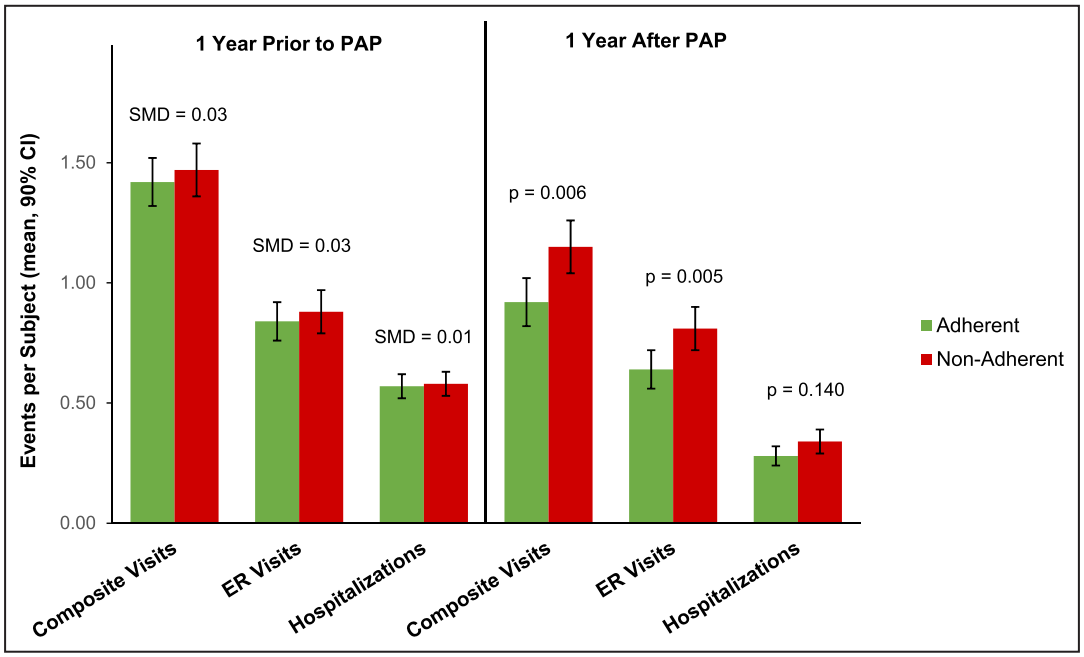

Figure 2. Health care resource utilization 1 year before and 1 year after initiating positive airway pressure therapy.
ER indicates emergency room; PAP, positive airway pressure; and SMD, standardized mean difference.

research efforts in this context. Second, we examined a survivor cohort and therefore did not examine the impact of OSA on mortality.[35] We recognize that mortality is clearly important, but our goal was to assess outcomes such as emergency room visits, hospitalizations, and costs.[39] Although the overall sample size was large, the study was underpowered for certain outcomes such as cardiovascular hospitalizations, highlighting the need for further study. Third, given the nature of administrative claims data, we were limited in our clinical knowledge on the manifestation of both OSA and HFrEF. Knowing that obstructive and central apneas frequently coexist in this population, we were able to exclude patients with the *ICD* diagnosis of central sleep apnea, yet these patients with OSA could still be experiencing central apneas. While PAP devices do collect information on residual apneas, analyzing those data as well as diagnostic OSA data was outside the scope of this investigation but should be considered in future work. Fourth, we recognize that adherence to therapy may be associated with improved outcomes beyond the impact of therapy itself on sleep apnea. For example, Platt et al showed an association between PAP use and statin therapy, suggesting that motivated patients may have improved health outcomes for reasons beyond PAP adherence per se.[40] We modeled this healthy user effect by assessing adherence to β-blocker therapy and did not detect a major impact of the healthy user effect on our main findings. However, we were unable to account for other factors that may be related to patient motivations for being adherent. We acknowledge the need for further data to confirm our findings and support efforts to optimize PAP adherence. Moreover, there is the potential to utilize novel patient engagement tools that may improve PAP adherence[19] or effective non-PAP therapies (eg, weight loss, pharmacotherapy, and oxygen) that could help to improve outcomes.[41–48]

CONCLUSIONS

The results of this study showed improved outcomes in patients with OSA and HFrEF who were adherent to PAP therapy. These data provide additional real-world evidence for the role of PAP therapy in reducing health care resource use. Therefore, assessment of OSA in patients with heart failure should be encouraged until more definitive outcomes data emerge.

APPENDIX

medXcloud Group

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. medXcloud investigators include authors Peter Cistulli, Atul Malhotra, Jean-Louis Pépin, Adam V. Benjafield, as well as Kimberly L. Sterling, Carlos M. Nunez, Meredith Barrett (ResMed

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Independent medical writing support was provided by Nicola Ryan. Representatives of the study sponsor were involved in the study design, collection, analysis and interpretation of data, writing of the report, and in the decision to submit the paper for publication. Atul Malhotra wrote the first draft of the manuscript and had final responsibility for the decision to submit for publication.

Conception and design: KVC, ASM, FHSK, AVB, VKS; Analysis: ASM; Interpretation: AM, KVC, ASM, JLP, FHSK, PAC, AVB, VKS; Drafting the first version of the manuscript: AM, VKS; Review and editing of the manuscript: AM, KVC, ASM, JLP, FHSK, PAC, AVB, VKS.

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Supplemental Material

Tables S1–S4

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics by positive airway pressure therapy adherence.

	Adherent (n=1,252)	Intermediate (n=935)	Non-Adherent (n=995)	*P* Value
Female, n (%)	342 (27.3)	309 (33.0)	308 (31.0)	0.012
Age, years	60.9±10.6	59.8±11.2	58.1±11.9	<0.001
Payer				**<0.001**
Commercial	802 (64.1)	514 (55.0)	477 (47.9)	
Medicaid	151 (12.1)	191 (20.4)	304 (30.6)	
Medicare Advantage	299 (23.9)	230 (24.6)	214 (21.5)	
Obesity				**0.90**
Morbidly obese	495 (39.5)	353 (37.8)	394 (39.6)	
Obese	370 (29.6)	269 (28.8)	285 (28.6)	
Overweight	67 (5.4)	61 (6.5)	60 (6.0)	
Healthy weight	17 (1.4)	11 (1.2)	9 (0.9)	
Not categorized	303 (24.2)	241 (25.8)	247 (24.8)	
Comorbid conditions				
Number	5.5±2.2	5.7±2.3	5.7±2.3	0.028
Comorbidity, n (%)				
Hypertension	1,127 (90.0)	869 (92.9)	931 (93.6)	0.004
Pulmonary hypertension	189 (15.1)	147 (15.7)	163 (16.4)	0.71
Atrial fibrillation	597 (47.7)	378 (40.4)	360 (36.2)	<0.001
Atrial flutter	63 (5.0)	22 (2.4)	34 (3.4)	0.004
Other arrhythmia	525 (41.9)	367 (39.3)	364 (36.6)	0.036
Coronary artery disease	796 (63.6)	616 (65.9)	671 (67.4)	0.15
Cerebrovascular disease	193 (15.4)	134 (14.3)	163 (16.4)	0.46
Asthma	218 (17.4)	193 (20.6)	225 (22.6)	0.008
COPD	351 (28.0)	293 (31.3)	340 (34.2)	0.007
Pneumonia	182 (14.5)	165 (17.6)	181 (18.2)	0.041
Psychotic disorders	29 (2.3)	39 (4.2)	46 (4.6)	0.007
Other mood disorders	52 (4.2)	67 (7.2)	64 (6.4)	0.006
Depression	228 (18.2)	239 (25.6)	245 (24.6)	<0.001
Anxiety	209 (16.7)	190 (20.3)	234 (23.5)	<0.001
Type 2 diabetes	583 (46.6)	472 (50.5)	493 (49.5)	0.15
Hyperlipidemia	983 (78.5)	718 (76.8)	752 (75.6)	0.25
GERD	359 (28.7)	311 (33.3)	306 (30.8)	0.071
Cancer	164 (13.1)	102 (10.9)	90 (9.0)	0.010
Heart failure variables, n (%)				
Implanted cardiac device	335 (26.8)	258 (27.6)	275 (27.6)	0.87
Cardiomyopathy type				**0.71**
Ischemic	252 (20.1)	160 (17.1)	191 (19.2)	
Dilated	260 (20.8)	194 (20.7)	211 (21.2)	
Heart failure medications*				

ACEI	452 (44.4)	345 (44.4)	400 (48.2)	0.20
ARB	264 (26.0)	202 (26.0)	206 (24.8)	0.82
ARNI	45 (4.4)	54 (6.9)	62 (7.5)	0.013
Beta-blocker	811 (79.7)	623 (80.2)	668 (80.5)	0.92
MRA	281 (27.6)	273 (35.1)	246 (29.6)	0.002
Diuretic	645 (63.4)	505 (65.0)	554 (66.7)	0.33
Vasodilator	69 (6.8)	65 (8.4)	73 (8.8)	0.24
SGLT2 inhibitor	18 (1.8)	14 (1.8)	14 (1.7)	0.98
Digoxin	100 (9.8)	58 (7.5)	81 (9.8)	0.16
Has Rx data, no HF Rx	121 (11.9)	89 (11.5)	85 (10.2)	0.52
No Rx data	235 (18.8)	158 (16.9)	165 (16.6)	0.33
Adherent to beta-blocker†				**0.001**
Yes	391 (73.6)	307 (70.6)	290 (63.2)	
No	140 (26.4)	128 (29.4)	169 (36.8)	
Prior year HCRU visits, n (%)				
Composite	855 (68.3)	675 (72.2)	747 (75.1)	0.002
Emergency room	580 (46.3)	496 (53.0)	574 (57.7)	<0.001
All-cause hospitalization	513 (41.0)	389 (41.6)	466 (46.8)	0.012
Cardiovascular hospitalization	348 (27.8)	217 (23.2)	265 (26.6)	0.048

Values are mean ± standard deviation or number of patients (%).

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; HCRU, health care resource utilization; MRA, mineralocorticoid receptor antagonist; Rx, prescription; SGLT2, sodium-glucose cotransporter-2; SMD, standardized mean difference.

* Medication percentages (other than 'No Rx data') are based on patients with Rx data.

† Adherence to beta-blocker percentages are based on those who filled a prescription for beta-blocker medication in the 181-360 days before starting positive airway pressure therapy.

Table S2. Baseline characteristics by cardiomyopathy subgroup.

	Overall (n=3,182)	Ischemic (n=603)	Dilated (n=665)	P Value
Female, n (%)	959 (30.1)	117 (19.4)	192 (28.9)	<0.001
Age, years	59.7±11.2	62.8±10.6	56.0±10.5	<0.001
Payer				**<0.001**
Commercial	1,793 (56.3)	318 (52.7)	446 (67.1)	
Medicaid	646 (20.3)	109 (18.1)	121 (18.2)	
Medicare Advantage	743 (23.4)	176 (29.2)	98 (14.7)	
Obesity				**<0.001**
Morbidly obese	1,242 (39.0)	175 (29.0)	287 (43.2)	
Obese	924 (29.0)	203 (33.7)	195 (29.3)	
Overweight	188 (5.9)	43 (7.1)	34 (5.1)	
Healthy weight	37 (1.2)	11 (1.8)	3 (0.5)	
Not categorized	791 (24.9)	171 (28.4)	146 (22.0)	
Comorbidities				
Number	5.6±2.3	6.5±2.1	5.1±2.1	<0.001
Comorbidity, n (%)				
Coronary artery disease	2,083 (65.5)	603 (100.0)	354 (53.2)	<0.001
Atrial fibrillation	1,335 (42.0)	243 (40.3)	292 (43.9)	0.19
Hypertension	2,927 (92.0)	569 (94.4)	595 (89.5)	0.002
Pulmonary hypertension	499 (15.7)	77 (12.8)	119 (17.9)	0.012
Cerebrovascular disease	490 (15.4)	155 (25.7)	53 (8.0)	<0.001
Atrial flutter	119 (3.7)	18 (3.0)	38 (5.7)	0.018
Asthma	636 (20.0)	114 (18.9)	144 (21.7)	0.22
COPD	984 (30.9)	212 (35.2)	158 (23.8)	<0.001
Pneumonia	528 (16.6)	118 (19.6)	92 (13.8)	0.006
Psychotic disorders	114 (3.6)	20 (3.3)	21 (3.2)	0.87
Other Mood disorders	183 (5.8)	29 (4.8)	44 (6.6)	0.17
Depression	712 (22.4)	147 (24.4)	120 (18.0)	0.006
Anxiety	633 (19.9)	136 (22.6)	116 (17.4)	0.023
Type 2 diabetes	1,548 (48.6)	351 (58.2)	282 (42.4)	<0.001
Hyperlipidemia	2,453 (77.1)	553 (91.7)	464 (69.8)	<0.001
GERD	976 (30.7)	212 (35.2)	183 (27.5)	0.003
Cancer	356 (11.2)	80 (13.3)	49 (7.4)	<0.001

Values are mean ± standard deviation or number of patients (%).
COPD indicates chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease.

Table S3. Baseline characteristics by positive airway pressure therapy adherence level after inverse probability treatment weighting.

	Adherent (n=1,252)	Intermediate (n=935)	Non-Adherent (n=995)	SMD		
				A-N	A-I	I-N
Female, n (%)	383 (30.6)	283 (30.3)	301 (30.3)	0.01	0.01	0.00
Age, years	60.1±11.0	59.6±11.2	59.5±11.6	0.05	0.04	0.01
Payer				**0.01**	**0.01**	**0.00**
Commercial	709 (56.7)	526 (56.3)	561 (56.3)			
Medicaid	249 (19.9)	189 (20.2)	201 (20.2)			
Medicare Advantage	293 (23.4)	220 (23.5)	233 (23.4)			
Obesity				**0.01**	**0.02**	**0.02**
Morbidly obese	493 (39.3)	362 (38.7)	394 (39.6)			
Obese	359 (28.7)	271 (29.0)	285 (28.7)			
Overweight	75 (6.0)	56 (6.0)	58 (5.9)			
Healthy weight	15 (1.2)	11 (1.2)	12 (1.2)			
Not categorized	310 (24.7)	236 (25.2)	245 (24.6)			
Comorbid conditions						
Number	5.6±2.3	5.6±2.3	5.6±2.3	–0.02	0.01	–0.03
Comorbidity, n (%)						
Hypertension	1,150 (91.8)	860 (92.0)	919 (92.4)	–0.02	–0.01	–0.01
Pulmonary hypertension	193 (15.5)	148 (15.8)	153 (15.3)	0.00	–0.01	0.01
Atrial fibrillation	527 (42.1)	391 (41.8)	420 (42.2)	0.00	0.01	–0.01
Atrial flutter	52 (4.1)	23 (2.5)	39 (4.0)	0.01	0.09	–0.08
Other arrhythmia	487 (38.9)	367 (39.3)	392 (39.4)	–0.01	–0.01	0.00
Coronary artery disease	814 (65.1)	611 (65.4)	652 (65.5)	–0.01	–0.01	0.00
Cerebrovascular disease	195 (15.6)	142 (15.2)	155 (15.6)	0.00	0.01	–0.01
Asthma	249 (19.9)	186 (19.9)	202 (20.3)	–0.01	0.00	–0.01
COPD	382 (30.5)	288 (30.8)	306 (30.8)	–0.01	–0.01	0.00
Pneumonia	199 (15.9)	154 (16.4)	164 (16.5)	–0.02	–0.01	0.00
Psychotic disorders	47 (3.8)	36 (3.8)	38 (3.8)	0.00	0.00	0.00
Other Mood disorders	75 (6.0)	54 (5.8)	62 (6.2)	–0.01	0.01	–0.02
Depression	287 (22.9)	208 (22.2)	225 (22.6)	0.01	0.02	–0.01
Anxiety	249 (19.9)	184 (19.7)	199 (20.0)	0.00	0.01	–0.01
Type 2 diabetes	608 (48.6)	457 (48.8)	491 (49.4)	–0.02	–0.01	–0.01
Hyperlipidemia	959 (76.6)	719 (76.9)	770 (77.4)	–0.02	–0.01	–0.01
GERD	383 (30.6)	286 (30.6)	308 (30.9)	–0.01	0.00	–0.01
Cancer	144 (11.5)	103 (11.0)	116 (11.7)	–0.01	0.01	–0.02
Heart failure variables, n (%)						
Implanted cardiac device	339 (27.0)	255 (27.2)	267 (26.8)	0.01	0.00	0.01
Cardiomyopathy type					0.02	0.02
Ischemic	240 (19.2)	175 (18.7)	184 (18.5)			
Dilated	260 (20.8)	197 (21.1)	210 (21.1)			
Heart failure medications*						

ACEI	475 (45.9)	341 (44.2)	382 (46.4)	–0.01	0.04	–0.04
ARB	264 (25.5)	197 (25.6)	218 (26.5)	–0.02	0.00	–0.02
ARNI	48 (4.6)	54 (7.0)	59 (7.1)	–0.11	–0.10	–0.01
Beta-blocker	826 (79.9)	616 (79.9)	659 (80.1)	0.00	0.00	0.00
MRA	305 (29.5)	270 (35.0)	239 (29.1)	0.01	–0.12	0.13
Diuretic	665 (64.3)	497 (64.3)	546 (66.3)	–0.04	0.00	–0.04
Vasodilator	80 (7.8)	65 (8.4)	69 (8.4)	–0.02	–0.02	0.00
SGLT2 inhibitor	18 (1.8)	13 (1.6)	14 (1.8)	0.00	0.01	–0.01
Digoxin	102 (9.8)	57 (7.4)	86 (10.5)	–0.02	0.09	–0.11
Has Rx data, No HF Rx	120 (11.6)	90 (11.7)	87 (10.5)	0.03	0.00	0.04
No Rx data	218 (17.4)	164 (17.5)	172 (17.3)	0.00	0.00	0.01
Adherent to beta-blocker†					0.01	0.01
Yes	386 (69.8)	292 (69.5)	303 (69.2)			
No	167 (30.2)	129 (30.5)	135 (30.8)			
Prior year HCRU visits, n (%)						
Composite	885 (70.7)	674 (72.1)	701 (70.5)	0.00	–0.03	0.04
Emergency room	637 (50.9)	485 (51.9)	509 (51.2)	–0.01	–0.02	0.02
All-cause hospitalization	526 (42.0)	398 (42.6)	423 (42.5)	–0.01	-0.01	0.00
Cardiovascular hospitalization	345 (27.6)	227 (24.3)	249 (25.0)	0.08	0.06	–0.02
Prior year HCRU visits, number						
Composite	1.63±1.88	1.70±2.07	1.70±2.17	–0.04	–0.04	0.00
Emergency room	1.05±1.61	1.11±1.81	1.09±1.78	–0.02	–0.04	0.01
All-cause hospitalization	0.58±0.85	0.59±0.87	0.62±0.90	–0.04	–0.01	–0.03
Cardiovascular hospitalization	0.32±0.57	0.28±0.55	0.31±0.59	0.07	0.02	–0.04

Values are mean ± standard deviation or number of patients (%).

A indicates adherent; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; HCRU, health care resource utilization; I, intermediate adherence; MRA, mineralocorticoid receptor antagonist; NA, non-adherent; Rx, prescription; SGLT2, sodium-glucose cotransporter-2; SMD, standardized mean difference.

*Medication percentages (other than 'No Rx data') are based on patients with Rx data.

† Adherence to beta-blocker percentages are based on those who filled a prescription for beta-blocker medication in the 181-360 days before starting positive airway pressure therapy.

Table S4. Mean number of healthcare resource use visits and positive airway pressure therapy usage by cardiomyopathy subgroup.

	Overall (n=3,182)	Ischemic (n=603)	Dilated (n=665)	P Value
Prior year				
Composite	1.71±2.11	1.88±2.18	1.73±1.96	0.39
Emergency room	1.10±1.76	1.17±1.78	1.06±1.62	0.15
All-cause hospitalization	0.61±0.89	0.71±0.99	0.68±0.86	0.81
Cardiovascular hospitalization	0.31±0.58	0.33±0.59	0.41±0.65	0.021
Year 1, number				
Composite	1.24±2.25	1.29±2.37	1.18±2.07	0.086
Emergency room	0.89±1.81	0.90±1.89	0.82±1.69	0.064
All-cause hospitalization	0.35±0.90	0.40±0.96	0.36±0.86	0.66
Cardiovascular hospitalization	0.12±0.48	0.12±0.46	0.14±0.53	0.83
PAP hours per day	3.6±2.9	3.7±3.0	3.5±2.8	0.49
PAP days per week	4.0±2.6	4.0±2.7	4.0±2.6	0.71
PAP hours per use day	5.2±2.2	5.3±2.3	5.2±2.2	0.39

Values are mean ± standard deviation.
PAP, positive airway pressure.