ORIGINAL RESEARCH

Diagnosing and Treating Sleep Apnea in Patients With Acute Cerebrovascular Disease

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***Background*—**Obstructive sleep apnea (OSA) is common among patients with acute ischemic stroke and transient ischemic attack. We evaluated whether continuous positive airway pressure for OSA among patients with recent ischemic stroke or transient ischemic attack improved clinical outcomes.

***Methods and Results*—**This randomized controlled trial among patients with ischemic stroke/transient ischemic attack compared 2 strategies (standard or enhanced) for the diagnosis and treatment of OSA versus usual care over 1 year. Primary outcomes were National Institutes of Health Stroke Scale and modified Rankin Scale scores. Among 252 patients (84, control; 86, standard; 82, enhanced), OSA prevalence was as follows: control, 69%; standard, 74%; and enhanced, 80%. Continuous positive airway pressure use occurred on average 50% of nights and was similar among standard (3.9±2.1 mean hours/nights used) and enhanced (4.3±2.4 hours/nights used; P=0.46) patients. In intention-to-treat analyses, changes in National Institutes of Health Stroke Scale and modified Rankin Scale scores were similar across groups. In as-treated analyses among patients with OSA, increasing continuous positive airway pressure use was associated with improved National Institutes of Health Stroke Scale score (no/poor, −0.6±2.9; some, −0.9±1.4; good, −0.3±1.0; P=0.0064) and improved modified Rankin Scale score (no/poor, −0.3±1.5; some, −0.4±1.0; good, −0.9±1.2; P=0.0237). In shift analyses among patients with OSA, 59% of intervention patients had best neurological symptom severity (National Institutes of Health Stroke Scale score, 0–1) versus 38% of controls (P=0.038); absolute risk reduction was 21% (number needed to treat, 4.8).

***Conclusions*—**Although changes in neurological functioning and functional status were similar across the groups in the intention-to-treat analyses, continuous positive airway pressure use was associated with improved neurological functioning among patients with acute ischemic stroke/transient ischemic attack with OSA.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT01446913. **(*J Am Heart Assoc*. 2018;7: e008841. DOI: 10.1161/JAHA.118.008841.)**

Key Words: acute ischemic stroke • sleep apnea • transient ischemic attack

Sleep apnea is common among patients with acute ischemic stroke and transient ischemic attack (TIA) (60–80%),[1,2] and preliminary data have suggested that treatment of obstructive sleep apnea with continuous positive airway pressure (CPAP) may improve patient outcomes.[3] Several randomized controlled studies have evaluated the use

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Accompanying Tables S1 through S3 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.008841

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Clinical Perspective

What Is New?

- This randomized controlled trial evaluated whether continuous positive airway pressure for obstructive sleep apnea among patients with ischemic stroke or transient ischemic attack improved neurological symptom severity (measured by the National Institutes of Health Stroke Scale) and functional status (measured by the modified Rankin Scale).
- We examined the effect of continuous positive airway pressure among patients with ischemic stroke or transient ischemic attack (intention-to-treat analysis) and among patients with stroke or transient ischemic attack who had obstructive sleep apnea (as-treated analysis).
- In intention-to-treat analyses, changes in National Institutes of Health Stroke Scale and modified Rankin Scale scores were similar across groups.
- In as-treated analyses, increasing continuous positive airway pressure use was associated with improvements in National Institutes of Health Stroke Scale and modified Rankin Scale: 59% of intervention patients had best neurological symptom severity (National Institutes of Health Stroke Scale score, 0–1) versus 38% of controls (P=0.038); absolute risk reduction was 21% (number needed to treat, 4.8).

What Are the Clinical Implications?

- Patients with ischemic stroke and transient ischemic attack should receive screening for sleep apnea in the short-term event period, and patients with obstructive sleep apnea should receive treatment with continuous positive airway pressure.

of CPAP among patients with acute ischemic stroke or TIA, but they have been limited by short follow-up or small sample size.[1,3–5] The largest of the randomized trials observed (N=126) patients with acute stroke with sleep apnea over a 2-year period.[6] Patients were randomly assigned to receive either fixed-pressure CPAP or usual care. The mean time from stroke onset to the first cardiovascular event was longer in the CPAP group: 15 versus 8 months (P=0.044). Two randomized trials evaluated the use of early CPAP therapy for the purpose of improving stroke severity, as measured by the National Institutes of Health (NIH) Stroke Scale (NIHSS). One trial of (N=56) patients with acute stroke demonstrated a greater improvement in NIHSS with early CPAP compared with usual care (improvement of 3.0 versus 1.0 points; P=0.03) over a 1-month period.[2] Similarly, Minnerup et al found that the NIHSS improvement was largest among patients with the greatest CPAP use over the first 8 days after stroke (improvement of 2.3 versus 1.4 points; P=0.022).[7] The largest of the cohort studies (N=189) had a follow-up of 7 years and found that patients with sleep apnea who did not use CPAP had higher recurrent stroke rates than patients who used CPAP (32% versus 14%; P=0.021) and a higher adjusted incidence of nonfatal vascular events (hazard ratio, 2.87; 95% confidence interval [CI], 1.11–7.71).

The main study had 3 primary objectives: to evaluate whether a diagnosis and treatment intervention strategy for sleep apnea resulted in reduction in 5 domains of vascular risk (inflammatory, autonomic activity, insulin resistance, endothelial injury, and atherosclerosis); to determine the level of CPAP use that corresponded to greatest improvements in markers of vascular risk; and to determine whether an enhanced intervention protocol resulted in improved long-term CPAP adherence compared with a standard intervention protocol.[8] This article describes the results of the secondary objective, which was to examine the relationship between CPAP use and clinical outcomes, including neurological symptom severity, functional status, and recurrent vascular events.

Methods

The methods used in the analysis and the materials used to conduct this trial will be made available on request; the data must remain on the current servers, but requests for analysis of the data can be made to the corresponding author. This randomized controlled trial among patients with TIA and ischemic stroke compared strategies for the diagnosis and treatment of sleep apnea with usual care. Patients were randomized to a control group (usual care) or to 1 of 2 intervention groups (standard or enhanced). The study was conducted at 5 participating hospitals in 2 centers in the United States (Yale School of Medicine [New Haven, CT] and Indiana University School of Medicine [Indianapolis, IN]). Randomization was stratified by center and by TIA versus stroke index event. The principal investigators (D.M.B., H.K.Y.) and one of the study statisticians (S.O.) were blinded to patient treatment assignment. A Data Safety Monitoring Board, assembled by the NIH, National Heart, Lung, and Blood Institute, convened every 6 months to review unblinded recruitment and safety data. Human subjects' approvals were obtained from the participating sites' Institutional Review Boards and by the Department of Veterans Affairs Research and Development committees.

Inclusion and Exclusion Criteria

Patients were included if they were ≥18 years, had a TIA or ischemic stroke, and were within 1 week of neurological symptom onset. Eligible patients had brain imaging within 48 hours of symptom onset. Patients were excluded for the

following reasons: known sleep apnea; suspected sleep disorder other than sleep apnea (eg, narcolepsy); hospice or receiving comfort measures only; unable to use a nasal or face mask (eg, facial trauma); mechanical ventilation; non-English language; inability to provide informed consent; active suicidal ideation; residence outside the recruitment area; or the provider did not allow research staff to contact the patient.

Unattended Polysomnography

The unattended type-2 polysomnography (Safiro; Compumedics) included the following: electroencephalography, electrooculography, electromyography, snore channel, oral thermistor, nasal pressure, chest and abdominal effort, leg movements, position, electrocardiography, and oxygen saturation. Polysomnographic data were scored by a single sleep laboratory (Harvard School of Medicine). Apnea was defined as complete cessation of airflow for ≥10 seconds and was classified as "obstructive" if respiratory effort was present or "central" in the absence of respiratory effort. Hypopnea was defined as a decrease in airflow of ≥30% from baseline associated with ≥3% oxygen desaturation or arousal.[9] Patients with an apnea-hypopnea index of ≥5 events/h were classified as having sleep apnea.[9] Central sleep apnea was defined as present when >50% of the events were classified as central.

Auto-Titrating CPAP

The Respironics M-series (System One; Phillips Respironics, North Ryde, Australia) CPAP machine produced a recording of the pressure that was delivered throughout the night, respiratory events (apneas and hypopneas), adherence (hours of use per night), and air leak. It used an algorithm to detect and distinguish obstructive from central events and responded accordingly. Phillips Respironics provided the CPAP machines but had no role in the design of the study, interpretation of results, or drafting of this article.

Intervention Protocols

Intervention patients received polysomnography as soon as possible after the index stroke/TIA event. Intervention patients with sleep apnea received auto-titrating CPAP. The 2 intervention protocols differed in both the frequency and content of the visits: the enhanced protocol focused on delivering the patient-tailored behavioral adherence program, and the standard protocol focused on technical issues related to the CPAP equipment. In both intervention groups, a final visit took place at the conclusion of the subject's participation for outcome assessment.

Standard intervention

The standard intervention consisted of 5 in-person contacts and 1 telephone contact over the up to 12-month follow-up. Research staff provided an educational session about sleep apnea and CPAP, the results of the polysomnography, and instruction about CPAP equipment during the initial in-person contact. In-person contacts at 1, 3, and 6 months postenrollment allowed for interrogation of the CPAP unit for adherence, discussions about symptom improvement and adverse effects, and encouragement of continued use.

Enhanced intervention

The enhanced adherence intervention protocol was based on the narrative model of patient decision making[10] and self-determination theory.[11] At the time of unattended polysomnography, patients received the standardized educational session (previously described). At the time of CPAP delivery, patients completed a questionnaire about attitudes and beliefs about sleep apnea, social supports, and individual risks for consequences of sleep apnea and the Self-Efficacy Measure in Sleep Apnea.[12] The staff was trained to identify patient-specific barriers and facilitators of CPAP adherence.

The key component of the enhanced intervention was the development of a Personalized Positive Pressure Plan for each patient by the intervention team that included a sleep medicine physician, a general internist with special experience in the care of patients with cerebrovascular disease, a doctoral-level specialist in health communications, a doctoral-level expert in adult learning, a respiratory technician, and members of the research staff (who were most familiar with the individual patient). A template that included patient-specific information served to organize the Personalized Positive Pressure Plan deliberations. A component of the template was a "balance sheet" of barriers and facilitators of CPAP adherence that team members used to brainstorm possible approaches that could be used to augment patient adherence. The staff implemented the suggestions and, if needed, reviewed the status of the patient at a future Personalized Positive Pressure Plan meeting.

During the first week after CPAP initiation, the patient had 1 in-person and 2 telephone contacts to deliver the behavioral adherence intervention. The patient received weekly in-person contacts during the first month to encourage CPAP adherence. Telephone contacts occurred at months 2, 4, 5, 7, 8, 9, 10, and 11 to serve as "booster sessions" for the targeted education and behavioral adherence intervention. In-person visits occurred at 3 and 6 months for detailed CPAP compliance downloads. Additional in-person and telephone visits occurred at the request of participants for additional support.

Usual Care

Control patients received unattended polysomnography at the end of the follow-up. Patients and their primary care providers were informed of polysomnographic results; patients with sleep apnea were encouraged to receive CPAP. Patients in the control group were neither dissuaded nor encouraged to seek polysomnography as part of usual care during the follow-up.

Safety

Safety monitoring on adverse events occurred at all scheduled follow-up visits. All adverse events were reviewed by the internal study safety committee. Adverse event data were provided to a safety monitor monthly, who was independent of the investigative team. Safety data were reviewed by the Data Safety Monitoring Board every 6 months.

Follow-Up

The study originally planned to include a 1-year follow-up for all participants. At an interim Data Safety Monitoring Board meeting, the decision was made to extend recruitment to achieve the planned sample size but to not extend the trial duration; therefore, enrolled patients had a theoretical minimum follow-up of 6 months and a maximum follow-up of 1 year. The recurrent vascular events were reported both as observed rates and per 100 person-years of follow-up; the latter was calculated as (number of events/total person-years of follow-up)$\times$100, where follow-up was calculated from randomization.

Outcomes

CPAP adherence

CPAP adherence was measured in terms of number of nights of any use and number of hours of use/night. CPAP adherence was classified as follows: "good" if [cumulative hours used/(total nights available$\times$0.70)] was $\geq$4 hours; "some" if [cumulative hours used/(total nights available$\times$0.70)] was <4 hours and the number of days used was >10% of the total nights available; and "none/poor" if the number of days used was $\leq$10% of the total nights available or if the patient did not use any CPAP.[13]

Neurological symptom severity

Neurological symptom severity was assessed using the NIHSS.[14] The NIHSS includes 11 domains of neurological functioning; normal neurological functioning receives a score of 0, and increasing scores signify greater neurological impairment. The best neurological outcome group was defined as an NIHSS at the time of follow-up of 0 to 1.[15]

Functional status

Functional status was assessed using the 7-level modified Rankin Scale (mRS) score.[16] Higher scores indicate worsening functional status, and a single point change is considered to be clinically important.[17] An mRS score of 0 indicates no symptoms; 1, no significant disability (able to perform usual activities despite some symptoms); 2, slight disability (able to look after own affairs without assistance, but unable to perform all previous activities); 3, moderate disability (requires some help, but able to walk unassisted); 4, moderately severe disability (unable to attend to own bodily needs without assistance and unable to walk unassisted); 5, severe disability (requires constant nursing care and attention, bedridden, and incontinent); and 6, patients who have died.

Recurrent vascular events

The combined recurrent vascular event end point included the following: stroke, acute myocardial infarction, unstable angina hospitalization, urgent coronary revascularization, and all-cause mortality. Potential vascular events were adjudicated by independent (blinded to treatment group) adjudicators (a vascular neurologist or cardiologist) using standard definitions.

Analysis Plan

The analysis plan included both an intention-to-treat analysis (which included all patients) and a prespecified as-treated analysis among patients with sleep apnea, with groups defined by CPAP use: intervention and control patients who did not use CPAP; intervention patients with some CPAP use; and intervention patients with good CPAP use. The rationale for this approach was based on the hypothesis that CPAP treatment would only be beneficial to patients with sleep apnea. In performing the as-treated analyses, we lost the comparability ensured by randomization and results are best suited for generating hypotheses for future research. We prespecified the plan to combine the standard and enhanced interventions groups, if we found no differences in CPAP use across the 2 groups.

The planned sample size of 255 patients (85 patients in each group) was designed to provide $\geq$80% power for the primary aims of the overall study; this article describes the results of the secondary aims. No testing of statistical significance was planned for the recurrent vascular event rate data because the study was not designed to be powered to detect differences in the recurrent vascular event rate.

No imputations were made for missing data. For comparison of demographics, χ^2 or Fisher's exact tests were used for categorical variables, and ANOVA or Kruskal-Wallis tests were used for continuous measures. Data analyses was performed using SAS/STAT software, SAS System for Windows Version 9.3 (SAS Institute Inc, Cary, NC).

To determine whether an enhanced intervention protocol resulted in improved long-term CPAP adherence rates compared with a standard intervention protocol, we restricted the analysis to intervention patients with sleep apnea and used logistic regression to model the proportion of patients with good CPAP use. We adjusted for length of CPAP use (defined as last CPAP use date minus CPAP delivery date), site, and stroke versus TIA index event.

For the comparison of the change in outcomes by CPAP adherence groups, we restricted analyses to intervention patients (enhanced and standard) with sleep apnea. We constructed models, as previously described. If the overall estimate of the effect for adherence group was statistically significant, we further assessed the differences between pairs of groups (eg, good versus some CPAP use).

To evaluate the change in outcomes, we used an ordinal change analysis (also known as shift analysis) (Mantel-Haenszel χ^2 test for ordered responses) to compare measurements obtained at the final visit by treatment arms.[18] Using categorization systems deployed in other acute stroke trials, we examined the mRS score across 5 ordinal categories (0 through ≥4) and the NIHSS score across 3 categories (mild, 0–1; moderate, 2–8; severe, ≥9).[19] NIHSS and mRS scores were modeled using a generalized estimating equation Poisson model with main effects. In the generalized estimating equation, the clusters were defined by each patient and an independent correlation structure was used in the primary analysis. In sensitivity analyses, we used alternative correlation structures and found nearly identical results (data not shown). The independent variables included the following: site, stroke/TIA diagnosis, treatment group, and the day of measurement. The main effects were selected on the basis of the design of this randomized study.

Role of Funding Source

Although the NIH/National Heart, Lung, and Blood Institute convened a data safety monitoring board, the funder had no role in the study design, data collection, data analysis, data interpretation, or writing of this article.

Results

A total of 1884 patients were screened for eligibility (2011–2013); 919 were excluded, and 332 refused to participate. A total of 252 patients were randomized (84, control; 86, standard intervention; and 82, enhanced intervention; Figure 1). Two control patients were withdrawn from the study per protocol because of suicidal ideation. Some patients refused specific elements of the baseline or final assessments (eg, the blood draw), but they were retained in analyses for which they had data; 11 control patients, 9 standard patients, and 9 enhanced patients were excluded from the analyses because of insufficient data (Figure 1). The reasons for withdrawal (Figure 1) included significant concurrent illness and "patient reasons" (eg, patients stating that the study did not relate to their health, or the patient was "too busy" to participate).

The baseline characteristics of the study population are provided in Table 1; overall, 41% were women, 36% were black, and for 80% the index event was stroke. There were few observed differences between patients with complete versus missing data (data not shown). The median time from symptom onset to enrollment was as follows: control, 74 hours; standard, 91 hours; and enhanced, 93 hours (P=0.65). The median time from symptom onset to polysomnography was 31 days in the standard group and 47 days in the enhanced intervention group; CPAP delivery took an additional month after polysomnography. The median follow-up was as follows: control, 360 days; standard, 346 days; and enhanced, 324 days (P=0.49).

The obstructive sleep apnea prevalence was as follows: standard, 39/53 (74%); enhanced, 45/56 (80%); and control, 20/29 (69%) (Table S1). All of the intervention patients who received polysomnography did so as part of the study protocol; 29 control patients received polysomnography at the end of the study per protocol, and an additional 8 control patients received polysomnography as part of routine clinical practice (1 patient had no sleep apnea; among the 7 patients with sleep apnea [8.3%], 5 had some CPAP use and 2 had no CPAP use). The mean apnea-hypopnea index for patients with sleep apnea was as follows: control, 28.5 (±SD, 21.1) events/h; standard, 23.7±19.6 events/h; and enhanced, 21.6±17.8 events/h (P=0.30), indicating that the sleep apnea in this population was of moderate severity.

CPAP Adherence

More than 70% of the intervention patients with sleep apnea had some or good CPAP use (Table 2): 25 of 36 with CPAP use data (69.4%) of standard patients and 34 of 45 with CPAP use data (75.6%) of enhanced patients. The median CPAP use per nights was 4.5 hours for both standard and enhanced patients; the enhanced protocol did not improve long-term CPAP adherence compared with the standard protocol.

Neurological Symptom Severity and Functional Status

In the intention-to-treat analysis (Table 3), changes in NIHSS score were modest and were similar across each of the 3 groups (mean±SD): control, −0.5±2.1; standard intervention,

−0.8±1.9; enhanced intervention, −0.7±2.1 (*P*=0.80) (Table 3). Similarly, changes in the mRS score were not statistically different across the 3 groups: control, 0.1±1.5; standard intervention, −0.6±1.2; enhanced intervention, −0.3±1.5 (*P*=0.60).

In the as-treated analysis among patients with sleep apnea (Table 4), increasing CPAP use was associated with improvements in NIHSS score: no/poor CPAP use, −0.6±2.9; some CPAP use, −0.9±1.4; good CPAP use, −0.3±1.0 (*P*=0.0064). Similarly, increasing CPAP use was associated with improvements in mRS score: no/poor CPAP use, −0.3±1.5; some CPAP use, −0.4±1.0; good CPAP use, −0.9±1.2 (*P*=0.0237).

Figure 2 displays the shift analyses of final visit measures among patients with sleep apnea. More intervention patients were observed to have the best neurological functioning (an NIHSS score of 0–1, indicated in dark shading), 59% compared with 38% for control patients (*P*=0.038 for the shift analysis); absolute risk reduction was 21% (number needed to treat of 4.8 [95% CI, 3.3–8.2]). Although fewer control patients had the best functional status on the mRS (indicated in dark shading) compared with intervention patients, the results were not statistically significant (*P*=0.068 for the shift analysis).

Recurrent Vascular Events

With regard to recurrent vascular events (Table S2): 13.1 events per 100 person-years of follow-up were observed in the control group, and 11.0 events per 100 person-years of follow-up were observed in the intervention groups. Six patients died during the study period, 2 in the control group, 0 in the standard intervention group, and 4 in the enhanced intervention group (Table S3).

Discussion

The current study is, to our knowledge, the largest randomized controlled trial to evaluate the effects of CPAP among patients with a recent stroke or TIA. The results demonstrate that CPAP therapy for patients with ischemic stroke or TIA who have sleep apnea was associated with statistically significant and clinically relevant improvements

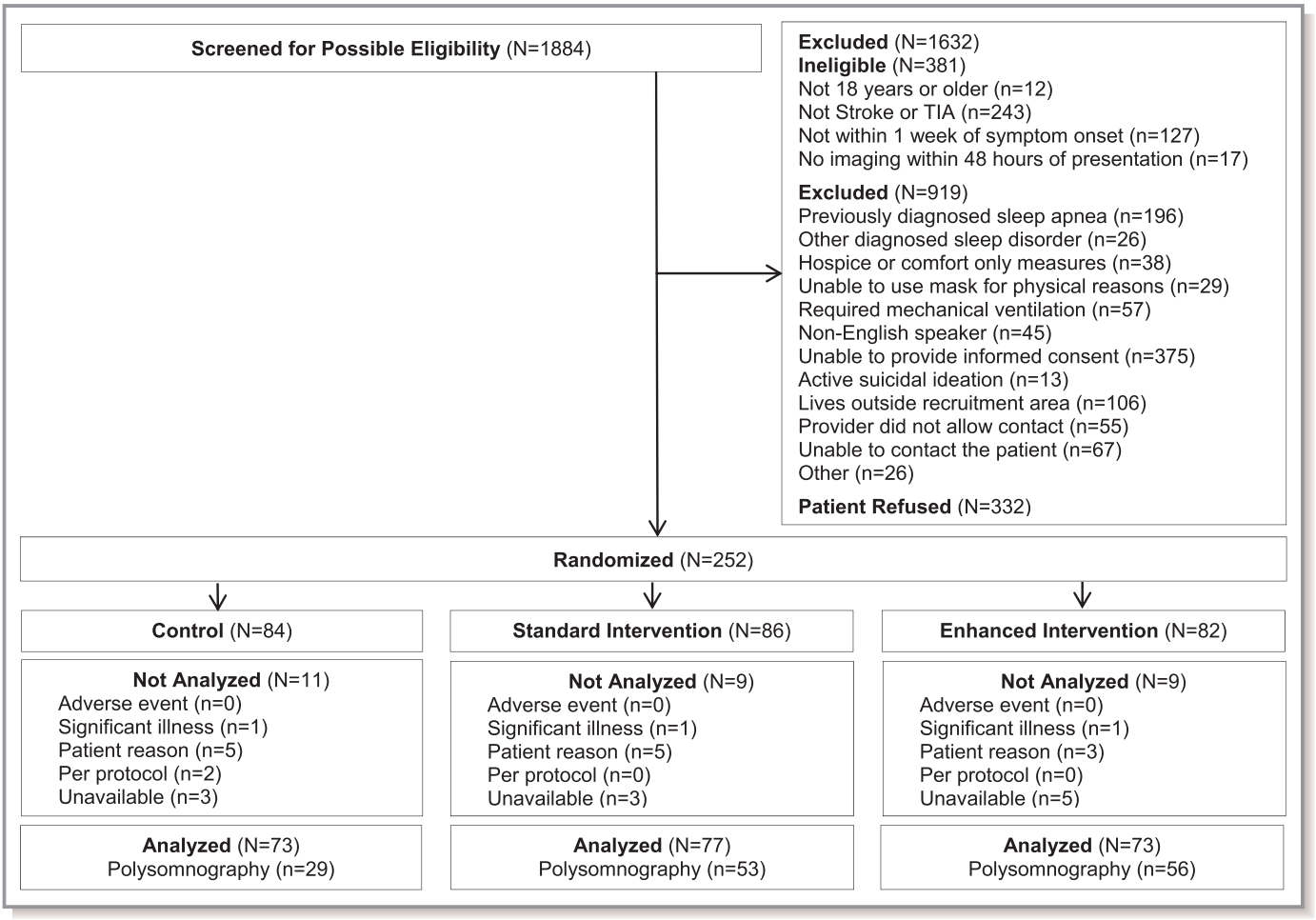

Figure 1. Patient flow. TIA indicates transient ischemic attack.

Table 1. Baseline Characteristics

Characteristic	Control (N=84)	Intervention	
		Standard (N=86)	Enhanced (N=82)
Age, y			
Median (range)	59 (26–85)	61 (30–94)	62 (32–96)
Mean±SD	60.3±12.5	60.0±13.2	61.3±12.8
Hispanic ethnicity, N (%)	4 (4.8)	2 (2.4)	2 (2.5)
White race, N (%)	48 (57.1)	52 (61.2)	56 (69.1)
Male sex, N (%)	48 (57.1)	51 (59.3)	50 (61)
Index cerebrovascular event, N (%)*			
Stroke	68 (81)	68 (79.1)	66 (80.5)
TIA	11 (13.1)	15 (17.4)	15 (18.3)
Other	5 (6)	3 (3.5)	1 (1.2)
Event classification			
Atherothrombotic/large vessel (eg, carotid stenosis)	18 (21.4)	9 (10.5)	16 (19.5)
Cardioembolic	11 (13.1)	21 (24.4)	14 (17.1)
Lacunar	20 (23.8)	16 (18.6)	15 (18.3)
Other classified (eg, dissection)	2 (2.4)	4 (4.7)	4 (4.9)
Unclassified	17 (20.2)	15 (17.4)	15 (18.3)
Missing	16 (19.0)	21(24.4)	18 (22.0)
Patient awoke with symptoms	20 (23.8)	26 (30.2)	22 (26.8)
Patient was found down	3 (3.6)	4 (4.7)	1 (1.2)
Seizure at symptom onset	2 (2.4)	1 (1.2)	0 (0)
Clinical features of index event			
Unilateral weakness with or without speech impairment	72 (85.7)	67 (77.9)	56 (68.3)
Speech impairment without weakness	3 (3.6)	8 (9.3)	14 (17.1)
Other	9 (10.7)	11 (12.8)	12 (14.6)
Duration of symptoms, min			
<10	2 (2.4)	2 (2.3)	3 (3.7)
10–59	6 (7.1)	14 (16.3)	8 (9.8)
>60	24 (28.6)	29 (33.7)	29 (35.4)
Possible permanence	52 (61.9)	41 (47.7)	42 (51.2)
Received thrombolysis	13 (15.5)	10 (11.6)	12 (14.6)
$ABCD^2$ score for patients with TIA, median (range)†	4 (1–5)	3 (2–5)	3 (0–5)
Comorbidity, N (%)			
Hypertension	62 (76.5)	54 (65.9)	50 (61)
Any antihypertensive medication	59 (70.2)	60 (69.8)	46 (56.1)
Hyperlipidemia	47 (59.5)	45 (57)	42 (51.9)
Diabetes mellitus	35 (41.7)	32 (37.2)	31 (37.8)
Chronic pain	17 (22.4)	15 (19.5)	14 (18.2)
Depression	19 (25.0)	23 (29.9)	24 (31.6)
Current tobacco smoking	18 (21.4)	27 (31.4)	29 (35.4)
Chronic obstructive pulmonary disorder	4 (5.0)	12 (14.6)	3 (3.8)
Myocardial infarction	9 (11.1)	16 (19.8)	12 (15.0)

Continued

Table 1. Continued

Characteristic	Control (N=84)	Intervention	
		Standard (N=86)	Enhanced (N=82)
Anxiety	16 (21.3)	17 (22.4)	14 (18.2)
Peripheral vascular disease	9 (11.5)	12 (15.2)	11 (13.9)
Atrial fibrillation	8 (10.3)	10 (12.7)	7 (8.9)
Chronic kidney disease	9 (10.7)	7 (8.1)	7 (8.5)
Dementia	3 (3.8)	0 (0.0)	1 (1.3)
Congestive heart failure	7 (8.6)	9 (11.4)	4 (5.1)
Charlson comorbidity score, median (range)	1.5 (0–15)	1 (0–12)	2 (0–16)
Sleep duration, mean±SD, h/d	7.0±1.8	6.8±1.5	7.3±1.8
Measurements, mean±SD			
Neck circumference, inches	15.9±2.0	15.8±1.9	15.6±1.9
Waist circumference, inches	42.2±6.6	42.4±6.5	41.7±6.8
Weight, pounds	192.8±46.8	201.2±51.4	188.4±47.8
Body mass index, kg/m^2	30.0±6.6	31.1±8.6	29.9±8.0
Index event evaluation, N (%)*			
Thrombolytic therapy given	13 (15.5)	10 (11.6)	12 (14.6)
Carotid artery imaging performed	79 (94)	84 (97.7)	76 (92.7)
Carotid endarterectomy or stenting	4 (4.8)	4 (4.7)	8 (9.8)
ECG performed	73 (89.0)	68 (80.0)	71 (91.0)
Echocardiography performed	71 (84.5)	72 (83.7)	74 (90.2)
Anticoagulation for patients with atrial fibrillation	5/9 (55.6)	6/11 (54.5)	3/5 (60)
Antiplatelet agent prescribed at discharge	71 (84.5)	73 (84.9)	74 (90.2)
Tobacco cessation counselling for smokers	15 (62.5)	19 (65.5)	11 (36.7)
Diabetes mellitus management plan for patients with diabetes mellitus	14 (48.3)	7 (35.0)	10 (35.7)
Lipid-lowering medication	60 (71.4)	50 (58.1)	55 (67.1)

TIA indicates transient ischemic attack.

*The classification of the index event was made on the basis of chart review at the end of the clinical evaluation and, therefore, differs from the original stroke vs TIA designation that was made at the time of randomization, which usually occurred early after presentation.

†The ABCD^2 score is a prognostic index used to identify patients with TIA who are at risk of recurrent vascular events and includes age, blood pressure, clinical features (speech vs weakness), duration of symptoms, and diabetes mellitus.

in neurological symptoms and functional status. The best neurological functioning outcome has been used in acute stroke therapy trials, including the original studies that demonstrated the effectiveness of thrombolytic therapy.[15] In the present study of the effect of CPAP therapy, the absolute risk reduction for the achievement of the best neurological functioning was 21%, indicating that the number needed to treat was 4.8 (95% CI, 3.3–8.2). The number needed to treat to achieve best neurological function associated with the diagnosis and management of sleep apnea among patients with stroke and TIA is exceptionally low. To provide context for this finding, the original thrombolytic therapy study demonstrated an 11% absolute increase in the proportion of patients achieving the best neurological functioning, indicating a number needed to treat of 9.1 for thrombolysis. Unlike other acute stroke therapies, CPAP has an established track record of safety and can be applied in addition to other effective interventions. These results demonstrate that this diagnosis and treatment strategy, which focuses on the timely identification and management of obstructive sleep apnea after stroke/TIA, can be implemented with excellent safety.

Our results add to the body of evidence that supports the diagnosis and treatment of sleep apnea early after a stroke or TIA event.[3] In addition to the robust literature that supports the treatment of sleep apnea in the general population,[20,21] emerging data have suggested that patients with cerebrovascular disease in the early poststroke period derive *neurological*

Table 2. CPAP Adherence Among Intervention Patients With Sleep Apnea

Outcome		Intervention Patients With Sleep Apnea		Unadjusted *P* Value*	Adjusted *P* Value*
		Standard (N=39)	Enhanced (N=45)		
Patients who had CPAP delivered and had CPAP use data, N (%)		36 (92.3)	45 (100.0)	0.06	0.90
CPAP adherence categories, N (%)†				0.81	0.95
Good		14 (38.9)	18 (40.0)		
Some		11 (30.6)	16 (35.6)		
None/poor		11 (30.6)	11 (24.4)		
CPAP use per CPAP-use night, h	N	35	45	0.46	0.65
	Mean±SD	3.9±2.1	4.3±2.4		
	Median (range)	4.5 (0.2–7.5)	4.5 (0.1–9.4)		
CPAP use per night, h	N	35	45	0.30	0.51
	Mean±SD	2.3±2.3	2.9±2.8		
	Median (range)	1.7 (0.0–7.6)	2.0 (0.0–8.8)		
Proportion of nights using CPAP	N	35	45	0.45	0.66
	Mean±SD	0.5±0.4	0.5±0.4		
	Median (range)	0.4 (0.0–1.1)	0.4 (0.0–1.1)		
Total cumulative time of CPAP per days in follow-up, h	N	35	45	0.75	0.95
	Mean±SD	1.6±1.8	1.8±2.0		
	Median (range)	0.8 (0.0–5.9)	1.4 (0.0–7.9)		
Patients who had CPAP delivered but without CPAP data, N (%)		2 (5.1)	0 (0.0)	0.12	…
Patients who did not have CPAP delivered, N (%)	Unable to contact	0 (0.0)	0 (0.0)	…	…
	Patient refused CPAP	1 (2.6)	0 (0.0)	0.46	…

CPAP indicates continuous positive airway pressure.

*Unadjusted *P* values were calculated from χ^2 or Fisher exact tests, or *t* tests (log transformations were used for nonnormal data). Adjusted *P* values were calculated from modeling (logistic, multinomial logistic, or linear regressions) after controlling for the covariates of time (length of CPAP use, except for the results related to the patients who had CPAP delivered and had CPAP use data, the total cumulative hours of CPAP per days in follow-up, and the patients who had CPAP delivered but who did not have CPAP data for whom time was the length of follow-up), site, and transient ischemic attack/stroke index event.

†CPAP adherence categories were calculated for patients with CPAP use data and classified into 3 groups: "good" if [cumulative hours used/(total nights available×0.70)] was ≥4 hours; "some" if [cumulative hours used/(total nights available×0.70)] was <4 hours and the number of days used was >10% of the total nights available; and "none/poor" if the number of days used was ≤10% of the total nights available or if the patient did not use any CPAP.

benefit from the treatment of sleep apnea. Three randomized controlled trials demonstrated improvements in the NIHSS score among patients treated in the acute stroke period; however, these studies were limited by small sample sizes (ranging from 32 to 55 patients) and short follow-ups (ranging from 8 to 90 days).[2,4,7] In contrast to the favorable evidence supporting the diagnosis and treatment of sleep apnea in the acute stroke or TIA period, randomized controlled trials evaluating the use of CPAP in patients with subacute and chronic stroke have reported mixed results.[3,22–24] The SAVE (Sleep Apnea Cardiovascular Endpoints) trial, for example, recruited patients with established cardiovascular disease or cerebrovascular disease, including patients who were at least 3 months poststroke.[25] The results of the SAVE trial were reported for the entire population (not just the enrolled patients with stroke or TIA). Despite demonstrating no difference in the primary end point of cardiovascular death, myocardial infarction, stroke, or hospitalization for acute coronary syndrome, heart failure, or TIA, the propensity-matched analysis demonstrated that CPAP use was associated with lower stroke risk than usual care (hazard ratio, 0.56; 95% CI, 0.32–1.00; *P*=0.05) and lower risk of cerebral events than usual care (hazard ratio, 0.52; 95% CI, 0.30–0.90; *P*=0.02).[4] Taken as a whole, the literature suggests that the sooner after a stroke or TIA that the CPAP can be initiated, the more substantial the improvement in clinical outcomes.

The long-term CPAP adherence rates observed in this study indicate that >70% of patients had some CPAP use over the ≈1-year follow-up; this suggests that it is feasible to provide CPAP therapy to patients with cerebrovascular disease. These observed rates are consistent with data from general sleep apnea populations; for example, McArdle et al conducted a study of 1155 patients with sleep apnea, but not with cerebrovascular disease, and found that 68% were using

Table 3. Clinical Outcome Changes: Intention-to-Treat Analysis

Outcome		Control (N=73)*	Intervention*		*P* Value				
			Standard (N=77)	Enhanced (N=73)	Overall	Control vs Standard	Control vs Enhanced	Standard vs Enhanced	Control vs Intervention
Modified Rankin Scale score	Baseline	65 1.6±1.4 1 (0, 5)	68 1.8±1.4 2 (0, 4)	68 1.9±1.5 2 (0, 6)	0.60	…	…	…	0.81
	Final	47 1.5±1.7 1 (0, 6)	50 1.0±1.1 1 (0, 4)	52 1.4±1.5 1 (0, 6)					
	Change	43 0.1±1.5 0 (−3, 4)	47 −0.6±1.2 0 (−3, 2)	49 −0.3±1.5 0 (−4, 4)					
NIH Stroke Scale score	Baseline	62 2.4±2.9 2 (0, 17)	59 2.2±2.3 2 (0, 10)	64 2.3±2.7 1 (0, 12)	0.80	…	…	…	0.71
	Final	44 2.0±3.2 1 (0, 20)	51 1.6±2.0 1 (0, 7)	50 1.5±1.5 1 (0, 5)					
	Change	39 −0.5±2.1 0 (−7, 3)	44 −0.8±1.9 0 (−8, 3)	46 −0.7±2.1 0 (−8, 5)					

*Data are given as number, mean±SD, and median (minimum, maximum). NIH indicates National Institutes of Health.

CPAP after 5 years.[26] Given that no differences in CPAP adherence were observed between the standard and enhanced protocols, future research could deploy the standard intervention approach (which may be of greater intensity than is typical in routine clinical care).

The major limitation of this study was missing data. Given that the design involved randomizing patients before polysomnography, we augmented the planned sample size to account for patients without sleep apnea who were unlikely to contribute a change in outcomes. Losses to follow-up were equally distributed across all 3 randomization groups; therefore, it is unlikely that missing data biased the results. The primary methodological risk of missing data was the potential for overlooking associations that might not achieve statistical significance because of reduced sample size. For example, losses to follow-up could potentially impair our ability to detect differences in outcomes across the 3 groups. We had final mRS data for 64% (47/73) of control group patients, 65% (50/77) of standard intervention patients, and 71% (52/73) of enhanced intervention patients. Similarly, we had final NIHSS data for 60% (44/73) of control group patients, 66% (51/77) of standard intervention patients, and 68% (52/73) of enhanced intervention patients. Therefore, although the losses were similar across the 3 groups, fewer control group patients had final outcome data compared with enhanced group data. If all of the missing patients in the control group

Table 4. Clinical Outcome Changes Among Patients With Sleep Apnea According to CPAP Use Category: As-Treated Analysis

Outcome	Intervention and Control Patients: No/Poor CPAP Use (N=39)*	Intervention Patients: Some CPAP Use (N=26)*	Intervention Patients: Good CPAP Use (N=32)*	*P* Value				
				Overall	None vs Some	None vs Good	Some vs Good	None vs Some or Good
Modified Rankin Scale score	33 −0.3±1.5 0 (−3, 4)	19 −0.4±1.0 0 (−3, 1)	28 −0.9±1.2 −1 (−4, 1)	0.0237	0.30	0.0064	0.15	0.0159
NIH Stroke Sale score	32 −0.6±2.9 −0.5 (−8, 5)	19 −0.9±1.4 0 (−4, 1)	27 −0.3±1.0 0 (−3, 2)	0.0064	0.13	0.0029	0.17	0.0048

CPAP indicates continuous positive airway pressure; NIH, National Institutes of Health.
*Data are given as number, mean change±SD, and median (minimum, maximum).

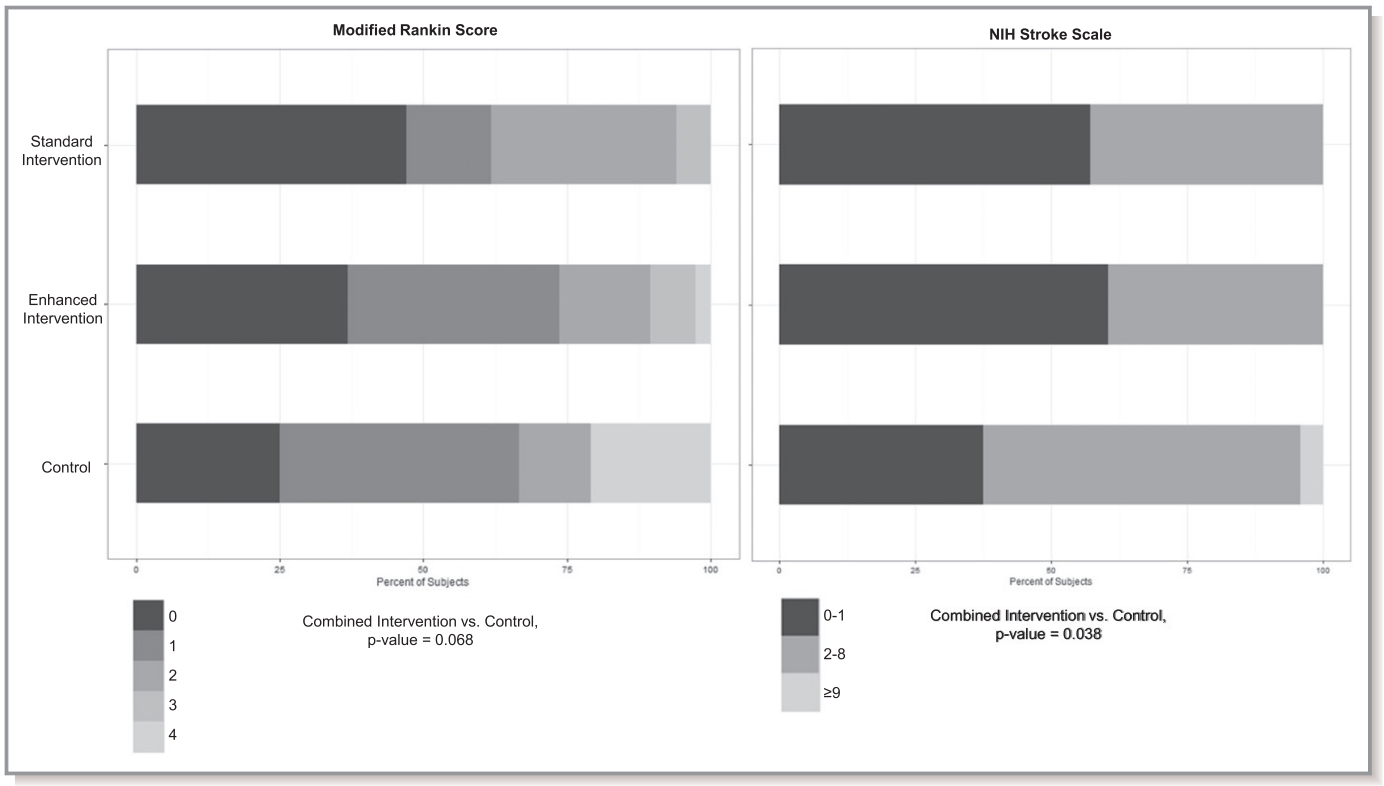

Figure 2. Final clinical outcomes among patients with sleep apnea. NIH indicates National Institutes of Health.

had a distribution similar to the control patients for whom we had complete data, the difference in the mRS score between the control and intervention groups would have been statistically significant (data not shown). Another limitation of the study was that it took ≈1 month to achieve CPAP delivery after polysomnography in the intervention groups. Although this is within the typical time it takes for CPAP delivery in routine clinical settings, earlier initiation of CPAP therapy might have produced greater changes in the vascular risk domains.

Sleep apnea was present in most of this population with stroke or TIA, with an overall prevalence rate of 76%; as expected, central sleep apnea was rare (present in 1 patient). However, only 8.3% of patients had sleep apnea as part of usual care, indicating that the guideline recommendations to screen and treat for sleep apnea are not being widely implemented.[3] Given the observed improvements in neurological symptoms and functional status, these data support the routine use of polysomnography for all patients with an ischemic stroke or TIA.[3]

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Disclosures

None.

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Supplemental Material

Table S1. Polysomnographic Data.

Polysomnographic Feature	Control* (n=29)	Intervention*		P-Value†
		Standard (n=53)	Enhanced (n=56)	
Obstructive sleep apnea: N (%)	20 (69.0)	39 (73.6)	45 (80.4)	0.35
Central sleep apnea: N (%)	1 (3.4)	0 (0)	0 (0)	
No sleep apnea: N (%)	8 (27.6)	14 (26.4)	11 (19.6)	
Apnea Hypopnea Index (AHI, events/hour)				
All Patients: median (range)	14.7 (0.5-87.9)	11.5 (0.3-67.7)	11.2 (0-66.3)	0.99
Mean ± standard deviation	20.3 ± 21.5	18.7 ± 19.4	17.8 ± 17.6	
Sleep Apnea Patients: median (range)	20.4 (7.8-87.9)	14.7 (5.2-67.7)	14.2 (5-66.3)	0.30
Mean ± standard deviation	28.5 ± 21.1	23.7 ± 19.6	21.6 ± 17.8	
Central Apnea Index (events/hour)				
All Patients: Mean ± standard deviation	1.8 ± 6.2	1.0 ± 4.1	1.3 ± 5.0	0.82
Sleep Apnea Patients: Mean ± standard deviation	0.8 ± 1.9	1.3 ± 4.6	1.6 ± 5.5	0.91
Oxygen Desaturation Index (number of desaturations ≥4%/hours sleep)				
All Patients: median (range)	10.6 (0.5-106.0)	11 (0.9-73.3)	10.2 (0.5-177.5)	0.89
Mean ± standard deviation	20.6 ± 25.8	17.4 ± 17.7	21.0 ± 32.1	
Sleep Apnea Patients: median (range)	19.4 (3.9-106.0)	13.7 (3.5-73.3)	12.4 (1.7-177.5)	0.39
Mean ± standard deviation	29.5 ± 27.6	21.5 ± 18.2	25.5 ± 34.4	
Percent time <90% oxygen saturation§				
All Patients: median (range)	0.3 (0-65.9)	0.4 (0-55.6)	0.6 (0-41.9)	0.84
Mean ± standard deviation	10.3 ± 18.3	4.9 ± 11.7	5.6 ± 10.3	
Sleep Apnea Patients: median (range)	6.8 (0-65.9)	0.6 (0-45)	1.2 (0-41.9)	0.26
Mean ± standard deviation	16.2 ± 21.2	4.8 ± 10.1	7.0 ± 11.2	

*The denominator for this table is the number of patients with a valid sleep study.

†Diagnoses frequencies were tested using Fisher's exact test. Polysomnographic measures were tested using the non-parametric Kruskal-Wallis test.

§The oxygen saturation measurements were made on ambient air without oxygen supplementation.

Table S2. Recurrent Vascular Events.

Endpoint		Control			Intervention (Standard & Enhanced)			CPAP Use Categories Among Intervention Patients with Sleep Apnea								
								None/Poor			Some			Good		
		N	% randomized	Rate per 100 person-years of follow-up	N	% randomized	Rate per 100 person-years of follow-up	N	% randomized	Rate per 100 person-years of follow-up	N	% randomized	Rate per 100 person-years of follow-up	N	% randomized	Rate per 100 person-years of follow-up
WHOLE COHORT		84	100		168	100		22	100		27	100		32	100	
All-cause Mortality	People	2	2.4	2.9	4	2.4	3.1	0	0	0	0	0	0	0	0	0
Vascular Death	People	0	0	0	3	1.8	2.4	0	0	0	0	0	0	0	0	0
Non-Vascular Death	People	2	2.4	2.9	1	0.6	0.8	0	0	0	0	0	0	0	0	0
Stroke	People	6	7.1		6	3.6		1	4.5		0	0		0	0	
	Events	6		8.7	7		5.5	1		4.8	0		0	0		0
Acute Myocardial Infarction (AMI)	People	1	1.2		0	0.0		0	0		0	0	0	0	0	0
	Events	1		1.5	0		0.0	0		0	0		0	0		0
Unstable Angina Hospitalization	People	0	0.0		0	0.0		0	0		0	0		0	0	
	Events	0		0	0		0.0	0		0	0		0	0		0
Coronary Revascularization Urgent	People	0	0.0		3	1.8		0	0	0	0	0		2	6.3	
	Events	0		0	3		2.4	0		0	0		0	2		7.3
Any Above Events	People	9	10.7		10	6.0		1	4.5		0	0		2	6.3	
	Events	9		13.1	14		11.0	1		4.8	0		0	2		7.3
STROKE PATIENTS ONLY		68	100		134	100		17	100		21	100		25	100	
All-cause Mortality	People	2	2.9	3.7	4	3.0	4.0	0	0	0	0	0	0	0	0	0
Vascular Death	People	0	0	0	3	2.2	3.0	0	0	0	0	0	0	0	0	0
Non-Vascular Death	People	2	2.9	3.7	1	0.7	1.0	0	0	0	0	0	0	0	0	0
Stroke	People	6	8.8		6	4.5		1	5.9		0	0		0	0	
	Events	6		11.0	7		7.0	1		6.4	0		0	0		0
Acute Myocardial Infarction (AMI)	People	1	1.5		0	0.0		0	0		0	0		0	0	
	Events	1		1.8	0		0.0	0		0	0		0	0		0
Unstable Angina Hospitalization	People	0	0		0	0.0		0	0		0	0		0	0	
	Events	0		0	0		0.0	0		0	0		0	0		0
Coronary Revascularization Urgent	People	0	0		1	0.7		0	0		0	0		1	4.0	
	Events	0		0	1		1.0	0		0	0		0	1		4.8
Any Above Events	People	9	13.2		8	6.0		1	5.9		0	0		1	4.0	
	Events	9		16.4	12		12.0	1		6.4				1		4.8
TIA PATIENTS ONLY		11	100		30	100		4	100		5	100		7	100	
All-cause Mortality	People	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0
Vascular Death	People	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0
Non-Vascular Death	People	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	00.	0	0.0	0.0
Stroke	People	0	0.0		0	0.0		0	0.0		0	0.0		0	0.0	
	Events			0.0	0		0.0			0.0	0		0.0	0		0
Acute Myocardial Infarction (AMI)	People	0	0.0		0	0.0		0	0.0		0	0.0		0	0.0	
	Events	0		0.0	0		0.0	0		0.0	0		0.0	0		0.0
Unstable Angina Hospitalization	People	0	0.0		0	0.0		0	0.0		0	0.0		0	0.0	
	Events	0		0.0	0		0.0	0		0.0	0		0.0	0		0.0
Coronary Revascularization Urgent	People	0	0.0		2	6.7		0	0.0		0	0.0		1	14.3	
	Events	0		0.0	2		8.3	0		0.0	0		0.0	1		15.6
Any Above Events	People	0	0.0		2	6.7		0	0.0		0	0.0		1	14.3	
	Events	0		0.0	2		8.3	0		0.0	0		0.0	1		15.6

Table S3. Adverse Events After Randomization.

Events		Control		Intervention				CPAP Use Categories					
				Standard		Enhanced		None/Poor		Some		Good	
		N	Rate per 100 person-years of follow-up	N	Rate per 100 person-years of follow-up	N	Rate per 100 person-years of follow-up	N	Rate per 100 person-years of follow-up	N	Rate per 100 person-years of follow-up	N	Rate per 100 person-years of follow-up
Serious & Related AE*	Expected	0	0·0	0	0·0	1	1·6	0	0·0	1	3·9	0	0·0
	Unexpected	0	0·0	0	0·0	0	0·0	0	0·0	0	0·0	0	0·0
Serious & Unrelated AE	Expected	18	26·5	8	12·3	13	21·3	4	19.1	5	19.4	4	14.8
	Unexpected	48	70·7	39	59·8	30	49·1	1	4·8	9	34·9	8	29·6
Non-serious & Related AE	Expected	0	0·0	6	9·2	11	18·0	2	9·6	1	3·9	14	51·8
	Unexpected	2	2·9	0	0·0	2	3·3	0	0·0	1	3·9	1	3·7
Non-serious & Unrelated AE	Expected	14	20·6	8	12·3	8	13·1	7	33·5	3	11·6	5	18·5
	Unexpected	72	106·1	56	85·8	50	81·9	15	71·7	29	112·4	32	118·3
Total of serious AE		66	97·3	47	72·0	44	72·1	5	23·9	15	58·2	12	44·4
Total of non-serious AE		88	129·7	70	107·3	71	116·3	24	114·8	34	131·8	52	192·2
Total of related AE		2	2·9	6	9·2	14	22·9	2	9·6	3	11·6	15	55·5
Total of unrelated AE		152	224·0	111	170·1	101	165·4	27	129·1	46	178·4	49	181·1
Total of expected AE		32	47·2	22	33·7	33	54·0	13	62·2	10	38·8	23	85·0
Total of unexpected AE		122	179·8	95	145·6	82	134·3	16	76·5	39	151·2	41	151·6
Total AE		154	226·9	117	179·3	115	188·3	29	138·7	49	190·0	64	236·6

*AE refers to adverse events.