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Reducing Cardiovascular Risk through Treatment of Obstructive Sleep Apnea: Two Methodological Approaches

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Abstract

Obstructive sleep apnea (OSA) significantly impacts cardiovascular health, demonstrated by observational investigations showing an independently increased risk of ischemic heart disease, diabetes, hypertension, congestive heart failure, acute coronary syndrome, stroke, cardiovascular mortality, and all-cause mortality. Positive airway pressure (PAP), a medical therapy for sleep apnea, reverses airway obstruction and may help reduce cardiovascular risk. Prior to planning large Phase III randomized controlled trials to test the impact of PAP on cardiovascular outcomes, several gaps in knowledge need to be addressed. This paper describes two independent studies that worked collaboratively to fill these gaps. The populations, design features, and relative benefits/challenges of the two studies (SleepTight and BestAIR) are described. Both studies were

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NCT01446913 (SleepTight)

NCT01261390 (BestAIR)

encouraged to have multidisciplinary teams with expertise in behavioral interventions to improve PAP compliance. Both studies provide key information that will be useful to the research community in future large-scale, event-driven, randomized trials to evaluate the efficacy and/or effectiveness of strategies to identify and treat significant obstructive sleep apnea for decreasing risk of major adverse cardiovascular events in high-risk patients.

Keywords

Sleep Apnea Syndromes; Cardiovascular Diseases; Positive Airway Pressure; Stroke; TIA

BACKGROUND

Obstructive sleep apnea (OSA) is common in the general population. Prevalence rates of mild to moderate OSA of about 15% are reported; and approximately 4 to 5% of the population is classified as having severe OSA.[1-3] Among patients at risk for or with established cardiovascular disease (CVD), OSA prevalence rates are even greater.[4, 5] Untreated OSA in the US is estimated to contribute $3B in medical costs related to greater health care utilization.[6-8] In particular, OSA significantly impacts cardiovascular health, demonstrated by observational investigations showing an independently increased risk of ischemic heart disease, diabetes, hypertension, congestive heart failure, acute coronary syndrome, stroke, cardiovascular mortality, and all-cause mortality.[9-13] Mechanistic studies suggest several plausible biologic mechanisms for this risk, including recurrent hypoxia, frequent arousal from sleep, intrathoracic pressure changes, vascular inflammation, autonomic activation, and metabolic dysregulation.[14]

Positive airway pressure (PAP) reverses airway obstruction and may represent and important treatment to reduce cardiovascular risk. However, essential information is needed prior to conducting a large Phase III trial to directly address gaps in knowledge regarding the impact of PAP on cardiovascular risk. For example, whereas short-term studies suggest that increased duration of effective CPAP use may translate into greater vascular risk reduction,[15] more research is warranted to determine both key strategies for improving CPAP adherence over the long-term, and whether there is a minimal dose of PAP needed to alter vascular risk. This need is especially true of high risk vascular populations, and enrollees in clinical trials in research settings, who may be less sleepy than patients referred through sleep- related clinical pathways. Additionally, design considerations regarding equipoise and the selection of appropriate control groups as well as the feasibility of recruitment, randomization, and retention of study populations must also be addressed. Information about effect size of PAP therapy is also required, and can be inferred by corresponding changes in pathophysiologic markers of cardiovascular and cerebrovascular disease.

In response to these needs, the National Heart, Lung and Blood Institute (NHLBI) at the National Institutes of Health (NIH) released a Request for Applications (RFA) on “Reducing Cardiovascular Disease Risk Through Treatment of Obstructive Sleep Apnea (U34)” (RFA-HL-10-023) to 1) encourage research to establish the feasibility of conducting long-term PAP treatment in research settings among individuals with increased cardiovascular risk

profiles, 2) evaluate the potential for such treatment to produce changes in cardiovascular disease risk profiles, 3) identify feasibility of study design strategies for future event-driven Phase III trials, and 4) include multidisciplinary teams with expertise in behavioral interventions to improve PAP compliance. An additional stipulation of this mechanism was that research activities were to be coordinated through a Joint Steering Committee process that would facilitate developing and reporting standardized measures of key common variables, such as population characteristics and entry criteria, PAP adherence, key protocol characteristics, and common biological outcomes, to facilitate comparison of study outcomes. The request was for three-year randomized controlled trial (RCT) planning grants that focused on PAP treatment, for the purpose of conducting preliminary studies that could guide the research community in the design of Phase III clinical trials to test whether PAP treatment of OSA reduces vascular events. The alternative populations, design features, and relative benefits/challenges of the two studies funded under this mechanism (Sleep Tight-U34HL105285 and BestAIR-U34HL105277) are described below. The authors of this paper are solely responsible for the design and conduct of the respective studies, the drafting and editing of this manuscript and its final content.

SLEEPTIGHT

Overall Trial Design

The “Sleep Apnea in TIA: Reducing Cardiovascular Risk with Positive Airway Pressure” (SleepTight) study is a prospective, randomized controlled planning trial among patients with transient ischemic attack (TIA) and ischemic stroke, comparing the effectiveness of strategies for the diagnosis and treatment of sleep apnea with usual care, over 12 months at centers in Connecticut and Indiana (Table I, Figure 1). The eligibility criteria are specified in Table II. The target population was selected because of their high prevalence of obstructive sleep apnea (60-80%),[4, 16] and their heightened risk for recurrent cerebrovascular and cardiovascular events despite current prevention strategies.

255 patients with TIA or stroke are randomly assigned using a 1:1:1 (control:standard PAP: enhanced PAP) randomization scheme to either usual care or a home-based diagnosis and treatment approach that includes ambulatory polysomnography and initiation of PAP for patients with sleep apnea (Figure 1). Control patients could undergo diagnosis and treatment of sleep apnea if suspected as part of usual clinical care. The randomization is stratified by center (Connecticut or Indiana) and neurologic event type (TIA or stroke). Intervention patients with sleep apnea receive either a standard PAP treatment intervention or an enhanced protocol designed to increase long-term PAP adherence.

The primary aims consist of seeking to evaluate: whether the intervention results in significant reductions in several markers of cardiovascular risk; the optimal adherence levels to achieve these improvements; and whether an enhanced intervention protocol results in improved long-term PAP adherence rates. The secondary aims are to collect cerebrovascular and cardiovascular event rates as pilot data for a potential future event-driven trial. Patients are recruited in the acute hospital environment, but the major setting of the study is the patient's home. This setting was intended to facilitate the participation of an acute TIA/ stroke population with limited mobility and competing demands.

Baseline Assessments

Data collected at baseline include demographics, co-morbidities, medications (using the WHO classification), blood pressure, heart rate, and anthropometrics. The $ABCD^2$ score, a system used to predict short-term recurrent event rates among patients with TIA, and the NIH Stroke Severity (NIHSS) score, are also calculated. Patients are interviewed to complete measures of self-efficacy in sleep apnea, sleepiness, sleep duration, functional status, and mood. Physiologic measurements include unattended full polysomnography, 24-hour holter monitoring, 24-hour ambulatory blood pressure, phlebotomy, flow-mediated vasodilation, and carotid doppler ultrasonography (Table III).

Study Interventions

Polysomnography is performed using the Safiro™ type 2 sleep monitor (Compumedics, Victoria Australia). Scoring conforms to standards of the American Academy of Sleep Medicine (AASM); hypopneas are scored using the AASM alternative definition of (≥3% oxygen desaturation or arousal).[17] Patients with an apnea hypopnea index (AHI) of ≥ 5 events/hour are diagnosed as having sleep apnea and are initiated on auto-pap titration protocols using the System One® PAP device (Phillips Respironics).

The *Standard Intervention* is intended to approximate “real world” PAP support, and consists of three in-person contacts and telephone contacts throughout the 12-month follow-up period. The initial in-person contact focuses on providing the results of the diagnostic sleep study and instruction regarding PAP equipment. The second and third in-person contacts occur at one and three months, respectively, allowing for interrogation of the PAP unit for adherence data questioning regarding symptom improvement, trouble shooting, and encouragement of continued PAP use. Interim regular telephone contact is made to inquire regarding adverse events. A final visit occurs at one year for outcome assessment.

The *Enhanced Intervention* adds three components: (1) targeted education, (2) behavioral adherence intervention, and (3) increased PAP support. The intervention protocol is based on the conceptual frameworks of the narrative model[18] and self-determination theory,[19, 20] and consists of intensive in-person patient contact during the first month of PAP treatment, with subsequent follow-up telephone/in-person contact for continuing support. These data are used to identify potential barriers and facilitators of PAP use. A video for participant viewing was developed (for use by both studies) that features a real-life role model who demonstrates ambivalence around PAP use and the resolution of this ambivalence- resulting in enhanced motivation and efforts adhere to PAP, successful problem solving, increased confidence, and ultimately PAP adherence. Starting within the first week and then weekly for the first month, the focus is on adherence interventions designed to “link” PAP use to intrinsically motivating factors of the patient. Subsequently, the patient receives monthly phone contacts, with an in-person contact at 3 and 6 months to serve as “booster sessions” for the targeted education and behavioral adherence intervention. A final visit takes place at 12 months for outcomes assessment.

Outcomes

The outcomes in SleepTight were based on biologically plausible mechanisms by which OSA may lead to cardiovascular risk. These pathways include intermittent hypoxia, heightened sympathetic activity, inflammation, metabolic dysregulation, leading downstream to endothelial injury, and atherosclerosis.

Endpoints include change (baseline to follow-up) in markers of inflammation, autonomic activity, insulin resistance, flow mediated vasodilation, and carotid intima-media thickness (Table III). The primary comparison is an intention-to-treat analysis of changes in vascular disease biomarkers between patients enrolled in the two intervention groups versus those enrolled in the control group. Given that only patients with sleep apnea in the intervention groups will receive CPAP, the initial power calculation was based on an estimated prevalence of sleep apnea of 60%[21,22] and a retention rate at one-year follow-up of 0.90. The power calculation was based on a method by Hedeker et al.[23] A sample size of 255 provided at least 80% power for each of the primary aims. Although patients are un-blinded, key investigators ascertaining outcomes remain blinded.

BESTAIR

Overall trial Design

The “Best Apnea Intervention in Research” (BestAIR) trial (Table I, Figure 2) is a planning study to evaluate the merits of alternative study design features for later, large-scale, Phase 3 RCTs that address the role of sleep apnea treatment on reducing CVD morbidity. The study design is a 12-month parallel, randomized, double-blind, multicenter Phase-2 efficacy trial, with 24-hour systolic blood pressure as the primary physiological endpoint and a number of process measures as secondary outcomes. The study was designed to enroll 225 patients with moderate to severe sleep apnea (AHI >15), and with CVD risk factors or established CVD, whose treating physician had clinical equipoise, into a two week run-in period, and then to randomize an estimated 80% (n=180) of these participants into a 12-month, 4-arm intervention study. The run-in trial requires participants to apply nasal dilator strips (Breathe Right®), and a PAP mask nightly (open to the atmosphere), and complete a sleep diary. After demonstration of adherence with these procedures, patients are invited to a baseline visit at a clinical research center and subsequently randomized. Participants are then followed by phone and interim visits (at 6 and 12 months) until study completion. The eligibility criteria for the trial are specified in Table II.

Baseline Assessments

Baseline visits are conducted in the morning, following an overnight fast where urine and venous blood samples are obtained. Other measurements include ambulatory 24h blood pressure monitoring, radial artery tonometry (to assess arterial stiffness and pulse wave velocity), resting 12-lead electrocardiogram and 2-D echocardiography, and questionnaires on medical history, lifestyle, and sleep habits.

Study Interventions

The study includes four groups: (1) Conservative Medical Therapy (CMT) alone; (2) CMT plus sham PAP delivered by a trained sleep technician; (3) CMT plus active PAP delivered by a trained sleep technician; and (4) CMT plus active PAP enhanced through behavioral support provided a psychologist providing a standardized PAP behavioral promotion intervention. Groups 1 and 2 are considered alternative control conditions and groups 3 and 4 are considered alternative active treatments. The primary physiological, various process measures, and other clinical endpoints will be compared for groups 1 and 2, vs. groups 3 and 4.

CMT—The participant is instructed on sleep hygiene, including specific techniques to reduce apnea, as well as healthy lifestyle guidelines. In addition, participants are provided a supply of nasal dilator strips to use nightly.

Active PAP and Sham-PAP Arms—In addition to receiving CMT, participants randomized to sham or active-PAP interventions meet with a trained sleep technician. PAP levels are determined through overnight laboratory titrations or through auto-PAP titration protocols. The core intervention delivered by the sleep technician includes education on PAP and mask use, information on side effects, and feedback on PAP use based on adherence data available through wireless tele-monitoring. Participants are scheduled to meet with the sleep technician at set-up, and again one week after initiating PAP, to reinforce PAP use and make any adjustments in the mask or pressure setting. Thereafter, the sleep technician meets with the participant in-person at months 1, 3, 6, and 9, using the available data from the PAP monitor on PAP use, mask leak, and residual AHI, to assist with troubleshooting.

Participants randomized to active PAP with enhanced behavioral support receive the sleep technician-delivered intervention described above plus a specific behavioral protocol. Participants speak with the behavioral interventionist 6 times, through phone or other contact, at weeks 3, 4, 8, 12, and 32 after beginning PAP. This strategy allows mechanical issues related to PAP to be addressed early (by the sleep technician), while timing the delivery of the behavioral intervention to times after the patient has had a chance to experience PAP. The enhanced intervention is based on social cognitive theory and feedback concerning adherence, with targeted problem solving-training. The motivational enhancement intervention is adapted from the motivational enhancement treatment protocol for PAP adherence (ME-PAP) developed by Aloia et al.[24-27]

Outcomes

The primary physiological outcome (see Table III) is an intermediate marker of CVD risk: change in 24-hour mean systolic blood pressure, measured at 6 and 12 months following randomization. A broader set of intermediate markers of CVD and patient-reported outcomes are also identified as secondary outcomes. The *primary process measures* are recruitment yields, crossover rates, retention rates, and adherence. Adherence in both PAP arms will be assessed through electronic wireless downloads. CMT adherence will be measured by responses obtained at the quarterly follow-up visits, summarizing self-reported

use of nasal dilators. Adjudication of *clinical endpoints* occurs through review of medical records and other data.

COMMON FEATURES AND KEY DIFFERENCES

The investigative teams collaborated throughout the duration of the projects to ensure several key common features between studies (Table IV), both studies use two active PAP intervention groups with more-versus-less intensive adherence approaches, as well as similar behavioral adherence approaches in the more intensive adherence protocols. Definitions, endpoints, trial administrative procedures, and tools are harmonized, where possible, between the two studies. Identical sleep study scoring procedures are used. Considerable overlap also exists among selected intermediate measures of cardiovascular risk, including inflammatory markers, insulin/glucose homeostasis, lipids, BNP, and heart rate variability. Both studies have identical definitions and assessment of vascular outcomes. There are several patient reported outcomes common to both studies, including the Epworth Sleepiness Scale, PHQ depression scale, and the Self Efficacy Measure for Sleep Apnea (SEMSA). Both studies utilize identical PAP adherence measures. Both studies utilize blinded ascertainment of outcomes. These efforts at harmonization are aimed to enhance comparability across the two studies and foster future joint analyses.

Important differences between the two studies (Table V) are also noteworthy. SleepTight targets high risk patients with TIA/stroke in the acute hospital setting, with follow-up in the home. The SleepTight study does not involve patients who have been diagnosed with sleep apnea (and may be symptomatic) to a control group that does not receive PAP. It is strategy-based, randomizes prior to polysomnography, and compares the *effectiveness* of a diagnosis and treatment approach for sleep apnea versus usual care. Usual care patients may undergo diagnostic testing treatment for sleep apnea post-stroke/TIA, however in our experience this is rare<5%). This approach addresses potential ethical and safety considerations regarding randomizing symptomatic or high risk patients over the long-term to a control arm that does not include active PAP treatment. By treating soon after an acute event, the risk of recurrent event is high, which may decrease the total sample size required to power a study, and may result in a lower number needed to treat/number needed to harm (NNT/NNH). By randomizing to testing vs. no testing, SleepTight addresses a clinical question facing stroke patients and their clinicians. It asks the question: Does a strategy of polysomnography and PAP treatment, if indicated by at least mild OSA, reduce vascular risk in an acute post-stroke/TIA population?

In contrast, BestAIR targets patients who have lower CV event risk profiles who are indetified through outpatient clinic settings, is treatment-based, randomizes after polysomnography, and examines the *efficacy* of CPAP, sham CPAP, or CMT on cardiovascular risk. BestAIR evaluates the safety and utility of sham CPAP and CMT control regimens. This approach preserves double blinding (in one arm), and addresses safety issues through close monitoring of adverse events and excluding severely symptomatic patients. By randomizing stable CVD patients and those with CVD risk factors, a larger sample size is required, but this focus has the potential to generalize to a larger group of patients. By randomizing after a positive sleep study and run-in, it focuses on

the physiological effect of PAP treatment. It asks the question: Does treatment with PAP reduce risk among patients with at least moderate OSA and either established CVD or CV risk factors.

Overall, both studies will inform the research community regarding key information relevant to the planning of future large-scale, event-driven, randomized trials to evaluate the efficacy or effectiveness of treating significant obstructive sleep apnea to decrease major adverse CVD events in high-risk patients. More generally, given the growing interest in pragmatic trials, the alternative use of effectiveness and efficacy in these two studies will provide opportunities to consider the impact of major design differences on study implementation, efficiency, outcomes, features, and generalizability.

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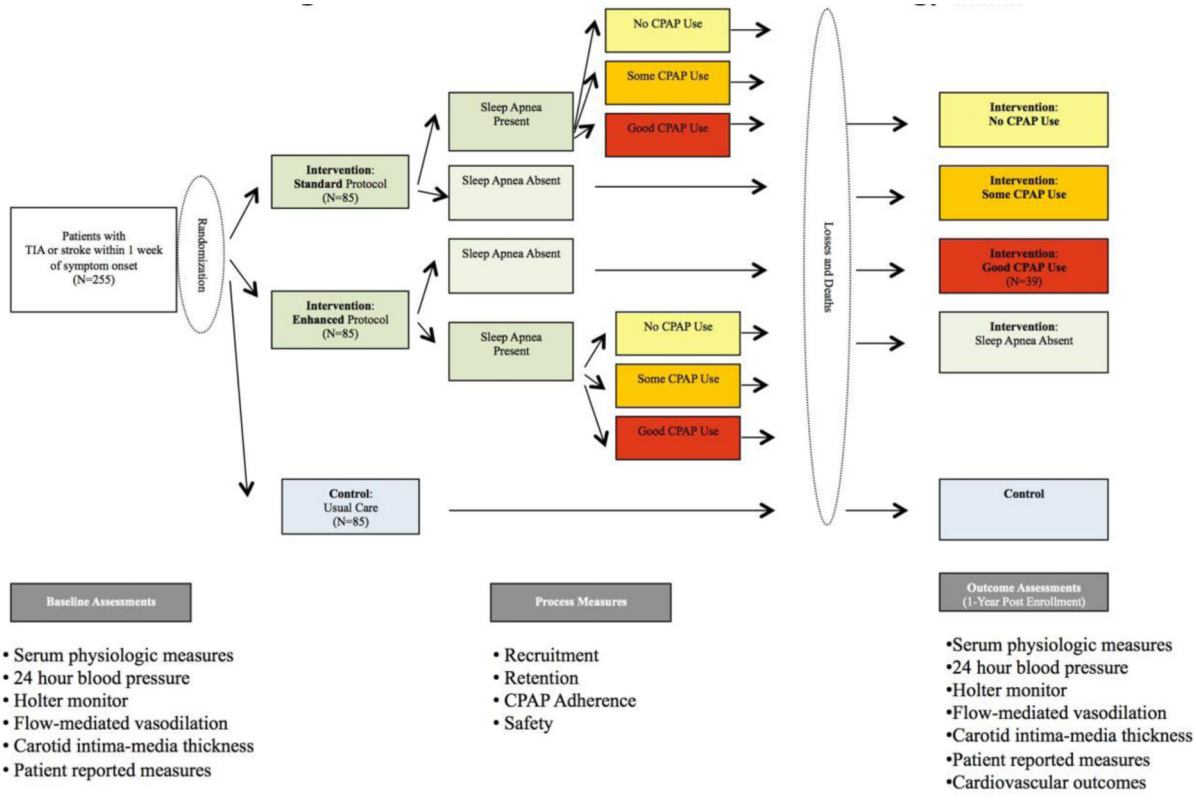

Figure 1.
SleepTight Study Design

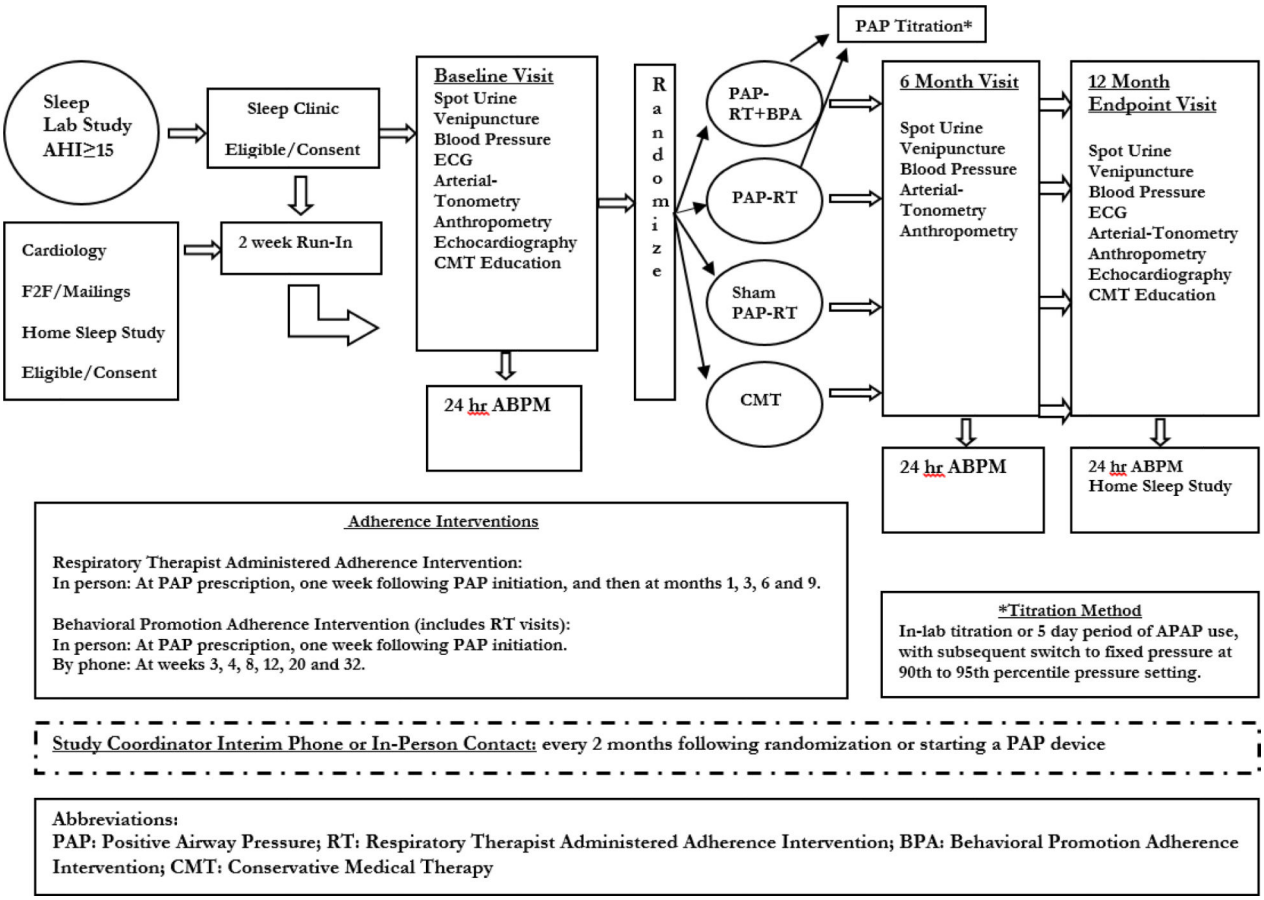

Figure 2.
BestAIR Study Design

Table I

Key Design Features of Each Study

	SleepTight (NCT01446913)	**BestAIR (NCT01261390)**
Grantee Institutions	Yale School of Medicine; Indiana School of Medicine	Brigham and Women's Hospital; Beth Israel Deaconess Medical Center
Target Population	Patients with recent (within 1 week) TIA or ischemic stroke	Patients with established CVD; diabetes; or 3+ CVD risk factors; free of an acute cardiac event for prior 4 months
Overall Design	Phase 2 randomized controlled trial	
Recruitment Site	Hospital, all follow-up occurs in patient's home	Outpatient (sleep, cardiac clinics)
Run-In	None	2 weeks of wearing a PAP mask open to the room
Sleep Apnea Entry Criteria	AHI ≥5 events/hour	AHI ≥15 events/hour
Primary Outcomes	Change in five domains of cardiovascular risk markers (inflammatory, autonomic, metabolic, endothelial, and atherosclerotic)	24-hour mean systolic BP at 6 and 12 months
Secondary Outcomes	Combined endpoint of 1-year vascular events or death rate	Arterial stiffness; cardiac function and structure (echocardiography); biochemical markers of glucose control; lipid levels, inflammation
Process Outcomes	PAP adherence; recruitment yie ds; cross-over rates; retention rates, sleep apnea prevalence	
Patient Reported Outcomes	Stroke severity; functional status; sleepiness; mood, self-efficacy	Generic and sleep specific quality of life; sleepiness; mood; self-efficacy
Active Interventions	Auto-titrating PAP (Standard vs. Enhanced Intervention)	
Control	Usual Care	Sham-PAP; Nasal Dilator Strips, sleep education

CVD=cardiovascular disease; TIA=transient ischemic attack; AHI=apnea hypopnea index; BP=blood pressure; PAP=positive airway pressure

Table II

Eligibility Criteria

	SleepTight	BestAIR
Inclusion	18 years or older	45-75 years or older (or 55-75 if without established CVD)
	TIA/ischemic stroke within 1 week of symptom onset	Diagnosed with moderate to severe OSA (AHI ≥ 15 events/hr)
	Brain imaging within 48 hours of symptoms onset	Either: Established CVD; Diabetes; or Three or more established CVD risk factors
Exclusion	Known sleep apnea	Working as professional driver
	Suspected sleep-disorder other than sleep apnea	Diagnosed heart failure with EF of <35% or NYHA class 3 or 4 status
	Hospice or patients receiving comfort measures only	Less than 4 months since MI, stroke, revascularization procedure
	Patients unable to use either a nasal or face mask	Poorly controlled hypertension (>170/>100)
	Patients who require mechanical ventilation	Prior stroke with functional impairment
	Non-English language patients	Severe uncontrolled medical problems or medications that may influence study exams
	Inability to provide informed consent	Resting oxygen saturation <90% or nocturnal oxygen saturation <85% for >10%
	Active suicidal ideation	Prior use of prescribed PAP for sleep apnea
	Lives outside the recruitment area	Report of inability to spend ≥6 hours in bed
	Provider does not allow research staff to contact the patient	Severe sleepiness defined by an Epworth Sleepiness Score of >14 or report of trouble staying awake while driving in the past 2 years
		Low risk of having sleep apnea defined by a Berlin Score of <2
		Central sleep apnea, with >50% of respiratory events classified as central apneas
		Refusal to consider PAP use after an initial split-night PAP study (pre-randomization)
		Concurrent involvement in another research study that will result in a conflict determined by study doctors

OSA= obstructive sleep apnea; CVD=cardiovascular disease; TIA=transient ischemic attack; AHI=apnea hypopnea index; BP=blood pressure; PAP=positive airway pressure

Table III

Outcomes

	SleepTight	BestAir
Physiologic Endpoints	Inflammation	Primary Endpoint
	High sensitivity CRP	24h SBP
	IL-6	Secondary Endpoints
	Autonomic	Blood Pressure Profile
	Plasma catecholamines	Nocturnal BP
	Heart rate variability	Mean 24h BP
	24hr ambulatory BP	BP dipping status
	Insulin resistance	Inflammation
	HOMA-IR	CRP
	HbA1c	IL-6
	Atrial pressure	Fibrinogen
	BNP	PAI-1
	Endothelial Injury	MRP 8-14
	Flow-mediated vasodilation	Vascular Stiffness
	Atherosclerosis	Augmentation Index
	Carotid intima-media thickness	Pulse Wave Velocity
		Cardiac Function/Morphology
		NT pro BNP
		Renal function
		Urinary albumin/creatine
		Dyslipidemia/Metabolism
		Total LDL and HDL
		Triglyceride
		Fasting insulin/glucose
	SEMSA	SEMSA
	ESS	ESS
	Modified Rankin Scale	SAQLI
	NIHSS	MOS-SF36
	ABCD2	PHQ-8
	Sleep duration	
	Concomitant medical care	
Process Measures	Recruitment rates	Recruitment rates
	Retention rates	Retention rates
	Safety	Safety
	Sleep Apnea Prevalence	PAP Adherence
	PAP Adherence	Cross-Over rates
		Run-in rates

	SleepTight	**BestAir**
Cardiovascular Outcome Events	Stroke, TIA, Acute coronary syndrome, Hospitalization for congestive heart failure, Death (CV or non-CV)	

CVD=cardiovascular disease; TIA=transient ischemic attack; AHI=apnea hypopnea index; SBP=systolic blood pressure; PAP=positive airway pressure

Table IV

Common Elements of the SleepTight and BestAIR

Study Leadership	Multi-PI model: sleep and cardio/cerebrovascular expertise
Exclusion Criteria	Known sleep apnea/prior PAP use
	Co-morbid sleep disorder
Target population	Established cardiovascular disease
Measurements	24-hour mean systolic blood pressure
	Lipid profiles, glucose, insulin
	CRP, IL-6, Pro-BNP
	Epworth Sleepiness Score, PHQ-9
	Self Efficacy Measure of Sleep Apnea
	PAP Adherence hours of use
	WHO Classification of Medication Use
	AHI scored in same center with same scoring criteria
Clinical Endpoints	Use common adjudication procedure
Active Interventions	PAP Behavioral support with enhanced education and motivation Both direct and phone contact support Common patient role-model video

Table V

Distinct Features of Each Study

	SleepTight	**BestAIR**
Type of Study	Effectiveness study	Efficacy study
Intervention	Strategy-based	Treatment-based
Randomization	Randomization to screen and treat vs usual care	Active PAP vs no PAP
Target Population	Acute stroke/TIA	Established CVD or high risk, no recent acute event
Recruitment	Large inpatient population; setting of acute stroke centers is optimal.	Large outpatient program following patients with established cardiovascular disease and CVD risk factors
Risk Level of Patients	By randomizing soon after an acute CVD, the risk of recurrent event is high. This decreases the total sample size required to power a study and may result in lower NNT/NNH	By randomizing stable CVD patients and those with CVD risk factors, a larger sample size is required, but may benefit a larger group of patients.
Sleep Apnea Severity	OSA may or may not be present (randomization pre-polysomnography); AHI ≥ 5	OSA present (randomization post-polysomnography); ESS ≤ 14; no drowsy driving; AHI ≥15
Timing of Randomization	By randomizing to testing vs. no testing, addresses clinical question facing stroke patients and their clinicians	By randomizing after (+) sleep study and run-in, addresses the biological effect of PAP treatment
Question addressed:	Does a strategy of polysomnography and PAP treatment, if indicated by at least mild OSA, reduce risk in an acute post-stroke/TIA population	Does treatment with PAP reduce risk among patients with at least moderate OSA and either established CVD or CV risk factors
Control Conditions	Usual Care (unblinded)	One control group (sham PAP) blinded, but assesses potential impact on retention in an unblinded control group as well
In-home vs In-clinic follow-up	Burden on study staff	Burden on study participant

CVD=cardiovascular disease; TIA=transient ischemic attack; AHI=apnea hypopnea index; BP=blood pressure; PAP=positive airway pressure; NNT=number needed to treat;NNH=number needed to harm