The Determining Risk of Vascular Events by Apnea Monitoring (DREAM) Study: Design, Rationale and Methods

Brian B Koo, MD;[1,2] Christine Won, MD, MPH;[3,4] Bernardo J Selim, MD;[5] Li Qin, PhD;[6] Sangchoon Jeon, PhD;[7] Nancy S Redeker, PhD, RN, FAHA, FAAN;[7] Dawn M. Bravata, MD;[8-12] Kingman P Strohl, MD;[13,14] John Concato, MD;[15,16] Henry K Yaggi, MD, MPH.[3,4]

[1]Department of Neurology, Yale University, New Haven, CT; [2]Department of Neurology, Connecticut Veterans Affairs Health System, West Haven, CT; [3]Department of Pulmonary, Critical Care, and Sleep Medicine, Yale University, New Haven, CT; [4]Department of Pulmonary, Critical Care, and Sleep Medicine, Connecticut Veterans Affairs Health System, West Haven, CT; [5]Department of Pulmonary, Critical Care, and Sleep Medicine, Mayo Clinic, Rochester, MN; [6]Department of Biostatistics, Yale School of Public Health, New Haven, CT; [7]Division of Acute Care/Health Systems, Yale School of Nursing, New Haven, CT; [8]Department of Neurology, Indiana University School of Medicine, Indianapolis, IN; [9]VA HSR&D Center for Health Information and Communication (CHIC); Richard L. Roudebush VA Medical Center, Indianapolis, IN; [10]Department of Internal Medicine, Indiana University School of Medicine, Indianapolis, IN; [11]Regenstrief Institute, Indianapolis, IN; [12]Department of Medicine, Richard L. Roudebush VA Medical Center; Indianapolis, IN; [13]Department of Pulmonary, Critical Care, and Sleep Medicine, Case Western Reserve University, Cleveland, OH; [14]Department of Pulmonary, Critical Care, and Sleep Medicine, Louis Stokes Veterans Affairs Medical Center, Cleveland, OH; [15]Department of Internal Medicine, Yale University, New Haven, CT; [16]Clinical Epidemiology Research Center (CERC), Connecticut Veterans Affairs Health System, West Haven, CT.

Correspondence:

Brian B Koo, M.D.
950 Campbell Avenue
West Haven, CT 06516

Phone: 203-932-5711 x 5416
Fax: 203-785-3826
(koobri@gmail.com)

This is the author's manuscript of the article published in final edited form as:
Koo, B. B., Won, C., Selim, B. J., Qin, L., Jeon, S., Redeker, N. S., … Yaggi, H. K. (2015). The Determining Risk of Vascular Events by Apnea Monitoring (DREAM) study: design, rationale, and methods. Sleep and Breathing, 20(2), 893–900. http://doi.org/10.1007/s11325-015-1254-3

ABSTRACT

Purpose: The goal of the Determining Risk of Vascular Events by Apnea Monitoring (DREAM) Study is to develop a prognostic model for cardiovascular outcomes, based on physiologic variables—related to breathing, sleep architecture, and oxygenation—measured during polysomnography in U.S. veterans.

Methods: The DREAM Study is a multi-site, retrospective observational cohort study conducted at three Veterans Affairs (VA) centers (West Haven, CT; Indianapolis, IN; Cleveland, OH). Veterans undergoing polysomnography between January 1, 2000 and December 31, 2004 were included based on: referral for evaluation of sleep-disordered breathing; documented history and physical prior to sleep testing; and ≥2 hours sleep monitoring. Demographic, anthropomorphic, medical, medication, and social history factors were recorded. Measures to determine sleep apnea, sleep architecture, and oxygenation were recorded from polysomnography. VA Patient Treatment File, VA–Medicare Data, Vista Computerized Patient Record System, and VA Vital Status File were reviewed on dates subsequent to polysomnography, ranging from 0.06 to 8.8 years (5.5±1.3 yrs; mean±SD).

Results: The study population includes 1,840 predominantly male, middle-aged veterans. As designed, the main primary outcome is the composite endpoint of acute coronary syndrome, stroke, transient ischemic attack or death. Secondary outcomes includes incidents of neoplasm, congestive heart failure, cardiac arrhythmia, diabetes, depression, and post-traumatic stress disorder. Laboratory outcomes include measures of glycemic control, cholesterol, and kidney function. (Actual results are pending.)

Conclusions: This manuscript provides the rationale for the inclusion of veterans in a study to determine the association between physiologic sleep measures and cardiovascular outcomes, and specifically the development of a corresponding outcomes-based prognostic model.

Keywords: sleep apnea; OSA; epidemiology; veterans; cardiovascular

INTRODUCTION

A recent Institute of Medicine report, entitled '*Sleep Disorders and Sleep Deprivation: an Unmet Public Health Challenge*', estimated that 50-70 million Americans suffer from a chronic sleep disorder [1]. Major aspects of this "unmet public health challenge" are the cardiovascular and cerebrovascular health consequences of sleep-disordered breathing. Obstructive sleep apnea (OSA), a common form of sleep-disordered breathing, has a high and rising prevalence (17%) in the general adult population, attributable in part to enhanced awareness and the emerging epidemic of obesity [2-4]. OSA has also been independently linked to important health outcomes, including hypertension [5], fatal and nonfatal cardiovascular events [6, 7], stroke[8], and metabolic dysfunction [9].

The prevalence of OSA is believed to be even higher among U.S. veterans [10, 11], due to major risk factors for OSA that are common in this population (e.g. increasing age, male gender, obesity, and alcohol use) [12]. Furthermore, because of a high prevalence of other cardiovascular risk factors and metabolic co-morbidities, veterans may be more vulnerable to some of the health consequences of OSA [13]. Accordingly,

significant resources are now being dedicated in the Veterans Health Administration to improving access to the diagnosis of OSA.

Although significant efforts are being made to increase diagnostic capacity, our understanding of the polysomnographic measures that best predict the adverse health consequences of OSA remains poorly developed. OSA is characterized by repeated upper airway occlusion during sleep which results in airflow cessation (apnea) or reduction (hypopnea). The enumeration of these events-per-hour of sleep yields the apnea-hypopnea index (AHI). Clinically, this metric defines sleep apnea severity, but it has also been shown to relate to cardiovascular disease, including hypertension [5], coronary heart disease [14], and stroke[8]. Standard polysomnography also records a rich array of other physiologic measurements. Although the AHI is important, as a single metric, it does not take into account other physiologic factors, such as oxygen desaturation severity, overall arousal frequency, cardiac arrhythmia, or degree of sleep disruption.

Embedded within the collection of various physiologic polysomnographic components lies information that may predict adverse health outcomes more accurately than the AHI. Measurements of physiologic components other than breathing—including sleep disruption, heart rate variability, or periodically occurring limb movements—have been shown to track with hypertension and cardiovascular disease [15-17]. Previous research, however, has not adequately integrated these diverse physiologic measures to evaluate potential cardiovascular associations in a combined approach; instead, most studies have focused on singular measures, usually AHI. A gap

in knowledge, therefore exists regarding how different physiologic factors measured during sleep, when "combined," may be associated with disease outcomes.

The goal of the Determining Risk of Vascular Events by Apnea Monitoring (DREAM) Study is to develop a prognostic model for cardiovascular and mortality outcomes, based on physiologic variables measured during polysomnography in U.S. veterans. The DREAM study is composed of a large U.S. veteran study population that has undergone in-laboratory polysomnography for suspected sleep-disordered breathing and has been followed for the development of cardiovascular disease and mortality. The objectives of this manuscript are to: describe the goals of the DREAM study; outline its methodological approach; and provide the rationale for the inclusion of U.S. veteran patients undergoing polysomnography for suspected sleep disordered breathing.

DESIGN AND METHODS

Overall Trial Design/Specific Aims

The DREAM Study is a multi-site, retrospective, observational cohort study. The primary objectives of the DREAM Study are to determine the polysomnographic variables that are most predictive of incident cardiovascular outcomes. The DREAM Study includes data from three Veterans Health Administration (VHA) medical centers (West Haven, CT; Indianapolis, IN; Cleveland, OH). The Institutional Review Boards at each of the sites approved the conduct of this research.

At the time of the sleep study, medical, anthropomorphic and demographic characteristics were abstracted from the VA electronic medical record for visits most recent (and prior to) the sleep study. Data from the sleep study were also abstracted at this time. All medical record and polysomnographic abstraction was performed at the central clinical research center at the Clinical Epidemiology Research Center (CERC) at the West Haven VA. (The CERC is a collaboration among the VA Cooperative Studies Program, VA Connecticut Healthcare System, and Yale University which seeks to improve the healthcare of U.S. veterans by coordinating and supporting nationally funded VA research involving large observational cohorts.)

The DREAM study was designed and collected with the overall goal of developing a clinical prognostic model of cardiovascular disease in patients undergoing sleep testing for suspected sleep disordered breathing, and who are at risk for developing such events. The initial aim of this study was to identify polysomnographic and sleep measures—including AHI, oxygen desaturation frequency, arousal index and periodic limb movement index—that best predict incidence of stroke, acute coronary syndrome and mortality. With the identification of polysomnography-related cardiovascular risk variables from the DREAM study, the subsequent aim was to validate this model in a non-veteran observational cohort of patients studied with polysomnography for sleep-disordered breathing. The final aim was to determine to what degree do polysomnography-related measures add to the prognostic value of more conventional risk factors of cardiovascular disease, including smoking, hypertension, diabetes, age, hyperlipidemia, and alcohol use.

Inclusion and Exclusion Criteria

U.S. veterans undergoing in-laboratory polysomnography for the evaluation of sleep-disordered breathing between January 1, 2000 and December 31, 2004 were eligible for inclusion (Table 1). Eligible patients included those referred for suspected sleep-disordered breathing who had a history and physical documented in the electronic medical record prior to the sleep study, and who underwent at least 2 hours of attended sleep monitoring using full polysomnography (full night or split night protocols). The inclusion of veterans undergoing split night studies in the cohort reflects the wide use of combined diagnostic and therapeutic sleep testing throughout the VA system. Patients were excluded if: they were referred for reasons other than the evaluation of suspected sleep-disordered breathing (e.g., narcolepsy or movement disorder); the study was done with a tracheostomy that was “open” or “unplugged”; or the study was performed entirely with airway pressurization. Veterans were not excluded if they received therapy by oral appliance or surgery.

Polysomnography Data Acquisition

Digital in-laboratory polysomnographic data from the Indianapolis, Cleveland, and West Haven VAMCs, from 01/01/2000 through 12/31/04 (n=1840 out of approximately 2,200 available) were rescored by an independent certified sleep technologist at the CERC in West Haven. Participants underwent overnight, attended, in-laboratory polysomnography, which included at least 2 hours of sleep without positive airway pressure (PAP) utilization. Polysomnogram acquisition software included Grass data-acquisition systems (Astro-Med; Warwick, RI) for West Haven,

CompuMedics PS (Melbourne, Australia) for Indianapolis, and Embla (Pleasanton, CA) for Cleveland.

The recording montage included frontal (F3, F4), central (C3, C4) and occipital (O1, O2) electrodes referenced to contralateral auricular leads, bilateral electrooculographic channels, 2 submental electromyographic channels, electrocardiography, nasal pressure transduction, oronasal thermistry, chest/abdomen respiratory inductance plethysmography, finger pulse oximetry, body position (by a mercury gauge sensor), and bilateral anterior tibialis electromyography.

Sleep stages were scored using 30-second epochs according to Rechtschaffen and Kales criteria [18, 19]. and sleep architecture variables were noted as percent total sleep time for stages NREM 1, NREM 2, NREM 3, and REM sleep. Arousals were scored according to published guidelines and summarized as the total number of arousals per hour of sleep (arousal index) [20].

Apnea was defined as near complete reduction in thermocouple, lasting longer than 10 seconds, and was classified as obstructive or central depending on whether respiratory effort was present or absent, respectively. Hypopnea was scored according to American Academy of Sleep Medicine (AASM) recommended: ≥30% decrement in amplitude of nasal pressure flow signal for at least 10 seconds associated with a 4% oxygen desaturation, and alternative criteria: ≥50% decrement in amplitude of nasal pressure flow signal for at least 10 seconds associated with a 3% oxygen desaturation or arousal, based upon criteria accepted at the time of scoring.[19]

Apneas and hypopneas were categorized as obstructive or central based on AASM criteria. The apnea-hypopnea index (AHI) was calculated as the total number of apneas

and hypopneas per hour of sleep. Nocturnal pulse oximetry was used to measure oxygenation, and oxygen saturation was noted as the number of 3% desaturations per hour of sleep, oxygen desaturation 3% index; and 4% desaturations per hour of sleep, oxygen desaturation 4% index. Oxygenation was further measured as percent of total sleep time spent below 90% saturation. Periodic limb movements were scored according to AASM guidelines: 8μV increase in anterior tibialis EMG amplitude from baseline for 0.5 to 10.0 seconds, occurring a minimum of four movements in succession, no less and no more than 5 and 90 seconds apart, respectively [19]. The periodic limb movement index (PLMI) was computed as the total number of periodic leg movements per hour of sleep.

The different sleep-related polysomnographic and questionnaire variables are displayed in Table 2.

Designation of Sleep Apnea Treatment

For patients in this VA cohort, treatment was recommended according to consensus guidelines, and appliances and supplies were ordered by the institution through a single respiratory supply service. Importantly, the orders for these services are documented in the electronic medical record. In addition, patients are followed closely for the assessment of efficacy and treatment compliance through established sleep medicine and pulmonary clinics where positive airway pressure use is documented. Two physician investigators, blinded to outcome status, categorized each patient's airway pressurization treatment use in categories of: (1) not ordered; (2) no use; (3) intermittent use; and (4) continuous or "regular" use of positive airway

pressure. For the purposes of these analyses, airway pressurization compliance was documented into (1) “regular use” or (2) “not regular use”. “Regular use was approximated by the Centers of Medicare & Medicaid definition of CPAP compliance of 4 hours per night for 70% of nights or by regular issuance of supplies. It should be noted that many of the times, such precise data were not available for compliance, as CPAP use was information was provided by patient self-report then further by provider documentation of this.

Covariates

A distinctive feature of this study is the use of the robust VA databases across different VA sites, taking advantage of the centralized electronic medical record [Vista Computerized Patient Record System (CPRS/Vista Web)] that is shared by each of the sites. Experienced and trained research staff, blinded to study hypotheses, manually abstracted demographic, anthropomorphic and medical data. Covariate data is listed in Table 3. Baseline data were abstracted from clinical visits directly preceding the polysomnography date (time zero), and included measurements of age, sex, race, height, weight, blood pressure, smoking status (yes, no, pack years), and alcohol use (yes, no).

Past medical history was also abstracted, including histories of: hypertension, hyperlipidemia, congestive heart failure, cardiac arrhythmia (atrial fibrillation/flutter, second degree atrioventricular block, third degree atrioventricular block, QT prolongation), pacemaker, percutaneous angioplasty, coronary artery bypass graft, angina, arterial claudication, stroke, transient ischemic attack, diabetes, end stage renal disease, human immunodeficiency virus, cancer (and type), dementia, depression, and

post-traumatic stress disorder. Using this information, the Charlson Comorbidity Index was calculated for each patient [21].

Medical data at baseline also included three clinical blood pressure measurements (occurring on three consecutive clinical visits), cardiac echocardiography (if completed), electrocardiography, and several laboratory values: two fasting blood glucose values, hemoglobin A1c, total cholesterol, HDL cholesterol, LDL cholesterol, creatinine, blood urea nitrogen, and thyroid stimulating hormone levels. Medications were also inventoried, with doses of anti-hypertensive medication noted.

Primary Outcomes

Follow-up events that occurred any time from time zero (polysomnography day) through the date of participant's last visit were included, so that participants had follow-up ranging from 0.06 to 8.8 years (5.5 ± 1.3 yrs; mean±SD). The main primary outcome is the composite endpoint of acute coronary syndromes, stroke, transient ischemic attack or death (Table 4) [22]. The choice of composite endpoint is based on an accepted methodological practice; when outcomes are hierarchic, lower order events (stroke, myocardial infarction) should be assessed with higher order ones (death) to avoid inferential errors (e.g., people who die can no longer have cardiovascular events) [23].

Acute coronary syndrome, stroke, and death events were ascertained by review of the VA Patient Treatment File, VA Outpatient Clinic File, VA–Medicare Data, the Vista Computerized Patient Record System (CPRS/Vista Web), and the VA Vital Status File. The VHA Patient Treatment File (PTF=inpatient) and Patient Clinic Encounter (PCE=outpatient) were searched for appropriate International Classification of

Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes for TIA/stroke (434.XX, 435.X, and 436) and acute coronary syndrome (410.XX excluding history code 411). These codes are both sensitive and specific for the diagnosis of stroke and ACS [24]. Overall mortality was ascertained using the VA Vital Status File; this file combines death dates from several sources including the Patient Treatment File, Beneficiary Identification and Record Locator Subsystem death file, Medicare Vital Status, and Social Security Administration Death File. Mortality was further divided into fatal events attributable to myocardial infarction, stroke, cardiac arrest, arrhythmia, congestive heart failure, cancer, or suicide.

Secondary outcomes included incidents of neoplasm, congestive heart failure, cardiac arrhythmia, peripheral vascular disease, end stage renal disease, pulmonary hypertension, deep vein thrombosis, diabetes, human immunodeficiency virus, dementia, depression, and post-traumatic stress disorder. Laboratory outcomes included measures of glycemic control, including hemoglobin A1c and fasting glucose levels, total cholesterol, HDL cholesterol, LDL cholesterol, creatinine, blood urea nitrogen, and thyroid stimulating hormone levels.

All outcomes were adjudicated by an internal medicine trained physician who verified their occurrence by reviewing the medical record. Exact times of each of the events, including death, were recorded. Time-to-event was defined as the time from overnight polysomnography (time zero) to the time of a patient's confirmed first cardiovascular event (CHD or stroke) or death, or to the end of follow-up (10/14/2011). Patients not found to have had a vascular event or death, and who had not been seen in

an outpatient visit since the end of follow-up (12/31/07), were censored at the last point of contact (e.g., last outpatient visit).

Sampling and Sample Size

Participants were included based upon their completion of an attended overnight sleep study for the evaluation of sleep-disordered breathing. Given that both Indianapolis and West Haven VA participants were predominantly Caucasian, the Cleveland VA was chosen specifically to broaden inclusion of minorities, in particular African-Americans. Prevalent cardiovascular disease and hypertension were not excluded; this approach allows for a determination of whether primarily incident disease differs from secondary or recurrent disease.

The source population includes approximately 2,200 veterans at VA Connecicut Healthcare System (N~800), the Richard L. Roudebush Indianapolis VAMC (N~900), and the Louis Stokes Cleveland VAMC (N~500). Based on an accrual interval of 4 years, a mean follow-up interval of 5 years, and a median time to event of 3 years (estimated from previous work) a sample size of 2200 allows for a minimal detectable hazard ratio of 1.15 with 80% power and α=0.05 [8]. The study is therefore powered adequately to detect an association between individual sleep variables and the development of acute coronary syndrome (which represents the most conservative estimate of the three primary endpoints). For patients in the DREAM study, the mortality rate is 13.2%.For the general male population aged 60 years (in DREAM study, 94.4% are male and average age is 58.1 years old), the mortality rate is 1.1%

(www.ssa.gov/oact/STATS/table4c6.html).[25] Based on the above information, the standardized mortality ratio is 13.2/1.1= 12.0.

From this approximately 2,200 available participants, demographic, medical, and polysomnographic data have been abstracted for 1,840 veterans. Table 5 outlines some baseline demographic and abbreviated polysomnographic characteristics of the cohort.

DISCUSSION

The DREAM Study is a multi-site, retrospective, observational cohort study designed to determine if various physiologic sleep study variables predict cardiovascular events, such as stroke, CHD or mortality. This research is based upon the growing need to identify therapeutic targets to reduce cardiovascular disease, the leading cause of mortality in the United States [26]. Better understanding the connection between OSA and cardiovascular disease represents one such strategy. In the U.S., obesity and OSA are both on the rise. But only about 20% of OSA is diagnosed, and even a smaller percentage is effectively treated [27-30]. OSA is a well-known independent risk factor for a variety of diseases related to cardiovascular disease, including hypertension, diabetes, cardiac arrhythmia, stroke, and coronary heart disease [5, 8, 9, 14, 31]. For these reasons, increasing the understanding of physiologic interactions among sleep-related breathing parameters and the cardiovascular system is of substantial importance.

This project extends previous research by examining the prediction of cardiovascular and cerebrovascular outcomes, and is based on consideration of multiple

polysomnographic measures of sleep apnea severity (including frequency of apneic episodes, type of respiratory events, event duration, oxygen desaturation severity, and degree of sleep fragmentation). This research has the potential to refine the current concept of sleep apnea severity, by yielding a better understanding of prognosis for important clinical outcomes and by identifying key polysomnographic prognostic variables.

From the proposed research, a novel prognostic system will be developed and validated that will have clinical, policy, and research implications. With respect to clinical care, this research will yield a better understanding of prognosis for individuals regarding clinical outcomes, which will help to inform treatment decisions. The proposed work also has research implications. For example, knowledge of high risk groups will identify those most likely to benefit from treatment; thus, this study can serve as a prelude to future randomized controlled trials exploring the impact of sleep apnea therapy on the risk of cardiovascular outcomes. In addition, the research can further the understanding of the mechanisms mediating cardiovascular risk in patients with OSA, by identifying specific polysomnographic variables that explain variability in cardiovascular outcomes.

The DREAM study has several methodological strengths. The inclusion of participants from three different VA sites promotes population diversity, while maintaining consistency of access to government funded healthcare. The VA system has a robust electronic medical record system used at all sites, allowing for consistent and accurate adjudication of outcomes. Data were collected and scored using standardized criteria, with trained scorers at a central clinical research center, allowing for further

consistency and reliability. This method of research has the advantage of utilizing an established healthcare system and leveraging a robust electronic medical record for the collection of data. Of course, there are limitations to this approach as well, which include the use of billing codes as surrogate for cardiovascular outcome and selection bias inherent to collecting data based upon whether clinical follow-up occurred. CPAP compliance data was collected by documentation of a self-report through usual clinical care and also as surrogate of reissue of positive airway pressure supplies.

To date, this project has assembled a large U.S. veteran sleep disorders "cohort," and extensive polysomnographic data has been collected. As stated previously, the veteran population is particularly important to study the relationship between disordered sleep and cardiovascular disease, given that veterans are at high risk for having both cardiovascular disease and poor sleep, in part secondary to OSA. The primary limitation of the DREAM study database is the lack of gender diversity, which reflects the composition of the U.S. veteran population. For this reason, findings from this study have uncertain generalizability to women.

In summary, the DREAM study analyzes detailed sleep and breathing metrics for their association with outcomes of cardiovascular, cerebrovascular, and mortality events. A broad array of secondary outcomes will also be available, making this study applicable to other topics in neurology and psychiatry. The data from this study can provide valuable information regarding associations among different polysomnographic metrics of sleep apnea and cardiovascular outcomes.

ACKNOWLEDGEMENTS

We would like to acknowledge the research teams at all three VA sites: West Haven VAMC, Cleveland VAMC, and Indianapolis VAMC, and the veterans who participated in these studies. Thank you for your service.

CONFLICT OF INTEREST STATEMENT

All authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

REFERENCES

[1] Colten H, Altevogt B,(2006) Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem. National Academies Press (US)National Academy of Sciences, Washington DC.

[2] Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S,(1993) The occurrence of sleep-disordered breathing among middle-aged adults, N Engl J Med, 328: 1230-1235.

[3] Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP,(2001) The continuing epidemics of obesity and diabetes in the United States, Jama, 286: 1195-1200.

[4] Punjabi NM, Welch D, Strohl K,(2000) Sleep disorders in regional sleep centers: a national cooperative study. Coleman II Study Investigators, Sleep, 23: 471-480.

[5] Peppard PE, Young T, Palta M, Skatrud J,(2000) Prospective study of the association between sleep-disordered breathing and hypertension, N Engl J Med, 342: 1378-1384.

[6] Marin JM, Carrizo SJ, Vicente E, Agusti AG,(2005) Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study, Lancet, 365: 1046-1053.

[7] Gami AS, Howard DE, Olson EJ, Somers VK mers,(2005) Day-night pattern of sudden death in obstructive sleep apnea, N Engl J Med, 352: 1206-1214.

[8] Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V,(2005) Obstructive sleep apnea as a risk factor for stroke and death, N Engl J Med, 353: 2034-2041.

[9] Punjabi NM, Polotsky VY,(2005) Disorders of glucose metabolism in sleep apnea, J Appl Physiol (1985), 991998-992007.

[10] Fung CH, Martin JL, Dzierzewski JM, Jouldjian S, Josephson K, Park M, Alessi C,(2013) Prevalence and symptoms of occult sleep disordered breathing among older veterans with insomnia, J Clin Sleep Med, 9: 1173-1178.

[11] Samson P, Casey KR, Knepler J, Panos RJ,(2012) Clinical characteristics, comorbidities, and response to treatment of veterans with obstructive sleep apnea, Cincinnati Veterans Affairs Medical Center, 2005-2007, Prev Chronic Dis, 9:E46.

[12] Hirshkowitz M KS, Littner M, Kuna S, Weaver E, Kryger MH, Yaggi, Bishop M, Almenoff P. The VA Sleep Field Advisory Group.,(2014) Sleep-related Breathing Disorders: Sourcebook, 3rd Edition (Version 2.1).

[13] Sharafkhaneh A, Richardson P, Hirshkowitz M,(2004) Sleep apnea in a high risk population: a study of Veterans Health Administration beneficiaries, Sleep Med, 5: 345-350.

[14] Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, Redline S, Resnick HE, Tong EK, Diener-West M, Shahar E,(2010) Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study, Circulation, 122: 352-360.

[15] Jamasebi R, Redline S, Patel SR, Loparo KA,(2008) Entropy-based measures of EEG arousals as biomarkers for sleep dynamics: applications to hypertension, Sleep, 31: 935-943.

[16] Thomas RJ, Weiss MD, Mietus JE, Peng CK, Goldberger AL, Gottlieb DJ,(2009) Prevalent hypertension and stroke in the Sleep Heart Health Study: association with an ECG-derived spectrographic marker of cardiopulmonary coupling, Sleep, 32: 897-904.

[17] Koo BB, Blackwell T, Ancoli-Israel S, Stone KL, Stefanick ML, Redline S, (2011) Association of incident cardiovascular disease with periodic limb movements during sleep in older men: outcomes of sleep disorders in older men (MrOS) study, Circulation, 124: 1223-1231.

[18] Rechtschaffen A, Kales A,(1968) A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects, National Institutes of Health, Washington DC.

[19] Iber C, Ancoli-Israel S, Chesson A,(2007) The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specifications, 1st ed., American Academy of Sleep Medicine, Westchester, IL.

[20] Amerian Academy of Sleep Medicine,(1992) EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association, Sleep, 15: 173-184.

[21] Charlson ME, Pompei P, Ales KL, MacKenzie CR,(1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, J Chronic Dis, 40: 373-383.

[22] Cannon CP, Brindis RG, Chaitman BR, Cohen DJ, Cross JT, Drozda Jr. JP, Fesmire FM, Fintel DJ, Fonarow GC, Fox KA, Gray DT, Harrington RA, Hicks KA, Hollander JE, Krumholz H, Labarthe DR, Long JB, Mascette AM, Meyer C, Peterson ED, Radford MJ, Roe MT, Richmann JB, Selker HP, Shahian DM, Shaw SE, Sprenger S, Swor R, Underberg JA, Van de Werf F, Weiner BH, Weintraub WS,(2013) ACCF/AHA key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes and coronary artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Acute Coronary Syndromes and Coronary Artery Disease Clinical Data Standards), Crit Pathw Cardiol, 12: 65-105.

[23] Gent N, Sackett DL,(1979) The qualification and disqualification of patients and events in long-term cardiovascular clinical trials, Thromb Haemost, 41:123-134.

[24] Reker DM, Hamilton BB, Duncan PW, Yeh SC, Rosen A, (2001) Stroke: who's counting what?, J Rehabil Res Dev, 38: 281-289.

[25] S.S. Administration, Actuarial Lift Table,(2010) in: O.S.S. Website (Ed.), www.ssa.gov/oact/STATS/table4c6.html. Accessed July 10, 2015.

[26] Mozaffarian D, Benjamin EJ, Go AS, et al,(2015) Executive summary: heart disease and stroke statistics-2015 update: a report from the american heart association, Circulation, 131: 434-441.

[27] Mokdad AH, Serdula MK, Dietz WH, Bowman BA, Marks JS, Koplan JP,(1999) The spread of the obesity epidemic in the United States, 1991-1998, Jama, 282: 1519-1522.

[28] Young T, Evans L, Finn L, Palta M,(1997)Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women, Sleep, 20: 705-706.

[29] Kapur V, Strohl KP, Redline S, Iber C, O'Connor G, Nieto J,(2002) Underdiagnosis of sleep apnea syndrome in U.S. communities, Sleep Breath, 6: 49-54.

[30] Weaver TE,(2006) Adherence to positive airway pressure therapy, Curr Opin Pulm Med, 12: 409-413.

[31] Mehra R, Benjamin EJ, Shahar E, Gottlieb DJ, Nawabit R, Kirchner HL, Sahadevan J, Redline S,(2006) Association of nocturnal arrhythmias with sleep-disordered breathing: The Sleep Heart Health Study, Am J Respir Crit Care Med, 173: 910-916.

TABLES

Table 1. Inclusion and Exclusion Criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
U.S. veteran in-lab PSG	PSG to evaluate hypersomnia

Evaluation for SDB	PSG to evaluate parasomnia
Jan. 1, 2000-Dec 31, 2004	PAP Titration study
History/physical in chart	Tracheostomy
At least 2 hours of PSG	No follow-up after PSG

PSG=polysomnography; SDB=sleep-disordered breathing; PAP=positive airway pressure

Table 2. Polysomnographic Variables

VARIABLES	**OPERATIONAL COMMENT**	**TIME OBTAINED**
Respiratory		
Apnea Hypopnea Index (AHI)	# Respiratory Events / hour of total sleep time	Zero time
Apnea Duration (sec)	Mean and longest duration of respiratory events	Zero time
Hypoxia		

Oxygen Desaturation Index 4%	# oxygen desaturations ≥4%/ total sleep time	Zero time
Oxygen Desaturation Index 3%	# oxygen desaturations ≥3%/ total sleep time	Zero time
T_{90}	Percent of total sleep time with SaO2 <90%	Zero time
T_{80}	Percent of total sleep time with SaO2 <80%	Zero-time
Average SaO_2	Average oxygen saturation during sleep	Zero-time
Minimum SaO_2	Lowest oxygen saturation	Zero-time
Sympathetic Activity		
Arousal Index	Total # arousals/hrs sleep	Zero-time
Other		
Sleep duration	Average number of sleep hours per night	Pre-zero time
Sleep Efficiency	Total sleep time /time in bed	Zero-time
Periodic limb movement index	Total # periodic limb movements / hour of sleep	Zero-time

Epworth Sleepiness Scale	Validated Clinical scale assessing sleepiness	Pre-zero-time

Table 3: Risk Adjustment Variables

VARIABLES	**OPERATIONAL COMMENT**	**DATA SOURCE**	**TIME OBTAINED**	**VARIABLE TYPE**
Framingham Stroke				
Age	In years	Medical record	Pre-zero time	Dimensional
Systolic BP (mmHg)	BP prior to zero time	Medical Record	Pre-zero time	Dimensional
Antihypertensive Rx	Currently on any medication to treat high blood pressure	Medical Record	Pre-zero time	Binary

Diabetes Mellitus	Diabetes history, on diabetic medication, or fasting blood sugar >126 mg/dL	Medical record	Pre-zero time	Binary
Cigarette Smoking	Any cigarette smoking at visit prior to zero time	Medical record	Pre-zero time	Binary
Cardiovascular Disease	See Framingham Project	Medial Record	Pre-zero time	Binary
Atrial Fibrillation	History atrial fibrillation	Medical Record	Pre-zero time	Binary
Left Ventricular Hypertrophy	By EKG	Medical Record	Pre-zero time	Binary
Framingham ACS				
Gender	Male or Female	Medical record	Pre-zero time	Binary
Total Cholesterol (mg/dL)	avg. of two measurements obtained from lipoprotein analysis	Medical record	Pre-zero time	Dimensional
HDL Cholesterol (mg/dL)	avg. of two measurements obtained from lipoprotein analysis	Medical record	Pre-zero time	Dimensional
Charlson	Comorbidty Adjustment	Medical Record	Pre-zero time	Dimensional

Comorbidity Index				
Additional Variables				
Race	Black ,White, Hispanic, Other	PTF†	Pre-zero time	Nominal
Socio-economic status	Eligibility for VA services	PTF†	Pre-zero time	Dimensional
Sleep Apnea Treatment status	Evidence of CPAP use, weight loss>20%,	Medical record Prosthetic data	Post-Zero time	Binary
† =Patient Treatment File				

Table 4. Primary Outcomes

OUTCOMES	OPERATIONAL COMMENT	DATA SOURCE
Primary Outcomes		
Acute Coronary Syndrome	According to Guidelines of the American College of Cardiology[22]	Medical record, PTF,* PCE ,¥ VA-Medicare
Stroke	Persistent focal neurologic deficit of presumed ischemic origin	Medical record, PTF,* PCE ,¥ VA-

	lasting > than 24 hours	Medicare
Transient Ischemic Attack	Persistent focal neurologic deficit of presumed ischemic origin lasting < than 24 hours	Medical record, PTF,* PCE ,¥ VA-Medicare
Death	Patient died before 12/31/07	VA Vital Status
*=Patient Treatment File ¥=Patient Clinic Encounter		

Table 5. Baseline Characteristics of Cohort

PARTICIPANT CHARACTERISTICS	**COHORT (N=1840)**
Age	58.1 ± 11.6
Sex, male, n (%)	1268 (94.4)
Race (n=1250)	-
Caucasian, n (%)	1053 (84.2)
Black, n (%)	171 (13.7)
Hispanic, n (%)	26 (2.1)
Body Mass Index, kg/m^2	34.7 ± 6.8

Smoking Status, n (%) (n=1139)	-
Never	374 (32.8)
Past	299 (26.3)
Current	466 (40.9)
Drink alcohol, n (%) (n=1277)	-
Never	449 (35.2)
Past	639 (50.0)
Current	189 (14.8)
Atrial Fibrillation, n (%)	103 (7.7)
Diabetes, n (%)	431 (32.1)
Use of anti-hypertensive, n (%)	933 (70.2)
Hypertension, n (%)	1184 (88.2)
Apnea-hypopnea Index	18.6 ± 24.3
Periodic Limb Movement Index	11.6 ± 23.7
Arousal Index	42.4 ± 27.8