Arrhythmia Detection In Obstructive Sleep apnea (ADIOS)

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A. BACKGROUND

Obstructive sleep apnea (OSA) is characterized by repetitive interruption of ventilation during sleep due to collapse of the pharyngeal airway. A diagnosis of OSA is established when a patient has an apnea-hypopnea index (AHI) >5 and symptoms of excessive daytime sleepiness[1]. OSA affects an estimated 15 million adults and is prevalent in a large percentage of patients with hypertension and other forms of cardiovascular disease[1]. Obesity and male sex are recognized risk factors for the presence of sleep-disordered breathing[2].

OSA is a recognized risk factor for ischemic stroke[3, 4]. The mechanisms whereby OSA increases the risk of stroke are complex, including hypoxia, increased likelihood of arrhythmia and congestive heart failure, increased atherosclerosis, and production of inflammatory changes in the blood[5]. Although OSA is well recognized as an independent stroke risk factor, little focus has been devoted to modifying potential stroke risk factors in patients with OSA.

One of the mechanisms whereby OSA can lead to ischemic stroke is via atrial fibrillation (AF). AF is the leading cause of cardioembolic stroke and there is an important bidirectional relationship between these two conditions[6, 7]. OSA is present in up to 50% of patients with AF[8]. Also, when patents with OSA are followed longitudinally, up to 15% will develop AF over a five year period[9].

In addition to overt AF, performance of the polysomnogram (PSG) will allow the detection of premature atrial contractions (PACs). PACs are a recognized potential predictor for AF[10].

Early detection of AF in patients with OSA is important since oral anticoagulants are extremely effective for stroke prevention in patients with nonvalvular AF[7]. Institution of anticoagulation in the patient population with coexistent AF and OSA represents a significant opportunity for primary stroke prevention.

B. METHODS

The specific goal of this study is to assess the frequency of AF in patients with OSA using a cardiac event monitor (www.lifewatch.com). We will specifically target OSA patients with a $CHADS^2$ score of ≥2.

Patients who are newly diagnosed with OSA (within the last 12 months) based on a PSG at one of our participating hospitals will be eligible. Patients with a $CHADS^2$ score of ≥2 will be approached for evaluation with a two week cardiac event monitor. The target sample size is 200 patients. The rationale for this sample size is provided below.

Inclusion and Exclusion Criteria

Inclusion Criteria

1. Diagnosis of OSA within the last 12 months

2. No previous diagnosis of atrial fibrillation

3. Able and willing to follow-up as an outpatient

4. Age 40-85 years

Exclusion criteria

1. Life expectancy < 2 years

2. Dementia or other neurologic condition which would make outpatient follow-up difficult

3. CHADS score <2

4. Alcohol or drug abuse which would interfere with outpatient follow-up

5. Severe CHF (NYHA class 3 or 4) or use of LVAD

6. Current dialysis treatment or planned treatment within 12 months

7. Known bleeding disorder or prothrombin time >15 seconds

8. Mechanical heart valve requiring anticoagulation

9. Moderate to severe mitral stenosis or regurgitation

10. Prior clinical diagnosis of ischemic stroke (radiologic infarcts are not excluded)

11. COPD with oxygen dependence

12. Pregnant patients or patients that plan to become pregnant within the course of the study*.

13. Patients with anticipated need for a pacemaker during the course of the study

*If any patients become pregnant during the course of the study, pregnancy outcomes will not be followed

Treatment Plan and Dosing Regimen

Patients will be screened for atrial fibrillation with the Lifewatch ACT MCT monitor. If positive for AF, results will be provided to the patient's primary care physician and outpatient antithrombotic medication use in the following six months will be recorded. The Lifewatch interpretation will be sent by FAX to the patient's primary care physician for patients recruited at the University of Miami Sleep Center.

Cardiology consultation will be encouraged for patients with newly detected AF.

Subject Recruitment

The study coordinator will work with the PI and co-investigators to institute screening procedures for eligible subjects at the two sites, also, protected health information will be access prior as well during

the course of the proposed research. All newly diagnosed OSA patients who meet the study criteria will be invited to join the study. In addition, patients with a diagnosis of OSA within the previous 12 months will also be asked to participate if they meet all the study criteria. Patients who will be approached for participation in the study are already under the care of the sleep physicians who are co-investigators in the study.

Prior to study initiation, an educational presentation will be provided to the Sleep Program personnel (including staff physicians, fellows) to review the nature and purpose of the study. The physicians involved in the Sleep Program have regular conferences in which the study will be highlighted. The PI will work with the study coordinator and co-investigators to review study enrollment on a biweekly basis. Any obstacles to enrollment will be addressed by the study staff.

A summary of the study schedule of events is provided in Appendix one.

Description of cardiac monitoring device

The Lifestar ACT MCT monitor is a continuous ECG monitor and arrhythmia detector that is designed for self-testing by patients at home and for analysis by medical professionals at a remote Monitoring Center. The chest-worn sensor is utilized for the acquisition, recording, and transmission of the ECG signal. The device is equipped with four electrodes on a harness and it houses a 3.6V AA battery, a Bluetooth transceiver and a buzzer Patients will be monitored over a 2 week of period.

The ECG signals are transmitted via Bluetooth to a handheld device with a proprietary interactive application, arranged to process and transmit the ECG recordings. The handheld device is mobile computing device with a display and a touch input such as a cell phone. It has adequate memory and processing capability to run the proprietary application. This device is already used for routine clinical care at both the University of Miami Hospital and the Miami VA Hospital. A patient quick start guide is attached as an appendix.

Outcome Measures

After completion of the four week cardiac event monitor, we will record the frequency of abnormalities such as:

1. Frequent premature atrial contractions
2. Frequent ventricular premature contractions
3. Definite AF (defined as an irregularly irregular rhythm with absence of p waves)
4. Longest duration of AF
5. AF episodes lasting more than six minutes

Initial interpretation of the cardiac monitor is provided by Lifewatch technicians and the reports will be confirmed by the study assigned cardiologist. The Lifewatch technicians receive ECG information only and no identifiable information. We will follow patients for six months after the placement of the cardiac event monitor. We will document selection of antithrombotic therapy including the following:

1. Novel oral anticoagulant (NOAC)
2. Warfarin
3. Antiplatelet therapy
4. No antithrombotic therapy

After all patients have completed the six month follow-up period, we will record the following:

1. Frequency of undetected AF
2. AF frequency according to baseline $CHADS^2$ score
3. Rate of utilization of anticoagulants in patients with AF
4. Rate of utilization of antiplatelet therapy in patients with AF
5. Predictors of AF based on baseline variables (age, sex, history of CHF, BMI, etc.)

If we find that >5% of patients with OSA and $CHADS^2$ score of ≥2 have undetected AF, then this would support a larger multi-center study of screening OSA patients for AF and identifying predictors of AF in this population.

Risk/benefit considerations

No benefit can be guaranteed to study participants. However, if they do have early detection of AF, they can be placed on appropriate antithrombotic treatment to prevent stroke, which is a potential benefit.

There are no major risks with the device. Some patients may have skin irritation and special "sensitive skin" leads are available for these patients. There is no restriction with the use of the device with pacemakers or other implanted devices since only surface recordings are made.

C. SAMPLE SIZE CONSIDERATIONS

The frequency of AF in the general population is likely to be <1%. Our hypothesis is that 5% of OSA patients screened with a four week monitor will have AF.

If p = the percent of patients with sleep apnea who have afib, then the z-test will assess the following hypotheses:

H0: $p <= 1\%$

H1: $p > 1\%$

If the true value of p is 5%, then a study with 200 patients has power = 97%. That is, the probability is 0.97 that the null hypothesis (H0) will be rejected at a significance level of 5% in favor of the alternate hypothesis (H1).

The sample size needed for 80% power is 59 patients. The higher sample size is justified since the point estimate of AF frequency will be more precise with the larger sample size. Further, analysis of the predictors of AF according to baseline variables will be more fruitful with a larger sample size.

D. Performance sites

Patients with OSA will be identified and recruited for the study at The University of Miami Sleep Center, which is accredited by the American Academy of Sleep Medicine.(http://uhealthsystem.com/sleep-center). The UM Sleep Center has an eight bed sleep lab and performs over 1000 sleep studies per year and diagnoses over 500 patients per year with OSA. There is ample volume of clinical patients for study recruitment.

E. Study Procedures and Timeline

See Table 1

F. Data Management Plan

The Department of Neurology at the University of Miami Miller School of Medicine has a full time statistician and has served as the clinical coordinating center for previous multi-center trials. The research infrastructure is excellent. The Neurology Department participates in two major NIH-sponsored clinical trial consortia, the NeuroNext Initiative and the Stroke Trials Network (StrokeNet).

With regard to data collection and adequacy, data will be obtained directly from the study participants via office visits or through phone follow-up, and thus we feel that the data source for those elements will be quite accurate. The electronic medical record (EMR) at the two facilities will be another source for obtaining information on any medical encounters for cardiac issues such as atrial fibrillation. Electronic case report forms will be created for data collection in the study.

Although all measures will be undertaken to prevent missing data, it is likely that there will be some missing data elements due to patients who drop out of the study. Due to the relatively short duration of study participation and the patient stipend being offered, we expect a dropout rate of <2%. To handle missing data, we will first examine the characteristics of those who are missing outcome data compared to those who are not, as well as those who were lost-to-follow-up and those who were not, to determine whether there are differences in important characteristics between the groups (e.g. age, race). To deal with missing data in the outcome, we will employ methodology such as the use of multiple imputation.

G. Drug Supply Request

None

H. Adverse Events

MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

1.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction (ADR)

An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medical product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event

A serious adverse event is defined as any AE which

- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization, but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

1.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

INSTITUTION/Investigator will be responsible for reporting AEs which occur during the conduct of the Study to the competent regulatory authorities, accredited Institutional Review Boards and/or Independent Ethics Committee(s) ("IRB/IEC(s)") in accordance with the applicable laws and regulations.

1.3 ADVERSE EVENT REPORTING TO BOEHRINGER-INGELHEIM (BI)

Dabigatran is not part of the protocol but the following section is added at the request of the sponsor in case patients receive dabigatran.

INSTITUTION shall report

(i) all ADRs, serious and non-serious

(ii) all fatal AEs

(iii) pregnancies in female subjects and partners of male subjects

which are associated with dabigatran by fax the BI Unique Entry Point (Fax : 1-203-837-4329) using BI NIS SAE report form in following timelines.

All Serious ADRs and AEs with fatal outcome shall be forwarded immediately (within twenty four (24) hours or next business day whichever is shorter).

All non-serious ADRs shall be forwarded within seven (7) days

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Causal relationship of adverse event

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Reporting of related Adverse Events associated with any other BI drug

The investigator is encouraged to report all adverse events related to any BI drug other dabigatran than the according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms.

I. Regulatory Considerations

1. Institutional Review Board (IRB)

Written informed consent will be obtained from study participants at each of the two performance sites. All study personnel will be trained in Good Clinical Practices (GCP) and fulfill other requirements of the University of Miami and Miami VA Hospital Research Committees.

2. Subject confidentiality

In order to maintain participant confidentiality, any records that leave the center will be identified only by the Study Identification number (SID). All records will be kept in a locked file cabinet. All computer entry will be done using SIDs only. Clinical information will not be released without the written permission of the participant. The patient contact information and restricted clinical information will be maintained by the study coordinator in a password-protected file on a laptop computer which will be kept in a locked office (CRB 1362).

3. Study Registration

The study will be registered at www.clinicaltrials.gov prior to initiation.

4. Study Modification/Discontinuation

The study may be discontinued at any time by the sponsor as per the contract.

J. Future Directions

In order to have the greatest impact on stroke prevention, it is important to have AF patients on the most effective antithrombotic medication[7]. Furthermore, it is important to have the anticoagulant medication started before a stroke to avoid permanent neurologic injury. Screening high risk patients for AF is one method to identify AF patients prior to the development of a disabling stroke.

We feel that the group of patients with OSA represents an excellent target population for AF screening due to their high frequency of multiple stroke risk factors (hypertension, diabetes mellitus, obesity, etc.). If we are able to establish that the frequency of AF in this population is at least 5%, then a larger study can be justified. Screening of OSA patients would also be a novel method for early identification of individual patients at elevated risk for ischemic stroke. Future studies could also investigate genetic polymorphisms which are associated with an increased propensity for AF[11, 12]. By combining genetic predisposition with environmental factors and conventional risk factors, an “AF prediction” score could be developed for patients with OSA and other conditions such as congestive heart failure.

K. Publication Plan

Our study team is multidisciplinary, including representatives from neurology, cardiology, and pulmonary/sleep medicine. It is likely that this study will be of interest to multiple audiences. Therefore, we would like to target abstract presentations for meetings such as the American College of Cardiology conference, American Academy of Neurology conference, and the meeting of the Associated Professional Sleep Societies.

Journals targeted for publication include the *Journal of the American College of Cardiology* (JACC), *Neurology*, and *Sleep*.

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APPENDIX ONE

Visit schedule and tasks for completion

Time	**Tasks for completion**
Baseline evaluation	• CHADS score calculation* • Obtain informed consent • Arrange cardiac monitor for patient • Explain plan for outpatient follow-up • Complete baseline data collection form • Heart monitor will be placed
1week	• Contact subject to verify that they are wearing the cardiac monitor. • Ask subject about any adverse events. • Remind subject to return the heart monitor (in person or via USPS or UPS) • Schedule 6-month phone call follow-up. This phone call will serve as the study close-out visit.
6 months	Contact subject for study close-out visit