ARIC Manuscript Proposal #1867

PC Reviewed: 11/8/11 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: The association between obstructive sleep apnea, biomarkers of myocardial stress and of inflammation, and cardiovascular outcomes in the Atherosclerosis Risk in Communities study.

b. Abbreviated Title (Length 26 characters): **OSA, cardiac biomarkers, and cardiovascular outcomes in the community**

2. Writing Group:
Gabriela Querejeta, Susan Redline, Naresh Punjabi, Christie Ballantyne, Scott D. Solomon, Amil M Shah; Others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _GQ____ **[please confirm with your initials electronically or in writing]**

First author: **Gabriela Querejeta, MD**
Address: 75 Francis Street, Boston, MA

Phone: 617-732-2733 Fax: 617-582-6027
E-mail: gquerejetaroca@partners.org

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
Name: **Amil M Shah, MD MPH**
Address: 75 Francis Street, Boston, MA

Phone: 617-525-9678 Fax: 617-582-6027
E-mail: ashah11@partners.org

3. Timeline: Analysis will begin once this proposed analysis is approved (anticipate Winter 2011). We aim to complete analysis and submit an abstract of the results to the 2012 American Heart Association Annual Meeting (abstract deadline June 2012). We anticipate a manuscript will be prepared within one year after proposal approval.

4. Rationale:

Obstructive sleep apnea (OSA) is prevalent and frequently asymptomatic in the general population.[1] OSA has been associated with an increased risk of cardiovascular (CV) mortality[2] and morbidity, including coronary artery disease,[3] pulmonary hypertension,[4] heart failure (HF),[5,6] and stroke.[7] However, the pathophysiologic mediators of this increased risk are not well defined.

OSA is associated with both an increased prevalence of systemic hypertension[8] and an increased risk of incident hypertension.[9] Although less well established, OSA has also been associated with a higher prevalence of pulmonary hypertension and interventions to treat OSA (CPAP) have been associated with reduction in pulmonary pressure.[4,10] Although the mechanisms are unclear, OSA is associated with intermittent hypoxemia and the burden of OSA associated hypoxemia, quantified as the percentage of sleep time spent at an oxygen saturation less than 90% (TST_{90}), has been associated with an increased risk of mortality.[11] These processes can place a hemodynamic load on both the left and right ventricle. Indeed, OSA has been associated with increased left ventricular mass[12] and increased right ventricular wall thickness[13] by echocardiography. The resulting myocardial stress and/or subclinical injury may partially mediate the observed increase risk for CV morbidity, particularly heart failure.

Both left and, to a lesser extent, right ventricular wall stress are triggers for the release of brain natriuretic peptide (BNP) and its precursor NT-proBNP.[6] Both are well established markers of increased risk across the spectrum of CV disease.[14-17] Similarly, cardiac troponin (Tn) is an intracellular myocardial protein that is a sensitive marker of myocardial injury.[18] While most commonly used as a measure of ischemia/injury in the setting of acute coronary syndromes (ACS), recent studies with high sensitivity assays demonstrate a surprisingly high frequency of detectable Tn in asymptomatic community dwelling persons.[19] Like NT-proBNP, Tn is emerging as an important risk marker of CV events across the spectrum of CV disease, beyond just ACS. Among persons with OSA, NT-proBNP and Tn may therefore reflect both the burden of increased hemodynamic load associated with OSA and the effectiveness of myocardial adaptation to this load. A limited number of small single center studies have evaluated the relationship between OSA, these biomarkers of myocardial stress/injury, and CV events with controversial results.[20-27] The largest of these involved 623 participants in the Framingham Heart Study and found no relationship between OSA severity and levels of either atrial natriuretic peptide (ANP) or BNP.[28] An integrated analysis incorporating both markers of myocardial stress and injury, and an assessment of their relationship with clinical outcomes, has not been previously examined in a large cohort of community dwelling individuals.

OSA has also been associated with increased markers of systemic inflammation,[29,30,31] in particular high sensitivity C-reactive protein (hsCRP), although this finding has not been universal.[32] The causal mechanisms between OSA and inflammation remain obscure, although one causal factor may be the hypoxia-hyperoxia cycles that occur in OSA patients during apnea and hypopnea.[33] Obesity may also be an important confounding comorbidity.[34] CRP is a well-established risk marker for incident CV events, including ischemic heart disease,[35] heart failure,[36] and stroke.[37] Pro-inflammatory effects therefore represent an addition pathway by which OSA may increase risk of CV

events. However, the association between OSA, inflammatory markers, and risk of CV events has not been evaluated in a large populations-based cohort study.

We propose to harness the wealth of data on sleep disordered breathing by polysomnography, biomarkers of myocardial stress (NT-proBNP), myocardial injury (high sensitivity TnT), and systemic inflammation (hsCRP), and clinical co-mordibities available in the 1,920 ARIC participant who also participated in the Sleep Heart Health Study (SHHS) and who now have over 10 years of follow-up surveillance for incident CV events since undergoing polysomnography and biomarker measurement. Specifically, we aim to assess (1) whether OSA is associated with increased levels of NT-proBNP, cTnT, and hsCRP, (2) whether the severity of OSA as measures by the apnea-hypopnea index (AHI) is associated with the degree of elevation in these biomarkers, and (3) whether NT-proBNP, cTnT, and hsCRP allow for improved risk discrimination among persons with OSA beyond AHI and clinical variables alone.

5. Main Hypothesis/Study Questions:

We hypothesize that:

a) The presence and severity of OSA will be associated with higher levels of NT-proBNP (reflecting greater myocardial stress), cTnT (reflecting subclinical myocardial injury), and hsCRP (reflecting greater systemic inflammation) compared to persons without OSA even after adjustment for relevant comorbidities.
b) Among persons with OSA, levels of NT-proBNP, cTnT, and hsCRP will improve prediction of risk for CV events beyond clinical covariates and AHI.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study Design

To address hypothesis (a), we will perform a cross-sectional study of the association between OSA presence and severity, as reflected by AHI (primary analysis) and TST_{90} (secondary analysis), and levels of NT-proBNP, cTnT, and hsCRP in univariate and adjusted analyses.

To address hypothesis (b), we will perform an analysis of the relationship between each biomarker of interest and incident CV events (heart failure and coronary heart disease) stratified by groups of OSA severity based on AHI (primary analysis) and TST_{90} (secondary analysis).

Inclusion/Exclusion Criteria

The analysis population will include ARIC participants with hs-cTnT, NT-proBNP and hs-CRP measured in the ARIC study at Visit 4 (1996-1998) who also participated in the SHHS and had AHI measured by polysomnography between 1995-1998. Analysis will

be restricted to participant without established heart failure or coronary heart disease at Visit 4.

Variables of Interest

Exposure variables:

(1) OSA group based on AHI level measured between 1995-1998. Groups will be defined by AHI as follows: <=5 (no OSA, n=1,036), 5-15 (mild OSA, n=557), 15-30 (moderate OSA, n=208), and >30 (severe OSA, n=119).
(2) Levels of pro-BNP and hs-CRP measured at Visit 4 will be expressed as continuous variables. For biomarker values that are not normally distributed, log transformation will be performed to achieve normality. For hsTnT, given the frequency of undetectable levels, hsTnT will be modeled as a continuous variable in the analysis for hypothesis (a), and as a categorical variable for hypothesis (b) dividing participants into 4 groups: hsTnT undetectable and 3 groups based on tertiles of detectable hsTnT levels.

Outcome variables:

(1) All cause mortality
(2) Incident heart failure hospitalization based on diagnosis codes from hospital discharges (ICD-9 code 428) [38]
(3) Total incident CHD events (fatal CHD, definite or probable MI, or coronary revascularization) ascertained per ARIC study procedures [39,40]

Covariates of interest:

The associations described for both hypothesis (a) and (b) will be evaluated after multivariable adjustment for potential confounding factors, including age, gender,[41] BMI,[28] and kidney function (eGFR and urine albumin-to-creatinine ratio).[42] Analysis will also be performed with additional adjustment for potential causal intermediaries, including hypertension, diabetes, and dyslipidemia. All covariate values will be drawn from ARIC Visit 4.

Summary of Data Analysis

To address hypothesis (a), levels of hs-cTnT, NT-proBNT and hs-CRP will be compared between the 4 AHI groups, using a p for trend analysis. These associated will also be evaluated after multivariable adjustment for potential confounding factors and subsequently for possible causal intermediaries, as listed in the 'Covariates of interest' section above. As a secondary analysis, a similar analysis will be performed dividing the study population into 2 groups based on TST_{90} (TST_{90}<1% [n=1,336] and $TST_{90}\geq$1% [n=583]).

To address hypothesis (b), univariate and multivariable Cox proportional hazards models will be generated to determine the association between each biomarker and incident mortality or CV event stratified by AHI-based OSA category. As a secondary analysis, a similar analysis will be performed based on TST_{90} groups.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ____ Yes ____ No
(This file ICTDER03 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes __X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
____ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

___X___ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

MS#1811- (Oluleye et al) Association of high sensitive Troponin T (hs-cTnT),N-Terminal pro- brain natriuretic peptide (NT-proBNP) and high sensitivity C- reactive protein (hs-CRP) with cause- specific mortality: ARIC study

MS#1808- (Nambi et al) The utility high sensitivity cardiac troponin t in the prediction of heart failure risk

MS#1757 (Nambi et al) The association of high sensitivity troponin with heart failure, mortality and recurrent coronary heart disease (CHD) in individuals with prevalent CHD

MS#1564 (Saunders et al) Correlation of High Sensitivity Troponin-T (hs-cTnT) and Amino Terminal pro-Brain Natriuretic Peptide (NT-proBNP) with Renal Function Parameters; and Association with Mortality and Adverse Cardiovascular Events

MS#1172 (Nambi et al) Lp-PLA2 and hs-CRP as Predictors of Ischemic Stroke

MS#940 (Ballantyne et al) Lipoprotein-associated phospholipase A2, high sensititivity c-reactive protein, and risk for ischemic stroke

MS#934 (Folsom et al) An assessment of incremental coronary risk prediction using C-reactive protein and other novel risk markers

MS#889 (Ballantyne et al) Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein and risk for incident coronary heart disease in middle-aged men and women in Atherosclerosis Risk in Communities Study

MS#606 (Folsom et al) C-reactive protein and incident cornary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ **Yes** ____ **No**

11.b. If yes, is the proposal

_X__ **A. primarily the result of an ancillary study (list number*** 1995.12 and 2008.10**)**

___ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)**

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire..

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