

ARIC Manuscript Proposal #2317

PC Reviewed: 2/11/14
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Prognostic importance of dyspnea in the community: The ARIC study

b. Abbreviated Title (Length 26 characters):
Dyspnea and prognosis in ARIC

2. Writing Group:

Writing group members: Mario Santos, Dalane Kitzman, Kunihiro Matsushita, Laura Loehr, Carla A Sueta, Amil M Shah; Others welcome.

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

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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).

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3. Timeline:

Analysis will begin once this manuscript proposal is approved. Anticipate initial manuscript completion in approximately 3 months following proposal approval with final manuscript completion in 5/2014.

4. Rationale:

Chronic dyspnea occurs in approximately 10%,^{1,2} and is particularly common among the elderly, with at least moderately severe dyspnea reported in approximately 25% of persons >65 years of age.^{3,4,5} Among the elderly, dyspnea is also associated with

worse functional capacity and a higher prevalence of anxiety and depression.⁵ Existing studies also suggest that participant-reported dyspnea is associated with a higher risk of mortality,⁶ the majority of which appear to be cardiovascular in origin.⁴ Indeed, in the Framingham Heart Study, participant reported dyspnea appeared to be a more powerful predictor of clinical outcomes than objective physiologic measures such as pulmonary function/spirometry.⁷

Although common, there is limited data regarding the prognostic relevance of participant reported dyspnea for non-fatal cardiovascular outcomes, including heart failure (HF), coronary heart disease (CHD), and recurrent hospitalizations. Even with respect to mortality, the relative contribution of cardiovascular versus non-cardiovascular deaths has not been well described. In addition, there is sparse data regarding the prevalence and prognostic significance of dyspnea in African Americans, a population that carries a sizable proportion of the HF and pulmonary disease burden.

A better understanding of the prognostic relevance of dyspnea in the community will provide novel insight into a common, but poorly understood, symptom that adversely impacts quality of life. The well characterized ARIC cohort offers the unique opportunity to define the prognostic relevance of dyspnea, identify clinical and laboratory predictors of risk among persons reporting dyspnea, and investigate race/ethnicity-based differences in these relationships.

5. Main Hypothesis/Study Questions:

We hypothesize that, compared to the participants without significant dyspnea, persons with dyspnea will have a higher risk of death, incident HF, incident MI, and all-cause hospitalization.

Specifically, we aim to:

1. Define the prevalence and clinical correlates of any dyspnea and dyspnea of at least moderate severity in the study cohort overall, and stratified by gender, race/ethnicity, and age category.
2. Determine the unadjusted and multivariable adjusted association of dyspnea with: (1) mortality (all-cause, cardiovascular, non-cardiovascular); (2) incident HF; (3) incident CHD; and (4) all hospitalizations.
3. Identify characteristics predictive of incident death or cardiovascular events among participants reporting dyspnea.

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:

This will be a time-to-event analysis based on data collected at ARIC Visit 4.

Inclusion/exclusion criteria:

All participants with dyspnea scale data will be included in this analysis.

Key variables of interest:

1. Dyspnea scale (visit 4): Based on Respiratory Questionnaire items 5-10.
2. Anthropometrics (visit 4): height, weight, BMI, BSA, waist:hip ratio
3. ECG variables (visit 4): (1) LVH by Cornell criteria; (2) presence of BBB (LBBB, RBBB); (3) rhythm other than sinus
4. Cardiac biomarkers of stress and injury (visit 4): NT-proBNP, hs-TnT
5. Vascular function variables (visit 4): systolic blood pressure, diastolic blood pressure, mean arterial pressure, pulse pressure
6. Pulmonary function variables (visit 4): FEV₁, FVC, FEV₁/FVC ratio
7. Renal function variables (visit 4): eGFR, urine albumin:creatinine ratio
8. Hematologic variables (visit 4): hemoglobin and hematocrit
9. Clinical covariates (visit 4): age, gender, race/ethnicity, heart rate, history of hypertension, diabetes, dyslipidemia, coronary artery disease, prior MI or revascularization procedure, prior stroke or TIA, peripheral arterial disease, heart failure, prior hospitalization for heart failure

Data analysis:

The prevalence and severity of dyspnea will be defined based on items 5 – 10 of the Respiratory Questionnaire, which is an approximation of the MRC breathlessness scale.⁸ This is a 5 level scale, with the participant score based on the question that best described the participants level of activity. This scale has been widely applied^{1,2,3,4,5,6} and has demonstrated prognostic relevance in COPD and coronary artery disease.³ For the primary analysis, dyspnea will be defined dichotomously (yes/no) based on a MRC score of ≥ 2 (breathlessness related to exercise intolerance or at rest). In a secondary analysis, we will define three groups: no dyspnea (MRC score 1), dyspnea with exertional limitation (MRC score 2-3), and severe dyspnea (MRC score ≥ 4). Participants reporting dyspnea will be compared to all cohort participants not reporting dyspnea. In a sensitivity analysis, we will compare participants reporting dyspnea to cohort participants not reporting dyspnea who are age, gender, and race/ethnicity matched.

Basic descriptive statistics will be performed in the population stratified by presence of dyspnea or not. Between-group comparisons will be performed using a Fisher's exact test for categorical variables, t-test for normally distributed continuous variables, and Wilcoxon rank sum test for non-normally distributed continuous variables. To quantify the relationship between dyspnea at Visit 4 and subsequent events we will use Cox proportional hazards models. Endpoints to be evaluated include (1) mortality (all-cause, cardiovascular, non-cardiovascular); (2) incident HF; (3) incident CHD; and (4) all hospitalizations. The presence of dyspnea will be the primary response variable. Multivariable adjustment will be performed, adjusting first for age, gender, and race/ethnicity, then additionally by BMI and clinical variables that differ significantly between the two groups. Additional sensitivity analysis will be performed restricting the above comparison to persons reporting dyspnea compared to age, gender, and race/ethnicity matched individuals not reporting dyspnea. Both univariate and multivariable analysis will be performed as described above. We will assess for effect

modification of gender and race/ethnicity on the dyspnea-outcomes relationship. Finally, among participants reporting dyspnea, we will identify significant predictors of subsequent events using multivariable Cox proportional hazards models with a stepwise selection procedure, with demographic, clinical, and laboratory variables as candidate predictors. Secondary analysis 3 categories of dyspnea (none, with exertional limitation, severe) will then be performed to evaluate the relationship of dyspnea severity with clinical outcomes, using a similar analytic approach.

Anticipated methodologic limitations:

Limited data will be available regarding the underlying etiology of dyspnea, particularly as cardiac function was not assessed in all participants at Visit 4. Participants reporting dyspnea may differ systematically – for example in demographics and co-morbidities – from those not reporting dyspnea. Therefore, residual confounding despite efforts to optimally adjust for potential confounder may be a limitation. Participants may develop dyspnea during the follow-up period, which would not be captured in this analysis.

7.a. Will the data be used for non-CVD analysis in this manuscript? Yes
 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
 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.csc.unc.edu/ARIC/search.php>
 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)?

References

- ¹ Bowden JA, To THM, Abernethy AP, Currow DC. Predictors of chronic breathlessness: a large population study. *BMC Public Health* 2011;11:33.
- ² Currow DC, Plummer JL, Crockett A, Cert G, Abernethy AP. A community population survey of prevalence and severity of dyspnea in adults. *J Pain Symptom Manage* 2009;38:533-45.
- ³ Huijnen B, van der Horst F, van Amelsvoort L, Wesseling G, Lansbergen M, Aarts P, Nicolson N, Knottnerus A. Dyspnea in elderly family practice patients: Occurance, severity, quality of life and mortality over an 8-year period. *Family Practice* 2006;23:34-9.
- ⁴ Tessier JF, Nejari C, Letenneur L, Filleul L, Marty ML, Gateau PB, Dartigues JF. *Eur J Epidemiol* 2001;17:223-9.
- ⁵ Ho SF, O'Mahony S, Steward JA, Breay P, Buchalter M, Burr ML. Dyspnoea and quality of life in older people at home. *Age and Ageing* 2001;30:155-9.
- ⁶ Frostad A, Soyseth V, Andersen A, Gulsvik A. Respiratory symptoms as predictors of all-cause mortality in an urban community: a 30-year follow-up. *J Internal Med* 2006;259:520-9.
- ⁷ Sorlie PD, Kannel WB, O'Connor G. Mortality associated with respiratory function and symptoms in advanced age: The Framingham Study. *Am Rev Respir Dis* 1989;140:379-84.
- ⁸ Stenton C. The MRC breathlessness scale. *Occup Med (Lond)* 2008;58:226-7.