ARIC Manuscript Proposal #2653

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SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Manifestations of mild ventricular dysfunction and risk of HF

b. Abbreviated Title (Length 26 characters): VD signs and symptoms


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

First author: Anna Kucharska-Newton
Address: Cardiovascular Epidemiology Program
Department of Epidemiology
Gillings School of Global Public Health
University of North Carolina at Chapel Hill
Chapel Hill, NC 27514

Phone: 919 966 4564  Fax: 919 966 9800
E-mail: anna_newton@unc.edu

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: Gerardo Heiss
Address: Cardiovascular Epidemiology Program
Department of Epidemiology
Gillings School of Global Public Health
University of North Carolina at Chapel Hill
Chapel Hill, NC 27514

Phone: 919 962 3252  Fax: 919 966 9800
E-mail: gerardo_heiss@unc.edu

3. Timeline: Proposed analyses are part of a R21 NIA grant submission (October 2015). Ancillary Study approval (AS 2015.22) has been granted by the ARIC Steering Committee.

4. Rationale:
Changes in cardiac structure and function that occur as part of normal aging and in the setting of conditions such as hypertension or diabetes, manifest along a continuum of initially subclinical
ventricular dysfunction and mild structural abnormalities to an overt clinical heart failure (HF) syndrome. Signs and symptoms that are part of the HF syndrome, including shortness of breath, edema, and fatigue, occurring in persons at increased risk of HF (and in the absence of a clinical diagnosis of HF), are as common among patients seen in ambulatory care practice as they are non-specific, presenting a challenge with respect to clinical decision making. Current HF stage classification describes persons who have a risk factor burden suggestive of HF risk in the absence of HF signs and symptoms as HF Stage A and those with evidence of structural changes in the heart, again in the absence of HF signs and symptoms as HF Stage B. Persons who present with signs and symptoms of HF (and are therefore not in HF Stage A or B) and who do not yet have a diagnosis of HF (therefore are not classified as being in Stage C HF) are outside of the existing classification schemes. We thus propose to classify individuals presenting with shortness of breath, edema, and fatigue who are at risk of developing HF and do not have a HF diagnosis as being in “pre-HF”, an undiagnosed HF condition. Referrals from primary care to cardiology for echocardiographic imaging, which may aid in the identification potential cardiac function abnormalities among persons in pre-HF, are expensive and often cannot be provided in a timely manner. Early identification of patients at risk for HF, however, is critical to clinical management, prevention of progression and eventual decompensation, and avoidance of unnecessary hospitalizations.

To add specificity to the signs and symptoms potentially associated with HF, several biomarkers of cardiac function have been identified which may aid in the differential diagnosis of patients with cardiac and/or pulmonary causes of breathlessness, edema, and fatigue. Of those, NT-proBNP, the biochemically inert degradation product of the natriuretic peptide synthesized by cardiomyocytes in response to volume overload, has been tested extensively as a diagnostic, prognostic and disease management tool. Despite low cost and guideline recommendations, adoption of NT-proBNP outside of the Emergency Department and inpatient settings is limited. Relative novelty of the test, lack of clarity with respect to diagnostic cut points applicable to the ambulatory care setting, and inter and intra-individual variability of NT-proBNP levels may all be barriers to its wider use. Further improvement in the prediction of the risk of HF hospitalization can be achieved by inclusion in prognostic models of information on levels of cardiac troponin T (cTnT) a marker of cardiomyocyte damage. A HF risk prediction model that includes both NT-proBNP and cTnT has been found to achieve the best statistical model fit. In contrast to NT-proBNP, levels of cTnT are not subject to high intra-individual variability. To our knowledge no studies have formally tested the utility of NT-proBNP and cTnT in the identification of pre-HF. Such assessments are, however, needed for effective implementation of simple HF risk scores in routine outpatient clinical practice. Validated and easy to use HF prognostic models optimized for the assessment of HF risk in complex patients with early signs of ventricular dysfunction would be instrumental to primary care prevention of HF.

5. Main Hypothesis/Study Questions: The proposed study is motivated by limited data on the long-term risk of heart failure among patients who present with manifestations potentially associated with ventricular dysfunction and/or pulmonary disease in the absence of a clear heart failure syndrome. Specifically, we propose to use ARIC cohort data to study the association of self-reported shortness of breath, lower extremity edema and of fatigue with (a) serum levels of NT-proBNP and cTnT with (b) the risk of subsequent
hospitalized heart failure as modified by NT-proBNP and cTnT levels, and (c) with echocardiographic measures of cardiac structure and function.

Our objectives are to:

**Aim 1:** Quantify the association of serum NT-proBNP and cTnT with shortness of breath, edema, and fatigue among older adults.

**Sub-aim 1a:** Assess the effect of age, gender, BMI, kidney function, diabetes, and medication use on the observed associations.

**Aim 2:** In race and gender strata, identify the most parsimonious set of clinically-relevant variables that optimize the risk stratification of a first HF hospitalization among adults with pre-HF.

**Sub-aim 2a:** Develop a risk score predicting 5- and 10-year risk of HF hospitalization among older adults with symptoms of pre-HF.

**Sub-aim 2b:** Assess the calibration and risk discrimination performance of the developed HF risk prediction model.

**Aim 3:** Characterize the cross-sectional association of symptoms of pre-HF among older adults with echocardiographic parameters of cardiac structure and function.

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 population**

Main analyses will be conducted in follow-up through 2012 among study participants who completed the Visit 2 assessments of respiratory status and the Maastricht vital exhaustion questionnaire, who had non-missing information concerning lower extremity edema assessment, and who had non-missing NT-proBNP and cTnT data. Excluded from analyses will be persons of race other than black or white and blacks from the Minnesota and Washington County study centers.

We will further examine the association of signs and symptoms of mild ventricular dysfunction with echocardiographic evidence of ventricular remodeling among study participants who completed the Visit 5 examination, using as exposure the Visit 5 repeat assessment of shortness of breath and edema.

**Exposure**

*Shortness of breath:* Self-report of shortness of breath will be based on results obtained from the breathlessness component of the respiratory assessment, which was modeled on the Epidemiology Standardization Project (Comstock 1987) and conducted at Visit 2 and Visit 5. Participants who responded “Yes” to the first question listed below were asked to respond to the subsequent four questions which assess increasing breathing difficulty, from breathlessness on exertion to difficulty breathing at rest.

1. Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill?
2. Do you ever have to stop for breath when walking at your own pace on the level?
3. Do you have to walk slower than people of your age on the level because of breathlessness?
4. Do you ever have to stop for breath after walking about 100 yards (or after a few minutes) on the level?

5. Are you too breathless to leave the house or breathless on dressing or undressing?

A continuous score (range 0-5)\textsuperscript{11} will be constructed for all participants and used as a continuous variable or as tertiles of the distribution, with the highest tertile reflecting clinically manifest dyspnea.

We will also examine associations of shortness of breath with the proposed outcomes using a binary categorization of this exposure (response “Yes” to any of the above questions).

**Edema:** Presence of bilateral lower extremity pitting edema, based on the physical examination conducted at Visit 2 and Visit 5, will be categorized as a binary variable.

**Fatigue:** Fatigue is one of two main domains assessed by the Maastricht Vital Exhaustion Questionnaire (MVEQ) which was administered at Visit 2. The following questions of the 21-item MVEQ will be used to ascertain levels of fatigue among study participants:

<table>
<thead>
<tr>
<th>Question</th>
<th>Item on the MVEQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you often feel tired?</td>
<td>1</td>
</tr>
<tr>
<td>Do you have a feeling that you have not been accomplishing much lately?</td>
<td>5</td>
</tr>
<tr>
<td>Do you feel weak all over?</td>
<td>4</td>
</tr>
<tr>
<td>I feel fine (reverse).</td>
<td>14</td>
</tr>
<tr>
<td>Do you feel more listless lately than before?</td>
<td>8</td>
</tr>
<tr>
<td>Do you have a feeling these days that you just do not have it anymore?</td>
<td>17</td>
</tr>
<tr>
<td>Do you sometimes feel that your body is like a battery that is losing its power?</td>
<td>15</td>
</tr>
</tbody>
</table>

Fatigue ascertained at Visit 2 will be operationalized as response “Yes” to the first of the above listed questions (“Are you often feeling tired?”).

In sensitivity analyses, a continuous fatigue score will be constructed on the basis of responses to the above 7 questions using the following classification criteria: “No”=0 points; “Do not know”=1 point; “Yes”=2 points. The final score (range 0-14) will be used as a continuous exposure as well as tertiles of the distribution, with the highest tertile indicative of clinically manifest fatigue.

At Visit 5, fatigue was considered present if the participant provided the response "some of the time" or "much or all the time" to the following two statements: "I felt everything I did was an effort" and "I could not get ‘going’".

The three listed above signs and symptoms of ventricular dysfunction; shortness of breath, edema, and fatigue, will be assessed as independent exposures and as a composite measure of exposure. Components of the composite measure will be determined on the basis of the analysis of variance and principal components analysis.

**NT-proBNP and cTNT:** Serum NT-proBNP and cTNT levels were measured at Visit 2 as part of ARIC Ancillary study 2009.16 (PI: E. Selvin) and at the Visit 5 clinical examination using the Roche Elecsys2010 immunofluorescent assay. The high sensitivity assay was used to measure cardiac troponin levels (hs-cTnT). In keeping with the convention adopted in extant studies, half of
the lowest NT-proBNP detection limit (5 pg/L) will be assigned as the serum level of this marker for study participants with undetectable NT-proBNP levels. Correlation between NT-proBNP and hs-cTnT will be examined using the Spearman correlation coefficient.

**Outcomes**
The main outcome of interest in this analysis will be incident HF hospitalization, which will be ascertained from the presence of ICD-9 code 428.x in any position in participants’ records of hospitalizations occurring in follow-up through December 31, 2012. Study participants with prevalent HF at ARIC Visit 2, ascertained on the basis of HF prevalence at ARIC study baseline Visit and HF incidence in follow-up through the Visit 2 examination date, will be excluded from analysis. Likewise, participants with prevalent HF at visit 5 will be excluded from analyses.

Echocardiographic measures of cardiac structure and function – the outcome for Aim 3 - will be based on the comprehensive tissue Doppler echocardiography performed at Visit 5 and will include measures of LV structure (left ventricular (LV) mass, mean LV wall thickness, relative wall thickness, LV end-diastolic diameter) as well as measures of LV diastolic function (left atrial volume and relaxation velocity). LV ejection fraction and the global longitudinal strain will be considered as markers of systolic function.

**Covariates**
Serum NT-proBNP levels are known to be affected by age, gender, BMI, kidney function, and medication use. Those covariates, ascertained from Visit 2 data, will be examined as effect modifiers of the observed associations. Kidney function will assessed on the basis of the estimated glomerular filtration rate which will be calculated using the CKD-EPI equation. Medications considered in analyses will include diuretics, b-blockers, ACE inhibitors, and anti-arrhythmic agents.

Selection of the most parsimonious set of clinically relevant covariates for inclusion in the proposed HF risk score will be based on the ARIC HF risk prediction model developed by Agarwal et al. Additionally, we will examine potential effect modification of observed associations of HF signs and symptoms with the risk of HF hospitalization by prevalent comorbidities, including diabetes, hypertension, and atrial fibrillation which will be assessed in follow-up from baseline prevalent disease status (as applicable) through the Visit 2 date.

**Analytical considerations**
Gender- and race-specific generalized linear models will be constructed for the cross-sectional analyses of the association of shortness of breath and edema ascertained during Visit 5 with echocardiographic measures of ventricular function assessed at that visit and for the cross-sectional analysis of the association of NT-proBNP and hs-cTnT levels with shortness of breath, edema, and fatigue ascertained at Visits 2 and 5. In analyses focused on Visit 5 data, propensity scores will be constructed from available demographic and comorbidity participant characteristics to account for selection bias due to attrition.

Age-adjusted incidence rates of HF-related hospitalizations among those with signs and symptoms of ventricular dysfunction, as compared to those without, will be estimated using gender- and race-specific Poisson regression models. Relative risk of incident HF hospitalization will be estimated...
using Cox proportional hazard multivariable regression models. Proportional hazard assumptions for all variables will be evaluated by plotting Shoenfeld residuals against time.

Construction of the most parsimonious model of the risk of HF hospitalization will be based on variables identified through univariate Cox proportional hazard regression models with the significance value set at 0.05. Model fit will be examined using likelihood ratio tests.

The following methods will be used to assess the performance of the HF risk prediction model in pre-HF:

- **Model calibration** – graphical examination of the observed, relative to the predicted, probabilities. Hosmer-Lemeshow statistic
- **Model discrimination** – Harrel’s c-statistic\(^\text{15}\); area under the curve analysis\(^\text{16}\); predictiveness curves, ranking predicted risk probabilities against risk quantiles\(^\text{17}\)
- **Classification** – net reclassification index\(^\text{18}\)
- **Clinical usefulness of the model** - decision curve analysis methods to identify clinically relevant diagnostic thresholds\(^\text{19-21}\)

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 ICTDER 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](http://www.csc.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 # 1376 Agarwal S. et al., Optimal predictors of incident hospitalized heart failure: the ARIC cohort study. (published)

MS# 1808 Nambi V. et al., The utility high sensitivity cardiac troponin t in the prediction of heart failure risk (published)
MS# 1917 Shah A. et al., Association of diastolic dysfunction with high sensitivity troponin T and NT-proBNP across left ventricular geometries in the community – A preliminary analysis from the ARIC study

MS# 2219 Shah A., et al., Pathophysiologic characterization of dyspnea in the elderly: The 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*  2009.16 (PI: E. Selvin); 2015.22 (PI: Kucharska-Newton))
   ___  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.csc.unc.edu/aric/forms/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.csc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript _____ Yes ____ No.

References