ARIC Manuscript Proposal # 3345

PC Reviewed: 02/12/2019   Status: _____   Priority: 2
SC Reviewed: _____   Status: _____   Priority: ____

1.a. Full Title: Prevalence, Characteristics, and Outcomes of Subclinical, Undiagnosed, and Established Heart Failure with Preserved Ejection Fraction in the Community: The Atherosclerosis Risk in Communities Study

  b. Abbreviated Title (Length 31 characters): **HFpEF Diagnostic Scores in ARIC**

2.   Writing Group:
        Writing group members:

Senthil Selvaraj and Peder Langeland Myhre (co first-authors), Muthiah Vaduganathan, Brian Claggett, Amil Shah, Scott Solomon; others welcome

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

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3.   Timeline: We will begin work on the analysis immediately after obtaining approval and data. We estimate the time to journal submission will be less than 6 months from data acquisition

4.   Rationale:
Exertional dyspnea is common in the elderly. A study of ARIC participants from visit 2 noted significant dyspnea in 22% which portended worse outcomes, including higher incidence of all

cause mortality, among those without a known cardiopulmonary cause of dyspnea (Santos et al., PLoS One, 2016). Given the broad differential diagnosis of dyspnea, establishing a diagnosis can be challenging though is critical to appropriate clinical management. Heart failure with preserved ejection fraction (HFpEF) is common, costly, and increasing in prevalence (Owan et al., NEJM, 2006; Redfield et al., JAMA 2016). Diagnosing HFpEF can be challenging in some patients and can necessitate invasive hemodynamic assessment, the gold standard, to establish a diagnosis, particularly among euvolemic and compensated patients. Broad use of cardiac catheterization among all patients with unexplained dyspnea, however, is not feasible for widespread use in the community.

Fortunately, a Bayesian approach to the diagnosis of HFpEF has recently been developed by invasive hemodynamic exercise testing in patients with unexplained dyspnea free of pulmonary disease (Reddy et al, Circulation, 2018). The H_2FPEF score uses routinely obtained clinical variables as well as echocardiographic data to provide a probability of HFpEF among those with unexplained dyspnea. These variables include obesity, atrial fibrillation, age >60 years, treatment with ≥2 antihypertensives, echocardiographic E/e' ratio >9, and echocardiographic pulmonary artery systolic pressure >35 mm Hg. Test characteristics are excellent, with an area under the curve of 0.84 with preserved replication statistics in an independent cohort. If externally validated, clinicians may be able to non-invasively estimate the probability a patient with dyspnea has HFpEF using this instrument. It is noteworthy that the score was derived from a relatively modest sample of patients from a single, referral tertiary care center.

In addition, the European Society of Cardiology (ESC) has published consensus guidelines on the diagnosis of HFpEF (Pieske et al. How do Diagnose Heart Failure with Preserved Ejection Fraction – The HFA-PEF$_2$ Diagnostic Algorithm. A *Consensus Recommendation from the Heart Failure Association of ESC 2018*). This algorithm is based on a staged diagnostic process that takes into account demographics, functional, morphologic, and biomarker characteristics to diagnose HFpEF. Both the H_2FpEF score and the HFA-PEF$_2$ Diagnostic Algorithm are important tools used to establish a HFpEF diagnosis. This algorithm has been presented at an international meeting and a manuscript is currently in peer review.

While data exist on prevalence of patients discharged from hospitalizations for acutely decompensated HFpEF, few data exist regarding the burden of HFpEF, both undiagnosed and established, in the community. In addition, characteristics of individuals with risk factors for HFpEF without symptoms (hereafter referred to as "subclinical HF") are not well studied. Finally, whether individuals with subclinical HF by H_2FPEF score and those with undiagnosed HFpEF have similar outcomes to those with established HFpEF is unknown. Understanding the total burden of those at risk for HFpEF hospitalization is important, as it can underscore the need to prevent HF hospitalization and use of targeted therapies to reduce HF hospitalization, including SGLT2 inhibitors (Zelniker TA et al. Lancet 2018).

5.   Main Hypothesis/Study Questions:
 The main study questions are:
   1.) Among patients with unexplained dyspnea without known HF, how do the H_2FPEF and the HFA-PEF$_2$ scoring systems compare in predicting incident HFpEF?

2.) What is the burden of subclinical and undiagnosed HFpEF in the community and associated clinical characteristics?

3.) What is the risk for incident HFpEF hospitalization of subclinical and undiagnosed HFpEF compared with those with established HFpEF?

We hypothesized that the H_2FPEF scoring system predicts HF hospitalization more accurately than the ESC scoring system. We also hypothesized that subclinical and undiagnosed HFpEF is common in the community, and that there is a graded risk in adverse outcomes by H_2FPEF score and the presence of symptoms.

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).
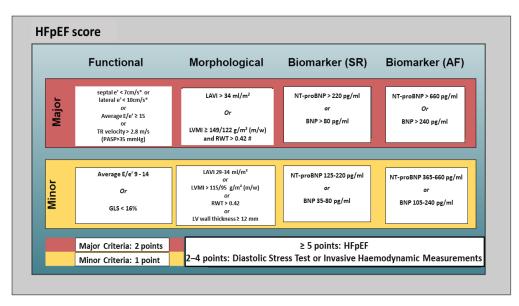
Study design and inclusion/exclusion criteria: We will perform a cross-sectional and prospective analysis of ARIC participants at visit 5, for whom echocardiography and dyspnea data are available, as these are necessary for analysis of the H_2FPEF score. We will include those with available echocardiographic data and dyspnea data from the modified Medical Research Council (mMRC) score form. We will exclude those with reduced EF ($<50\%$), severe valvular disease, or those with underlying pulmonary disease (COPD or asthma), as this analysis will focus on those with unexplained dyspnea.

Exposure variable: The H_2FPEF score. The variables included in the score are obesity (BMI>30 kg/m^2), atrial fibrillation (paroxysmal or persistent), age >60 years, treatment with ≥ 2 antihypertensives, echocardiographic E/e' ratio >9, and echocardiographic pulmonary artery systolic pressure >35 mm Hg.

Pasted below from the Reddy et al. paper is the scoring system. The probability of HFpEF is noted at the bottom by number of total points.

	Clinical Variable	Values	Points
H₂	**H**eavy	Body mass index > 30 kg/m²	2
	Hypertensive	2 or more antihypertensive medicines	1
F	Atrial **F**ibrillation	Paroxysmal or Persistent	3
P	**P**ulmonary Hypertension	Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure > 35 mmHg	1
E	**E**lder	Age > 60 years	1
F	**F**illing Pressure	Doppler Echocardiographic E/e' > 9	1
H₂FPEF score			**Sum (0-9)**

Total Points: 0 1 2 3 4 5 6 7 8 9

Probability of HFpEF: 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 0.95

For comparison we have pasted step 2 of the ESC HFA-PEF₂ algorithm:

HFpEF score

	Functional	Morphological	Biomarker (SR)	Biomarker (AF)
Major	septal e' < 7cm/s* or lateral e' < 10cm/s* or Average E/e' ≥ 15 or TR velocity > 2.8 m/s (PASP>35 mmHg)	LAVI > 34 ml/m² Or LVMI ≥ 149/122 g/m² (m/w) and RWT > 0.42 #	NT-proBNP > 220 pg/ml or BNP > 80 pg/ml	NT-proBNP > 660 pg/ml Or BNP > 240 pg/ml
Minor	Average E/e' 9 - 14 Or GLS < 16%	LAVI 29-34 ml/m² or LVMI > 115/95 g/m² (m/w) or RWT > 0.42 or LV wall thickness ≥ 12 mm	NT-proBNP 125-220 pg/ml or BNP 35-80 pg/ml	NT-proBNP 365-660 pg/ml or BNP 105-240 pg/ml

Major Criteria: 2 points
Minor Criteria: 1 point

≥ 5 points: HFpEF
2–4 points: Diastolic Stress Test or Invasive Haemodynamic Measurements

Outcome: The primary outcome will be time to HF hospitalization or death. We will also examine time to HF hospitalization and death as separate end points.

Variables of interest:
1. Clinical covariates (visit 5): age, gender, race/ethnicity, 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
2. Dyspnea scale (visit 5): Based on Respiratory Questionnaire items 5-10.
3. Anthropometrics (visit 5): height, weight, BMI, waist:hip ratio
4. Echocardiographic variables (visit 5 echo): (1) LV structure (LV end-diastolic and end-systolic volumes and dimensions), wall thickness, relative wall thickness, and mass); (2) LV diastolic function (E wave, A wave, E wave deceleration time, TDI E', E/e, and LAVi); (3) LV systolic function (LVEF, global longitudinal strain, global circumferential strain); (4) pulmonary hemodynamics (estimated PASP based on TR jet velocity and assumed right atrial pressure) and right ventricular function (TDI tricuspid annular S')
5. Cardiac biomarkers (visit 5): NT-proBNP, hs-cTnT
6. Hemodynamic (visit 5): systolic blood pressure, diastolic blood pressure, mean arterial pressure, pulse pressure, heart rate
7. Renal function variables (visit 5): eGFR based on serum creatinine
8. Hematologic variables (visit 5): hemoglobin and hematocrit
9. Measures of glycemic control (visit 5): hemoglobin A1C, fasting glucose

Analysis
Objective 1: We will first identify all patients with unexplained dyspnea without HF at baseline. We will describe the distributions of the H_2FPEF score and the ESC HFA-PEF$_2$ score in these patients. We will use Cox proportional hazards models and cumulative incidence curves to assess the association between both scores and incident adjudicated HFpEF risk. We will assess the predictive capacity of the scores as continuous variables and by established cut-offs (≥ 5 points). We will also compare the predictive value of both scores in predicting HFpEF using C-statistics.

Objective 2: This analysis will focus on the H_2FPEF score. We will categorize patients into the following group: 1) asymptomatic with H_2FPEF score<5, 2) asymptomatic with H_2FPEF score≥ 5, 3) dyspnea with H_2FPEF score<5, 4) dyspnea with H_2FPEF score≥ 5, and 5) established HFpEF. We have chosen 5 as the cutoff since this yields >80% probability of HFpEF. Baseline characteristics will be summarized using descriptive statistics for continuous variables and counts and percentages for categorical variables. We will determine the distribution of the H_2FPEF score in those without symptoms (subclinical HFpEF) and those with symptoms but no diagnosis of HF (undiagnosed HFpEF).

Objective 3: We will perform univariate Cox proportional hazards models to determine the relationship between the H_2FPEF score categories and adverse outcomes. The referent arm will be no dyspnea and H_2FPEF score<5. Hazard ratios and associated 95% confidence intervals will be calculated using Cox proportional hazards regression. Patients will be censored if they were lost to follow-up or died (for non-mortality analyses). Cumulative incidence curves will be calculated for each outcome.

All analyses will be performed using STATA version 14 (StataCorp LLC; College Station, TX, USA), and a two-sided p-value < 0.05 will be considered statistically significant.

Limitations: The major limitations of the study are lack of data on inferior vena cava (IVC) diameter, which is a surrogate of right atrial pressure and used for calculations of the pulmonary artery systolic pressure (used in the H_2FPEF score). We will assume a right atrial pressure of 5 mmHg, which is consistent with previous echocardiographic studies when IVC diameter is not available (Selvaraj et al., Circ HF, 2015). In addition, the tricuspid regurgitant velocity jet is needed to calculate pulmonary artery systolic pressure but is unable to be measured in roughly 1/3 of the general population. We will perform sensitivity analyses using complete case analysis as well as multiple imputation for this variable among those with missing data.

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 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   _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/mantrack/maintain/search/dtSearch.html

____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)?

#2219: Amil M Shah, Brian Claggett, Hicham Skali, Dalane Kitzman, Kunihiro Matsushita, Laura Loehr, Scott D. Solomon. The Relationship of Unexplained Dyspnea in Late Life With Cardiovascular and Non-Cardiovascular Dysfunction: the Atherosclerosis Risk in Communities (ARIC) Study

The senior author of this study, Amil Shah, will be a co-author for the present study. While this study examines dyspnea in the elderly, it does not utilize the H_2FPEF score or the ESC HFA-PEF$_2$ algorithm, which is unique to our analysis.

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

11.b. If yes, is the proposal
   ___   **A. primarily the result of an ancillary study (list number* _____)**
   ___   **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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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.

We aim to submit the manuscript for ARIC review within 6 months of obtaining data.

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.cscc.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.

The authors are aware of this policy.