ARIC Manuscript Proposal #3557

PC Reviewed: 2/11/20 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:
Longitudinal changes in left ventricular diastolic function in late life - the ARIC study

b. Abbreviated Title (Length 26 characters):
Changes in diastolic function in late life

2. Writing Group:

Writing group members:
Li Zhao, Brian Claggett, Kunihiro Matsushita, Dalane Kitzman, Suma Konety, Thomas Mosley, Amil Shah; others welcome

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

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3. Timeline:
Analysis will begin once the proposal is approved. We expect that the data analysis will be completed in 2 months after beginning, and we anticipate that the manuscript will be completed for submission in approximately 4 to 6 months.

4. Rationale:

Heart failure (HF) prevalence and incidence is highest in late life, and accounts for significant morbidity and mortality [1]. Heart failure with preserved ejection fraction (HFpEF) accounts for approximately half of all HF [2], and is associated with similar morbidity and mortality as HF with reduced ejection fraction (HFrEF) [3]. Importantly, unlike HFrEF, there are no effective therapeutic options for HFpEF to improve clinical outcomes [4-9]. While HFpEF is clinically and pathophysiologically heterogeneous, left ventricular diastolic dysfunction is consistently considered a key pathophysiologic contributor to HFpEF development and outcomes [10]. Several cross-sectional studies have demonstrated that common measures of LV diastolic function are worse at older age [11-14]. However, limited data are available regarding longitudinal changes in diastolic function – and its predictors – in late life, when the risk of HF generally and HFpEF in particular is highest. Longitudinal data from the Olmsted County Heart Function Study (OCHFS), with average age of 61 years old at baseline, demonstrated that among persons with normal diastolic function at baseline, higher age and E/e' at baseline were predictive of worsened diastolic function over 4 years interval [15]. In the community based FLEMENGHO study, with mean age of 51 years old, measures of left ventricular diastolic function tended to worsen over time and was associated with advanced age, higher baseline insulin level, and hemodynamic parameters, such as heart rate and blood pressure [16]. A similar study from the Framingham Heart Study, with mean age of 64 years old, found that both cardiometabolic risk factors and noncardiac comorbidities were associated with diastolic dysfunction progression over 5.6 years interval [17]. However, changes in diastolic function in late life (e.g. among persons 70 - 80 years old) have not been previously studied to our knowledge.

Longitudinal echocardiographic data from the 5th and 7th visits of the Atherosclerosis Risk In Communities (ARIC) study are a unique resource to address this gap in knowledge [11, 18]. The objective of this analysis is to characterize the changes of diastolic function in late life and to identify the clinical and imaging predictors of this change.

5. Main Hypothesis/Study Questions:

The objectives of this analysis are: (1) To quantify the 'expected' changed in echo diastolic measures over ~5 years in late life in a low risk subgroup of ARIC participants; (2) Characterize longitudinal changes in diastolic function over ~5 years in late-life among ARIC participants attending both Visits 5 and 7; and (3) Identify clinical and imaging predictors of longitudinal changes in LV diastolic function.

We hypothesize that:

(a) Measures of diastolic function will worsen over ~5 years in late life.
(b) Participants with higher burden of cardiovascular co-morbidities at Visit 5 will demonstrate greater worsening in diastolic function.
(c) Participants with evidence of structural heart disease (e.g. LV hypertrophy or remodeling) at Visit 5 will demonstrate greater worsening in diastolic 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 design
The proposed study will be an observational study utilizing longitudinal data on echocardiograms and clinical characteristics from ARIC Visits 5 and 7.

Inclusion/exclusion
Major inclusion criterion is available echocardiographic data at ARIC Visits 5 and 7. Participants with evidence of moderate or greater left-sided valvular heart disease at either Visit 5 or 7 will be excluded.

Outcome
The changes of left ventricular diastolic function parameters between ARIC visit 5 and visit 7. Primary diastolic function variables of interest include: TDI e', E/e' ratio, LA volume and volume index, LA width.

Variables of interest:
1. Echocardiographic variables (Visits 5 and 7): (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, TDI E', E/e' ratio, LAVi, and LA diameter); (3) LV systolic function (LVEF, global longitudinal strain, global circumferential strain); (4) pulmonary hemodynamics (estimated PASP based on TR jet velocity) and right ventricular function (RV fractional area change, TDI tricuspid annular s')
2. Clinical covariates (Visits 5 and 7): age, gender, race/ethnicity, BMI, blood pressure, heart rate, history of hypertension, diabetes, dyslipidemia, coronary artery disease, prior MI or revascularization procedure, atrial fibrillation, prior stroke or TIA, heart failure, spirometry (including FEV1/FVC ratio and FVC) at Visit 5, eGFR, serum creatinine, hemoglobin, hematocrit, hemoglobin A1C, fasting glucose, NT-proBNP, hs-cTnT
3. Outcome variable: Adjudicated incident HF post Visit 5, including adjudicated HFpEF and HFrEF.

Summary of data analysis
Objective 1:
We will characterize the distribution of change in diastolic measure from Visits 5 to 7 amongst a low risk subgroup of participants at Visit 5. This subgroup will be defined based on absence of cardiovascular disease or risk factors as previously published [6]. Because empirical estimates of distribution limits can vary substantially in small to moderate-sized samples, we will use quantile regression (STATA qreg) to define 10th, 50th, and 90th percentile limits of changes of diastolic functional parameters, with associated 95% confidence interval (CI). Limits will be defined in this low-risk reference subgroup overall and stratified by sex.

Objective 2:
We will describe the distribution of change in diastolic measures from Visits 5 to 7 among the study sample overall. Given the important potential impact of rhythm on Doppler-based

measures [19], analyses will be stratified based on rhythm at time of echo: sinus rhythm at both visits; atrial fibrillation at both visits; sinus rhythm at Visit 5 and atrial fibrillation at Visit 7. We will further describe the prevalence of both 'abnormal' changes in diastolic measures (defined using the 90th percentile limit of change defined in Objective 1 above) and the prevalence of 'lack of decline' in diastolic measures (defined using the 10th perctile limit of change defined in Objective 1 above). Values will also be defined in subgroups based on sex and race.

Objective 3:
We will define clinical and imaging predictors of worsening diastolic function, and preservation of diastolic function, from Visit 5 to 7. Key clinical predictors assessed at Visit 5 will include: age, gender, race/ethnicity, chronic kidney disease, history of atrial fibrillation, history of coronary artery disease including myocardial infarction, hypertension, diabetes, BMI, and smoking status. Key imaging predictors at Visit 5 will include LVEF, LV mass index, LV longitudinal and circumferential strain, and the baseline value of the diastolic parameter of interest. Key model covariates will include the following variables from both Visits 5 and 7: systolic BP, diastolic BP, heart rate, cardiovascular medications. Additional models will further adjust for interval myocardial infarction and incident heart failure between Visits 5 and 7. For predictors of change in diastolic measures as continuous variables, we will employ multivariable linear regression. For predictors of abnormal change in diastolic measures as a dichotomous variable, we will employ multivariable logistic regression. As in Objective 2 above, analyses will be stratified by rhythm at time of echo. Additional analyses will be performed stratified by (1) ACCF/AHA Heart Failure Stage at Visit 5 as previously defined [20], and (2) development of interval adjudicated HF between Visit 5 and Visit 7. Analyses will be performed with STATA software. Additional sensitivity analyses will be performed excluding participants with interval myocardial infarction and heart failure between Visits 5 and 7. Finally, additional analyses will be performed quantifying change in diastolic measures as 'change per year' in each diastolic measure, as time between Visits 5 and 7 may vary from ~5 to 8 years.

Methodologic limitations and challenges
The major limitations of this analysis are attendance bias and survival bias. We anticipate that survival bias will likely lead to underestimation of the longitudinal changes in diastolic function. We also suspect that attendance bias will similarly lead to underestimation of the magnitude of change to the extent that healthier participants choose to attend at Visit 7. We will attempt to mitigate the impact of attendance bias by performing sensitivity analyses using inverse probability weighting. Probability weights will be based on clinical, echocardiographic, and biomarker values at Visit 5. The number of participants in our low risk reference group may be limited, and will likely preclude defining race-specific reference limits.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes ____ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 current derived consent file ICTDER05 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

_____ 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)?

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes ____ 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 https://sites.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.

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.

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