ARIC Manuscript Proposal Form

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Publication Committee Review Date: **06/11/24**
ARIC Manuscript Proposal Number: **# 4478**

1.a. Full Title: Prevalence and correlates of tricuspid regurgitation in late-life: the ARIC study

b. Abbreviated Title (Length 26 characters): TR prevalence

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:
Writing group members: Khush M. Kharidia, Fernando R. Giugni, Victoria Lamberson, Yimin Yang, Amil M. Shah, Hicham Skali, Brian Claggett, Pamela Lutsey, Lynne Wagenknecht, Thomas Mosley, OTHERS WELCOME

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

First author [please provide a middle initial; EX: Adam L Williams]:

Khush	**M**	**Kharidia**
First name	Middle initial	Last name

Address: 5323 Harry Hines Blvd, Dallas, TX, 75390

Phone: 408-807-9260
E-mail: khush.kharidia@utsouthwestern.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (The ARIC author should be involved enough in ARIC to be able to point the lead author to appropriate ancillary study PIs and to be able to search ARIC manuscript proposals if the lead author doesn't have the access needed to do such a search).
Name: Amil M. Shah
Address: 5323 Harry Hines Blvd, Dallas, TX, 75390

Phone: 214-648-3111
E-mail: amil.shah@utsouthwestern.edu

3. Timeline: Data analysis will start once the proposal is approved. We anticipate the manuscript will be prepared within the next 6 months.

4. Rationale: Once thought to be an innocent bystander of cardiopulmonary disease, tricuspid regurgitation (TR) is now known to be associated with significant morbidity and mortality. While the prevalence of moderate to severe TR in the general population is estimated at 3%, this estimate increases to 7% in those > 75 years old[1]. Lesser severity of TR is even more common, estimated to be detectable in 82% of men and 86% of women[2]. The burden of tricuspid regurgitation is expected to grow substantially as the population ages, with persons >65 years old anticipated to account for 20% of the US population by 2030[3].

TR is a physiologically complex process that involves altered leaflet structure, tricuspid annular size, and right-sided cardiac hemodynamics.[4] Among patients clinically referred for echocardiography, greater prevalence and severity of TR is associated with female sex, prevalent atrial fibrillation, left-sided heart disease including lower left ventricular ejection fraction and mitral and aortic valve disease, and pulmonary hypertension.[5–7] Similarly, in studies largely drawing from clinically referred samples, the presence of severe TR has been associated with greater risk of mortality,[5–8] but the clinical importance of mild and moderate TR remains controversial.[6,8,9] Furthermore, the extent to which TR is independently associated with functional decline and greater mortality beyond frequent associated co-morbidities – including left heart dysfunction and valvular dysfunction – is not known.

To our knowledge, there is no contemporary study quantifying the burden of tricuspid regurgitation in older adults in the general population not referred for clinically indicated echocardiography. We propose to leverage the detailed clinical and echocardiographic phenotyping in ARIC to (1) estimate the prevalence of TR in a diverse community-based cohort of older adults, (2) identify clinical and echocardiographic correlates of TR presence and severity in this population, and (3) determine the association of TR severity with functional impairment (2-minute walk test), incident cardiovascular disease, and mortality.

5. Main Hypothesis/Study Aims: We hypothesize that greater TR severity is associated with older age, female gender, higher prevalence of comorbidities, worse left and right ventricular function on echocardiography, worse functional capacity, higher incidence of cardiovascular diseases, and greater mortality in late-life.

The aims of the study include:

(1) estimate the prevalence of TR in a diverse cohort of older adults in the community
(2) identify clinical and echocardiographic correlates of TR in this population
(3) determine the association of TR severity with functional impairment, incident cardiovascular disease and mortality

6. Design and analysis - please address the following aspects:

a) inclusion/exclusion

a. Inclusion: ARIC study participants who underwent echocardiography at study Visit 7
b. Exclusion: Participants with prior tricuspid valve surgery or inadequate echo imaging. For associations with incident HF, patients with prevalent HF will be excluded; for associations with incident AF, patients with prevalent AF will be excluded.

b) study design

This proposal includes cross sectional and longitudinal analyses using data from ARIC Visit 7. First, we will estimate TR prevalence in ARIC participants at Visit 7 stratified by sex, age group, and race (Analysis 1). Second, we will evaluate the cross-sectional association of TR severity at Visit 7 with clinical characteristics and echocardiographic measures (Analysis 2). Third, we will evaluate the associations of TR severity at Visit 7 with 2-minute walk distance at Visit 7 and with incident cardiovascular disease events (HF, AF) post-Visit 7 (Analysis 3).

c) outcome and other variables of interest with specific reference to the time of their collection

Analysis 1

TR severity measures at Visit 7: Qualitative TR severity by visual estimation
Stratification variables at Visit 7: sex, race, age groups (<80, 80-85y, ≥85).

Analysis 2

Exposures:

Demographic at Visit 7: age, sex, race, Visit Center

Clinical at Visit 7: smoking status, systolic blood pressure, diastolic blood pressure, prevalent hypertension, prevalent diabetes, prevalent chronic kidney disease, estimated glomerular filtration rate (eGFR), prevalent coronary artery disease (CAD), previous myocardial infarction (MI), previous stroke, prevalent atrial fibrillation (AF), prevalent peripheral artery disease, diuretic use, body mass index (BMI), hemoglobin, HbA1C, NT-proBNP, hs-troponin

Echocardiographic at Visit 7: mitral stenosis moderate/severe, mitral regurgitation moderate/severe, aortic stenosis moderate/severe, aortic regurgitation moderate/severe, LVEDV, LVEDD, MWT, LVMi, LV ejection fraction, global longitudinal strain, global circumferential strain, LA volume index, e' septal, e' lateral, E/e', E/A, RVEDA, RVESA, PASP, TAPSE, FAC, S' wave, TR jet area (TRJA), TRJA/right atrial area (TRJA/RAA).

Outcomes: Qualitative TR severity at Visit 7

Covariates: For associations with clinical variables at Visit 7, multivariable models will adjust for age, sex, race, visit center (model 1); For associations with echocardiographic measures, additional models will further adjust for BMI, eGFR, prevalent hypertension, prevalent diabetes, prevalent CAD, prevalent HF, prevalent AF (model 2)

Analysis 3
Exposure: Qualitative TR severity at Visit 7
Outcomes: incident HF post Visit 7, incident AF post Visit 7, mortality post Visit 7, 2-minute walk test at Visit 5, dyspnea score at Visit 5
Covariates: age, sex, race, visit center (model 1); age, sex, race, visit center, BMI, eGFR, prevalent hypertension, prevalent diabetes, prevalent CAD, prevalent HF, prevalent AF (model 2)

d) summary of data analysis

In Analysis 1, we will describe TR severity prevalence in the sample overall and stratified by age-group, sex and race. In Analysis 2, we will describe comorbidities and echocardiographic measures by grade of TR severity and will test for associations using adjusted trend tests based on multivariable linear regression models with TR grade modeled as a continuous exposure. In Analysis 3, associations of TR severity with 2MWT will similarly be assessed with multivariable linear regression. Associations of TR severity with incident AF, HF and mortality will be assessed using multivariable Cox PH models.

e) Any anticipated methodologic limitations or challenges if present

1. TR severity will be based on qualitative assessment, which may result in some misclassification. However, there is a lack of widely accepted quantitative criteria for TR severity.
2. High proportion of missing data for some echo variables, and for PASP in particular, may limit power for these analyses
3. Relatively low number of HF and AF events given limited follow-up available post-Visit 7 will limit power to detect associations with incident HF and AF.

f) Will the author need Limited data to complete the proposed manuscript? ☐ Yes, Limited data is needed (Provide a brief (2-3 sentences) justification for requesting PHI data) . ☒ No, De-identified data will be sufficient.

*Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded, Proteomics/Somalogic, and other -omic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? (Non-ARIC analysis means that the authors are not regarded as ARIC investigators and the "ARIC author" is essentially just a facilitator rather than an integral part of the writing group.) ☐ 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 is distributed to ARIC PIs annually, 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 or the "sponsoring" ARIC 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 website at: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website□Publications□Proposal Search]

☒ 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)?
MP#1158 Prevalence and correlates of mitral, tricuspid, and aortic regurgitation in middle aged and elderly African-Americans: the ARIC study.
MP#2739 Valvular heart disease and cardiac remodeling, damage, and overload in older Adults
MP#2807 Valvular heart disease and cardiac remodeling, damage, and overload in older adults

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use current [or ongoing] ancillary study data (this includes ACHIEVE)? ☒ **Yes** ☐ **No → Skip to question 12**

11.b. If yes to 11.a., is the proposal
☒ **A. primarily the result of an ancillary study**
☐ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables)**

11.c. If yes to 11.a., list number* _2015.34_

*ancillary studies are listed by number
https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website□Ancillary Studies□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 https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC Website□Publications□Publication Policies, Forms, and Guidelines]. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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