ARIC Manuscript Proposal Form

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Publication Committee Review Date: **12/10/24**
ARIC Manuscript Proposal Number: **# 4576**

1.a. Full Title: Association of PREVENT-HF with Preclinical Heart Failure and Implications for Clinical Risk Prediction: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): PREVENT-HF and Preclinical HF

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. JKG **[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 (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).

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3. Timeline: We aim to complete the manuscript within 3 months from the time of approval.

4. Rationale: Heart failure (HF) represents a major public health challenge in the United States, with significant morbidity, mortality, and healthcare costs.[1] In response, the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure[2] emphasized HF prevention as a priority. A central component of HF prevention is identifying individuals at highest risk who are most likely to benefit from targeted interventions. To support this effort, a staging framework for HF has been developed,[2] ranging from Stage A (at risk for HF) to Stage D (end-stage HF). Stage B, or preclinical HF, encompasses individuals with structural heart disease but no HF symptoms, who are at the greatest risk for progressing to clinical HF. This definition of preclinical HF now includes elevated cardiac biomarkers (such as natriuretic peptides or high-sensitivity cardiac troponin) in addition to imaging evidence of structural or hemodynamic cardiac abnormalities.[2] Screening for cardiac biomarkers and initiating targeted interventions has been shown to delay the onset of left ventricular dysfunction and symptomatic HF.[3] However, the optimal strategy for identifying individuals with preclinical HF at highest risk remains unclear.

The 2022 AHA/ACC/HFSA Heart Failure Guideline also recommends the use of multivariable risk models to more accurately assess the absolute risk of HF in at-risk populations.[2] In this context, the AHA introduced the PREVENT (Predicting Risk of Cardiovascular Events) risk algorithm in November 2023 to enhance the prediction of long-term cardiovascular and HF risk.[4] PREVENT integrates traditional cardiovascular risk factors, measures of metabolic and kidney health,[5,6] and social determinants of health to predict 10- and 30-year risks. This model extends beyond the focus on atherosclerotic cardiovascular disease (ASCVD) to also predict HF (PREVENT-HF) and total cardiovascular disease (PREVENT-CVD). Despite its risk-prediction potential, the relationship between PREVENT-HF risk estimates and preclinical HF remains unclear, as does the impact of preclinical HF measures on prognosis and risk reclassification within PREVENT-HF categories.

To address these gaps, we aim to use data from the Atherosclerosis Risk in Communities (ARIC) study to 1) evaluate the association between PREVENT-HF risk estimates and preclinical HF; 2) to assess the incremental predictive information added by preclinical HF measures beyond PREVENT-HF; and 3) to investigate how preclinical HF influences HF risk reclassification within the PREVENT-HF risk categories. We hypothesize that considering preclinical HF measures in concert with PREVENT-HF risk estimates will improve clinical HF risk prediction and classification, ultimately informing strategies to prevent the progression of HF.

5. Main Hypothesis/Study Aims:

1) To assess the prevalence and association of preclinical HF, identified by elevated cardiac biomarkers and/or abnormal echocardiographic findings, with higher categories of

estimated HF risk by PREVENT-HF (<7.5%; ≥ 7.5 to < 10%; ≥ 10 to < 15%; ≥ 15 to < 20%; and ≥ 20%).

2) To assess whether preclinical HF measures add predictive information beyond that provided by PREVENT-HF risk estimates
3) To evaluate the incidence rates (IR) of clinical HF (Stage C) across different PREVENT-HF risk categories and determine whether incorporating preclinical HF measures refines estimation of absolute HF risk

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

a) inclusion/exclusion

The baseline (indexed) visit for this study is Visit 5. To focus on the primary prevention population for which PREVENT-HF was developed, we will exclude participants with known ASCVD, defined as coronary heart disease or ischemic stroke, or with a history of HF prior to Visit 5. We will also exclude individuals missing follow-up data after Visit 5, those with missing echocardiographic or cardiac biomarker data, and participants missing PREVENT-HF score parameters or other key covariates. Additionally, we will exclude individuals aged 80 or older, or those ineligible for PREVENT due to risk factor parameters outside of established normal ranges (e.g., total cholesterol: 130-320 mg/dL, high density lipoprotein cholesterol (HDL-C): 20-100 mg/dL, systolic blood pressure: 90-200 mmHg, body mass index (BMI): 18.5-39.9 kg/m^2, and estimated glomerular filtration rate (eGFR): 15-140 mL/min/1.73m^2).

b) study design

This analysis will include both cross-sectional and prospective components. In the cross-sectional analysis at ARIC Visit 5 (2011-2013), we will examine the association between higher levels of predicted HF risk using the PREVENT-HF risk categories (<7.5%, ≥7.5% to <10%, ≥10% to <15%, ≥15% to <20%, and ≥20%) and the presence of preclinical HF, defined by elevated cardiac biomarkers and/or echocardiographic abnormalities. In the prospective analysis, we will assess the impact of adding preclinical HF measures to PREVENT-HF risk estimation on risk prediction for HF, and assess how preclinical HF measures relate to the absolute risk of developing HF within PREVENT-HF risk categories assessed at the Visit 5 baseline.

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

Exposure:

In the cross-sectional analyses, the primary exposure will be predicted risk using the PREVENT-HF score. PREVENT-HF risk will be modeled both continuously and categorically, using the following risk categories: <7.5%, ≥7.5% to <10%, ≥10% to <15%, ≥15% to <20%, and ≥20%. In the prospective analyses, the primary exposures will include the PREVENT-HF risk score and measures of preclinical HF, defined as abnormal cardiac biomarkers and/or abnormal cardiac function or structure on echocardiography. Abnormal biomarkers will be defined as N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥125 pg/mL or high-sensitivity troponin T ≥22 ng/L in men and ≥14 ng/L in women. Cardiac biomarkers will also be log transformed and modeled continuously in assessing their impact on HF risk prediction. Abnormal cardiac function or structure on echocardiography performed at Visit 5 will be defined according to clinical guidelines and prior ARIC analyses (used to define the thresholds for “abnormal” in the

ARIC population)[7]. Quantitative measures will be assessed in accordance with American Society of Echocardiography guidelines.[8,9] We will define abnormal cardiac structure and function based on any of the following criteria: left ventricular ejection fraction (LVEF) <50%, global longitudinal strain <16%, regional wall motion abnormalities, left ventricular mass index >116 g/m² in men and >95 g/m² in women, left ventricular end-diastolic volume index ≥75 mL/m² in men and ≥62 mL/m² in women, left atrial volume index ≥29 mL/m², average E/e' ≥15, tricuspid regurgitant velocity >280 cm/s, or the presence of a valvular abnormality. Valvular abnormalities will be defined as: peak aortic valve velocity ≥300 cm/s, mitral regurgitation jet area ≥4 cm², moderate or greater aortic insufficiency, or moderate or greater mitral stenosis.

Outcomes:

In the cross-sectional analysis, the outcome of interest will be measures of preclinical HF, specifically cardiac biomarkers and echocardiographic findings. In the prospective analysis, the primary outcome will be incident HF events, defined as hospitalization for HF or mortality due to HF, occurring after Visit 5 through 12/30/2021. Potential incident HF events have been adjudicated by an expert panel (for events occurring after 2005) using a standardized protocol. These events were categorized as definite acute decompensated HF, probable acute decompensated HF, chronic HF, non-HF events, or unclassifiable. For the purposes of this analysis, cases classified as definite or probable acute decompensated HF, or new diagnoses of chronic HF, will be considered incident HF events.

Covariates: Age, sex, race, education, smoking status, alcohol use, systolic and diastolic blood pressures, blood pressure medication use,non-HDL-C, low density lipoprotein cholesterol (LDL-C), triglycerides (TGs), HDL-C, BMI, obesity, diabetes, and eGFR.

d) summary of data analysis

We will categorize participants into PREVENT-HF 10-year risk categories of: <7.5%; ≥ 7.5 to < 10%; ≥ 10 to < 15%; ≥ 15 to < 20%; and ≥ 20%. Then, we will compare participant characteristics across the risk categories, using the chi-squared test for categorical variables and analysis of variance (ANOVA) for continuous variables.

To assess the cross-sectional association of PREVENT-HF with measures of subclinical HF, we will compare the prevalence of elevated cardiac biomarkers alone, abnormal echocardiographic measures alone, and the combination of abnormal cardiac biomarkers plus abnormal echocardiographic measures, across PREVENT-HF risk categories using the chi-squared test. We will perform multivariate logistic regression to assess the odds of preclinical HF across PREVENT-HF categories, using those with PREVENT-HF <7.5% as the reference. We will also model PREVENT-HF score continuously in restricted cubic spline models to assess the continuous association of PREVENT-HF with preclinical HF measures. We will conduct sensitivity analyses in participants with very high-risk chronic kidney disease (stage G4, or stage G3 or worse with significant proteinuria [ACR > 300 mg/g]) to evaluate whether advanced chronic kidney disease modifies the relationship between cardiac biomarkers and clinical heart failure risk.

In prospective analyses, we will use adjusted Cox regression models to assess the relative risk associations of higher PREVENT-HF scores with incident HF. We will also assess average HF incidence rates (per 1,000 person years) for individuals in each PREVENT-HF risk category. Within each of the PREVENT-HF risk categories, we will compare HF incidence across 4 groups related to the presence and degree of preclinical HF:
1) normal cardiac biomarkers and echocardiographic measures
2) abnormal cardiac biomarkers but normal echocardiographic measures
3) abnormal echocardiographic measures but normal cardiac biomarkers
4) abnormal cardiac biomarkers and abnormal echocardiographic measures

Lastly, to assess and compare the predictive performance of the PREVENT-HF risk model alone to prediction metrics after the addition of preclinical HF measures to PREVENT, we will assess for changes in risk discrimination (as reflected by the C-statistic), risk reclassification (as reflected by the Net Reclassification Index (NRI)) and risk calibration (ratio between observed and predicted HF risk). These will be used to evaluate the additive predictive value added by preclinical HF measures to the PREVENT score. The three prediction models to be compared are:

1. PREVENT-HF Alone: The PREVENT-HF score
2. PREVENT-HF + Cardiac Biomarkers: this will included the PREVENT-HF score plus log transformed NT-proBNP and high-sensitivity cardiac troponin.
3. PREVENT-HF + Cardiac Biomarker Testing + Echocardiographic measures: This model adds dichotomized echocardiographic measures (abnormal versus normal) to PREVENT-HF and cardiac biomarker levels.

e) Any anticipated methodologic limitations or challenges if present

- The guideline definition of cardiac structural and functional abnormalities is broad, encompassing not only additional echocardiography parameters, but also include those that may be derived from cardiac magnetic resonance or invasive catheterization assessment, which are not available in our study.
- Incident HF in our study is defined as adjudicated hospitalization for decomensated HF, thus we are not able to account for milder HF decompensation that may be managed in the outpatient setting.
- Echocardiography data is only available at ARIC visit 5 and thus, our analysis will primarily focus on older adults. The prevalence of preclinical HF will likely be lower in a younger population.

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)?

- Jia, X, Al Rifai, M, Ndumele, C. et al. Reclassification of Pre-Heart Failure Stages Using Cardiac Biomarkers: The ARIC Study. J Am Coll Cardiol HF. 2023 Apr, 11 (4) 440–450. https://doi.org/10.1016/j.jchf.2022.12.005

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* __

*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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