ARIC Manuscript Proposal Form

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Publication Committee Review Date: **10/08/24**
ARIC Manuscript Proposal Number: **#4553**

1.a. Full Title: Natriuretic Peptide Cutpoints for Heart Failure Classification in Individuals with and without Obesity

b. Abbreviated Title (Length 26 characters): Obesity and Stage B Heart Failure

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:

Writing group members: Mandana Chitsazan, Juhi K. Parekh, Leah B. Kosyakovsky, Emily S. Lau, James L. Januzzi Jr, Thomas J. Wang, Daniel Levy, Bruce M. Psaty, John S. Gottdiener, Jorge R. Kizer, Christopher R. deFilippi, Elizabeth Selvin, Christie M. Ballantyne, Norrina B. Allen, Rudolf A. de Boer, Sanjiv J. Shah, Chiadi E Ndumele, and Jennifer E. Ho

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _MC____ **[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: Data analyses: 6 months; manuscript preparation: 6 months

4. Rationale: The prevalence of heart failure is on the rise due to the aging population. Based on the 2015-2017 data, approximately 6 million American adults aged 20 years and older had HF (2). The prevalence of HF is estimated to increase by 46% between 2012 and 2030(3). The definition and staging of heart failure (HF) have undergone recent revisions in two distinct documents: the 2021 Universal Definition and Classification of Heart Failure and the 2022 American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA) guideline for the management of heart failure. Compared with the 2013 ACC/AHA guideline, the updated 2022 ACC/AHA/HFSA guidelines have modified the terminology of heart failure stages and added elevated biomarkers (natriuretic peptides (NPs) and persistent elevation of troponin) as new criteria for classification as stage B (pre-HF)(4). B-type natriuretic peptide (BNP) levels above 35 pg/mL and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels above 125 pg/mL were used to define elevated NP levels (4).

In a previous study applying updated criteria to individuals from three community-based cohorts (Framingham Heart Study (FHS), Multi-Ethnic Study of Atherosclerosis (MESA), and Cardiovascular Health Study (CHS)), we noted substantial reclassification of participants from the healthy and stage A HF (at risk) categories to stage B HF (pre-HF), with a resultant increase in the proportion of total individuals with stage B HF from 15.9% (2013) to 43.2% (2022).(5) Of note, the largest shift was attributable to those with elevated NP levels.

Given known NP deficiency in obesity and complex associations with HF,(6)(7) the use of a single NP cut-point to identify individuals with obesity and pre-HF (i.e., stage B HF) may under-recognize true risk. For example, a recent study demonstrated that implementation of reduced NT-proBNP cutoffs for individuals with elevated BMI resulted in improved diagnostic accuracy in the setting of acute HF (8). In preliminary studies, we identified optimal NT-proBNP cutpoint to predict the future risk of heart failure (HF) among normal-weight individuals without prevalent HF was 123 pg/ml. In contrast, the optimal NT-proBNP cutpoints were lower for overweight individuals (75 pg/ml) and for individuals with obesity (94pg/ml) (9). We now seek to expand our sample by adding another independent cohort (ARIC) and perform similar analyses to confirm their accuracy and applicability across different populations, thereby enhancing their utility in clinical settings for early identification and intervention. Additionally, validating these cutpoints will help determine whether BMI- adjustments are necessary to identify stage B HF in individuals with obesity.

5. Main Hypothesis/Study Aims: We hypothesize that lower NP cutpoints should be considered among individuals with obesity, thus allowing appropriate classification of individuals with obesity to stage B HF.

Aim 1: To examine the reclassification of individuals with and without obesity from stage A to stage B HF based on natriuretic peptide cutpoints endorsed by the 2022 ACC/AHA heart failure definitions.

Aim 2:
To estimate the optimal natriuretic peptide cutpoint for predicting future risk of incident heart failure (HF) among obese and non-obese individuals.

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

a) **inclusion/exclusion**
b) **study design**
c) **outcome and other variables of interest with specific reference to the time of their collection**
d) **summary of data analysis**
e) **Any anticipated methodologic limitations or challenges if present**

Methods:
Study sample: Our previous analysis included FHS offspring cohort exam 6 (1995-1996), MESA baseline exam (2000-2002), CHS baseline exam (1989-1990;1992-1993 for supplemental African American cohort), and Prevention of Renal and Vascular End-stage Disease (PREVEND) exam 1 (1997-1998). We now seek approval to examine individuals enrolled in the Atherosclerosis Risk in Communities Study (ARIC) visit 2 (1990-1992). The ARIC data will be pooled and harmonized with other cohorts' data. The final harmonized dataset will be divided into test and validation datasets (80% for the test dataset and 20% for the validation dataset).

We will exclude the following participants:

1) Missing NP levels
2) Prevalent HF at baseline exam
3) Missing key clinical covariates

Statistical Plan:

Outcome variable: Incident HF

- Participants were followed longitudinally within each cohort, with a formal review of hospital and outpatient records and event adjudication according to established protocols
- Predictor variables: Natriuretic Peptide level
  BNP was measured in FHS using high-sensitivity immunoradiometric assays. NT-proBNP was measured with electrochemiluminescence immunoassays in PREVEND, CHS, and MESA and with sandwich immunoassay in ARIC. NP concentrations will be logarithm (log)-transformed and then standardized to mean=0 and SD=1 within the cohort and subsequently pooled across cohorts for primary analyses.

Statistical analyses:

- We will examine the proportion of individuals who meet NP cutpoints for 'stage B HF' based on the 2022 ACC/AHA guideline, stratified by obesity class across the test dataset.
- We will examine whether BMI modifies the association of NT-proBNP with incident HF outcomes. Specifically, multivariable Cox models will be used to examine the association of NT-proBNP, BMI (continuous and categorical), and multiplicative NP*BMI interaction terms
    - Models will also be adjusted for age, sex, race/ethnicity, current smoking, diabetes, hypertension, dyslipidemia, and prevalent MI.
      - Diabetes mellitus is defined as random glucose ≥200 mg/dL, fasting glucose ≥126 mg/dL, hemoglobin A1c≥6.5%, or taking glucose-lowering medications. Hypertension is defined as systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥80 mm Hg, or taking blood pressure-lowering medications. Hyperlipidemia is defined as taking cholesterol-lowering medications. Prevalent MI will be defined based on each cohort's report of a prior history of MI. Each cohort also reports the smoking status of participants.
- We will use the receiver operating characteristic (ROC) curve to estimate optimal NP cutpoints for incident HF prediction for each obesity class in the test dataset. On the ROC curve, the Youden index (sensitivity + specificity - 1) is used to identify the threshold that maximizes the balance between sensitivity and specificity.
- The estimated optimal NP cutpoints for incident HF prediction in the test dataset will then be validated in the validation dataset. To validate our estimated NP cutpoints, we will classify participants into obesity classes (normal, overweight, obese). Using our derived NP cutpoints, we will categorize participants within each obesity class as above or below the cutpoints. During follow-up, we will identify those who develop incident stage C/D HF. We will then fit our Cox models to examine the association of elevated NP levels and incident HF within each obesity class.
- To evaluate model performance, we will generate ROC curves to evaluate the predictive performance and create calibration plots to compare predicted probabilities with observed outcomes. Key validation metrics such as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratios will be calculated. Finally, we will compare the validation cutpoints with those derived from the test dataset to assess consistency and robustness.

Anticipated limitations:

- The specificity of low NPs is limited (NPs can be low in younger age, not necessarily obesity exclusively).
- given a predominantly white sample, the generalizability of our findings may be limited.

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)?
Ndumele CE, Matsushita K, Sang Y, et al. N-Terminal Pro-Brain Natriuretic Peptide and Heart Failure Risk Among Individuals With and Without Obesity: The Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2016;133(7):631-638. doi:10.1161/CIRCULATIONAHA.115.01729

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* 2009.15 __

*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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2. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart Disease and Stroke Statistics—2021 Update. Circulation. 2021;143(8):e254-e743.
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5. Mohebi R, Wang D, Lau ES, Parekh JK, Allen N, Psaty BM, et al. Effect of 2022 ACC/AHA/HFSA Criteria on Stages of Heart Failure in a Pooled Community Cohort. Journal of the American College of Cardiology. 2023;81(23):2231-42.
6. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nature Reviews Cardiology. 2017;14(10):591-602.
7. Suthahar N, Meijers WC, Ho JE, Gansevoort RT, Voors AA, van der Meer P, et al. Sex-specific associations of obesity and N-terminal pro-B-type natriuretic peptide levels in the general population. European Journal of Heart Failure. 2018;20(8):1205-14.
8. Kozhuharov N, Martin J, Wussler D, Lopez-Ayala P, Belkin M, Strebel I, et al. Clinical effect of obesity on N-terminal pro-B-type natriuretic peptide cut-off concentrations for the diagnosis of acute heart failure. European Journal of Heart Failure. 2022;24(9):1545-54.

9. Chitsazan, M., Parekh, J., Kosyakovsky, L., Lau, E. S., Januzzi, J. L., Wang, T. J., Levy, D., Psaty, B., Mohebi, R., Gottdiener, J. S., Kizer, J. R., DeFilippi, C. R., Allen, N. B., Shah, S. J., and Ho, J. E. Applicability of the 2022 ACC/AHA/HFSA Natriuretic Peptide Cutpoints for Heart Failure Classification in Obese Individuals. Poster presentation at the American College of Cardiology 75th Annual Scientific Session, Atlanta, GA, 7 Apr. 2024.

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