ARIC Manuscript Proposal Form

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Publication Committee Review Date: **08/13/24**
ARIC Manuscript Proposal Number: **# 4445**

1.a. Full Title: Cardiovascular-kidney-metabolic syndrome stages, echocardiographic characteristics, and cardiovascular risk

b. Abbreviated Title (Length 26 characters): CKM stages: echo findings and CVD risk

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:
Writing group members: Mats C. H. Lassen, John W. Ostrominski, Brian Claggett, Chiadi Ndumele [others welcome], Tor Biering-Sørensen, Scott D. Solomon, Muthiah Vaduganathan

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _MCHL_ **[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: Analysis will begin following proposal approval with the aim of completing analysis and a manuscript within 6 months of data becoming available.

4. Rationale:

Cardiovascular-kidney-metabolic (CKM) health represents the clinical presentation of the interactions between metabolic risk factors including obesity, diabetes, chronic kidney disease (CKD), and the cardiovascular system[1–5]. Poor CKM health becomes increasingly prevalent with age and has important clinical implications including an increased risk of premature death, excess morbidity, multiorgan disease, and high healthcare cost[1,6]. Nearly every major organ system is affected by poor CKM health but the greatest clinical impact of CKM syndrome with regard to morbidity and premature mortality is through the disproportionate burden of cardiovascular disease including heart failure and almost all other types of cardiovascular disease phenotypes[4,7–9]. Importantly, persons with poor CKM health are often undertreated despite the existence of core disease-modifying therapies known to improve heart, kidney, and metabolic health[1,10]. There is therefore a growing need for a better understanding of how to identify poor CKM health, the longitudinal impact on cardiac structure and function, and the association between CKM health and prognosis in relation to cardiovascular risk.

The importance of CKM health has been amplified by the American Heart Association (AHA), which recently introduced a novel CKM-oriented staging system combined with guidance on risk stratification approaches and collaborative management strategies[1]. Among individuals with heart failure, CKM multimorbidity is highly prevalent and a previous study has found that more than 4 in 5 patients with heart failure with mildly reduced or preserved ejection fraction have concurrent CKM conditions[11]. International heart failure clinical practice guidelines have also acknowledged the link between poor CKM health and heart failure and have implemented prevention and treatment strategies in the most recent guidelines[12–17].

Despite the increased attention on poor CKM health, studies contextualizing the CKM syndrome framework with prospective cohort studies are lacking. Furthermore, no studies have yet assessed the association of specific CKM stages with patient-centered clinical outcomes, such as risk of new-onset heart failure, and with changes in cardiac structure and function over time as assessed by echocardiography. The ARIC study represents an ideal cohort for addressing these important questions, which may improve understanding of how the interplay of CKM risk factors and conditions affect cardiac structure and function longitudinally, as well as the risk of new-onset heart failure and other adverse cardiovascular events. This of utmost importance, especially when considering the growing elderly population, the increasing prevalence of poor CKM health and the array of known beneficial therapies which could help turn the tide.

5. Main Hypothesis/Study Aims:

We hypothesize that poor CKM health is prevalent among older adults enrolled in ARIC and that higher CKM stages are associated with impaired cardiac function as assessed by

echocardiography and that these functional changes translates into an increased risk of new-onset heart failure and other adverse cardiovascular events, such as atherosclerotic cardiovascular disease (ASCVD) events and incident atrial fibrillation (AF).

Specific hypotheses:

1. Poor CKM health, as assessed by CKM staging at visit 5, is prevalent among older adults enrolled in ARIC.
2. A large proportion of those with CKM stage 1 and 2 (cardiovascular risk factors) at visit 5 will have progressed to CKM stage 3 (subclinical cardiovascular disease) and 4 (clinical cardiovascular disease) at visit 7.
3. Higher CKM stage at visit 5 is associated with impaired echocardiographic parameters of structure and function and this cardiac remodeling translates into a higher rate of new-onset heart failure other incident cardiovascular diseases (stroke, coronary artery disease, peripheral artery disease, and AF) during follow-up.
4. Worse CKM stage at visit 5 is associated with increasingly impaired cardiac structure and function as assessed by echocardiography at visit 7.

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

a) Inclusion/Exclusion

This analysis will include all ARIC participants who underwent echocardiography at Visit 5. Participants with missing data for key variables used for CKM staging (BMI, waist circumference, HbA1c, triglycerides, HDL cholesterol, total cholesterol, blood pressure, eGFR, diabetes, CKD, and hypertension history, NT-proBNP) will be excluded from this analysis.

A subgroup will consist of those participants who underwent echocardiography at both Visit 5 and Visit 7.

For analyses evaluating clinical outcomes, those with established cardiovascular disease at visit 5 will be excluded.

b) Study design

This will be a longitudinal analysis of the participants with echocardiography performed at Visit 5. These participants will be staged according to the recent guidelines on CKM staging proposed by the AHA[1] and the risk of incident HF and other adverse cardiovascular events during follow-up will be assessed. Furthermore, progression in CKM stage and changes in echocardiographic parameters will be assessed for those participants who participated in Visit 5 and Visit 7 and had an echocardiography performed at both visits.

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

1. Clinical and anthropometric variables (Visit 5 and Visit 7): age, sex, race/ethnicity, height, weight, waist circumference, hip circumference, blood pressures, heart rate, history of hypertension, diabetes, dyslipidemia, chronic kidney disease, and prior

cardiovascular disease (coronary artery disease, MI or revascularization procedure, heart failure, atrial fibrillation, stroke, peripheral artery disease).

2. Laboratory values (Visit 5 and Visit 7): NT-proBNP, eGFR, high sensitivity troponin T, serum albumin and creatinine, urine albumin and creatinine, HbA1c, fasting glucose, high-sensitivity C-reactive protein, lipoprotein (a), triglycerides, LDL, HDL, and total cholesterol.

3. Echocardiographic variables (Visit 5 and Visit 7): LV structure (wall thickness, relative wall thickness, systolic and diastolic diameters and volumes, LV mass), LV systolic function (LVEF, stroke volume, mitral annular systolic velocities, global longitudinal strain), LV diastolic function (E wave, A wave, E wave deceleration time, TDI e', E/e', and left atrial [LA] volume), and, RV measures (TAPSE, RV fractional area change, tricuspid annular TDI s', pulmonary artery systolic pressure, and pulmonary vascular resistance). Volumetric and mass parameters will be indexed to both BSA and allosteric powers of height, respectively, and currently reported reference ranges for both will be implemented to ascertain the impact of reclassification to CKM stage 3. In the event insufficient data are available, an ancillary analysis within ARIC will be performed to identify appropriate threshold values for height-indexed parameters.

d) Summary of data analysis

At Visit 5, all participants will be grouped according to CKM stage (stage 0-4)[1]. Baseline characteristics and baseline echocardiographic characteristics will be compared using trend tests across CKM stages. Uni- and multivariable linear regressions will be used to assess associations between echocardiographic parameters and CKM stage. Adjustments for differences in clinical characteristics (based upon $P < 0.05$ and/or clinically important covariates) will be performed. Cox proportional hazard regression models will be used to assess the association between CKM stages and risk of incident HF and other adverse cardiovascular events during follow-up. For participants who underwent echocardiographic examination at both Visit 5 and visit 7, changes in echocardiographic parameters will be calculated and linear regression adjusted for the baseline value will be used to assess associations between CKM stage at Visit 5 and longitudinal changes in echocardiographic parameters. Linear and logistic regression will be used to assess progression in CKM stage from Visit 5 to Visit 7.

e) Any anticipated methodologic limitations or challenges if present

An important limitation to this study in relation to assessing longitudinal changes in echocardiography and CKM stage progression is attrition bias as not all participants survived until Visit 7 or did not choose to participate in Visit 7 and it is expected that these participants were significantly different from those who did participate at both visits. As this is a prospective cohort study, an inherent limitation is that we can assess associations but never establish causality.

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)?

The two most related ARIC manuscripts are included below. Our proposal is distinct from other CKM focused works in progress as it focuses on visit 5 and beyond and has a specific echocardiographic focus.

Ndumele CE, Matsushita K, Lazo M, Bello N, Blumenthal RS, Gerstenblith G, Nambi V, Ballantyne CM, Solomon SD, Selvin E, Folsom AR, Coresh J. Obesity and Subtypes of Incident Cardiovascular Disease. J Am Heart Assoc 2016;5:e003921.

Echouffo-Tcheugui JB, Ndumele CE, Zhang S, Florido R, Matsushita K, Coresh J, Skali H, Shah AM, Selvin E. Diabetes and Progression of Heart Failure: The Atherosclerosis Risk In Communities (ARIC) Study. *J Am Coll Cardiol* 2022;**79**:2285–2293.

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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6. Ostrominski JW, Arnold SV, Butler J, et al. Prevalence and Overlap of Cardiac, Renal, and Metabolic Conditions in US Adults, 1999-2020. *JAMA Cardiol*. Published online September 27, 2023. doi:10.1001/jamacardio.2023.3241
7. Pandey A, Vaduganathan M, Arora S, et al. Temporal Trends in Prevalence and Prognostic Implications of Comorbidities Among Patients With Acute Decompensated Heart Failure: The ARIC Study Community Surveillance. *Circulation*. 2020;142(3):230-243. doi:10.1161/CIRCULATIONAHA.120.047019
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12. Joseph JJ, Deedwania P, Acharya T, et al. Comprehensive Management of Cardiovascular Risk Factors for Adults With Type 2 Diabetes: A Scientific Statement From the American Heart Association. *Circulation*. 2022;145(9):e722-e759. doi:10.1161/CIR.0000000000001040
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16. Writing Committee, Birtcher KK, Allen LA, et al. 2022 ACC Expert Consensus Decision

Pathway for Integrating Atherosclerotic Cardiovascular Disease and Multimorbidity Treatment: A Framework for Pragmatic, Patient-Centered Care: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2023;81(3):292-317. doi:10.1016/j.jacc.2022.08.754
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