1.a. Full Title: High-sensitivity cardiac troponin-T and I for cardiovascular risk characterization in middle-aged adults with kidney disease.

b. Abbreviated Title (Length 26 characters): Hs-troponins in chronic kidney disease

2. Writing Group:
   Writing group members: Olive Tang; Kunihiro Matsushita; Josef Coresh; Morgan Grams; Chiadi Ndumele; Ron Hoogeveen; Christie Ballantyne; Elizabeth Selvin; others welcome

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

First author: Olive Tang
   Address: Johns Hopkins University
   2024 E Monument Street, Suite 2-600
   Baltimore, MD 21205
   Email: otang@jhmi.edu
   Phone: 617-671-0790

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
   Name: Elizabeth Selvin
   Address: Johns Hopkins University
   2024 E Monument Street, Suite 2-600
   Baltimore, MD 21205
   Phone: 410-614-3752    Fax: 410-955-0476
   E-mail: eselvin@jhu.edu

3. Timeline:
   All measurements required for this proposal have been collected. We aim to complete the manuscript <1 year from the time of approval and release of the data.

4. Rationale:
   High-sensitivity assays detect minute elevations in cardiac troponin I (hs-cTnI) and T (hs-cTnT). Hs-cTnI and hs-cTnT have been approved for use in diagnosing acute myocardial
infarctions. These more sensitive assays allow for the reliable measurement of very low concentrations of these proteins, potentially reflective of subclinical myocyte damage, which is informative, even in the general population. Among middle-aged individuals without coronary heart disease, hs-cTnI and hs-cTnT are strongly associated with future cardiovascular risk. Despite being derived from the same protein complex, hs-cTnI and hs-cTnT are only moderately correlated with one another.

Both troponins are elevated in the setting of kidney dysfunction. In the acute setting, where high sensitivity troponins are increasingly used as rule-out test for myocardial infarctions, there is growing interest in differentiating troponin patterns of chronic kidney disease from those associated with an acute coronary event. In the general population, both troponins are higher among those with chronic kidney disease. Early work suggests that among those with stable kidney disease but no prevalent cardiovascular disease, both troponins were cross-sectionally associated with kidney function markers (estimated glomerular filtration rate and urine albumin ratio) as well as cardiovascular markers including left ventricular mass index.

Our objective is to leverage the simultaneous measurements of hs-cTnI and hs-cTnT available at ARIC visit 4 to: 1) assess whether the associations of other cardiovascular risk factors (age, sex, blood pressure, cholesterol, smoking, diabetes) with hs-cTnI and hs-cTnT differ by kidney disease status; 2) characterize whether measures of hs-cTnI or hs-cTnT can be used as a simple strategy to stratify cardiovascular and mortality risk among patients with chronic kidney disease.

5. Main Hypothesis/Study Questions:
We aim to assess the utility of hs-cTnT and hs-cTnI in the risk stratification of participants with chronic kidney disease, defined as a low estimated glomerular filtration rate <60mL/min/1.73m² or albuminuria (>30mg/g Cr), and assess whether the observed relationship with subsequent cardiovascular and mortality risk differ from that observed in participants without chronic kidney disease. We will also compare the prognostic power of hs-cTnT compared to hs-cTnI, overall and by clinically defined subgroups.

Hypothesis 1: Both low eGFR and albuminuria may be associated with elevations in hs-cTnI and hs-cTnT. Among cross-categories of low estimated glomerular filtration rate and albuminuria, those with a low glomerular filtration rate and albuminuria will have the highest mean hs-cTnI and hs-cTnT as compared to those with intact kidney function.

Hypothesis 2: While hs-cTnI and hs-cTnT will be higher among those with chronic kidney disease, single measurements of hs-cTnT and/or hs-cTnI will be remain independent predictors of cardiovascular and mortality outcomes beyond traditional risk factors among those with chronic kidney disease.

Hypothesis 3: hs-cTnI and hs-cTnT will perform similarly in improving cardiovascular and mortality risk stratification in middle age adults with and without chronic kidney disease.

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:** Prospective cohort study

**Inclusion:** All black and white participants at ARIC visit 4

**Exclusions:** We will apply the standard ARIC exclusions and exclude participants with missing hs-cTnT or hs-cTnI measurements.

**Key exposures:**
High-sensitivity troponin T was measured in stored frozen plasma samples on a Cobas e411 analyzer using the Roche Elecsys Troponin T assay (Indianapolis, IN), with a lower limit of blank of 3 ng/L. High-sensitivity troponin I was measured in stored frozen plasma samples on an Architect i2000sr analyzer using an Abbott Architect Stat Troponin I double chemiluminescent immunoassay (Abbott Park, IL), with a lower limit of blank of 1.2 ng/L.

1) Elevated hsTnT defined as:
   a. Tertiles
   b. Percentile categories (<40th, 40th to <55th, 55th to <70th, 70th to <85th, ≥85th)
   c. Continuous
2) Elevated hsTnI defined as:
   a. Tertiles
   b. Percentile categories (<40th, 40th to <55th, 55th to <70th, 70th to <85th, ≥85th)
   c. Continuous

**Outcomes:**
Among those without prevalent cardiovascular disease (ASCVD + heart failure)
   1) Incident global cardiovascular event (MI, stroke, heart failure)
   2) Component cardiovascular events
      a. MI or revascularization or Stroke (ASCVD)
      b. Heart failure
Among the full population:
   3) Cardiovascular mortality
   4) All-cause mortality

**Important covariates:** age, sex, race-center, total cholesterol, LDL, HDL, Triglycerides, SBP, DBP, hypertension medication use, cholesterol medication use, current smoking status, diabetes status

**Analyses:**
We will compare baseline characteristics by levels of the novel cardiovascular biomarkers, using the definitions indicated above. We will use Kaplan-Meier survival analysis to compare the cumulative incidence of cardiovascular events and mortality by troponin categories independently and in combination. We will use Cox proportional hazards models to compare hazard ratios and corresponding 95% confidence intervals to characterize the association of troponin levels with cardiovascular risk and mortality with adjustment for relevant covariates. We will test for interaction by sex, race, and chronic kidney disease status using the likelihood ratio test. To assess the prognostic performance of these novel biomarkers, changes in the C-
statistic and net reclassification improvement will be compared between models with the troponin measurement compared to those based on previously published risk equations.

**Key subgroups:**
We will conduct analyses stratified by chronic kidney disease status (low estimated glomerular filtration rate or albuminuria) and in the full cohort using an interaction term to assess for effect modification. We will also consider cross-categories of kidney disease status (no chronic kidney disease; normal estimated glomerular filtration rate/albuminuria; low estimated glomerular filtration rate/no albuminuria; low estimated glomerular filtration rate/albuminuria). We will conduct primary analyses using estimated glomerular filtration rate based on creatinine, as this is more common clinically, but will conduct a sensitivity analysis using estimated glomerular filtration rate based on creatinine and cystatin C.

**Limitations:**
1) Given the observational nature of ARIC, there is the possibility of residual confounding.
2) There will be reliance on single measurements of the cardiac biomarkers at visit 4 made in stored samples.
3) Participants may have troponin values below the lower limit of detection. For these participants, we will assign a value that is half the lower limit of detection for continuous analyses.

7.a. Will the data be used for non-CVD analysis in this manuscript? _____ Yes  ____ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used? _____ Yes  _____ No
(This 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 file ICTDER03 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](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)?
Proposal # 1915: Novel cardiac and kidney markers and cardiovascular prediction in individuals with and without chronic kidney disease: the Atherosclerosis Risk in Communities (ARIC) Study (First author: Kunihiro Matsushita)

Proposal # 1808: The utility high sensitivity cardiac troponin t in the prediction of heart failure risk (First author: Vijay Nambi)

Proposal # 2319: Does cardiac troponin T help identify subjects with metabolic syndrome at higher risk of cardiovascular events? An analysis from the ARIC study (First Author: Vijay Nambi)

Proposal # 1757: The association of high sensitivity troponin with heart failure, mortality and recurrent coronary heart disease (CHD) in individuals with prevalent CHD (First Author: Vijay Nambi)

Proposal # 2775: High-sensitivity troponin I and incident heart failure hospitalization, myocardial infarction, stroke and cardiovascular disease mortality in ARIC (First Author: Christie Ballantyne)

Proposal # 2295: Predictive value of changes in BNP, Troponin, Hemoglobin and Serum Sodium in patients with acute decompensated heart failure (First Author: Jan Griffin)

Proposal # 1811: Association of high sensitive Troponin T (hs-cTnT), N-terminal pro-brain natriuretic peptide (NT-proBNP) and high sensitivity C-reactive protein (hs-CRP) with causespecific mortality: ARIC study (First Author: Oludamilola Oluleye)

Proposal # 2707: Hypoglycemia and Subclinical Myocardial Damage in Older Adults with Diabetes (First Author: Alexandra Lee)

Proposal # 1563: Novel highly sensitive cardiac Troponin-T (hs-cTnT) assay, mortality, and major adverse cardiovascular events in the ARIC Study (First Author: Justin Saunders)

Proposal # 2765: Relationship of Blood Pressure Parameters with High Sensitivity Cardiac Troponin-T and N-Terminal Prohormone of Brain Natriuretic Peptide in the Elderly: The Atherosclerosis Risk in Communities Cohort Study (First Author: Nidhi Madan)

Proposal # 1899: Troponin T, NT-proBNP and stroke incidence (First Author: Aaron Folsom)

Proposal # 2129: Diabetes and prediabetes and the incidence and progression of subclinical myocardial injury (First Author: Elizabeth Selvin)

Proposal # 3018: Evaluation of novel circulating biomarkers in the prediction of adverse cardiovascular events including heart failure (First Author: Vijay Nambi)
11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __x__ Yes  ____ No

11.b. If yes, is the proposal
   _x__  A. primarily the result of an ancillary study (list number* ___2013.21, ____)
   ____  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 at https://www2.csc.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.csc.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.

References: