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

b. Abbreviated Title (Length 26 characters): Hs-troponins in diabetes

2. Writing Group:
   Writing group members: Olive Tang; Kunihiro Matsushita; Josef Coresh; John W (Bill) McEvoy; A. Richey Sharrett; Christie Ballantyne; Ron Hoogeveen; 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]

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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:
Despite the abundance of cardiovascular risk equations in the literature, only the Framingham Risk Score\(^1\) and the ACC/AHA Pooled Cohort Equation\(^2\) are regularly used in the US to guide clinical practice for cardiovascular risk prevention. However, both of these equations have important limitations: the Framingham Risk Score does not account for differences by race, the Pooled Cohort Equation does not consider heart failure risk, and neither incorporate kidney function markers which have been shown to be associated with risk for adverse outcomes\(^3\). Moreover, both risk scores consider diabetes as a simple dichotomous factor (presence vs. absence), potentially limiting their ability to discriminate the risk and guide treatment within populations with diabetes. There has been growing recognition of the importance of incorporating measures of hyperglycemia to risk prediction equations. Newer equations, such as the Systemic Coronary Risk Evaluation (SCORE)\(^4\) and Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE)\(^5\) scores, incorporate glucose or hemoglobin A1c to better predict cardiovascular mortality risk. A study assessing these different scores in the UK Prospective Diabetes Study (UKPDS) cohort found that the Framingham, SCORE and DECODE equations either vastly overestimated or underestimated the observed 5- and 10-year risk depending on the subgroup and risk equation used\(^6\). Thus, there is substantial room for improvement in cardiovascular risk stratification in patients with diabetes.

At the same time, with the growing costs of new diabetic medications and the clinical heterogeneity of the diabetic population, there is increasing need for improving risk characterization among patients with diabetes, who until recently, have been uniformly considered at high risk of cardiovascular events. In an effort to differentiate risk among the diabetes population, data from the Swedish National Diabetes Register was used to create an equation to predict incident cardiovascular events\(^7\). As with the Pooled Cohort Equation, heart failure is not included in the composite outcome, despite the robust association of diabetes with heart failure risk\(^8\). Furthermore, despite good calibration, this diabetes-specific equation only achieved modest discrimination (AUC = 0.70) even in the cohort used to derive this score\(^7\).

Several biomarkers have emerged reflecting previously undetectable processes including subclinical myocardial damage and fibrosis. However, most are not clinically available (e.g. ST2, GDF15) and others are not widely utilized despite being cleared by the Food and Drug Administration (e.g. galectin-3). New high sensitivity assays for cardiac troponins (T and I), on the other hand, are approved for use in diagnosing acute myocardial infarctions\(^9\). These new and more sensitive assays allow for the reliable measurement of very low concentrations of these proteins, suggesting subclinical levels of myocyte damage, which is informative even in the general population\(^10\). Among middle-aged individuals without coronary heart disease, high sensitivity troponin T (hs-cTnT) has been strongly associated with future cardiovascular risk, especially heart failure. Hs-cTnT is also strongly associated with HbA1c levels\(^11\) and individuals with diabetes or prediabetes are far more likely to have elevated hs-cTnT and be at a higher cardiovascular risk compared to normoglycemic adults\(^12\). Some preliminary work in stable patients attending a cardiology clinic suggest a single measurement of hs-cTnT may predict risk just as well as the more complex SCORE algorithm\(^13\). Whether measures of hs-cTnT or high-sensitivity troponin I (hs-cTnI) can be used as a simple strategy to stratify risk among patients with diabetes remains to be evaluated.

5. **Main Hypothesis/Study Questions:**
We aim to assess the utility of hs-cTnT and hs-cTnI in the risk stratification of participants with diabetes, compared to established risk equations, and assess whether the observed relationship with subsequent cardiovascular and mortality risk differ from that observed in participants without diabetes. We will also compare the prognostic power of hs-cTnT compared to hs-cTnI, overall and by clinically defined subgroups.

Hypothesis 1: Single measurements of hs-cTnT and/or hs-cTnI will be independent predictors of cardiovascular and mortality outcomes beyond traditional risk factors or established risk scores such as the Framingham Risk Score and ASCVD Pooled Cohort Equation.

Hypothesis 2: Hs-cTnT and hs-cTnI may differentially improve the risk stratification of different clinical subgroups.

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, or prevalent cardiovascular disease.

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 detection 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 detection of 1.2 ng/L.

1) Elevated hsTnT defined as:
   a. > 14 ng/L
   b. Categorically: < 5ng/L, 5ng/dL – Upper Limit of Normal (according to age- and sex- specific cutoffs), > Upper Limit of Normal
   c. Quintiles
   d. Continuous
2) Elevated hsTnI defined as:
   a. > 25 ng/L
   b. > 34 ng/L for men and > 16 ng/L for women
   c. Quintiles
   d. Continuous

Outcomes:
1) Incident global cardiovascular event (MI, stroke, heart failure)
2) Component cardiovascular events
a. MI or revascularization
b. Stroke
c. Heart failure
3) Incident fatal global cardiovascular event
4) All-cause mortality

Important covariates (modeled individually or as part of composite risk score): age, sex, race-center, total cholesterol, LDL, HDL, Triglycerides, SBP, DBP, hypertension medication use, cholesterol medication use, family history of diabetes, family history of hypertension, current smoking status, diabetes duration, hypertension duration, blood glucose

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 diabetes 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. We will conduct a sensitivity analyses among participants who fasted at least 8 hours prior to their visit.

We will further extend these analyses to assess whether hs-cTnT and hs-cTnI reflect distinct underlying cardiovascular phenotypes. Capitalizing on the wealth of glycemic, kidney, and cardiac markers in ARIC, we will explore the utilization of alternative analysis techniques such as structural equation modeling to explore the common risk indicated by both hs-cTnT and hs-cTnI and whether they represent risk beyond renal function or glycemic status.

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    __x__ 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    __x__ 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

___x___ 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 # 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 # 2055: Assessing cardiovascular risk in diabetics using traditional indicators of target organ damage and serum biomarkers: the ARIC study (First Author: Mauro Gori)

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.cscc.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.cscc.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:


