ARIC Manuscript Proposal #2129

PC Reviewed: 5/14/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Diabetes and prediabetes and the incidence and progression of subclinical myocardial injury

b. Abbreviated Title (Length 26 characters): Change in hs-cTnT and CVD risk

2. Writing Group:

Writing group members: Elizabeth Selvin; Andreea M. Rawlings; Mariana Lazo; Jonathan Rubin; Ron C. Hoogeveen; Christie M. Ballantyne; Josef Coresh; others welcome

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

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3. Timeline: We aim to submit this paper for ARIC review <1 year from approval of the manuscript proposal

4. Rationale:

Cardiovascular disease is the leading cause of death among persons with diabetes and there is evidence that cardiac damage is often present at the time of clinical diagnosis of diabetes (1, 2). Persons with hyperglycemia below the threshold for the diagnosis of diabetes are know to be at high risk for cardiovascular events (3-5). Hyperglycemia is thought to induce myocardial injury and result in hyperglycemia-mediated coronary microvascular dysfunction (6, 7). Previous studies have shown that persons with pre-diabetes or diabetes have an increased risk for subclinical atherosclerosis as measured by carotid intimal thickness or coronary artery calcium (8-12). Much less is known about the association of pre-diabetes and diabetes with subclinical myocardial damage.

Cardiac troponins are elevated in the setting of myocardial damage and are the standard measures used for diagnosis of myocardial infarction. There have been several generations of increasingly sensitive tests that reliably detect lower and lower levels of troponin in the blood. A novel (pre-commercial) high-sensitivity assay for cardiac troponin T (hs-cTnT) developed by Roche Diagnostics allows for measurement of troponin levels far below the conventional limit of detection (13). It has been suggested that the minor elevations in cardiac troponin detected with this novel assay may represent subclinical myocardial injury (14, 15).

Our objective is to test the hypothesis that diabetes and chronic hyperglycemia (among persons without diabetes) are associated with the incidence and progression of subclinical myocardial injury in a community-based population without clinically evident cardiovascular disease or heart failure.

5. Main Hypothesis/Study Questions:

Hypothesis 1: The prevalence of subclinical myocardial injury—as indicated by detectable and elevated cardiac troponin T measured using a novel highly sensitive assay—will be higher among persons with diagnosed diabetes, undiagnosed diabetes, and pre-diabetes compared to persons without diabetes, even after adjustment for traditional cardiovascular risk factors.

Hypothesis 2: Diagnosed diabetes and chronic hyperglycemia (as indicated by HbA1c) in persons without diagnosed diabetes will be associated with higher incidence and greater progression of subclinical myocardial damage as indicated by elevations in cardiac troponin detected with a novel highly sensitivity assay (hs-cTnT) before and after adjustment for cardiovascular risk factors, compared to normoglycemic persons.

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: We will conduct 1) a cross-sectional analysis to quantify the prevalence of detectable and elevated hs-cTnT by categories of diabetes status (no diabetes, pre-diabetes, undiagnosed diabetes, diagnosed diabetes) at visit 2; and 2) a prospective analysis to characterize the association of diabetes status and HbA1c with the incidence and progression of myocardial injury, as indicated by changes in hs-cTnT from visit 2 to

visit 4. All analyses will be conducted among persons with no history of cardiovascular disease or heart failure and normal kidney function at baseline (visit 2).

Hs-cTnT: Cardiac troponin T was measured at two time points using the same highly sensitivity (pre-commercial) Roche assay.

Visit 2: cardiac troponin T levels were measured from stored (visit 2) serum samples using a sandwich immunoassay method (Roche Diagnostics) implemented on a Roche Elecys 2010 Analyzer in 2012-2013 at the University of Minnesota as part of Dr. Selvin's ancillary study.

Visit 4: cardiac troponin T levels were measured from stored (visit 4) plasma samples using the same sandwich immunoassay method implemented on a Cobas e411 analyzer in 2010 at the Baylor College of Medicine as part of Dr. Ballantyne's ancillary study (#2008.10).

Calibration of visit 2 and 4 measurements: A calibration study is currently underway to test the comparability of different laboratory assays between different ARIC visits (V1-V5), including the Roche hs-cTnT assay at visit 2 (serum, Roche Elecsys2010 at UMN) and visit 4 (plasma, Cobas e411 at Baylor). Anticipated completion date of the calibration study is ~May 2013. If systematic differences are observed between hs-cTnT values obtained using the method at UMN in serum compared to the method used at Baylor in plasma, we will use a statistical calibration to align the measurements and correct for the bias ("drift").

Exclusions: Persons who did not attend visits 2 or 4, were missing information on exposures or covariates of interest, who had a history of cardiovascular disease (coronary heart disease, stroke, or heart failure) or chronic kidney disease at or before visit 2, persons whose race was reported to be other than white or black, and blacks in the Minneapolis and Washington County cohorts.

Statistical analyses: We will first characterize the prevalence of detectable and elevated hs-cTnT by diabetes status (diagnosed diabetes, undiagnosed diabetes, pre-diabetes, and no diabetes) at visit 2. We will use logistic regression models to evaluate the independent association of diabetes status with detectable and elevated levels of hs-cTnT before and after adjustment for traditional cardiovascular risk factors. For example, multivariable logistic regression models will be used to estimate odds ratios and corresponding 95% CIs for the association of diabetes status with detectable hs-cTnT and "elevated hs-cTnT" above the 99% percentile (both the "true" 99th percentile and also the arbitrary 99th percentile for the Roche reference population). HbA1c will be modeled in clinical categories in persons without a history of diabetes (<5.7, 5.7-<6.4, ≥6.5%) and in persons with diagnosed diabetes (<7, 7-<8, ≥8%). Second, we will characterize the association of diabetes status (defined by history of diabetes and HbA1c categories) at visit 2 with incidence and progression of myocardial injury, as indicated by change in hs-cTnT levels from visit 2 to visit 4. Among persons with no detectable levels of hs-cTnT at visit 2, we will examine risk factors for incident detectable hs-cTnT at visit 4 (binary variable).

Among persons with detectable levels of hs-cTnT, we split the population into approximate thirds as per previous analyses of hs-cTnT in ARIC (16). We will characterize change across these categories (i.e., movement across categories of detactable and thirds of detectable hs-cTnT at visit 2 to these categories at visit 4). For simplicity, we may also compare the association of diabetes status across categories of change from undetectable, detectable, and elevated at visit 2 to visit 4 (3x3 grid). All covariates will be assessed at visit 2. We will consider the following core models:

Model 1: age, sex, race-center.
Model 2: age, sex, race-center, total and high-density cholesterol levels, body mass index, systolic blood pressure, hypertension medication use, smoking status, and C-reactive protein.
Model 3: all variables in Model 2 + estimated GFR

To characterize the continuous associations, we will generate piece-wise linear splines with knots corresponding to the cutoffs in our categorical models and we will also implement restricted cubic splines to obtain a smoother fit to the data.

Sensitivity analyses: We will conduct sensitivity analyses to address the possibility of a small number of incident clinical cases of cardiovascular disease that may occur between baseline (visit 2) and the follow-up visit (visit 4). We will also address the potential impact of the small number of deaths that may have occurred after visit 2 but before the visit 4. We will also conduct sensitivity analyses incorporating fasting glucose into our definition of diabetes.

Limitations:
- Single measurement of HbA1c at visit 2 only
- Measurements of hs-cTnT at only two time points, 6 years apart.
- As with all observational studies, we will not be able to eliminate the possibility of residual confounding despite rigorous adjustment for known risk factors.

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/search.php

___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)?

Folsom AR, Nambi V, Bell EJ, Oluleye OW, Gottesman RF, Lutsey PL, Huxley RR, Ballantyne CM. Troponin T, N-Terminal Pro-B-Type Natriuretic Peptide, and Incidence of Stroke: The Atherosclerosis Risk in Communities Study.
Stroke. 2013 Mar 7. [Epub ahead of print] PMID: 23471272

Rubin J, Matsushita K, Ballantyne CM, Hoogeveen R, Coresh J, Selvin E.
Chronic hyperglycemia and subclinical myocardial injury. J Am Coll Cardiol. 2012 Jan 31;59(5):484-9. doi: 10.1016/j.jacc.2011.10.875. PMID: 22281251

Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, Hoogeveen RC, Liu X, Astor BC, Mosley TH, Folsom AR, Heiss G, Coresh J, Ballantyne CM. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. Circulation. 2011 Apr 5;123(13):1367-76.

Agarwal SK, Avery CL, Ballantyne CM, Catellier D, Nambi V, Saunders J, Sharrett AR, Coresh J, Heiss G, Hoogeveen RC. Sources of variability in measurements of cardiac troponin T in a community-based sample: the atherosclerosis risk in communities study. Clin Chem. 2011 Jun;57(6):891-7. doi: 10.1373/clinchem.2010.159350. Epub 2011 Apr 25. PMID: 21519038

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

___ A. primarily the result of an ancillary study (list number* __ 2006.15, 2009.16 and 2008.10_____)

___ 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 http://www.cscc.unc.edu/aric/forms/

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.

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16. Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. Circulation. 2011;123(13):1367-76. PMCID: PMC3072024.