ARIC Manuscript Proposal # 1596

1.a. Full Title: Hyperglycemia and risk of subsequent elevation of NT-proBNP and hs-cTnT

  b. Abbreviated Title (Length 26 characters): **HbA1c and cardiac damage**

2.   Writing Group:
       Writing group members:
Jonathan Rubin, MD; Kunihiro Matsushita, MD, PhD; Christie M. Ballantyne, M.D.; Ron Hoogeveen, Ph.D.; Josef Coresh, MD, PhD; Elizabeth Selvin, PhD, MPH; others welcome.

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

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3.   Timeline: Analysis is to start as soon as data are available (~ Feb 2010). We plan to submit the manuscript for ARIC review <1 year from approval / data availability.

4.   **Rationale**:

Cardiovascular disease is the leading cause of morbidity and mortality in persons with diabetes mellitus [1]. Diabetes confers approximately a 2-fold increase in risk of cardiovascular events, not entirely explained by traditional risk factors.

Epidemiologic studies have demonstrated an association between measures of glycemia and cardiovascular disease in persons with and without diabetes. Hemoglobin A1c (HbA1c), a marker of chronic hyperglycemia, is associated with incident coronary heart disease [2, 3], stroke [3-6], peripheral arterial disease[2, 7], heart failure [8] , total cardiovascular events, and all-cause mortality [9-12].

Hyperglycemia is also associated with echocardiographic subclinical left ventricular dysfunction [13-16]. Interestingly, HbA1c has also been shown to be associated with increased left ventricular mass in non-diabetics persons [17].

Newly identified biomarkers have improved the accuracy in the diagnosis of subclinical ventricular dysfunction. B-type natriuretic peptide is closely associated with left ventricular mass index [18] and accurately detects heart failure [19]. N-terminal pro-brain natriuretic peptide (NT-proBNP) is also associated with cardiovascular risk [20] and mortality [21, 22]. When compared to BNP, NT-proBNP was superior in the prediction of death in the general population[23]. NT-proBNP is elevated in patients with diabetes [24, 25] and has been demonstrated to detect subclinical left ventricular dysfunction[24]. It is also a reliable marker of future cardiac and all cause mortality in persons with diabetes [26].

Cardiac Troponin-T (cTnT) is associated with cardiovascular disease risk and adverse outcomes in both the general population and in high-risk groups [27]. Newer highly sensitive cardiac troponin-T (hs-cTnT) assays have demonstrated greater sensitivity as compared to earlier cTnT assays [28] and have also shown to be associated with cardiovascular death and heart failure in subjects with stable coronary artery disease [29].

Measurement of NT-proBNP and hs-cTnT from stored samples from all participants who attended the fourth ARIC visit will provide a population-based sample in which to assess the relationship of hyperglycemia to these markers of myocardial damage. We therefore propose to test the hypothesis that chronic hyperglycemia, as assessed by hemoglobin A1c, is associated with subclinical myocardial damage indicated by elevated NT-proBNP and hs-cTnT values, after controlling for covariates of interest.

5.   Main Hypothesis/Study Questions:

Hypothesis 1: HbA1c will be positively associated with subsequent elevations in hs-cTnT
      a) The association above will be present both in persons with and without diabetes.
      b) The association will be present independent of known cardiovascular risk factors.

Hypothesis 2: HbA1c will be positively associated with subsequent elevations in NT-proBNP

a) The association will be present both in persons with and without diabetes.
b) The association will be present independent of known cardiovascular risk factors.

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 with baseline at visit 2.

Exposure: Hemoglobin A_{1c} (HbA1c) (available at visit 2 only)
We measured HbA1c from stored whole blood specimens in ARIC as part of ARIC Ancillary Studies #2003.5 and #2006.15. HbA1c data are available on all participants at ARIC Visit 2.

Outcomes:
NT-proBNP and hs-cTnT measured in all participants with stored samples at Visit 4

Inclusions
All black and white ARIC subjects with data on HbA1c at visit 2 who subsequently attended visit 4 and have data on NT-proBNP and hs-cTnT available (n ≈ 11,500).

Exclusions:
Ethnicity other than black or white, missing HbA1c at visit 2, missing hs-cTnT at visit 4 (for hypothesis #1), missing data on NT-proBNP at visit 4 (for hypothesis #2), or missing covariates of interest.

Definition of Diabetes
Subjects will be classified as having a history of diabetes at Visit 2 if they report a physician diagnosis of diabetes or medications for diabetes at either Visit 1 or Visit 2. Undiagnosed diabetes will be defined as a fasting glucose >=126 mg/dl or non-fasting glucose >=200 mg/d at Visit 2, with sensitivity analyses using the Visit 1 glucose measurements to identify diabetes cases.

Covariates
Other variables of interest will include age, sex, race, center, smoking status, body mass index, waist-hip ratio, blood pressure, hypertensive medication use, diabetes medication use, education, triglycerides, HDL and LDL cholesterol and kidney function (estimated GFR from serum creatinine).

Potential effect modifier: cardiovascular disease history (self-reported history of CHD, stroke/TIA, or incident adjudicated non-fatal event prior to Visit 2).

Statistical Analysis
We will use linear and logistic regression models to assess the association between baseline HbA1c (Visit 2) and later measurements of hs-cTnT and NT-proBNP (Visit 4). For example, multivariable logistic regression models will be used to estimate odds ratios and corresponding

95% CIs for hs-cTnT or NT-proBNP levels above the 99% percentile, respectively, by categories of HbA1c . (NOTE: In the recent Omland et al paper in NEJM [29], hs-cTnT was associated with cardiovascular morbidity below the 99th percentile). Due to the nature of its distribution, log transformation of NT-proBNP may be indicated for regression modeling. HbA1c will be modeled as: (1) a continuous variable; and (2) in clinical categories in persons without a history of diabetes (<5, 5-<5.5, 5.5-<6, 6-<6.5 ≥6.5%) and in persons with diagnosed diabetes (<7, 7-<8, ≥8%). We will also conduct analyses implementing linear splines (e.g., knots at quartiles or at clinical cut-points) and restricted cubic splines in multivariable models to characterize the shape of the association with HbA1c. We will first conduct all analyses stratified by diagnosed diabetes status; then, second, we will generate diabetes-specific categories of HbA1c (and fasting glucose) at baseline to assess the relationship of hyperglycemia with hs-cTnT and NT-proBNP across the entire spectrum of impaired glucose homeostasis. We will formally test for interaction between HbA1c level and prevalent cardiovascular disease at baseline. If effect modification is present, we will conduct all analyses stratified by cardiovascular disease status at baseline.

We will also conduct sensitivity analyses censoring those persons with incident cardiovascular events during follow-up (i.e., incident cardiovascular disease occurring between Visit 2 and Visit 4). Additional sensitivity analyses will be conducted excluding individuals taking blood pressure lowering medications at baseline and exploring different definitions of diabetes (e.g., using glucose data from Visit 1, for example).

Limitations
Because hs-cTnT and NT-proBNP data will only be available at Visit 4 and HbA1c data are only available at Visit 2, we will not be able to establish the temporality of any observed associations. Despite adjustment for known risk factors for cardiovascular disease, we will also not be able to rule out the possibility of residual confounding in the interpretation of our results.

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 ICTDER03 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)?

Proposals on the association between HbA1c and cardiovascular disease
MP#1024: Glycemic Control (HbA1c) and Coronary Heart Disease Risk in Persons with and Without Diabetes: The Atherosclerosis Risk in Communities Study
MP#1056r: Hemoglobin A1c (HbA1c) and Peripheral Arterial Disease in Diabetes: The Atherosclerosis Risk in Communities (ARIC) Study
MP#1067: Glycemic Control and Risk of Ischemic Stroke: The Atherosclerosis Risk in Communities (ARIC) Study

Proposals on the association of hs-cTnT or NT-proBNP to cardiovascular or kidney disease
MP#1564: Correlation of High Sensitivity Troponin-T (hs-cTnT) and Amino Terminal pro-Brain Natriuretic Peptide (NT-proBNP) with Renal Function Parameters; and Association with Mortality and Adverse Cardiovascular Events
MP#1563: Novel highly sensitive cardiac Troponin-T (hs-cTnT) assay, mortality, and major adverse cardiovascular events in the ARIC Study

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?   __X__ Yes ____ No
ARIC Ancillary Study #2006.15, "Hemoglobin A1c (HbA1c), Incident Diabetes, and Major Causes of Morbidity and Mortality in Non-Diabetic Participants (HbA1cDM)."
ARIC Ancillary Study #2008.11, "Measurement of NT-pro-BNP and troponin T at visit 4 for the full ARIC cohort"

11.b. If yes, is the proposal
     _**X**_ **A. primarily the result of an ancillary study (list number** #2006.15 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/

12. 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.

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