ARIC Manuscript Proposal #1968

PC Reviewed: 7/10/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
The association of cardiac troponin T measured by a highly sensitive assay and incident diabetes

b. Abbreviated Title (Length 26 characters):
hs-cTnT and incident diabetes

2. Writing Group:
Writing group members:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. SPW **[please confirm with your initials electronically or in writing]**

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3. Timeline:
Data to be used in this proposal are already available. Analyses and manuscript preparation will be performed over the next six months.

4. Rationale:

Cardiovascular disease is the leading cause of death in patients with diabetes.[1] Randomized trials have demonstrated that improvements in glucose control can lead to a significant decrease in microvascular complications, but a similar decrease in macrovascular complications has not been observed.[2-4] In contrast, diabetic individuals who are treated for elevated traditional cardiovascular risk factors (e.g. blood pressure and hyperlipidemia) have a significantly reduced risk of macrovascular events.[5-8]

The "Common Soil hypothesis" suggests that macrovascular complications may not be directly attributable to the hyperglycemia of diabetes.[9] Instead, diabetes and macrovascular disease may arise from a similar set of underlying genetic and environmental risk factors. In particular, obesity, dyslipidemia, and hypertension are established risk factors for both diabetes and cardiovascular disease. These shared risk factors may indicate that diabetes and cardiovascular disease may develop in parallel, rather than macrovascular disease occurring as a result of diabetes induced hyperglycemia.

The "Ticking Clock hypothesis" is similar in that it does not attribute the increased risk for macrovascular disease to hyperglycemia. Instead, it proposes that the risk of developing macrovascular complications is due to traditional cardiovascular risk factors and begins long before an individual reaches the glycemic threshold for diabetes.[10] Individuals typically are obese, dyslipidemic, and have high blood pressure before they meet the diagnostic criteria for diabetes. This suggests that while a consistent state of hyperglycemia, which heralds the clinical diagnosis of diabetes, may increase the risk of microvascular disease it is not necessarily the major underlying risk factor for the development of macrovascular disease. Therefore, an increased risk for macrovascular disease due to an elevation of traditional cardiovascular risk factors may accrue for years before the clinical diagnosis of diabetes. In support of this hypothesis Hu et al noted that individuals who developed diabetes had a greater than two-fold risk for macrovascular complications at more than 15 years before their diagnosis of diabetes.[11]

Cardiac troponin is a highly specific marker of myocardial necrosis and a key component in the diagnosis of myocardial infarction.[12] A recently developed highly sensitive cardiac troponin assay (hs-cTnT) can detect cardiac troponin at levels approximately 10 times lower than traditional assays and in the general population an elevated level of hs-cTnT is associated with an increased risk of incident cardiovascular disease.[13, 14] Hs-cTnT has also been associated with transient myocardial ischemia and has been suggested as a marker of subclinical myocardial injury.[15, 16] Furthermore, individuals with diabetes have a significantly higher level of hs-cTnT compared to those without diabetes.[17, 18]

Previous studies have shown that individuals with impaired fasting glucose or diabetes have an increased risk for subclinical atherosclerosis as detected by coronary artery calcium scanning.[19-21] However, the association between the presence of subclinical damage to the myocardium and the subsequent risk of diabetes is uncharacterized. If myocardial damage precedes diabetes, this undermines the notion of a causal link between hyperglycemia and cardiovascular disease and might explain why tight glycemic control fails to modify cardiovascular disease risk in adults with long-standing diabetes.

5. Main Hypothesis/Study Questions:

Hypothesis:

1) Subclinical myocardial damage as indicated by the presence or elevation in hs-cTnT will be associated with an increased risk for incident diabetes among persons with no history of diabetes or cardiovascular disease at baseline.

2) Among participants with diabetes at baseline (Visit 4) the risk of developing coronary heart disease will be significantly attenuated after adjustment for hs-cTnT.

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 analysis with baseline at Visit 4

Inclusion criteria:

- Participants in whom a serum hs-cTnT was measured at Visit 4 (n~11,000) and with annual follow up data

Exclusion criteria:

- Participants with known coronary artery disease (history, EKG evidence of angina or myocardial infarction), participants with a known history of diabetes (self-report), participants without a recorded hs-cTnT measurement, and participants with an eGFR <60mL/min/1.73m^2. Participants with missing data on important confounders

Exposure Variable:

- hs-cTnT (by quintile) and modeled continuously. For the categorical analyses, those participants with undetectable levels (33.5% of all ARIC participants) will be the reference group (group 1). The remaining participants with detectable levels will be split into approximate thirds: cTnT levels 0.003 to 0.005 μg/L (group 2), 0.006 to 0.008 μg/L (group 3), and higher levels divided at approximately the 90th percentile of the ARIC general population (group 4: 0.009 to 0.013 μg/L), Those particpants with elevated hs-cTnT (group 5: ≥0.014 μg/L) will be defined as a level above the previously reported 99th percentile value (0.014 μg/L) in a healthy subpopulation aged 20–70 years (Roche Diagnostics, data on file). In addition, we will also model hs-cTnT as a continuous variable with undetectable levels of hs-cTnT assigned a value of 0.0015 μg/L (i.e., half the lower limit of detection).

Confounding/Interacting Variables:

-Age, sex, race, cholesterol levels (total, LDL, HDL), blood pressure, serum glucose, hypertension, body mass index (height, weight), waist to hip ratio, glomerular filtration

rate, cystatin C, smoking (current, former, never), hs-CRP, alcohol consumption, family history of diabetes, lactate, insulin, HOMA-IR

Outcome Variables:

- Primary: Incident diabetes, using information on diabetes diagnoses and diabetes medication use obtained during the annual telephone follow-up calls to all participants (AFU).

Analysis plan and methods:

Analyses will be conducted based on quintiles of detected hs-cTnT (as defined previously). We will also make comparisons for undetected versus detected levels of hs-cTnT. Baseline differences on continuous variables will be compared using one-way ANOVA testing and categorical variables will be compared with chi-squared testing. Hazard ratios and associated confidence intervals will be calculated for the primary endpoint (incident diabetes) by quintile of hs-cTnT. Additional models with progressive degrees of adjustment for established diabetes and cardiovascular risk factors will be performed. Model 1: sociodemographics, Model 2: Model 1 + lifestyle + risk factors + family history, Model 3: Model 2 + eGFR + novel biomarkers, Model 4: Model 3 + fasting glucose

hs-cTnT will also be modeled as a continuous variable using spline models and we will formally test the significance of deviation from linearity using a spline with a knot at the mean hs-cTnT.

An analysis examining the association between diabetes at baseline (Visit 4) with incident CHD before and after adjustment for hs-cTnT will be performed to examine if hs-cTnT can explain most of the association of DM with CVD outcomes. If true, this would support our hypothesis that cardiac damage pre-exists/co-exists with the development of diabetes.

Sensitivity analyses: We will conduct sensitivity analyses excluding individuals with baseline fasting glucose levels of ≥100 (pre-diabetics and undiagnosed diabetics) or >126 (undiagnosed diabetics) and for follow-up periods of <5 years and >5 years.

We will also use information on diabetes cases, blood glucose levels and HbA1c measurements obtained in a subsample of persons at the CARMRI visit in 2005-2006. Using the CARMRI subsample, we will examine the association of hs-cTnT with change in serum glucose level between Visit 4 and the CARMRI visit in 2005-2006. In addition we will examine the association of hs-cTnT with incident diabetes defined by a fasting glucose ≥ 126 mg/dl, HbA1c ≥6.5% obtained at the CARMRI visit.

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)?

MP# 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 cause- specific mortality: ARIC study

MP# 1596 Hyperglycemia and risk of subsequent elevation of NT-proBNP and hs-cTnT

MP# 1734 Biomarker, anthropometric parameters associated with highly sensitive cardiac troponin T

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 withMortality 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

11.b. If yes, is the proposal

_X__ A. primarily the result of an ancillary study (list number* _2007.09____)

___ 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.

References

1. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the who multinational study of vascular disease in diabetes. *Diabetologia*. 2001;44 Suppl 2:S14-21
2. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (ukpds 33). Uk prospective diabetes study (ukpds) group. *Lancet*. 1998;352:837-853
3. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *The New England journal of medicine*. 2008;358:2560-2572
4. Gerstein HC, Miller ME, Byington RP, Goff DC, Jr., Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH, Jr., Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. *The New England journal of medicine*. 2008;358:2545-2559
5. Collins R, Armitage J, Parish S, Sleigh P, Peto R. Mrc/bhf heart protection study of cholesterol-lowering with simvastatin in 5963 people with diabetes: A randomised placebo-controlled trial. *Lancet*. 2003;361:2005-2016
6. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the collaborative atorvastatin diabetes study (cards): Multicentre randomised placebo-controlled trial. *Lancet*. 2004;364:685-696
7. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: Ukpds 38. Uk prospective diabetes study group. *BMJ*. 1998;317:703-713

8. Patel A, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, Harrap S, Poulter N, Marre M, Cooper M, Glasziou P, Grobbee DE, Hamet P, Heller S, Liu LS, Mancia G, Mogensen CE, Pan CY, Rodgers A, Williams B. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the advance trial): A randomised controlled trial. *Lancet*. 2007;370:829-840

9. Stern MP. Diabetes and cardiovascular disease. The "common soil" hypothesis. *Diabetes*. 1995;44:369-374

10. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. Cardiovascular risk factors in confirmed prediabetic individuals. Does the clock for coronary heart disease start ticking before the onset of clinical diabetes? *JAMA : the journal of the American Medical Association*. 1990;263:2893-2898

11. Hu FB, Stampfer MJ, Haffner SM, Solomon CG, Willett WC, Manson JE. Elevated risk of cardiovascular disease prior to clinical diagnosis of type 2 diabetes. *Diabetes care*. 2002;25:1129-1134

12. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, Jr., Chavey WE, 2nd, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright RS, Smith SC, Jr., Jacobs AK, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Ornato JP, Page RL, Riegel B. Acc/aha 2007 guidelines for the management of patients with unstable angina/non st-elevation myocardial infarction: A report of the american college of cardiology/american heart association task force on practice guidelines (writing committee to revise the 2002 guidelines for the management of patients with unstable angina/non st-elevation myocardial infarction): Developed in collaboration with the american college of emergency physicians, the society for cardiovascular angiography and interventions, and the society of thoracic surgeons: Endorsed by the american association of cardiovascular and pulmonary rehabilitation and the society for academic emergency medicine. *Circulation*. 2007;116:e148-304

13. 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;123:1367-1376

14. Linssen GC, Bakker SJ, Voors AA, Gansevoort RT, Hillege HL, de Jong PE, van Veldhuisen DJ, Gans RO, de Zeeuw D. N-terminal pro-b-type natriuretic peptide is an independent predictor of cardiovascular morbidity and mortality in the general population. *European heart journal*. 2010;31:120-127

15. Sabatine MS, Morrow DA, de Lemos JA, Jarolim P, Braunwald E. Detection of acute changes in circulating troponin in the setting of transient stress test-induced myocardial ischaemia using an ultrasensitive assay: Results from timi 35. *European heart journal*. 2009;30:162-169

16. Morrow DA, Antman EM. Evaluation of high-sensitivity assays for cardiac troponin. *Clinical chemistry*. 2009;55:5-8

17. Everett BM, Cook NR, Magnone MC, Bobadilla M, Kim E, Rifai N, Ridker PM, Pradhan AD. Sensitive cardiac troponin t assay and the risk of incident cardiovascular disease in women with and without diabetes mellitus: The women's health study. *Circulation*. 2011;123:2811-2818

18. Rubin J, Matsushita K, Ballantyne CM, Hoogeveen R, Coresh J, Selvin E. Chronic hyperglycemia and subclinical myocardial injury. *Journal of the American College of Cardiology*. 2012;59:484-489

19. Meigs JB, Larson MG, D'Agostino RB, Levy D, Clouse ME, Nathan DM, Wilson PW, O'Donnell CJ. Coronary artery calcification in type 2 diabetes and insulin resistance: The framingham offspring study. *Diabetes care*. 2002;25:1313-1319

20. Moebus S, Stang A, Mohlenkamp S, Dragano N, Schmermund A, Slomiany U, Hoffmann B, Bauer M, Broecker-Preuss M, Mann K, Siegrist J, Erbel R, Jockel KH. Association of impaired fasting glucose and coronary artery calcification as a marker of subclinical atherosclerosis in a population-based cohort--results of the heinz nixdorf recall study. *Diabetologia*. 2009;52:81-89

21. Lee KK, Fortmann SP, Fair JM, Iribarren C, Rubin GD, Varady A, Go AS, Quertermous T, Hlatky MA. Insulin resistance independently predicts the progression of coronary artery calcification. *American heart journal*. 2009;157:939-945