1. a. Full Title:
Association of highly–sensitive cardiac troponins (hs-cTnT) with resting electrocardiographic (ECG) parameters in the Atherosclerosis Risk in Community (ARIC) Study.

b. Abbreviated Title:
hs-cTnT and ECG

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

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3. Timeline:
The resting electrocardiogram (ECG) and high sensitive troponin (hs-cTnT) data is already available and statistical analysis can be performed as soon as the manuscript proposal is approved. A draft manuscript will be presented to the steering committees within 12 weeks of analysis.

4. Rationale: Elevated serum troponins have been known to be a marker of acute myocardial damage as well as for poor outcomes in coronary heart disease (CHD) and heart failure (HF) patients. (1) Release of troponin is believed to be a result of cardiomyocyte necrosis and apoptosis in these conditions. With the advent of newer assays, characterized by a limit of detection at the picogram or subpicogram level, previously undetectable cardiac troponin levels can now be measured. (2) Recently, there have been studies suggesting that previously undetectable cardiac troponin levels, now measurable by the highly sensitive assays (hs-cTnT), are associated with worse outcomes in patients with chronic HF, stable CHD and unstable angina. (3, 4, 5, 6) In addition, these were shown to be associated with a higher risk for cardiovascular (CV) and all-cause mortality in the apparently healthy population cohorts. (7) A recent analysis found significant association of hs-cTnT with mortality and major CV events in the Atherosclerosis Risk in Communities (ARIC) population. (8, unpublished data) Electrocardiographic evidence of left ventricular hypertrophy (LVH) was associated with higher hs-cTnT levels. (8) However, the association of elevated hs-cTnT levels with other ECG parameters remains to be determined.

Independent of the traditional CV risk factors, several 12-lead resting ECG findings have been shown to have association with incident CHD, major adverse cardiovascular events (MACE), ischemic strokes and poor outcome in the ARIC study as well as other population cohorts. (9-12) Minor Q waves, possibly representing subclinical myocardial infarction, have been found to have a significant association with future CV events. (9, 10) While major and minor ST-segment depression has consistently been associated with MACE in most population cohorts, (9, 10, 11, 12) few studies have also found an inverse
association of ST-elevation with CV events. (11, 13) There are some reports suggesting ECG Cornell voltage evidence of LVH, (10, 11, 18, 19, 21, 22) LVH with strain (20) and major T-wave abnormalities (21) as risk factors for future CV events. Recent ARIC based study has linked premature ventricular contraction with incident stroke risk. (23) Similarly, there is some evidence suggesting the predictive value of major ventricular conduction delays (10, 11) and prolonged corrected QT interval for future CV events. (14, 15, 16, 17)

Though hs-cTnT and resting ECG parameters have individually shown to be risk predictors of CV disease in healthy adult populations, the association of hs-cTnT with resting ECG parameters is not known. It remains to be evaluated whether healthy asymptomatic adults showing elevation in hs-cTnT levels also have corresponding changes on their resting ECG. It is possible that certain electrophysiological changes, as yet considered innocuous or benign, may induce myocardial damage detectable by hs-cTnT assays.

5. Main Hypothesis/Study Questions:

We hypothesize that participants with even very low levels of troponins, as measured by high sensitivity assays, have characteristic ECG features at the same timepoint or had certain ECG changes before troponin assessment. The aims of this study are:

a. To evaluate the association of hs-cTnT with various resting ECG parameters in the ARIC study at the same timepoint.

b. To evaluate the association of hs-cTnT with a change in various resting ECG parameters over pre-defined visits in the ARIC study.

6. Data (variables, time window, source, inclusions/exclusions):

Highly sensitive cardiac troponins (hs-cTnT) assays were obtained from blood draw at visit 4 in the ARIC cohort.
Parameters from ECG performed at visits 1 and 4 in the ARIC cohort will be used for this study.

Inclusion Criteria:
- Available ECG data at visits 1 and 4
- Available hs-cTnT at visit 4

Exclusion Criteria:
- Participants with missing hs-cTnT assays at visit 4
- Participants with missing ECG variables at visits 1 and 4
- Participants using medications with potential effects on the ECG (types I and III antiarrhythmics, digoxin, haloperidol, methadone)
- Participants with thyroid dysfunction
Variables
A) The first part of the analysis will involve evaluating the association of hs-cTnT levels with resting ECG parameters at visits 1 and 4.

B) The second part of the study will involve evaluating the association of hs-cTnT levels with a change in resting ECG parameters between visits 1 and 4.

hs-cTnT will be used both as a continuous variable and a dichotomous variable (group with undetectable levels (<0.003 µg/L) and group with detectable levels).

ECG parameters (per Minnesota Codes) evaluated at visits 1 and 4 will include:

I) Conduction abnormalities
   1. Short PR interval
   2. Prolonged PR interval
   3. Ventricular Conduction Delays –major/minor (left, right, partial, complete)
   4. Left Axis Deviation
   5. Right Axis Deviation
   6. QRS duration
   7. Corrected QT interval
   8. Presence of U waves

II) Ischemic abnormalities
   1. Presence of Q wave –major /minor (in leads I, aVL, V6; II, III, aVF; and V1-V3)
   2. ST depression-major/minor (in leads I, aVL, V6; II, III, aVF; and V1-V5)
   3. T wave –major/minor (in leads I, aVL, V6; II, III, aVF; and V1-V5)
   4. ST segment elevation (in leads I, aVL, V6; II, III, aVF; and V1-V5)
   5. High T wave amplitude

III) Rate/Rhythm abnormalities
   1. Ventricular premature complex
   2. Heart rate (HR)
   3. Atrial premature complex
   4. Presence of atrial flutter or fibrillation
   5. Presence of sinus arrhythmia

IV) Structural/Infiltrative abnormalities
   1. Low QRS amplitude ( <5mm in -- leads I, II and III, and < 10mm in leads V1-V6)
   2. High R wave amplitude (in leads I, aVL, V6; II, III, aVF; and V1-V5)
   3. Left ventricular hypertrophy (LVH) by voltage criterion and LVH by ST-T inclusive –LVH criterion
4. Left atrial (LA) size and predictors of LV filling pressures-P wave terminal force, P-wave area, P wave duration

Each of the above mentioned ECG parameters will be individually assessed for a change between visit 4 and visit 1. For categorical parameters, the dichotomous response will be recorded as a ‘yes/1’ or ‘no/0’. The delta (value of parameter at visit 4 minus value of parameter at visit 1) will be recorded for continuous variables.

**Statistical Analysis**

Linear regression analyses will be performed to identify univariate and multivariate ECG predictors of hs-cTnT after adjusting for the effects of known or potential confounding variables. Linear regression model 1 will be used to adjust for demographic (age, gender, race, education, study center) variables, body mass index, height, chronic lung disease, medications and renal functions (estimated glomerular filtration rate) at baseline visit. Linear regression model 2 will adjust for variables used in model 1 and the traditional CV risk factors including smoking, alcohol intake, physical inactivity, diabetes mellitus, systolic blood pressure, diastolic blood pressure, use of anti-hypertensive medications, family history of premature coronary artery disease, lipid profile and body mass index at the baseline visit.

Similarly, logistic regression analyses will be performed for dichotomous hs-cTnT variable.

Analysis will be performed both including and after excluding patients with a history of CHD and heart failure.

This statistical methodology will be used to evaluate:

**A)** Association of hs-cTnT with ECG parameters at visits 1, and 4

**B)** Association of hs-cTnT with a change in ECG parameters between visits 4 and 1.

Once we have evaluated the association of hs-cTnT with resting ECG parameters, we also aim to determine whether a new risk model combining one or multiple ECG parameters with hs-cTnT improves risk prediction for CV disease in asymptomatic healthy population when compared to either parameters used alone.

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

7. b. If Yes, is the author aware that the file ICTDER02 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
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 ICTDER02 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)?

1- MS # 1563, Saunders et al (unpublished data)
2- MS# , Machado et al , Am J Cardiol 2006
3- MS# 300, Dekker et al, JACC 2004
4- MS# 1378, Aggarwal et al, Stroke 2010

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* __Saunders et al  MS#__)  ____ 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: