1.a. Full Title: Performance of highly sensitive cardiac troponin T when added to ECG for diagnosis of left ventricular hypertrophy and left atrial enlargement as confirmed by echocardiography: the ARIC study

b. Abbreviated Title (Length 26 characters): Biomarkers & ECG in LVH and LAE

2. Writing Group:

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3. Timeline: Analysis to start as soon as approval is obtained. Manuscript is to be prepared as soon as analyses are available. The analysis and manuscript preparation will take place within 1 year from approval of the proposal.

4. Rationale:
Left ventricular hypertrophy (LVH) is one of the markers of target organ damage from hypertension (HTN).\(^1,2\) LVH is independently associated with cardiovascular (CV) morbidity and mortality.\(^1,3-5\) Regression of LVH or prevention of further progression of LVH is also independently associated with reduction of CV events compared to persistent or newly developed LVH.\(^6,7\) Imaging modalities such as echocardiogram or cardiac magnetic resonance imaging (MRI) are mainly used for the diagnosis of LVH. These diagnostic modalities may not be easily available, and are expensive\(^8\) compared to electrocardiogram (ECG), which has high specificity for LVH (80-90%).\(^9,10\) Imaging modalities use LV mass for the diagnosis of LVH, whereas ECG uses cardiac electrical activity recorded on skin surface, a fundamentally different method for the detection of LVH. Cardiac electrical activity recorded at the skin surface can be attenuated by various factors such as body habitus, adipose and lung tissue, pericardial fluid, epicardial fat etc. Therefore, ECG has low sensitivity (<50%, and usually <30%)\(^9,11-12\) for the diagnosis of LVH, especially for mild to moderate LVH,\(^12\) which is the most prevalent form of LVH in the general population. However, ECG diagnosed LVH has been associated with adverse CV outcomes\(^4,13-16\) and regression of LVH on ECG has been associated with reduced adverse CV events.\(^17,18\) Critics argue that negative ECG criteria should not be used to rule out LVH.\(^9\) Some of the ECG abnormalities found in LVH (strain pattern such as J-point depression, upwardly convex down-sloping depression of the ST segment and asymmetrical inversion of the T wave; complete right bundle branch block; incomplete or complete left bundle branch block; left anterior fascicular block; left axis deviation; QRS duration of ≥90 milliseconds in V5 or V6; prolonged QT interval; p wave changes) (from now called “soft ECG changes”) may not have directly resulted from increased muscle mass, but could simply reflect conduction abnormality or subendocardial ischemia from increased muscle mass. This could explain why the non-voltage ECG abnormalities were shown to be strong and independent predictors of CV morbidity and mortality beyond that attributable to increased LV mass and other traditional CV risk factors.\(^13,19-21\) These “soft ECG changes” are not part of all the available ECG-LVH diagnostic criteria (Figure),\(^9,22,23\) and so this could account for the low sensitivity of the ECG-LVH diagnostic performance.
### Selected ECG criteria of left ventricular hypertrophy (LVH).

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis voltage</td>
<td>$R_I + S_{III} - S_I - R_{III} \geq 1.7 \text{mV}$</td>
</tr>
<tr>
<td>Gubner–Ungerleider</td>
<td>$R_I + S_{III} \geq 2.5 \text{mV}$</td>
</tr>
<tr>
<td>voltage</td>
<td></td>
</tr>
<tr>
<td>Sokolow–Lyon voltage</td>
<td>$S_{V1} + R_{V5} \geq 3.5 \text{mV}$</td>
</tr>
<tr>
<td>$R_{aVL}$</td>
<td>$R_{aVL} &gt; 1.1 \text{mV}$</td>
</tr>
<tr>
<td>Romhilt–Estes score</td>
<td>$\geq 5 \ (\text{LVH}); \geq 4 \ (\text{probable LVH})$</td>
</tr>
<tr>
<td>Cornell voltage</td>
<td>$S_{V3} + R_{aVL} &gt; 2.8 \text{mV} \ (\text{men}), &gt; 2.0 \text{mV} \ (\text{women})$</td>
</tr>
<tr>
<td>Cornell product</td>
<td>$(S_{V3} + R_{aVL}) \times \text{QRS duration} \geq 244 \text{mV} \times \text{ms}$</td>
</tr>
<tr>
<td>Left ventricular strain</td>
<td>ST-segment depression $\geq 0.1 \text{mV} + \text{T-wave}$</td>
</tr>
<tr>
<td></td>
<td>asymmetric inversion in $V_2-V_6$ and in peripheral leads (lateral or inferior)</td>
</tr>
<tr>
<td>$R_{V6} : R_{V5}$ ratio</td>
<td>$R_{V6} : R_{V5} &gt; 1$</td>
</tr>
<tr>
<td>Framingham criterion</td>
<td>$R_I + S_{III} \geq 2.5 \text{mV}, S_{V10} \geq 3.5 \text{mV}, S_{V1/V2} \geq 2.5 \text{mV}$</td>
</tr>
<tr>
<td>Perugia criterion</td>
<td>$S_{V3} + R_{aVL} &gt; 2.4 \text{mV} \ (\text{men}), &gt; 2.0 \text{mV} \ (\text{women})$, and/or $LV \text{ strain}, and/or \text{Romhilt–Estes score} \geq 5$</td>
</tr>
</tbody>
</table>

**Figure.** Several ECG-LVH criteria

Highly sensitive cardiac troponin T (hs-cTnT) and N terminal-pro beta natriuretic peptide (NT-proBNP) are very sensitive markers of myocardial injury$^{24}$ and myocardial stretch$^{35}$ respectively. They are associated with various incident CV events,$^{26-32}$ heart failure.$^{26,29,30,33}$ Both hs-cTnT and NT-proBNP are shown to be increased in LVH,$^{33,34}$ each reflecting different pathophysiology (myocardial injury and stretch respectively). Both are relatively inexpensive. Use of established ECG-LVH criteria plus these sensitive biomarkers for the diagnosis of LVH can be complementary and could increase the sensitivity for LVH diagnosis. In addition, some of the ECG-LVH criteria incorporate some of the ECG abnormalities mentioned in the “soft ECG changes”.$^{9,22,23}$ Testing performance of these specific criteria will allow us to assess the utility of “soft ECG changes” combined with voltage ECG criteria and biomarkers. This approach can have practical implication because the combined test using biomarkers for LVH diagnosis may be relatively inexpensive and will be easily available compared to echocardiogram. It will also avoid the need of any expertise that is needed to interpret echocardiogram. To our knowledge there are only few related such studies.$^{34,35}$ In one of these studies ECG performance was assessed using ECG voltage criteria.
only and test characteristics were compared using MRI as gold standard\textsuperscript{34} and not echocardiogram, which is the most widely used test in the assessment of LVH in clinical practice. Other study used only NT-proBNP, but in population with suspected heart failure.\textsuperscript{35}

There are several ECG abnormalities that suggest left atrial enlargement (LAE), such as the P terminal force, i.e. the product of the amplitude and the duration of the terminal negative component of the P wave in lead V1; duration of p wave ≥120 ms; and notched P wave ≥ 40 ms.\textsuperscript{22} The performance of these abnormalities when used in conjunction with hs-TnT and NT-proBNP has not been examined.

ARIC 5th visit has collected information on hs-cTnT, NT-proBNP, ECG and echocardiogram, and thus provides unique opportunity to test if addition of these biomarkers to ECG improves LVH and LAE diagnosis. Therefore, we decided to assess the test characteristics of the various ECG criteria for LVH (figure) and LAE when combined with hs-cTnT or NT-proBNP or both with echocardiogram used as the gold standard.

5. Main Hypothesis/Study Questions:

Primary aim:

1. To examine whether addition of hs-cTnT or NT-proBNP or both to the “traditionally” known ECG-LVH criteria would improve their diagnostic performance.
2. To examine whether addition of hs-cTnT or NT-proBNP or both to the “traditionally” known ECG abnormalities associated with LAE would improve the diagnostic performance.

Secondary aim:

To assess if there is any difference in the diagnostic performance of ECG-biomarker combined LVH and LAE criteria by various clinically relevant 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 methodological limitations or challenges if present).

Variables:

All the variables used in this analysis will be from Visit 5. NT-proBNP corresponding to the highest sex-specific quartile, i.e. 75\textsuperscript{th} percentile in a healthy subpopulation (ie after excluding those with prevalent CVD, see below) and the limit of hs-cTnT detection (5 ng/L) from ARIC visit 5\textsuperscript{th} will be used as a dichotomous variable. This is based on similar analysis from prior published study.\textsuperscript{34} LVH will be specific to gender, race and body surface area, and LAE will also be standardized. The various ECG-LVH criteria and ECG abnormalities associated with LAE and the echo criteria will be derived with advice from the ARIC ECG Reading Center (Soliman) and the ARIC ECHO Reading Center (Solomon) respectively.
Inclusion/Exclusion:

All ARIC 5th visit participants with available information on hs-cTnT, NT-proBNP, ECG and echocardiogram will be included except the following:

1. Standard ARIC exclusions (race/center)
2. Prevalent CVD (CHD, heart failure)
3. Aortic stenosis (of any severity)
4. Moderate to severe other valvular stenosis or regurgitation
5. Cardiac rhythm other than sinus or atrial pacing
6. On digoxin/digitalis and loop diuretics
7. Severe pulmonary hypertension (pulmonary artery mean pressure ≥50 mm Hg)

Since our goal is to examine test characteristics for LVH diagnosis resulting primarily from HTN, we decided to exclude causes other than HTN that may be associated with either LVH (e.g., aortic stenosis) or elevated biomarkers (e.g., prevalent CVD, other significant valvular abnormalities etc).

Analysis:

Descriptive statistics will be based on parametric or non-parametric tests based on Gaussian distribution of variables.

We will develop following logistic regression models in initial analyses to examine the association of exposure variables, first using ECG only, then combining ECG with biomarker(s) (NT-proBNP and hs-cTnT one at a time) for LVH (LAE) diagnosis (compared with the echo as the gold standard).

1. Age, race, gender,
2. Model 1 plus BMI, smoking status (current smoker, never smoked), HTN or on treatment for HTN, heart rate, Total cholesterol/high-density lipoprotein cholesterol, DM (or on treatment for DM), eGFR, LV ejection fraction (LVEF)

Then we will assess the test characteristic (for example, sensitivity, specificity, positive and negative predictive value, positive and negative likelihood ratios, receiver operating curve area) of the various ECG-LVH criteria (and LAE abnormality) in isolation or when combined with NT-proBNP and hs-cTnT one at a time to examine changes in test characteristics (as above plus c statistics and net reclassification index). In ROC analysis we will consider NT-proBNP and hs-cTnT as continuous variables to find the levels associated with best sensitivity and specificity. We will also examine the performance of the combined ECG and biomarkers for LV mass. In addition, we will also present number needed to screen, as defined by the number of participants needed to screen to detect 1 case of LVH (LAE), calculated using 1 divide by absolute rate of additional LVH (LAE) diagnosis made by the combined biomarker and ECG vs. that made by ECG alone.
As part of sensitivity analysis, stratified analyses will be performed by following status; race, gender, stage 3 CKD status (i.e. eGFR < or ≥ 60 mL/min/1.73m²), HTN, age < or ≥ 50 and LVEF < or ≥ 50%. Additional analyses will be performed using BMI categories (<25, 25-29.9, 30-34.9, 35-39.9, ≥40) to assess if there is any trend with BMI. In stratified analysis we will test the performance of the various LVH criteria mentioned above for diagnosis of concentric or eccentric LVH to assess if there is differential performance for these subtypes of LVH.

Methodological limitations or challenges:

The ARIC visit 5th population could potentially represent a healthier subset of the original ARIC cohort and thus the findings of our study may not have the best external validity in a relatively healthier population.

There could be differences in characteristics of individuals at V5 who had or did not have echocardiogram assessment. We will compare the difference in their V5 characteristics.

Unmeasured variables could still be associated with ECG and biomarker criteria for LVH.

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

 ____ Yes   ____X__ 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)?
11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ___ Yes ___ X ___ No

11.b. If yes, is the proposal
___ A. primarily the result of an ancillary study
___ 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.csc.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.csc.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.


19. Okin PM, Roman MJ, Lee ET, Galloway JM, Howard BV, Devereux RB. Combined echocardiographic left ventricular hypertrophy and electrocardiographic ST depression


