ARIC Manuscript Proposal # 1615

PC Reviewed: 2/9/10   **Status: A**   **Priority: 2**
SC Reviewed: _____   **Status: _____**   **Priority: ____**

1.a. Full Title: Components of variability in the measurement of high sensitive troponin T. The ARIC Study

  b. Abbreviated Title (Length 26 characters): Variability in hs-Trop T

   2.   Writing Group: Agarwal SK, Ballantyne CM, Catellier D, Hoogeveen RC, Nambi V, Rhodes CE, Sharrett RA, Avery CL, Heiss G

The first author_SKA_ confirms that all the coauthors have given their approval for this manuscript proposal.

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   3.   Timeline:
As part of ancillary study #2009.15, assay runs and data management are in progress; if approved, a draft of manuscript(s) can be submitted within six months.

   4.   Rationale:
Cardiac troponins are markers of myocardial injury commonly used for the diagnosis of acute coronary events [1-4]. Several studies [5-12] have reported an association between increased concentration of troponin measured in blood and HF, although concentrations are generally lower than those seen in patients with acute coronary syndromes [13]. The lower troponin concentrations associated with chronic HF necessitate a highly sensitive troponin assay, such as the high sensitivity troponin T (hsTNT) assay which can detect troponin concentrations >10-fold lower than traditional assays. In 2007, Latini et al. reported that while only 10.4% (n = 420) of HF patients had detectable troponin levels when the traditional assay was used, hsTNT was detectable in 92% of participants (n = 3,729). As with the traditional troponin assay, hsTNT was associated with the risk of death among HF patients and significantly improved prognostic discrimination even after adjustment for clinical covariates.

To our knowledge, only one study has been published to evaluate the variability of hsTNT since the publication of a review by National Academy of Clinical Biochemistry Standards of Laboratory

Practice in 1999 which emphasized the absence of such studies[14]. We will examine whether participant characteristics (e.g. variability (e.g. age, sex, race, body mass index and serum level of biomarker)) influence the variation in hsTNT, in individuals without heart failure or coronary artery disease. Briefly, in this study we propose to examine several components of variability (laboratory, process, and biological). Process variability (i.e., variability in blood processing, shipping, and laboratory handling and analysis) will be estimated from replicate plasma samples taken on 112 individuals in the ARIC Carotid MRI (CarMRI) study. Biologic + process variation will be estimated from 55 replicate plasma samples taken 4-8 weeks apart in the CarMRI study. Stability of hs-Troponin T will be estimated from ARIC visit 4 specimens.

5.   Main Hypothesis/Study Questions:

1.   Estimate laboratory variability by analyzing 30 split samples of hsTNT, from participants with HF (n = 15) and participants without evidence of HF (n = 15).
2.   Estimate process variability (i.e., variability in blood processing, shipping, and laboratory handling and analysis) from replicate plasma samples taken on 112 individuals.
3.   Estimate the biologic + process variation from 55 replicate plasma samples taken 4-8 weeks apart.
4.   Estimate variation due degradation:
    i.   Short-term degradation will not be assessed since expected to be of small magnitude
    ii.   Long-term degradation will be estimated from the different storage times of the specimens.

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).

Data: Assays done per design described in ancillary study #2009.15 will be used.

Statistical analysis: By treating paired measurements as a random effect in a linear mixed effects model, we were able to partition the total variance (σ^2_{TOT}) into a between-pair (or between-person, σ^2_{BP}) and within-pair component of variance. The within-pair variance derived from the first split-sample Sub-study 1 corresponds to the laboratory variability. The within-pair component of variance derived from the within-visit reliability Sub-study 2 , in which duplicate samples were obtained from participants on the same day, corresponds to an estimate of variation due to blood collection, processing and laboratory analysis (σ^2_e). In contrast, the within-pair component of variance derived from the between-visit reliability Sub-study 3, in which duplicate samples were obtained from participants at two separate visits, corresponds to an estimate of the within-person (biologic) variation over time plus method variation ($\sigma^2_{WP} + \sigma^2_e$). The proportion of the total variance attributable to between-person variability, or reliability coefficient (R = $\sigma^2_{BP}/\sigma^2_{TOT}$) can be interpreted as the correlation between paired measurements. The following benchmarks were used for characterization of the adequacy of reliability [15]: slight reliability, 0-0.2; fair reliability, 0.21-0.4; moderate reliability, 0.41-0.6; substantial reliability, 0.61-0.8; almost perfect reliability, 0.81-1.0. Based on our sample sizes of 112 and 55 for the two sub-studies, the 95% confidence interval assuming a moderate reliability of 0.60 will have lower limits

of 0.48 and 0.44, respectively. The coefficient of variation (CV) is defined as the square-root of the within-pair component of variance divided by the mean of the paired observations multiplied by 100. CV values greater than 10% are generally considered as cause for concern.

Ideally we would have assayed hsTNT levels at the time of specimen collection and then re-analyzed the samples at pre-specified time intervals to evaluate rates of sample degradation. While this is not possible, there are alternative methods that could suggest whether the samples have substantially degraded. For example, the ARIC Carotid MRI study participants contributed specimens over the course of three years during the Visit 4 examination. Since the order of the examination visit was selected at random participant characteristics no not systematically differ by study month it is possible to assess the analyte concentrations by month and analyze the association between times since specimen collection. A roughly flat slope would suggest little degradation, whereas a decreasing slope would suggest sample decay. Similarly, we will plot the percent of samples below the level of detection as an index of degradation through time.

Limitations: This study will utilize assays stored since ARIC's Visit 4 examination; hence we expect some degradation. This may result in measured values below the lower limit of detection for some specimens. This is especially so as the original value in individuals without heart disease is expected to be low, which will introduce some methodological challenges.

It is to be noted that the study sample for our between person variability is not same as laboratory/process variability. Hence, total variance would not be equal their sum of these variance component, however, given the samples were similar in attributes we can assume that this is so. These differences in the sample characteristics will also be explored.

7.a. Will the data be used for non-CVD analysis in this manuscript? No

b. NA

8.a. Will the DNA data be used in this manuscript? No

8.b. NA

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. No overlaps found.

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)?

None

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes, 2009.15

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.
      Agreed

References:

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