ARIC Manuscript Proposal # 1744

PC Reviewed: 1/11/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Does the association of biomarkers with incident cardiovascular disease vary depending on carotid IMT level

b. Abbreviated Title (Length 26 characters): Biomarkers and CIMT

2. Writing Group:

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Others are welcome.

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

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3. **Timeline**: Analysis is to start as soon as approval is obtained. Manuscript is to be prepared as soon as analysis is available. We hope that the manuscript will be prepared within one year from approval of the analysis.

4. **Rationale**: Several biomarkers such as high sensitivity C-reactive protein (hs-CRP), lipoprotein associated phospholipase A2 (LpPLA2), high sensitivity troponin T (cTnT), NT-pro B-type natriuretic peptide, lipoprotein (a) (Lp(a) have been shown to be associated with prevalent and incident cardiovascular disease (CVD) [coronary heart disease (CHD) and stroke (ischemic/thrombotic)].

   Similarly, sub-clinical atherosclerosis measured using imaging techniques such as ultrasound [carotid initima media thickness (CIMT)] and CT scan (coronary artery calcium score) is also associated with incident CVD.

   There is a debate as to which is a better predictor of adverse cardiovascular events: an adverse biomarker profile or imaging based identification of sub-clinical atherosclerosis burden.

   It has been argued that a certain level of inflammation (as marked by the adverse biomarker profile) is key in destabilizing a plaque, leading to an acute event. On the other hand data from studies such as CHS/MESA (Cao JJ ***Circulation*. 2007;116:32-38**) have shown that an association of markers such as hs-CRP with incident CVD events can be found only when sub-clinical atherosclerosis is present at a certain level of severity.

   Identifying whether the strength of association of biomarkers or degree of sub-clinical atherosclerosis with incident events is affected by the level of the other may have significant clinical and research implications.

   It will be of interest to evaluate if the burden of sub-clinical atherosclerosis as defined on imaging such as ultrasound mediates the association between the biomarker and cardiovascular outcomes or if an inflammatory mileu in the absence of identifiable level of sub-clinical atherosclerosis is sufficient to lead to adverse cardiovascular events. It will also be of interest to study the interaction between adverse levels of the biomarkers and burden of sub-clinical atherosclerosis with adverse events. It is likely that the association is not linear, i.e. at lesser degree of sub-clinical atherosclerosis; the association of markers with events is weaker than when there is increased sub-clinical atherosclerosis.

ARIC visit 4 has measured/ is measuring several of these biomarkers. Between ARIC visit 3 and visit 4 CIMT was measured in the ARIC participants.
This proposal aims to study the associations of biomarkers and CIMT with incident events after stratifying for the other variable and doing a formal interaction test

5. Main Hypothesis/Study Questions:

Hypothesis 1: The strength of association between biomarkers (described in the past to have association with incident CVD) and cardiovascular disease will be significantly weaker in individuals with a lesser burden of sub-clinical atherosclerosis on a carotid ultrasound than those with an increased burden. The association will be strongest in those with the greatest carotid IMT levels.
Hypothesis 2: The strength of association between CIMT/ plaque (described in the past to have association with incident CVD) and cardiovascular disease will be significantly weaker in individuals with "normal" biomarkers values than those with "abnormal" biomarker values. The association will be strongest in those with the greatest biomarker values.

Study Questions:
a. To determine if the association between the biomarkers and incident CVD events are modified by the level of sub-clinical atherosclerosis on a carotid ultrasound
b. To determine if the association between the CIMT and incident CVD events are modified by biomarker levels

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).

Inclusion criteria: Individuals with CIMT/ plaque evaluation in either visit 3 or visit 4 of ARIC will be eligible
Exclusion criteria: Standard ARIC exclusions will apply
Individuals with missing biomarker and covariate data will be excluded
Biomarkers of interest:

1. hs-CRP
2. LpPLA2
3. NT-proBNP
4. high sensitivity troponin T
5. Lipoprotein (a)
6. cystatin c
7. urine albumin to creatinine ratio

Carotid initima media thickness:

Visit 4 CIMT in those available and visit 3 CIMT in others will be used. Since visit 3 CIMT will be at a time point that is not congruent to the biomarker analysis we will need to account for this during the analysis
Mean of the CCA-IMT will be used as the IMT variable
Briefly, we will categorize CIMT stratified by sex and visit as $<25^{th}$ percentile, 25^{th}-75^{th} percentile and $>75^{th}$ percentile and adjust for the visit in the analysis
Presence or absence of plaque will be recorded as well.
Presence of plaque and CIMT $>75^{th}$ percentile will be considered to be evidence of significant burden of sub-clinical atherosclerosis. Absence of plaque + C-IMT $<25^{th}$ percentile will be considered as no significant sub-clinical atherosclerosis (i.e. least burden). All others will be considered to have evidence of mild sub-clinical atherosclerosis.

End points to be assessed:

1. Hard CHD ((fatal CHD, definite probable MI)
2. Stroke (ischemic/ thrombotic stroke)
3. Hard CVD (Hard CHD + stroke)

Analysis plan:

1. Cox proportional hazards models will be developed for each biomarker of interest (after identifying and performing necessary transformations as needed) to describe the hazard ratio for the various incident events. Both continuous and categorical analyses will be pursued. Model one will adjust for age, race and sex while model 2 in the CHD analysis will adjust for ARIC coronary risk score at visit 4. For stroke analysis, model 1 will be the same while model 2 will adjust for the ARIC stroke risk score at visit 4. For CVD analysis, model 1 will be the same while model 2 will adjust for component variables of both ACRS and the ARIC stroke risk score
2. Then we will stratify the individuals based on their CIMT and plaque presence as described above into those with minimal and those with significant sub-clinical atherosclerosis. Then we will re run the Cox models to evaluate the hazard ratios for the biomarker based on the burden (i.e. minimal to significant) of sub-clinical atherosclerosis and for sub-clinical atherosclerosis by levels of biomarker. When possible a 3x2 table as below will be constructed. When clear categories of biomarkers are not available, we will use tertiles for the analyses and/or evaluate the marker as a continuous variable

High Biomarker + significant sub-clinical Athero	Low Biomarker + significant sub-clinical Athero
High biomarker + Mild sub-clinical athero	Low biomarker +Mild sub-clinical athero
High biomarker + NO sub-	Low biomarker + NO sub-

clinical athero	clinical athero

3. Interactions between the biomarker and sub-clinical atherosclerosis will be evaluated (Additive and multiplicative by examining relative risks for each biomarker/ sub-clinical atherosclerosis alone and in combination as opposed to when neither is present). We will also test for statistical significance. Finally, if there is an interaction, we will examine the interaction stratifying by CHD and stroke risk (i.e. interactions in the low/ intermediate and high risk groups)
4. Kaplan Meier curves will be created

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 ___ 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

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
____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)?

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __x__ Yes _ __ No

ARIC Ancillary Study #2008.10, "Measurement of NT-pro-BNP and troponin T at visit 4 for the full ARIC cohort"
ARIC Ancillary Study "Measurement of hsCRP"
ARIC Ancillary Study "Measurement of cystatin C"
ARIC Ancillary Study #2009.06"Measurement of LpPLA2"
ARIC Ancillary Study # 2010.12 "Measurement of Lpa"

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* __2008.10, 2009.06, 2010.12_____)

___ 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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