ARIC Manuscript Proposal # 3019

PC Reviewed: 7/11/17       Status: _____       Priority: 2
SC Reviewed: _________       Status: _____       Priority: ____

1.a. Full Title:

Carotid Intima-Media Thickness, Plaque information and the prediction of 25 year cardiovascular risk in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters):

CIMT, plaque and CVD prediction

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. _____ [please confirm with your initials electronically or in writing]

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline:

The analysis will start immediately after approval with a plan to publish after analysis is complete (~1 year)

4. Rationale:

We have shown in the past that the addition of C-IMT/plaque information improves the prediction of coronary heart disease (CHD) risk in the ARIC study (Nambi V JACC 2010) which lead to its incorporation in the risk prediction guidelines (Goff et al). Since the publication of this analysis a newer CVD risk prediction score (pooled cohort risk equation or PCE) has been adopted for the estimation and prediction of 10-year cardiovascular disease (CVD) (CHD + ischemic stroke) risk. Furthermore, the recommendation for statin therapy has been expanded such that anyone with a 10 year estimated risk >5% could be candidates (based on risk-benefit estimation by the physician after discussion with the patient) for statin therapy. While coronary calcium score was suggested as a possible additional tool to consider for risk prediction in individuals with a 10-year CVD risk >2.5% -<5%, C-IMT was not endorsed. On the other hand, the use of plaque information in risk stratification was not considered and no recommendation provided.

Given the expanded indications for statins the role for additional risk stratification tools have now evolved to a) down grading risk and hence de-escalating therapy, b) identifying higher risk individuals in the lower ends of the risk spectrum, and c) providing additional context for the patient-physician risk discussion.

Additionally, heart failure (HF) is soon to become the leading CVD. The incremental value of C-IMT/plaque in prediction of HF risk (10 year or longer) has not been adequately explored. Finally atrial fibrillation (Afib) shares the “common soil” of risk factors with HF and atherosclerotic CVD and the association of CIMT/plaque with Afib could be additionally explored as well.

Given that in ARIC we now have almost 25 years of follow up, understanding and studying the value of CIMT and plaque information in the prediction of longer term CVD risk will be of value and therefore we propose to do the same. Furthermore in the past we just considered the addition of plaque information as present or absent. A plaque score based on number of segments with plaque can be evaluated as well and we will do the same in this analysis as well.

5. Main Hypothesis/Study Questions:
a. CIMT and plaque information will improve long term (~25 year) atherosclerotic CVD risk prediction in the ARIC study
b. CIMT and plaque information will improve HF risk prediction (10 year and 25 year) in the ARIC study
c. CIMT and plaque information will improve Afib risk prediction (10 year and 25 year) in the ARIC study

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:

ARIC visit 1 will serve as the baseline for this analysis.

Inclusion/Exclusion:

From the 15,792 individuals at the baseline ARIC visit we will exclude individuals

- missing information on prevalent CVD data
- missing CIMT or plaque data
- missing information on traditional CHD risk factors (TRF) including blood pressure information (including use of medications), tobacco use, lipid information (total cholesterol, HDL-c) and diabetes information for the CVD analysis and additional factors used in the HF prediction score for the HF analysis
- races other than black or white, and black participants from the Minnesota or Washington field center.
- subjects with prevalent CHD or prevalent stroke (ischemic or hemorrhagic stroke) will be excluded for the CVD analysis

For the HF analysis, individuals with prevalent HF will be excluded

For the Afib analysis, individuals with prevalent Afib will be excluded and similarly those who do not have variables for the estimation of Afib risk (age, race, height, smoking status, systolic blood pressure, hypertension medication use, precordial murmur, left ventricular hypertrophy, left atrial enlargement, diabetes, coronary heart disease, and heart failure) will be excluded

Outcome:

The outcome of interest for the CVD analysis will include incident CHD (definite or probable MI, CHD death or revascularization) and ischemic stroke. For the HF analysis, incident HF hospitalization will be the outcome of interest. For Afib, incident Afib will be the outcome of interest. For the combined analysis CVD+HF+Afib will be the outcome of interest.

Summary of Data Analysis:
Using the TRF the PCE will be estimated for the 10 year risk of CVD and CIMT/plaque information will be added to evaluate the additional value of CIMT/plaque for 10 year prediction of CVD risk. The beta coefficients for PCE will be estimated in ARIC and used in order to optimize the baseline model for optimal performance. Then using the variables used to derive the PCE, a 25 year risk will be obtained and CIMT/plaque information will be added to evaluate improvement in estimated risk.

Mean CIMT of the common carotid artery and maximum CIMT of the common carotid artery will be considered. CIMT will be classified as sex-specific <25th percentile, 25th-75th percentile or >75th percentile. Plaque will be considered as present/absent. Additionally, a plaque score- number of segments with plaque normalized to number of segments assessable will be evaluated.

Using Cox proportional hazards, several predictive models will be considered: 1) PCE plus (sex-specific) CIMT, categorized as <25th percentile, 25th to 75th percentile, and >75th percentile; 2) PCE plus carotid plaque; and 3) PCE plus CIMT (sex-specific and categorized as previously stated) plus plaque.

Categories of PCE considered will include <5%, 5-7.5% and >7.5% for the 10-year risk estimation and <12.5%, 12.5-15% and >=15% for the-25 year estimated CVD risk.

The area under the receiver-operating characteristic curve (AUC) will then be evaluated for a 25-year risk using methods that account for censoring for each of the models to describe the model predictivity (Nambi et al., 2010). Bootstrapping will then be performed to obtain confidence intervals (CI) for the differences in adjusted AUC between the models which will be adjusted for optimism.

To ensure proper model calibration, a goodness-of-fit of the observed and expected number of events within estimated risk groups using the Grønnesby-Borgan statistic will be used (Grønnesby et al., 1996).

We will then calculate the net reclassification index (NRI), which examines the net effect of adding a marker to the risk prediction scheme using a statistic described by (Pencina et al., 2010). A continuous NRI and NRI in the intermediate risk group will also be assessed.

For HF and Afib prediction similar analysis will be pursued except using the ARIC HF model and ARIC Afib model as the base model (Agarwal et al., 2012). In addition 10 year and 25 year improvement in risk will be pursued.

Finally for the “all CVD” (CHD + stroke + HF +Afib) analysis we will obtain a baseline model using factors used in the CVD and HF models and then add CIMT/plaque

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes   ____ 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  ____ 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.cscucc.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? ____ Yes  _x___ No
11.b. If yes, is the proposal
____ A. primarily the result of an ancillary study (list number*__________)
____ 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.cscucc.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
cacess.nih.gov/submit_process_journals.htm shows you which journals automatically upload
tables to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be
submitted by the Coordinating Center to CMS for informational purposes prior to publica-
tion. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I
will be using CMS data in my manuscript ____ Yes __X__ No.

References

(2010). Carotid Intima-Media Thickness and Presence or Absence of Plaque Improves Pre-
diction of Coronary Heart Disease Risk. Journal of the American College of Cardiol-
ogy, 55(15), 1600-1607. doi:10.1016/j.jacc.2009.11.075
ACC/AHA Guideline on the Assessment of Cardiovascular Risk A Report of the American
College of Cardiology/American Heart Association Task Force on Practice Guidelines. Cir-
culation, 127(23). doi:10.1161/01.cir.0000437741.48606.98
analysis based on the risk score. Lifetime Data Analysis, 2(4), 315-328.
doi:10.1007/bf00127305
tion improvement calculations to measure usefulness of new biomarkers. Statistics in Medi-
cine, 30(1), 11-21. doi:10.1002/sim.4085
. . Heiss, G. (2012). Prediction of Incident Heart Failure in General Practice: The Atheroscle-
doi:10.1161/circheartfailure.111.964841