1. **Full Title:** The Impact of Vascular Age Measured by Carotid Intima-Media Thickness on Coronary Risk Prediction in the ARIC Cohort.

   **Abbreviated Title:** Vascular age and coronary risk.

2. **Writing Group:** (list individual with lead responsibility first):

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3. **Timeline:** 8/04-10/04

4. **Rationale:**

   Cardiovascular disease (CHD) remains the number one overall cause of death in the United States, accounting for 39% of more than 2.4 million deaths annually.\(^1\) A key challenge in preventing first coronary events is identifying “high-risk” individuals who would be candidates for intensive medical intervention. Cardiovascular risk assessment traditionally has been based on identification of categorical risk factors for coronary heart disease (CHD).\(^2,3\) The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III recommended Framingham global CHD risk assessment to help classify an individual’s risk of future coronary events. Framingham CHD risk estimates are influenced strongly by chronological age; however, the atherosclerotic burden of individuals with the same chronological age and similar risk profiles can differ substantially.\(^4\) An imaging test that quantifies atherosclerotic burden and that can be integrated with existing risk stratification paradigms could be a very useful clinical tool.

   Measurement of carotid intima-media thickness (CIMT) with B-mode ultrasound is a noninvasive and highly reproducible technique for detecting and quantifying subclinical atherosclerosis. Data from ARIC as well as several other large, prospective epidemiological and interventional studies have shown that CIMT accurately identifies prevalent and incident cardiovascular disease, independent of traditional risk factors.\(^5-8\) Although it is a well-validated research tool, CIMT is still not used widely
clinically, even though the American Heart Association Prevention Conference V concluded that it “can now be considered for further clarification of CHD risk assessment”.

Recent studies, including some from ARIC, have integrated CIMT measurements into CHD risk prediction models in an attempt to improve risk prediction. In one paper, a modified CHD global risk formula for diabetic individuals was derived. Similar analyses integrating CIMT with CHD risk models in non-diabetic populations have revealed only marginal improvement in predicting CHD risk, therefore paradigms including CIMT have not yet been developed for use in a more general populations. The purpose of this proposal is to test a novel strategy by which CIMT could be integrated into global CHD risk assessment models and potentially improve CHD risk prediction.

CIMT measurements can be used in conjunction with previously published CIMT norms from the ARIC population to determine “vascular age” (VA). VA represents atherosclerotic burden, which varies between individuals with the same chronological age, despite similar CHD risk profiles. Thus, population-based risk estimates can be modified by this direct assessment of an individual’s personal atherosclerotic burden. In a feasibility study, we used CIMT values to determine VA in a group of patients referred for CIMT measurement to assist with clinical risk prediction. VA was determined by linear regression modeling using published nomograms of CIMT percentiles (5th, 10th, 25th, 50th, 75th, 90th, and 95th) according to chronological age, sex, and race. In this group, we substituted VA for chronological age in the Framingham CHD risk model. As expected, when VA replaced chronological age in the Framingham CHD risk model for this population, estimated CHD risk was altered substantially. Of 14 subjects initially at intermediate risk, 5 (36.2%) were re-classified as higher risk and 2 (14.0%) were re-classified as lower risk. The accuracy of the modified risk estimates could not be determined, however, as outcome data were unavailable.

This proposal, though similar to previous studies in its goal of improving CHD risk prediction in a general population with CIMT, differs enough to warrant further discussion and study. The limitations of the aforementioned studies should first be addressed. The paper by Chambless et al included high-risk subjects from the ARIC cohort with prevalent CHD or CHD risk equivalents, as defined by recent guidelines, total cardiovascular disease prevalence (including CHD, cerebrovascular disease, peripheral vascular disease, and diabetes) ranged from 9-12%. Additional risk stratification and imaging are not recommended for these patients. Their models may therefore have underestimated the true benefit of incorporating CIMT in a risk prediction paradigm. Despite this limitation, however, CIMT still improved the model, at least as well as age, which is known to be highly associated with incident CHD. We plan to restrict our analyses to intermediate-risk subjects and to integrate CIMT and age into a unified variable in order to augment the utility of the Framingham risk score, which is recommended by NCEP ATP III, is accurate in the ARIC cohort, and is already widely utilized clinically. In the Rotterdam Study, del Sol et al similarly included high-risk subjects in the development of a risk prediction model. Specifically, 37% of the subjects with incident myocardial infarction and 34% with incident strokes had either a previous MI or stroke, and 13-14% of the subjects had diabetes. Further, their risk prediction strategy involved extensive data manipulation and modeling. Finally, receiver operating characteristic (ROC) curve analysis was used in both studies. These analyses average changes over time and may not detect significant temporal changes, if present. Other approaches may therefore be more sensitive in detecting differences in risk prediction.

We plan to restrict analysis to intermediate-risk patients, defined as those with a 10-20% projected, 10-year risk by traditional Framingham risk assessment, and then alternatively as those with 6-20% 10-year Framingham risk with presence of family history of premature CHD, as recommended by the 34th Bethesda Conference. Among this population, we then plan to test a more clinically robust approach for CHD risk evaluation by integrating CIMT with age into the traditional Framingham risk calculation. In doing so, we ultimately aim to improve CHD prediction while maintaining the relative simplicity and clinical practicality of the traditional Framingham model.
5. Main Study Questions:
   a. Does VA substituted for chronological age in the Framingham global CHD risk model significantly change risk prediction among members of the ARIC cohort?
   b. Are a significant number of individuals re-classified into a different-risk group based on the change in age type used?
   c. Does VA substituted for chronological age in the Framingham global CHD risk model better predict CHD outcomes in the ARIC study population?
   d. Are there subsets of the study population in which VA assessment is better than Framingham global CHD assessment?

6. Data (variables, time window, source, inclusions/exclusions):
   a. Inclusions: ARIC Cohort Component participants with full set of CIMT measurements
   b. Exclusions: Subjects with diabetes, cardiovascular disease, peripheral vascular disease, cerebrovascular disease
   c. Time window: Time from initial CIMT assessments to final exams in 1998
   d. Independent variables: Chronological age, vascular age (see derivation below), family history, sex, total cholesterol, HDL cholesterol, smoking status, systolic blood pressure, concurrent antihypertensive therapy.

   Vascular age for each participant will be generated as follows. Linear and non-linear regression models will be constructed for each of the CIMT percentile functions for each carotid arterial segment (N=6, left and right common, bifurcation, and internal carotid arteries), by sex (male and female), race (white and black), and age (5-year increments from 45-65 years old). Composite CIMT values will be used to determine VA, defined as the age at which the composite CIMT value for an individual of a given race and sex would represent the median value (50th percentile) in the ARIC study. Specifically, the linear 50th percentile function by chronological age, sex, and race will be used to project the age of each subject based on their composite CIMT value. If each of a given subject’s segmental CIMT values were at the 50th percentile for their chronological age, sex, and race, then their composite CIMT would be at the 50th percentile and their VA would be equal to their chronological age. For example, a 45-year black female with a composite CIMT of 0.593 mm would have a CIMT percentile of 50% and a VA of 45 years; however, a 45-year black female with a composite CIMT of 0.678 mm would have a CIMT percentile of 71% and a VA of 55 years, representing the age at which a composite CIMT value of 0.678 mm represents the 50th percentile.

   e. Dependent variables: Framingham CHD risk scores; incidence of “hard” CHD and cerebrovascular disease events (fatal myocardial infarction, sudden cardiac death, fatal stroke); and incidence of “soft” events (nonfatal MI and stroke, hospitalizations for angina and transient ischemic attacks, revascularizations, etc.)
   f. Potential covariates: race, geographic location, family history of CHD, body mass index, total-to HDL-cholesterol ratio, use of cholesterol-lowering, anti-platelet, or other cardiac medications (i.e. statins, aspirin, beta-blockers), others.
   g. Analyses:
      1. General
         a. Overall and race- and sex-specific effects will be examined.
         b. Descriptives in means and proportions with standard deviations.
         c. Separate and combined analyses for incident “hard” and “soft” events (detailed above in 6e) for questions 5c-d.
         d. Cases = subjects with incident events; controls = subjects without incident events
      2. Specific
a. Question 5a: Distributional tests to assess for differences in Framingham risk scores generated using chronological compared to vascular age.

b. Question 5b: Tests for differences in proportions to assess change in Framingham risk classification (see schemes below) using vascular vs. chronological age.
   i. Scheme 1: <10% = low risk; 10-20% = intermediate risk; >20% = high risk
   ii. Scheme 2: <6% = low risk; 6-20% = intermediate risk; >20% = high risk

c. Question 5c:
   i. Appropriate tests of distributions and of differences in proportions using exact statistical procedures will compare vascular and chronological ages among both cases and controls.
   ii. Among cases: Distributional and difference-in-proportion tests will be conducted to compare event rates among Framingham risk-group classifications (defined in 6g2b) derived using vascular vs. chronological age, and Poissant regression models will assess for correlations between respective scores and event rates.
   iii. Among cases: Multivariable logistic regression models will be created to generate hazard risk ratios for events using vascular-age vs. chronological-age-defined Framingham risk scores and risk-group classifications.
   iv. Among cases: Additional longitudinal assessments via general linear modeling using mixed methods will also be done to see if a temporal difference in risk prediction arises in using vascular versus chronological age. Additional modeling and comparison with ROC analyses may also be conducted.

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 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
   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://bios.unc.edu/units/csec/ARIC/stdy/studymem.html ____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)? References 10 and 11 listed below and addressed in the Rationale.

11. 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


