

**ARIC Manuscript Proposal #1213**

**PC Reviewed:**   2  /  13  /07

**Status:**   A  

**Priority:**   2  

**SC Reviewed:** \_\_\_\_\_

**Status:** \_\_\_\_\_

**Priority:** \_\_\_\_\_

**1.a. Full Title:** The clinical utility of carotid intimal medial thickness in reclassifying risk for incident CHD and stroke in the ARIC study

**b. Abbreviated Title (Length 26 characters):** IMT and reclassifying risk

**2. Writing Group:**

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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 to start as soon as approval obtained. Manuscript is to be prepared as soon as analysis is available. We hope that the analysis and manuscript preparation will take place within one year from approval of the proposal.

**4. Rationale:** Recently the “Screening for Heart Attack Prevention and Education (SHAPE) Task Force” report recommended that non-invasive screening with modalities such as carotid intima medial thickness or coronary calcium score with computerized tomography be performed for all asymptomatic men and women between ages 45 and 75 years and ages 55 and 75 years respectively. This recommendation has however been made without any strong data to support the same and is yet to be tested. Hence the question remains as to whether a) such a strategy can make significant differences in our ability to predict cardiovascular risk given that novel biomarkers have been shown repeatedly to add minimally to the risk predicting ability of traditional risk factors b) if this strategy is useful in an entire population or selected subsets of the population and c) the cost effectiveness of such a strategy.

In regards to the non-invasive screening modalities available, computerized tomography can provide a direct estimation of the calcium in the coronary arteries, but the expense and possible long term side effects of radiation exposure may make it a less than ideal preventive screening tool. On the other hand carotid ultrasonography is safe and relatively less expensive (Medicare reimbursement for a carotid ultrasound is approximately \$125).

In evaluating a new biomarker one needs to assess the incremental utility of a biomarker vis a vis its ability to improve discrimination (change in c-statistic /AUC curve), improve calibration (refine estimated risk) and improve risk classification (refine classification of patients thought to be intermediate, low or high risk based on “traditional” risk factors using Framingham/ARIC risk scores). Carotid intimal medial thickness (CIMT) has already been shown to be an independent marker for coronary artery disease in several studies including the ARIC study where it has been associated with a higher hazard rate ratio (Chambless LE et al Am J Epidemiol 1997; 146:483-94). Similarly, the CIMT has been shown to improve the AUC of a ROC modestly. However, CIMT has not been examined with respect to its ability improve risk classification as those suggested by the ATP III guidelines. If CIMT does indeed help with reclassification, it is likely to do so in the group with intermediate risk.

The ARIC study will be an excellent population sample to test the ability of IMT to reclassify risk. Further, for the CIMT to be a clinically applicable tool and of public health importance it would likely need to be more acceptable to clinicians and interpreted as normal, abnormal or intermediate and not as a continuous variable. It is also known from the ARIC study (Hunt KJ et al, Ultrasound in med and biology 2001; 27(3): 357-65) that plaque in the carotid artery predicts incident CHD above and beyond IMT. Hence for clinical simplicity, a thin IMT with no plaque could be considered the lowest risk group while the group with thick IMT and plaque the highest risk. Similarly clinicians do not routinely use traditional risk scores such as the Framingham and ARIC risk scores in day to day practice since it is difficult to remember and calculate while consulting on a

patient. Instead, they generally count the number of risk factors and try to assess the risk. Hence it will be of immense value not only to apply the CIMT data in ARIC as one may see its use clinically, i.e. classifying patients in the various categories of being normal, abnormal or intermediate (using both CIMT and plaque), but in addition examining whether it could improve risk assessment using a simplified approach such counting the number of traditional risk factors. If CIMT is able to reclassify risk among patients categorized in various risk groups by currently used risk scores it could add to our ability to manage patients at risk for atherosclerosis related vascular disease.

## **5. Main Hypothesis/Study Questions:**

**Hypothesis:** Carotid artery IMT when added to traditional risk scores such as the ARIC risk score (ARS) will improve classification of patients in the various risk groups

### **Questions to be addressed in a step wise manner;**

1. If one defines the results of cIMT as a positive, negative or intermediate test using gender specific cutpoints for the 25 and 75 percentile, and similarly age and gender specific cutpoints for the 25<sup>th</sup> and 75<sup>th</sup> percentile what are the hazards ratio of a positive and negative test? A positive test will be one with a c-IMT > 75<sup>th</sup> percentile and a negative test one with an IMT < 25<sup>th</sup> percentile. What is the positive and negative predictive value of CIMT when analyzed as an AUC of a ROC?
2. Does the presence of plaque on a carotid ultrasound add to the predictive ability of CIMT (i.e. change the AUC of the ROC when added to the model obtained by answering question 1)? For example, does lower quartile of IMT without plaque have a lower risk than lower quartile with plaque, same question for upper quartile with or without plaque?
3. Does cIMT alone, and in addition to plaque interpreted as a negative, intermediate or positive test change risk classification in intermediate risk patients defined as 10 to 20 % risk in ATP III or as 6 to 20% risk as per Greenland et al.

## **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).**

After excluding patients with CHD and stroke at baseline, all the other patients in the ARIC study on whom ARS can be calculated and have available IMTs will be eligible for the analysis. Please note that all IMT analysis presented below will be done using IMT as both a continuous variable and in groups based on percentile as specified above. In addition IMT will also be evaluated specific for a particular age group (age groups will be classified as 45-54 and 55-64 years of age) and gender also.

We would:

1. Define the ARIC risk score at baseline and classify as low (10 year CHD risk less than or equal to 5%), intermediate (10 year CHD risk 6-20%) and high (10 year CHD risk

>20%). Also classify patients as defined in ATP III, i.e. intermediate risk as a 10 year CHD risk of 10-20%

2. Describe the incident CHD events (cardiovascular death, myocardial infarction, and revascularization) and stroke in the different categories of ARS and then stratify them based on a) the IMT as a continuous variable and b) as follows

IMT			
	<25 <sup>th</sup> percentile	25 <sup>th</sup> -75 <sup>th</sup> percentile	>75 <sup>th</sup> percentile
Low ARS			
Intermediate ARS			
High ARS			

3. Using the Cox proportional hazards model- fit models with traditional ARIC risk factors and then add CIMT both as a continuous variable and as categories described above and examine its effect in reclassifying risk of incident cardiovascular events including cardiovascular death, myocardial infarction, stroke and coronary artery or cerebrovascular revascularization. Compute the AUC for the models with and without CIMT. Then to assess model calibration or how closely the predicted probabilities reflect actual risk the following strategies will be applied:

i. Calculate the actual observed risk and then compute the Hosmer-Lemeshow calibration statistic comparing the observed and predicted risk using participant's actual follow-up time, with 10 categories based on 2% point increases in predicted risk ranging from less than 2% to 18% with and without CIMT. Also compute the statistic using decile categories of predicted probabilities. Clinical utility will be estimated by comparing predicted risk estimates based on models using ARS with and without CIMT and then using weighted *kappa* statistics to compare the predicted probabilities with and without CIMT. Group the predicted probabilities into 10 year risk categories of 0 to <6%, 6- <10%, 10%-<20% and 20% or greater. Generate a table as below to describe the same:

	10 year risk without CIMT		10 year risk with CIMT		total reclassified
	0 -<6%	6-<10%	10-<20%	>20%	
0 to <6%					
Total participants					
10 year risk					
6 to <10%					
Total participants					
10 year risk					
10 to <20%					
Total participants					
10 year risk					
>20%					
Total participants					
10 year risk					

In addition we will show percentages of people reclassified and their recomputed predicted risk.

ii. Another strategy that will be used to compare observed and predicted risk would be to use a Kaplan Meir curve (not modeling with risk factors) to get a 10 year observed risk estimation for the cells of the table. We can also obtain predicted risk using traditional risk factors. Following this we will obtain a 10 year predicted risk using the new risk score that has incorporated the C-IMT into it. We will then compare this to the 10 year observed risk based on the Kaplan Meir estimate. The problem with this strategy is that it may evidence the variability of the small samples.

4. Classify patients based on their IMT and presence of plaque on their carotid ultrasound in a table as follows

Plaque	IMT		
	<25 <sup>th</sup> percentile	25 <sup>th</sup> -75 <sup>th</sup> percentile	>75 <sup>th</sup> percentile
Yes			
No			

5. Evaluate if patients with IMT in the highest quartile (>75<sup>th</sup> percentile) with plaque have a significantly higher risk than patients in the other groups. Similarly evaluate if patients without plaque and IMT <25<sup>th</sup> percentile have the lowest risk.

6. Evaluate whether the addition of IMT, both as a continuous variable and as categories described above, and presence or absence of plaque will further reclassify the patient

7. Enumerate the number of traditional risk factors and then add CIMT (classify as abnormal (>75<sup>th</sup> percentile), normal (<25<sup>th</sup> percentile, no plaque) and intermediate (25<sup>th</sup> to 75<sup>th</sup> percentile or <25<sup>th</sup> percentile with plaque)) and evaluate the ability of the number of risk factors and IMT to predict risk

**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

(This file ICTDER02 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 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://www.csc.unc.edu/ARIC/search.php>**

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  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.csc.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.**