ARIC Manuscript proposal 1711

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1a. Full title: High-sensitivity C-reactive protein and family history and the classification of risk for coronary heart disease: The Atherosclerosis Risk in Communities Study

b. Abbreviated title: Validation of the Reynolds Risk Score

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. TP [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:** The Reynolds Risk Score has been proposed as an alternative risk assessment tool for the prediction of cardiovascular disease (CVD).\(^1\)\(^,\)\(^2\) The score builds on traditional risk prediction models by adding high sensitivity C-reactive protein (hsCRP) and family history of premature coronary heart disease. Compared to a model based on traditional risk factors alone the Reynolds Risk Score was associated with a small improvement in model discrimination (as measured by the c-statistic), and a modest improvement in the classification of risk (as measured by the net reclassification improvement). The authors suggested that application of the Reynolds Risk Score could allow more accurate targeting of lipid-lowering therapy. However, the Reynolds Risk Score was derived and validated in the Women’s Health and Physicians’ Health Studies, and it has not been evaluated in other cohorts.

In the ARIC study, the predictive capabilities of CRP and family history for incident coronary heart disease (CHD) have been examined separately, but not together. Folsom et al. found that 1 standard deviation higher CRP level was associated with a higher adjusted hazard ratio for CHD events, but a nonsignificant increase in the area under the receiver operating characteristic curve.\(^3\)\(^,\)\(^4\) Li et al. found that, even after adjusting for traditional risk factors and baseline carotid IMT, participants with a family history of premature CHD experienced an increased CHD event rate.\(^5\) Furthermore, these studies have not used contemporary statistical methodology in evaluating the value of a marker in risk prediction (i.e. net reclassification index, integrated discrimination, model calibration etc)

A previous proposal, #1485 by Nambi et al, was approved to evaluate the Reynolds Risk Score in African Americans. However, because hsCRP was first measured at exam 4 there were not enough events among African Americans for complete data analysis. Furthermore, the follow up at that time was only until 2005.

The following proposal is therefore focused on the utility of the Reynolds Risk Score among all ARIC participants (after discussion with Dr. Nambi we have decided to combine the analyses). The validation of the Reynolds score in the ARIC population will be important for several reasons: For example, the Reynolds Risk Score for Men was derived in physicians, and as a result may not apply to the general population. The ARIC cohort comprises a broad range of socio-demographic characteristics and may better represent patients to whom the score would be applied in everyday practice. Further, the study populations in the Physicians and Women’s Health Studies were predominantly white. A recent meta-analysis of hs-CRP levels showed that the levels vary significantly based on ethnicity.\(^6\) As a result, the cutoffs used in the Reynolds Risk Scores may not apply to African Americans. An additional issue is that in both the Women’s Health and Physician’s Health Studies blood pressure was not measured directly by study staff, but was rather ascertained by participant self-report of the blood pressure level. It is possible that relying on self-report may have diminished the association of blood pressure with incident CHD and thereby exaggerated the improvement in risk prediction when hsCRP and family history were added to the model. The ARIC study provides an ideal cohort in which to attempt to replicate the Reynolds Risk Score because all risk factors were measured directly.
5. Study questions/hypotheses:
   1. Does the Reynolds Risk Score improve prediction of incident CHD and CVD (CHD plus ischemic stroke) among participants in the ARIC study, compared to a model based on traditional risk factors (TRF) only as defined in the original publication of the Reynolds risk score?
      - Hypothesis: The Reynolds Risk Score will improve prediction of incident CHD and CVD.
   2. Does the addition of hsCRP and family history improve prediction of incident CHD when added to the ARIC Risk Score (i.e. best model in ARIC)?
      - Hypothesis: The Reynolds Risk Score will improve prediction of incident CHD compared to the ARIC Risk Score.
   3. If there is an improvement in risk prediction with the Reynolds Risk Score, is this driven primarily by the addition of family history, hsCRP or both?
      - Hypothesis: the improvement in risk prediction will be driven primarily by the addition of family history.
   4. Does the addition of known single-nucleotide polymorphisms (SNPs) associated with hsCRP levels to the model improve the prediction of CHD and CVD?
      - Hypothesis: the addition of SNPs for hsCRP will not substantially improve risk prediction.

6. Design/Analysis:
   Inclusion/exclusion criteria
   All participants with a complete family history measured at exam 2 (only the variable related to a family history of premature CHD would be used) and hsCRP measured at exam 4 will be eligible. Participants with prevalent CVD before exam 4 will be excluded. We will also exclude participants with absent information about traditional risk factors.
   Additional variables needed are:
   Age, sex, systolic blood pressure, total and HDL cholesterol, tobacco use, and antihypertensive medication use.

   Primary outcome measure
   Incident coronary heart disease (myocardial infarction, CHD death, or coronary revascularization) and cardiovascular disease (CHD plus ischemic stroke) using the most recent event data.

   Data Analysis
   1. We request that the data analysis be performed at the coordinating center.
   2. To analyze question #1 individuals with diabetes (defined as fasting glucose >126 mg/dL or on anti-diabetes medications) will be excluded, because they were excluded from the derivation of the Reynolds Risk Score for men. The prediction models for men only in Ridker et al. will be used as the TRF model. Model 1 will include age, sex, systolic blood pressure, total and HDL cholesterol, and tobacco use. Model 2 will include the variables from model 1, plus hsCRP (the best transformation/ fit of hs-CRP with outcomes will be determined and then used in this model) and family history of premature CHD. Models
1 and 2 will be used to estimate 10-year risk of CHD and CVD. Risk categories will be defined as 0-5%, >5-10%, >10-20%, and >20%.

a. We will evaluate model discrimination by comparing the area under the ROC curve using models 1 and 2 and furnish 95% confidence intervals.
b. We will calculate the Groonsby Borgan chi-square statistic to determine model calibration.
c. The net reclassification improvement (NRI) will be calculated. Briefly, cross tabulations of estimated risk using model 1 and model 2 will be performed to determine the proportion of participants correctly and incorrectly reclassified to higher and lower risk categories. In Ridker et al. the NRI was sensitive to the number of risk categories, and diminished with fewer categories. As a result, the NRI will be calculated a second time using 3 risk categories instead of 4 (0-5%, 5-<20%, ≥20%) so that only reclassification to the highest and lowest risk categories will be measured. Again, 95% confidence intervals will be furnished by bootstrapping.
d. The risk stratification capacity demonstrates the ability of a new risk marker to reclassify patients from intermediate risk to the more extreme risk categories. Ideally, the majority of individuals would be classified as high or low risk with the addition of a novel risk marker. The proportion of participants within each risk category, using the model with and without hsCRP and family history, will be compared.
e. All of the above will be repeated using CVD (CHD plus ischemic stroke) as the primary outcome.
f. Steps a-e will also be repeated after excluding participants on statins, and in African Americans only.

3. To address study question #2 (does the addition of hsCRP and family history improve risk prediction when added to the ARIC Risk Score?) the basic prediction model derived from ARIC participants by Chambless et al. for CHD and stroke will be used. This analysis will include both men and women. The basic ARIC prediction model differs from model 1 used to derive the Reynolds Risk Score because it includes antihypertensive medication use, whereas the Reynolds Risk Score does not include it. The ARIC risk score also includes diabetes, which is not included in the Reynolds Risk Score for Men, but is included in the score for women. Model 2 will include hsCRP (the best transformation/fit of hs-CRP with outcomes will be determined and then used in this model) and family history. The beta-coefficients will be derived from the ARIC cohort. The ARIC Risk Scores for both CHD and stroke will be used.
a. Discrimination, calibration, NRI and risk stratification will be assessed using models 1 and 2, as above. The analysis will be performed with and without participants with diabetes.
b. To determine the relative contribution of family history and hsCRP (question #3) the above analyses will also be done in which hsCRP and family history will be added to the model separately.
c. As a secondary analysis a-d in #2 will be repeated with the addition of African Americans.
4. To address question #4 (will the addition of SNPs associated with hsCRP levels to the model improve risk prediction?) we will add the SNPs that have been shown to be associated with hsCRP levels in the CHARGE analyses. The premise behind the question is that if an individual’s CRP reflects the presence of particular SNPs, rather than subclinical disease, then the relationship between the CRP level and CHD may be diminished. By adjusting for the presence of SNPs that predict CRP level (but not CHD events) then the relationship between CRP and CHD events may be altered. We will examine whether the hazard ratio associated with hsCRP level remains the same after the addition of the SNPs to the model. If the hazard ratio changes (increase or decrease) then we will use the revised ratio to calculate the net reclassification improvement, AUC, goodness of model fit and compare our results to that achieved when hsCRP level alone was included. Given that many SNPs differ based on race/ethnicity the analysis may only be feasible in white participants.

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

8a. **Will DNA data be used in this manuscript?** Yes
8b. **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

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 (other than proposal 1485, and we have agreed to collaborate on one unified proposal).

11a. **Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?** Yes
11b. **If yes, is the proposal primarily the result of an ancillary study?** Yes, study number 2006.16

References

