1a. **Full title:** Comparison of the Framingham and Reynolds Risk Scores and the Pooled Cohort Equations: the Atherosclerosis Risk and Communities Study

b. **Abbreviated title:** Comparison of multiple risk scores in ARIC

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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 3 months from approval of the analysis.

4. **Rationale:** The American College of Cardiology/American Heart Association recently introduced the Pooled Cohort Equations in the new Guideline on the Assessment of Cardiovascular Risk. The Pooled Cohort Equations are novel multivariable risk equations that were developed for the prediction of 10-year risk of an atherosclerotic cardiovascular disease (ASCVD) event. The equations were developed to address known limitations of the Framingham Risk Score (FRS) used in the Adult Treatment Panel Guidelines (III) – that the FRS was derived in a primarily white cohort, and that the primary outcome was restricted to coronary events. The Pooled Cohort Equations were derived using combined data from ARIC, CHS, and CARDIA, and therefore included a substantial proportion of African-American adults. ASCVD was defined as non-fatal myocardial infarction and coronary heart disease (CHD) death, as well as nonfatal or fatal stroke.

In the simultaneously released ACC/AHA Guideline on the Treatment of Blood Cholesterol a new paradigm to guide decisions about statin therapy was also developed. Under the older Adult Treatment Panel guidelines statin therapy was recommended for all patients whose estimated 10-year FRS was >20% for a CHD event. For lower risk patients the decision was based on their FRS and their baseline LDL level. Under the new guidelines, statin therapy is recommended for all adults whose 10-year ASCVD risk is above 7.5%, as long as the baseline LDL is above 70 mg/dl. If, after a quantitative risk assessment the treatment decision is still uncertain, the guidelines state that it is reasonable to measure markers of subclinical disease such as high-sensitivity C-reactive protein (hsCRP) and family history (FH). However, it is not known to what extent the use of additional risk markers might improve risk prediction beyond the Pooled Cohort Equations.

Health care providers also have other prediction models from which to choose when performing risk assessment. The Reynolds Risk Score (RRS) builds on traditional risk prediction models by adding high sensitivity C-reactive protein (hsCRP) and family history of premature coronary heart disease. Unlike the FRS or PCE, the primary outcome for the RRS includes revascularization, as well as MI and stroke. Compared to a model based on traditional risk factors 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, whose participants were predominantly Caucasian. The RRS for women was validated in the Women’s Health Initiative, but showed a similarly modest improvement in risk assessment. To our knowledge, the RRS has never been validated in another population of men.

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. 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. However, these studies have not used contemporary statistical
methodology in evaluating the value of a marker in risk prediction (i.e. net reclassification index, model calibration etc)

We had previously drafted a manuscript (MS1711) looking at whether the addition of hsCRP and FH improved risk prediction when added to a model based on traditional risk factors. We showed that while both hsCRP and FH provided an incremental improvement in discrimination, there was not a statistically significant improvement in the classification of risk. We used a baseline model derived within ARIC rather than the published Reynolds Risk Score, because we felt that would most objectively assess the value of adding hsCRP and FH to traditional risk factors. Our manuscript had several novel features: it was the first study of hsCRP with FH in a biracial cohort of men and women, and it was the first study to examine the individual contributions of hsCRP and FH. However, we submitted the manuscript to Circulation, Journal of the American College of Cardiology and European Heart Journal, without success. Reviewers commented that a comparison of the published Framingham and Reynolds Risk Scores would be of greater interest.

The following proposal is therefore a revision of our original proposal, and will include a direct comparison of the ARIC Risk Score, Reynolds Risk Scores, Framingham risk score (for CHD) and the Pooled Cohort Equations. We will not include the FRS for CVD (which also includes PAD, heart failure, hemorrhagic stroke, transient ischemic attack, angina and revascularization) as it has not been used in clinical practice guidelines. We will compare model fit, discrimination, calibration, and the distribution of risk achieved with the models. We will compare the proportion of participants who would qualify for statin therapy using each risk score, stratified by event status. Finally, we will examine whether risk prediction with the Pooled Cohort Equations improves when hsCRP and FH are added to the models.

5. Study questions/hypotheses:

1. How does the distribution of risk compare in the FRS (for CHD), the ARIC risk score, RRS and Pooled Cohort Equations (PCE)?
   - Hypothesis: The mean estimated 10-yr risk will be lower with the RRS, compared to the FRS and the Pooled Cohort Equations. More participants will be classified in the lowest risk category (10-year risk of ASCVD <5%) with the RRS than the FRS and PCE.

2. How does model fit and calibration compare between the ARIC risk score, FRS, RRS and PCE?
   - Hypothesis: compared to the ARIC risk score, the FRS, RRS and PCE will overestimate risk. However, the PCE will be the best calibrated, compared to the FRS and RRS.

3. What proportion of ARIC participants qualify for statin therapy using the FRS, RRS and PCE? (for this question we will only use risk scores that are commonly used in the clinical setting and have been recommended in practice guidelines, and so will not be including the ARIC risk score)
   - Hypothesis: substantially more ARIC participants will qualify for statin therapy using the PCE, compared to the FRS and RRS. The increase in participants who qualify for statin therapy also includes a greater number of adults who develop incident ASCVD.

4. Does the addition of hsCRP and family history improve prediction of incident ASCVD when added to the PCE?
   - Hypothesis: The Reynolds Risk Score will not significantly improve prediction of incident ASCVD.
5. Does the addition of revascularization to the primary outcome change model calibration, discrimination or reclassification?
   - Hypothesis: Model calibration, discrimination and reclassification for the RRS will improve with the addition of revascularization, but will not improve with the other risk models.

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, and those who were taking statins or other lipid-lowering therapy at the time of visit 4.
   Additional variables needed are: age, sex, systolic blood pressure, total and HDL cholesterol, tobacco use, antihypertensive medication use and diabetes status. The RRS for men excludes adults with diabetes. However, the RRS for women includes hemoglobin A1c for women with diabetes.

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

   Secondary outcome measure
   The primary outcome measure plus incident coronary revascularization

   Data Analysis
   1. We request that the data analysis be performed at Brigham and Women’s Hospital.
   2. To analyze question #1 we will use the published models for the FRS, RRS and PCE. The ARIC risk score will be derived using the subset of ARIC participants who qualify for the current analyses. We will use the same variables used in the PCE (age, sex, SBP, total and HDL cholesterol, smoking status, use of antihypertensive medications, presence or absence of diabetes).
      A. Framingham risk score for CHD: To evaluate the distribution of risk, model fit, discrimination and calibration we will use the following risk categories for the FRS: 0-5%, >5-10%, >10-20%, >20%. These are the categories used in the Adult Treatment Panel Guidelines. The primary outcome will be CHD events (fatal and nonfatal MI).
      B. ARIC, RRS and PCE: Because these scores are used for the prediction of atherosclerotic CVD we will use the categories outlined in the newest guidelines: 0-5%, >5-7.5%, >7.5%. The published RRS also includes revascularization in the primary outcome, and so this will require recalculation, so that the outcome is the same as that for the PCE and ARIC risk score.
         a. We will evaluate model discrimination by comparing the area under the ROC curve using all 3 models.
         b. We will calculate the Groovesby Borgan chi-square statistic to determine model calibration.
         c. We will calculate the Bayes Information Criterion to assess model fit.
3. To address study question #3 (what proportion of ARIC participants qualify for statins using the 3 scores?) we will use the cutoffs recommended in the ATP Guidelines and the most recent ACC/AHA guidelines.
   a. When using the FRS to assess statin eligibility we will use the following cutoffs: anyone with a FRS>20%, FRS 10-20% and LDL >100 mg/dl or FRS <10% but LDL >190 mg/dl.
   b. When using the RRS or PCE then anyone with a 10-year estimated risk >7.5% will be considered eligible for statin therapy.
   c. We will stratify participants by their event status.

4. To address question #4 (does the addition of hsCRP and FH improve risk prediction when using the PCE as the baseline mode?)
   a. We will compare model discrimination with and without the addition of hsCRP, and then FH, using the AUC
   b. Calibration will be assessed using the Gronnesby-Borgan statistic.
   c. We will assess classification of risk using the NRI, but will report the NRI for events and nonevents separately. Briefly, cross tabulations of estimated risk using the PCE with and without hsCRP and FH will be performed to determine the proportion of participants correctly and incorrectly reclassified to higher and lower risk categories. Given a recent paper challenging the validity of the NRI combined for events and nonevents, we will calculate the NRI for events and non events separately. Ninety-five percent confidence intervals will be furnished by bootstrapping.

5. To address question #5 (does the addition of revascularization to the primary outcome change model calibration, discrimination, or reclassification) we will perform the analyses above with an expanded primary outcome of coronary revascularization (with PCI or CABG), fatal and nonfatal MI, fatal and nonfatal stroke.

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

8a. **Will DNA data be used in this manuscript?** No.

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


