1.a. Full Title: Risk stratification in African Americans using C-reactive protein – an analysis from the ARIC study

b. Abbreviated Title (Length 26 characters): Reynolds Risk Score and African Americans

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 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 method of cardiovascular risk stratification. This risk stratification tool uses family history of CHD and hsCRP levels in addition to traditional risk factors in estimating risk and has been shown to be an improved model when compared to a traditional Framingham risk score in both men and women. The description and validation of the Reynolds risk score was however in a predominantly White population enrolled in the Physicians Health Study (Ridker PM *Circulation.* 2008;118:2243-2251) and Women’s Health Study (Ridker PM *et al* *JAMA.* 2007;297:611-619) respectively. Therefore evaluating its utility in an African American population will be important, as it is likely to be applied to the entire population.

In the ARIC study, both CRP and family history have been shown to be associated with CHD risk. In fact, family history has been studied separately in Whites and in African Americans and has been shown to be associated with CHD risk in both. However, combined use of CRP and family history as in the Reynolds risk score has not been evaluated in the stratification of risk. Given that family history (Li R Genet Epidemiol. 2000 Mar;18(3):236-50) and CRP (Folsom AR Arch Intern Med 2006;166:1368-1373, Folsom AR Am Heart Journal 2002; 144:233) are associated with CHD risk in the ARIC study, one would hypothesize that the addition of these two variables would improve risk prediction but will need to be tested formally. The Reynolds risk score described in men was a modification of the traditionally used Framingham risk score. Although the Framingham risk score derived coefficients in the ARIC study, were similar/comparable to those derived from ARIC for ARIC White participants, they were significantly different for the African Americans (D’Agostino RB Sr *et al* *JAMA.* 2001 Jul 11;286(2):180-7). Therefore we would need to test if adding hs-CRP and family history of CHD will improve both a) the Framingham Risk prediction model and b) the ARIC risk prediction model in African Americans enrolled in ARIC to evaluate if the addition of hs-CRP and family history improves both the “clinically used” model and to determine the best fitting model.

Finally, the Reynolds risk score has been evaluated for both CHD and CVD (ischemic stroke + CHD) end points. Although the prediction models will be different for CHD and CVD, we will need to evaluate both these outcomes to fully define and compare the utility of the Reynolds Risk Score in African Americans.

5. **Main Hypothesis/Study Questions:**
a) Does the addition of CRP and family history (Reynolds risk score) improve the prediction of CHD risk in an African American population when compared to i) the ARIC risk score based on traditional CHD risk factors and ii) the Framingham risk score?  
b) Does the Reynolds risk score improve the prediction of CVD risk when compared to i) ARIC risk score and ii) Framingham risk score in an African American population?  
c) How well does the Reynolds risk score do in African Americans when compared to Whites 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).

We will request that the analysis be done by the co-ordinating center

The ARIC study collected information about family history of CHD in visit 2 and hsCRP was measured in visit 4.

1. After standard ARIC exclusions, African American participants in the ARIC study at visit 4 will be eligible
2. All subjects with prevalent cardiovascular disease (strokes, coronary heart disease) or on lipid lowering therapy (statins and/or other lipid lowering medications) at visit 4 will be excluded from the analysis. All individuals with absent family history at visit 2 will also be excluded. The number excluded will be reported.
3. Using traditional risk factors from visit 4 data we will describe predictors of incident CVD using a Cox proportional hazards model. Then hsCRP categorized as < 1mg/L, 1-3 mg/L and >3 mg/L will be added along with family history to the traditional risk factors and a Cox proportional hazard model will be again defined. The AUC, adjusted for optimism, will be described, and the increase in AUC conferred by the model with hsCRP and family history will be calculated. Incident events between visit 4 and until December 2005 will be used for the analysis. The analysis will be repeated using the Framingham risk score
4. Reclassification tables will then be developed using clinically meaningful risk categories (i.e. those which may relate to indications for intervention).
5. Model fit will be evaluated using the Groobsby Borgan goodness of fit test statistic
6. Based on the reclassification tables, net reclassification index (including the clinical NRI) will then be calculated. In describing the NRI the number of individuals who had incident events among those reclassified to a higher risk group, the number among those reclassified to a lower risk group and similarly the number of individuals who did not have events who were reclassified to a lower or higher risk group will be described
7. The above will be repeated for ischemic stroke and then for combined events (CVD). Although the model to predict stroke is different from that which predicts CHD, especially with respect to the coefficients (for example the contribution of
blood pressure towards stroke is more powerful than for CHD) we will examine
the CVD prediction using this model as this was done for the Reynolds risk score

8. Finally, to evaluate the differences in the performance of the Reynolds Risk Score
between Whites and African Americans we will describe the Reynolds risk score
in the Whites meeting the same inclusion criteria as described above and describe
the improvement in AUC (adjusted for optimism), the reclassification table, the
goodness of fit and the NRI and compare with that obtained for African
Americans. Further we will compare the Beta coefficients for the various factors
in the models between the African Americans and Whites and test if these are
significantly different using the method as discussed by D’Agostino et al (JAMA. 2001;286:180-187). Briefly, a test statistic will be calculated as the difference in
the coefficients between the African Americans and Whites for a factor divided
by the standard error of the difference in the coefficients.

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 ICTDER03 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

8.c. If yes, is the author aware that the participants with RES_DNA = ‘not for
profit’ restriction must be excluded if the data are used by a for profit group?
 ____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.cscc.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?  
   __x__ Yes  ____ No

11.b. If yes, is the proposal
   __  A. primarily the result of an ancillary study (list number* ___ 2006.16 _______)
   ___ 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.cscc.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.