1.a. Full Title: The prognostic utility of high-sensitivity C-reactive protein when discordant with atherogenic lipoproteins in a primary prevention bi-racial population: The Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): hsCRP and lipid measurements

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. RQ [please confirm with your initials electronically or in writing]

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Background:
In the past 2 decades, several studies have accumulated evidence that inflammation has an independent causal role in atherosclerotic cardiovascular disease (ASCVD)\(^1\). In secondary prevention population studies, a post-hoc analysis from the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) showed that reaching dual LDL-C and hsCRP targets was associated with decreased risk for recurrent ASVD compared to those who achieved LDL target alone\(^2\). More recently, the landmark trial, The Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS)\(^3\), showed that treatment with the anti-inflammatory drug Canakinumab reduced recurrent ASCVD independent of lipid lowering.

In primary prevention, high-sensitivity C-reactive protein (hsCRP) has been proposed as an additional risk assessment tool, although data has been somewhat conflicting\(^1,4\). The best evidence comes from the 2008 Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, which showed that individuals with LDL<130 mg/dL and hsCRP ≥2 mg/L benefited from high-intensity statin therapy compared to placebo. However, the prognostic utility of high-sensitivity C-reactive protein (hsCRP) when discordant with other atherogenic lipoproteins such as LDL-C, non-HDL-C, apolipoprotein B (apoB) and TC/HDL-C in primary prevention is unknown. Moreover, the role of hsCRP in individuals with an optimal lipid profile is not well understood. Understanding the additive prognostic value of hsCRP beyond cholesterol and lipoprotein measurements may help inform worldwide guidelines, which currently do not recommend using hsCRP for risk assessment or management.

Aims:
To identify the prognostic utility of hsCRP for incident atherosclerotic cardiovascular events when discordant with one or more lipid measurements in ASCVD-free individuals from ARIC.
**Study Design:**
We will examine the discordance in prospective associations between several lipid measurements and hsCRP, and cardiovascular events. The baseline for this analysis will be ARIC visit 4. This is the visit that apoB was measured at.

**Inclusions:** We will include all participants free of an ASCVD event who attended ARIC visit 4.

**Exclusions:** We will exclude participants who had prevalent CHD at baseline or who had an incident ASCVD event before visit 4, our baseline. We will exclude individuals with missing data for standard lipid profile and apoB, as well as missing hsCRP at baseline. We will exclude participants who neither white nor black race, as well as blacks from MN and MD sites due to small numbers.

**Exposures:** The exposure of interest will be LDL-C (estimated by our novel equation that uses an adjustable TG:VLDL-C ratio), non-HDL-C (calculated as TC minus HDL-C), the TC/HDL-C ratio, apolipoprotein B (apoB), HDL-C on one hand and hsCRP on the other hand. All these variables will be dichotomized by low (below), or high (at or above) using the following cutpoints:

1) the median values
2) JUPITER-like cutpoints: LDL-C: 130 mg/dL (ARIC’s percentile 57), and percentile-equivalent non-HDL-C: 160 mg/dL, apoB: 102 mg/dL, TC/HDL: 4.4, HDL-C 50 mg/dL and hsCRP: 2 mg/L
3) high-risk cutpoints: LDL-C: 100 mg/dL (ARIC’s percentile 21), non-HDL-C: 130 mg/dL, apoB: 80 mg/dL, TC/HDL: 3.1, HDL 50 mg/dL and hsCRP: 2 mg/L

**Outcomes:** The primary outcome will be atherosclerotic cardiovascular disease (ASCVD) events, defined as incident coronary heart disease (CHD), fatal CHD, and stroke occurring after Baseline Visit through December 31, 2016 (or most recent follow-up available). Incident ASCVD will be defined as definite or probable nonfatal myocardial infarction or fatal CHD, definite or probable stroke (defined as sudden or rapid onset of neurological symptoms that lasted for 24 hours or led to death in the absence of another cause). As secondary outcomes, we will include total mortality occurring after baseline visit through December 31, 2016 (or most recent follow-up available).

**Covariates:** Other covariates that will be further included in models are: age, sex, race/center, BMI (in kg/m²), systolic blood pressure (in mmHg), use of antihypertensive medications, log-triglycerides, log-HDL-C (in analyses without HDL-C), diabetes
mellitus (defined as fasting plasma glucose ≥126 mg/dl, or self-reported physician
diagnosis of diabetes or use of diabetes medications), smoking status (in pack-years),
physical activity, use of lipid-lowering medication.

Main Analyses:
1) we will identify the number of individuals with concordance/discordance between
hsCRP and lipid variables following the same categories:
   - Individuals with low hsCRP and high hsCRP
   versus
   - Individuals with low LDL-C vs. high LDL-C
   - Individuals with low dual cutpoints (LDL-C and non-HDL-C) vs. high (LDL-C
and non-HDL-C)
   - Individuals with low triple cutpoints (LDL-C and non-HDL-C and apoB) vs. high
   (LDL-C and non-HDL-C and apoB)
   - Individuals with low quadruple cutpoints (LDL-C and non-HDL-C and apoB
and TC/HDL-C) vs. high (LDL-C and non-HDL-C and apoB and TC/HDL-C)
   - Individuals with low quadruple cutpoints /high HDL vs. high quadruple
cutpoints /low HDL-C

2) we will construct Cox proportional hazard models to estimate hazard ratios (95%
confidence intervals) for each outcome (primary and secondary) using the following
models:
   -Model 1: adjusted by age, sex and race/center
   -Model 2: Model 1 + smoking status + BMI+ systolic blood pressure + treatment
   for hypertension + diabetes + statin use
   -Model 3: Model 2 + log-triglycerides
   -Model 4: Model 3 + log-HDL-C

Finally, we will stratify the analyses above mentioned by race, sex, diabetes, use of
statins, and ASCVD risk categories based on the Pooled Cohort Risk Equations.

Limitations:
- There is the likelihood for some residual confounding by other risk factors not
  included in these models.
- Interim initiation of lipid lowering medication likely will modify the association
  between lipid discordance and ASCVD events.
- We will not have serial apoB measurements over the follow-up time.
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 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
____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 ICTDER03 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.csecc.unc.edu/ARIC/search.php

____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)?

Similar ARIC Manuscripts:
2753 (Quispe) The clinical impact of TC/HDL-C discordance with LDL-C, non-
HDL-C and apoB: The Atherosclerosis Risk in Communities (ARIC) Study
Notes: this proposal looked at discordance between TC/HDL-C vs. LDL-C and non-
HDL-C using median cutpoints in the overall population. ApoB discordance was not
assessed. The baseline population for this proposal was ARIC 1st visit, whereas for the
current proposal we will use ARIC 4th (where apoB data is available).
11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  
   Yes [ ] No [x] 

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.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.

References


