ARIC Manuscript Proposal # 1428

PC Reviewed: 09/09/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Elevated high sensitivity C-reactive protein in low LDL-c groups in the Atherosclerosis Risk in Communities population.

b. Abbreviated Title (Length 26 characters): high hs-CRP in low LDL-c groups

2. Writing Group:
Eric Yang, MD
Vijay Nambi, MD
Salim Virani, MD
Eric Boerwinkle, PhD
Brad C. Astor, PhD
Thomas H. Mosley, PhD
Josef Coresh, MD, PhD
Lloyd Chambless, PhD
Christie M. Ballantyne, MD
Others are welcome.

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

First author: **Eric Yang**
Address: 6565 Fannin Street
STE B 160/MS-A601
Houston, TX 77030

Phone: 713-798-3738 Fax: 713-798-4121
E-mail: eyyang@bcm.tmc.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
Name: Christie M. Ballantyne
Address: 6565 Fannin Street
STE B 160/MS-A601
Houston, TX 77030

Phone: 713-790-5800 Fax: 713-798-7885
E-mail: cmb@bcm.tmc.edu

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 Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial was a placebo controlled trial designed to assess the effect of rosuvastatin 20 mg daily on cardiovascular outcomes in 18,000 otherwise healthy subjects with low LDL-c (< 130 mg/dL) and elevated hs-CRP (≥ 2.0 mg/L) compared to placebo. Cardiovascular outcomes were defined as cardiovascular death, ischemic stroke, myocardial infarction, unstable angina requiring hospitalization, and arterial revascularization. The study design for this multicenter double-blinded placebo-controlled randomized trial has been published, and the inclusion and exclusion criteria are readily available (1, 2). Specifically, men aged 50 years or older and women aged 60 years or older with no prevalent cardiovascular disease, with initial screening LDL-c < 130 mg/dL, with hs-CRP ≥ 2.0 mg/L, and on no prior lipid lowering agents were included into the study.

The study was terminated early in March 2008 due to overwhelming benefit on primary outcomes in the statin group (3). Importantly, JUPITER has identified a a population not previously targeted for primary prevention with statin therapy by the current Adult Treatment Panel III guidelines (4). However, the prevalence of people meeting these criteria in a general population is currently unknown. The risk of such individuals for cardiovascular events compared to individuals who would not qualify for JUPITER because of hs-CRP < 2.0 is also unknown. Such a comparison is not possible with the JUPITER population due to its trial design. There are many individuals who have LDL-c less than 130 mg/dl who do not have CRP greater than 2 but who have other risk factors and may have increased risk for incident CHD.

We propose evaluating the number of individuals in ARIC who would meet JUPITER criteria for LDL-c and hsCRP. The ARIC Visit 4 participants would be an ideal population since hs-CRP levels and lipids were measured in all participants. Their age range would be similar to that of JUPITER. We propose to study the potential impact of JUPITER's lipid modifying therapy in the ARIC study.

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

a)Describe the number of individuals meeting JUPITER clinical and lipid inclusion criteria (i.e. no prior cardiovascular events, no prior lipid lowering therapy, LDL-c < 130 mg/dL) and then examine the numbers who also meet inclusion criteria versus exclusion criteria for CRP Examine Framingham Risk Score (FRS) (and ARIC risk score) in individuals meeting JUPITER clinical and lipid inclusion criteria and then examine FRS and ARIC risk score in individuals who meet inclusion criteria versus those who are excluded based upon CRP

b)

c)Describe incidence of cardiovascular events in ARIC participants meeting JUPITER inclusion criteria.
d)Describe the incidence of cardiovascular events in individuals meeting all JUPITER inclusion criteria except low hs-CRP (< 2.0 mg/L).
e)
f)Describe the risk and odds ratios in these populations compared to the age-matched ARIC visit 4 cohort.

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).

Individuals who completed Visit 4 of ARIC will be eligible. Inclusion and exclusion criteria from the JUPITER trial will be applied to the ARIC cohort as closely as possible to identify the population of interest. The prevalence of those meeting JUPITER criteria will be described. Incidence of cardiovascular events in this population will also be described. Individuals meeting JUPITER criteria will also have FRS calculated to estimate 10-year risk for CHD.

The population will be identified and analyzed as follows.

1. Individuals who participated in Visit 4 and had hs-CRP levels measured will be included who meet JUPITER clinical and lipid criteria, defined below.
    - JUPITER clinical criteria
        - Inclusion: men aged 50 years or older and women aged 60 years or older no prior history of cardiovascular disease or equivalent (ischemic strokes, coronary artery disease, history of myocardial infarction, peripheral vascular disease – ABI < 0.9, diabetes – fasting serum glucose ≥ 126 or clinical diagnosis).
        - Exclusion: individuals on any lipid lowering agents (niacin, statins, fibrates, bile acid sequestrants, ezetimibe) at time of Visit 4 or with creatinine > 2.0 mg/dL
    - JUPITER lipid criteria: LDL-c < 130 mg/dL, triglyceride levels < 500 mg/dL
2.
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    - .
3. This population will be classified into two groups based on hs-CRP levels to low levels (< 2.0 mg/L) or elevated levels (≥ 2.0 mg/L, meeting JUPITER randomization criteria).
4. Baseline characteristics of both groups will be described.
    - Characteristics will include age, gender, race, blood pressure, waste circumference, BMI, smoking, family history of CHD,

aspirin use, lipid profile (including non-HDL cholesterol), fasting glucose, hs-CRP

5. Calculation of the FRS (and ARIC risk score) for individuals meeting JUPITER clinical and lipid criteria will be done.
6. The population meeting JUPITER clinical and lipid criteria will be classified into two groups based on 10-year risk of CHD into low (0-5%) and low intermediate (5-10%) risk groups. This classification will be done with FRS as one set and ARIC risk core as another set, yielding four groups total.
7. Kaplan-Meier survival analysis to any cardiovascular events as defined by ARIC (ischemic strokes and myocardial infarctions) will be calculated for each group in step 2 and for step 5.
8. The total incidence of cardiovascular events as defined by ARIC will be described for the entire ARIC cohort at Visit 4 age-matched for JUPITER clinical criteria, and for each group in step 2 and for step 5.
9. Relative risk and odds ratios will be calculated between groups in step 2 and between individuals meeting JUPITER randomization criteria and the entire ARIC cohort at Visit 4 age-matched for JUPITER.
10.

11.
12.
13.

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

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

__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)?

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.

References:

1.Ridker PM on behalf of the JUPITER study group. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-Reactive protein: Rationale and design of the JUPITER. *Circulation* 2003; 108:2292-2297.
2.Ridker PM, et al. Baseline characteristics of participants in the JUPITER trial,a randomized placebo-controlled primary prevention trial of statin therapy among individuals with low low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein. *Am J Cardiol* 2007; 100:1659-1664.
3.AstraZeneca. Crestor outcomes study JUPITER closes early due to unequivocal evidence of benefit [press release]. March 31, 2008. Available at: http://www.astrazeneca.com/pressrelease/5385.aspx
4.Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation,

and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; 285:2486-2497.