ARIC Manuscript Proposal # 1504

PC Reviewed: 5/12/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: CRP, WBC and Heart Failure Incidence

b. Abbreviated Title (Length 26 characters): CRP, WBC and HF

2. Writing Group:

Writing group members: Aaron Folsom, Wobo Bekwelem, Pam Lutsey, Laura Loehr, Sunil Agarwal, Brad Astor, Christie Ballantyne

This likely will be an MPH project for Dr. Bekwelem.

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

First author:

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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:
Address:

Phone: Fax:
E-mail:

3. Timeline: finish by Dec 09

4. Rationale:

Inflammation, as reflected by elevated CRP or white blood count (WBC), is considered to be important in the etiology CHD. A few population studies have suggested that CRP may also be associated with risk of heart failure, including CHS, Framingham,

Rotterdam, MESA, and Health ABC (1-6). In many cases this association was independent of prevalent or incident CHD. CRP is known to be associated with hypertension and obesity, and inflammation accompanying these conditions could contribute to nonischemic heart failure. While evidence for a link between CRP and heart failure is growing, to our knowledge, no population study has examined the association of WBC, another marker of inflammation, with incident heart failure. A role for both WBCs and CRP is implicated by theories that the immune system is a modulator of myocyte injury (7).

The recent addition of CRP to the ARIC visit 4 measurements allows us to examine whether CRP is associated with risk of subsequent heart failure in ARIC. There are ample heart failure events in ARIC since visit 4 (n>850), which will provide adequate power for detecting a moderate association. In addition, ARIC measured WBC at baseline, permitting a test of the hypothesis that WBC is associated with increased risk of heart failure.

5. Main Hypothesis/Study Questions:

1. CRP at visit 4 is associated positively and independently with incidence of heart failure after visit 4
2. WBC at visit 1 is associated positively and independently with incidence of heart failure after visit 1

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).

Design: cohort
Endpoint: heart failure incidence after exposure assessment date
Exposures: visit 4 CRP; visit 1 WBC
Main covariates: age, race, sex, center, BMI, waist, smoking, lipids, hypertension, diabetes, GFR, CHD prevalence and incidence, possibly PFT values

Analysis: Cox proportional hazards, with CRP and WBC modeled as a continuous variable and as quartiles. Also look at high (e.g. >90%) biomarker levels vs. low. Separate analyses will be done for visit 1 WBC and visit 4 CRP. Race specific analyses for WBC may be important because of lower WBC values in blacks than whites. CHD will be a stratifying and/or time-dependent covariate. We will also consider a few other less specific makers of inflammation (fibrinogen, albumin) as well, perhaps as an "inflammation score" as Bruce Duncan had done for diabetes papers and as others had done for heart failure (8).

References

1. Hofman A, Grobbee DE, de Jong PT, et al. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol* 1991;7:403-22.

2. Gottdiener JS, Arnold AM, Aurigemma GP, et al. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. *J Am Coll Cardiol* 2000;35:1628-37.

3. Vasan RS, Sullivan LM, Roubenoff R, et al. Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. *Circulation* 2003;107:1486-91.

4. Cesari M, Penninx BW, Newman AB, et al. Inflammatory markers and onset of cardiovascular events: results from the Health ABC study. *Circulation* 2003;108:2317-22.

5. Kardys I, Knetsch AM, Bleumink GS, et al. C-reactive protein and risk of heart failure. The Rotterdam Study. *Am Heart J* 2006;152:514-20.

6. Bahrami H, Bluemke DA, Kronmal R, et al. Novel metabolic risk factors for incident heart failure and their relationship with obesity: The MESA (Multi-Ethnic Study of Atherosclerosis) Study. *J Am Coll Cardiol* 2008;51:1775-83.

7. Fildes JE, Shaw SM, Yonan N, et al. The immune system and chronic heart failure: Is the heart in control? *J Am Coll Cardiol* 2009;53:1013-20.

8. Engström G, Hedblad B, Tydén P, Lindgärde F. Inflammation-sensitive plasma proteins are associated with increased incidence of heart failure: a population-based cohort study. Atherosclerosis. 2009 Feb;202(2):617-22.

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)?

1342. Loehr LR et al. Potentially modifiable burden of incident HF due to obesity.
1184. Ballantyne C et al. LpPLA2, CRP and CVD

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __x__ No

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.