1.a. Full Title: C-Reactive Protein and the Change in Blood Pressure among Individuals Initially without Hypertension

b. Abbreviated Title (Length 26 characters): CRP and Blood Pressure Change

2. Writing Group (list individual with lead responsibility first):

   Lead: Abhijit V. Kshirsagar
   Address: C.B. 7155 348 MacNider Hall, Chapel Hill, NC 27599-7155
   Phone: 919.966.2561 x259   Fax: 919.966.4251
   E-mail: sagar@med.unc.edu

   Writing group members: Heejung Bang, Myra Carpenter, Aaron Folsom, Christie Ballantyne, Philip Klemmer

3. Timeline:

   Obtain data set: October 2004
   Begin statistical analysis: November 2004
   Complete statistical analysis: January 2005
   Complete manuscript: June 2005

4. Rationale:

   Systemic inflammation may be an important determinant of cardiovascular disease. C-reactive protein (CRP), arguably the most studied inflammatory marker, predicts the development of atheroembolic events (myocardial infarction, stroke) [1-3]

   Properties of C-reactive protein suggest that the acute phase reactant may also have an important role in the pathogenesis of elevated blood pressure. CRP has been shown to decrease nitric oxide production in endothelial cells [4] possibly by reducing expression of endothelial nitric oxide synthase (eNOS) [5]. Low levels of nitric oxide result in vasoconstriction. Furthermore, low levels of nitric oxide increase production of endothelin-1 [6,7], known to promote vasoconstriction, and fibrosis [8].

   Cross-sectional epidemiological studies have demonstrated a direct relationship of crp with blood pressure [9-11]. Recently, Sesso and colleagues [12] demonstrated a modestly elevated risk of incident self-reported hypertension associated with high C-
reactive protein among a population of healthy and predominantly white women (nurses cohort study). Information on the role of C-reactive protein and incident hypertension is incomplete however, especially among men, and African Americans. Both these groups are at a higher risk for the development of hypertension than white women.

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

   The *primary* hypotheses are that higher C-reactive protein is associated with greater blood pressure and with blood pressure change after adjustment for traditional cardiovascular disease risk factors. The *secondary* hypothesis is that high C-reactive protein is associated with incident hypertension.

6. **Data (variables, time window, source, inclusions/exclusions):**

   We plan to use the cohort random sample (CRS) from visit 2 as the study group. (Note that current case cohort designs were constructed for the studies of incident CHD or stroke, so additional cases will be ignored.)

   At visit 2, which is our baseline visit, the sample size of the CRS is 936. Necessary exclusions include individuals with missing or unmeasured CRP, n=151; individuals with hypertension at visit 1, n=268, and individuals with hypertension at visit 2, n=54. The target analysis dataset is comprised of 463 individuals. We will further apply a few minor exclusions based on races (other black and white) and missing covariates. Since the nature of random sampling is not preserved after major elimination process from the original CRS, sampling weights, which are equal to the inverse of stratum-specific selection probabilities, should be recalculated considering a target population being free of prior hypertension at visit 2. To examine the undue influence of some weights, we will repeat the whole analyses with and without considering the weighting scheme.

   Mathematically, the primary hypotheses are:

   **Hypothesis I:**
   \[ \text{BP} = f(\text{CRP}, \text{traditional risk factors}) \]

   **Hypothesis II:**
   \[ \text{BP slope} = f(\text{CRP}, \text{baseline BP}, \text{traditional risk factors}) \]

   The secondary hypothesis is:

   **Hypothesis III:**
   \[ \log(\text{hazard ratio of incident hypertension}) = f(\text{CRP}, \text{traditional risk factors}) \]

   where the function \( f \) will be based on linear models (i.e., including polynomials).
Hypotheses I and II will be evaluated with SBP and DBP separately. Hypothesis I will be analyzed by mixed model for repeated measures of BP with random slope and intercept. Hypothesis II will be analyzed by linear regression model using the BP slopes that are generated from hypothesis I. Hypothesis III will be analyzed by Cox proportional hazard regression using mid-point for the time of event.

For hypothesis I, we have 80% power to detect 20-23% of slope difference between two balanced CRP groups (high vs. low CRP group) for within-person correlation coefficient of 0.5-0.7 [14].

In all investigations, CRP will be treated as a continuous variable as well as a categorical variable. A previous investigation [13] using CRP in ARIC demonstrated that tertiles in ARIC (< 1.01, 1.10-2.82, and > 2.82 mg/L) are similar to cutpoints defined in AHA/CDC guidelines (< 1 mg/L, 1-3 mg/L, > 3 mg/L) [14]. We would like to use a three level CRP variable similar to the AHA/CDC guidelines. Incident hypertension, the outcome of interest for the secondary hypothesis, will be defined according to the standard ARIC definition (self-report, measurement $\geq 140$ mm Hg, a diastolic blood pressure $\geq 90$ mm Hg, use of antihypertensive medications). Additional consideration should be given to diabetes status and BMI condition. Some important interaction effects will be examined in an exploratory manner, and extensive multivariate adjustment or subgroup or strata-based analyses will not be conducted due to limited sample size. Except new weight assessment, we will follow a previous paper [2] as guidance for analytic strategy. Due to the serious interval censoring problem in survival analysis, we will additionally perform some sensitivity analysis using different event time.

Covariates to be considered in the analysis include gender, race, age, diabetes, insulin, glucose, cholesterol (LDL, HDL, triglycerides), BMI, family history of hypertension, smoking status, physical activity, initial blood pressure, waist/hip ratio, change in weight, caloric intake, and alcohol consumption.

In order to increase statistical power and efficiency, all ancillary covariates will be treated as continuous variables if at all possible.

All analyses will be done with SAS software (SAS Institute, Cary, N.C.). Two sided p-values will be used as criteria to assess statistical significance.

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 ICTDER02 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 ICTDER02 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 ICTDER02 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)?

MS # 606 – lead author, Aaron Folsom
MS # 889 – lead author, Christie Ballantyne

Note that both these individuals are part of the writing group of this proposal.

11. 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


