ARIC Manuscript Proposal # 1665

PC Reviewed: 7/13/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
C-reactive protein and mortality in individuals with atrial fibrillation: the ARIC study

b. Abbreviated Title (Length 26 characters):
CRP and AF in ARIC

2. Writing Group:
José Hermida, Faye Lopez, Kunihiro Matsushita, Brad Astor, Alvaro Alonso, others welcome

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

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3. Timeline:
Data analysis will start upon manuscript approval. We would expect to have a final draft of the manuscript by the end of September 2010. Data analysis will be

done at the University of Minnesota, and Dr. Hermida will be responsible for a first draft of the manuscript (assisted by Alvaro Alonso).

4. Rationale:

C-reactive protein (CRP) is a sensitive index of inflammation and its high level in plasma has been shown to predict myocardial infarction, stroke and cardiovascular death among both apparently healthy subjects and cardiovascular patients (1-5). Besides, high CRP levels are associated with deaths from non-vascular disease (including several cancers and respiratory diseases) even in subject without previous vascular disease (6).

There is considerable evidence that atrial fibrillation (AF) is associated with an inflammatory state and with an increased mortality and morbidity from stroke and thromboembolism (7). Less is known about the role of inflammation in patients with AF. One prospective study has evaluated the association of CRP with death in a population of patients with AF (8). The study, which included 880 AF patients recruited from subjects taking aspirin alone or combined with inefficacious doses of warfarin in the Stroke Prevention in Atrial Fibrillation (SPAF) III clinical trial, found that high levels of CRP (upper vs. lower tertile) were an independent predictor of all-cause mortality (HR 1.55, 95% CI 1.03-2.31), but not of vascular events or stroke. Generalizability of this study to the population of AF patients, however, might be limited since it included participants in a clinical trial and had a relatively short follow-up [mean time 453 (standard deviation, 229) days].

The CHADS2 score (congestive heart failure, hypertension, age under 75 years, diabetes, and previous stroke or transient ischemic attack) is a well-validated clinical score used to classify patients with AF according to future risk of thromboembolism; the score guides decisions about use of anticoagulant therapy (9). Recently this score has been suggested to be also an independent predictor of mortality in patients with AF (10). Most AF patients are classified as moderate risk and optimal thromboprophylactic care for these patients remains unclear (11). Additional methods to improve risk stratification in AF patients would have a major clinical impact. CRP could be useful for this purpose.

Therefore, we propose to examine the association of CRP plasma levels with the incidence of stroke, cardiovascular death and all-cause death in patients with AF in the ARIC study, independently of established cardiovascular risk factors. We will also evaluate whether the addition of CRP levels to the CHADS2 score improves the stratification of patients in terms of risk of stroke, cardiovascular death and all-cause death.

5. Main Hypothesis/Study Questions:

We hypothesize that AF patients with high levels of plasma CRP will have a higher risk of stroke, cardiovascular death and all-cause death, independently of other cardiovascular risk factors, compared to those with lower levels of CRP.

Additionally, we hypothesize that the addition of CRP levels to the CHADS2 score will improve the stratification of patients in terms of risk of stroke, cardiovascular death and all cause death.

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).

Study design

We will conduct a follow-up analysis of the ARIC cohort, using visit 4 as baseline.

Inclusion/exclusion criteria

Inclusion criteria. Whites and African-Americans who attended visit 4, with AF diagnosed at visit 4 or previously (defined by ECG at visits 1-4 or AF hospitalization before visit 4), and who had a measure of high sensitivity CRP.

Exclusion criteria. Race/ethnicity other than white and black, nonwhites in Minessota or Washington county; missing information in covariates of interest.

Variables of interest

Main outcome variable

Time from visit 4 to death, CV death, or stroke (depending on the analysis).

Main independent variable: CRP. In a primary analysis, we will include all CRP values. Then, we will conduct a secondary analysis excluding those with CRP > 10 mg/L, since those individuals might have clinically relevant inflammatory conditions.

Covariantes measured al visit 4: age, gender, race, center, body mass index, systolic blood pressure, use of antihypertensive medication, diabetes mellitus, prevalent stroke, prevalent heart failure (defined as prevalent HF at visit 1 according to Gothenburg criteria or incident HF between visit 1 and visit 4), prevalent CHD, use of antiplatelets, use of anticoagulants, use of statins, smoking status, ECG-based left ventricular hypertrophy.

Covariates measured at visit 1: education

Statistical analysis

We will assess the association between CRP and total mortality, CV mortality or stroke with Cox proportional hazards models. CRP will be modeled as a continuous variable and as quartiles

- Model 1: adjusting for age, sex, and race

- Model 2: adjusting for age, sex, race, center, education, systolic blood pressure, use of antihypertensive medication, diabetes mellitus, prevalent stroke, and prevalent heart failure [CHADS2 variables]
- Model 3: adjusting for age, sex, race, center, education, systolic blood pressure, use of antihypertensive medication, diabetes mellitus, prevalent stroke, prevalent heart failure, body mass index, prevalent CHD, use of antiplatelets, use of anticoagulants, use of statins, smoking status, alcohol intake, and ECG-based left ventricular hypertrophy.

Additionally, we will estimate the net reclassification improvement of adding CRP to the CHADS2 for the prediction of the main outcomes.

Power calculations

After applying exclusion criteria, 293 ARIC participants with AF will be eligible. Of these, 134 (46%) died during follow-up through 2007 (average follow-up: 8 years).

Assuming a two-tailed alpha error of 0.05, we will have 80% statistical power to detect a hazard ratio of 1.8 comparing extreme quartiles. Power for the detection of linear trends, if present, will be higher. We recognize that power for other outcomes will be limited.

Strengths and limitations

The main strengths of this study include: the long follow-up, and the population-based character of the sample. Our proposal, however, has two important limitations: the limited sample size and the ascertainment of AF. AF ascertainment in ARIC is mostly based on hospital discharges. However, we have shown previously an adequate validity of hospital discharge codes for the ascertainment of AF (12). Related to the ascertainment method, we will be unable to differentiate between paroxysmal, persistent or permanent AF. Finally, because CRP measures are not taken at the initial diagnosis of AF, we will be able to include only those ARIC participants with AF who survived through visit 4. To determine the impact of this problem, we will explore whether time since first diagnosis of AF affects our associations.

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.cscc.unc.edu/ARIC/search.php

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___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)?

No previous proposal in ARIC focus specifically on the association of CRP in subjects with atrial fibrillation and death or stroke.

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

_X_ A. primarily the result of an ancillary study
(list number* 2006.16, 2008.09, 2008.12)

___ 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

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