ARIC Manuscript Proposal #1980

PC Reviewed: 8/14/12  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Biomarkers CRP and BNP improve the prediction of AF risk on top of classic risk factors – the CHARGE-AF consortium

b. Abbreviated Title (Length 26 characters): CRP, BNP and AF prediction

2. Writing Group:
ARIC investigators: Alvaro Alonso, David Couper, Brad Astor, Christie Ballantyne, Ron Hoogeveen

Investigators from other CHARGE cohorts: Moritz F. Sinner, Michael Pencina, Katherine A. Stepas, Michiel Rienstra, Jared W. Magnani, João D. Fontes, Steven A. Lubitz, Patrick T. Ellinor, Vilmundur Gudnason, Jacqueline Witteman, Bouwe P. Krythe, Richard A. Kronmal, Christopher DeFilippi, Bruce M. Psaty, Susan R. Heckbert, Emelia J. Benjamin

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

First author: Alvaro Alonso
Address: 1300 S 2nd St, Suite 300
Sch of Public Health, University of Minnesota
Minneapolis, MN 55454
Phone: 612 626 8597  Fax: 612 624 0315
E-mail: alonso@umn.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: David Couper
Address: 137 E Franklin St Ste 203
Campus Box 8030
Chapel Hill 27599-8030
Phone: 919-962-3229  Fax: 919-962-3265
E-mail: david_couper@unc.edu

3. Timeline:
Analyses will be done in the next two months. A first draft of the manuscript is expected by the end of 2012.

4. **Rationale:**
Prediction of the risk to develop atrial fibrillation (AF) has been the focus of a number of recent reports. Based on factors collectable during a standard office visit, a first risk score was developed by investigators from the Framingham Heart Study (FHS).\(^1\) The score was subsequently validated in the Age Gene/Environment Susceptibility-Reykjavik (AGES) Study and the Cardiovascular Health Study (CHS),\(^2\) and different, yet comparable scores were established in the Atherosclerosis Risk in Communities (ARIC) Study,\(^3\) and the Malmö Cancer and Diet Study.\(^4\) Most recently, the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) AF consortium proposed a new risk score, which for the first time was based on a population of heterogeneous racial and geographic background.[REF: Alonso et al. Prediction of AF, ARIC MS #1578].

The current CHARGE AF risk score is comprised of clinical risk factors for AF, and in an extended version also includes electrocardiographic (ECG) parameters. Although such clinical risk factors already have good predictive abilities, we hypothesize that biomarkers would improve risk reclassification. Abundant literature is available regarding the relation between laboratory biomarkers and AF. Particularly, C-reactive protein (CRP),\(^5\)-\(^9\) and B-type natriuretic peptide (BNP),\(^4,5,10\)-\(^16\) two biomarkers routinely determined in clinical practice, have repeatedly been shown to be associated with or predict AF under various conditions. Other, innovative but less comprehensively studied biomarkers include apelin,\(^17\) urotensin II,\(^18\) soluble CD40 ligand,\(^19\) osteoprotegerin,\(^20\) troponin,\(^16,21\) endothelin,\(^16\) PAI-1,\(^22\) and YKL-40.\(^23\)

Here we aim to investigate whether the addition of CRP and BNP to the CHARGE AF risk score helps to improve the prediction of AF in a racially and geographically diverse population. We will use data from three community-based studies from the United States (ARIC, FHS and CHS), and subsequently will validate our findings independently in the European, community-based AGES Study and the Rotterdam Study (RS).

5. **Main Hypothesis/Study Questions:**
To assess the predictive ability of biomarkers CRP and BNP in the CHARGE cohorts, in addition to the previously reported CHARGE AF risk score.

We hypothesize that the biomarkers CRP and BNP, alone or in combination, improve AF risk prediction, when added to an established and validated risk score based on clinical variables.

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).**
Participants of the CHARGE cohorts AGES, ARIC, CHS, FHS and RS will be included. For ARIC, we will include participants recruited in visit 4 with data on CRP and NTproBNP available.

**Exclusions:**
- Participants with prevalent AF at visit 4
- Participants with relevantly impaired renal function (serum creatinine levels ≥ 2.0 mg/dl)
• Participants of non-whites or non-African-American race by self-report
• Participants with missing values for variables of interest, including missing data on biomarkers.

Follow-up duration:
A 5-year risk of incident AF.

Outcome variables:
Incident AF, as identified from hospital records and death certificates.

Predicting variables:

| Clinical variables (already included in the CHARGE-AF score) | 
|---|---|
| Age | continuous; years |
| Sex | dichotomous |
| Height | continuous; cm |
| Body mass index | continuous; kg/m² |
| Current smoker | dichotomous |
| Systolic blood pressure | continuous; mmHg |
| Diastolic blood pressure | continuous; mmHg |
| Hypertension treatment | dichotomous |
| Diabetes | dichotomous |
| ECG-derived LVH | dichotomous |
| PR interval | continuous; ms |
| Heart failure history | dichotomous |
| MI history | dichotomous |

| Biomarkers | 
|---|---|
| C-reactive protein | continuous; mg/L |
| Brain natriuretic peptide | continuous; pg/mL |

Statistical approach:
• Biomarkers CRP and BNP will be log-transformed to ensure normal distribution of the data.
• Cox proportional hazard models to assess prediction of incident AF by CRP and BNP during a 5-year follow-up. Clinical variables established within the initial CHARGE AF risk score (age, sex, race, height, BMI, systolic blood pressure, diastolic blood pressure, smoking, hypertension treatment, diabetes, heart failure, myocardial infarction) will be forced into the model, and biomarkers will be additionally added. Similarly, an extended model will additionally include ECG left ventricular hypertrophy and categorized PR interval before addition of biomarkers.
• Predictive ability will be assessed using:
  o C-statistics
  o Modified Hosmer-Lemeshow chi-square statistic for survival
  o Discrimination slopes
  o Integrated discrimination improvement (IDI)
  o Net reclassification improvement (NRI)
Data from ARIC will be pooled with data from CHS and FHS to create a joint US-based cohort. For validation, the identified prediction model will be assessed in European cohorts (AGES and RS).

**Anticipated Limitations:**
- Generalizability to other, non-white, non-African-American ethnicities
- Asymptomatic AF may be overlooked; paroxysmal, persistent and permanent AF and atrial flutter will be combined

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.cscucc.unc.edu/ARIC/search.php

  ____ X__ Yes  ______ No

  No overlap

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* __________)
B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)*2008.12, 2006.16, 2008.10)

*ancillary studies are listed by number at http://www.cscce.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.