ARIC Manuscript Proposal #2099

PC Reviewed: 3/12/13  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: _____

1. **a. Full Title:** Utility of biomarker panel, hsTnT, NT-proBNP, and cystatin C to prediction of ischemic stroke, and mortality in AF patients: the ARIC Study

   **b. Abbreviated Title (Length 26 characters):** AF, biomarkers, and risk of stroke and mortality

2. **Writing Group:**

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

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3. **Timeline:**

   Data analysis: 2-3 months from manuscript approval date.
   First draft of the manuscript: 4-5 months from the manuscript approval date.
4. Rationale:

Atrial fibrillation (AF) is a major and growing public health problem implicated in the causation of ischemic stroke and early death [1] [2]. Stroke prevention is of paramount importance in those with AF given the availability of anticoagulation therapy that can reduce stroke risk. In this context, CHADS2 and recently proposed CHADSVaSC scores are used to predict stroke risk to decide the risk/benefit of oral anticoagulation vs. anti-platelet therapy. Multiple biomarkers exists which may portend or identify AF patients at higher risk of adverse outcomes.

First, NT-proBNP is a functional peptide secreted mainly by ventricles [3] and also by atria especially in AF [4] [5], that may reflect underlying structural heart disease. BNP level is also a predictor of left atrial appendage (LAA) dysfunction[6]. Thus, it may portend a higher risk of stroke beyond the variables included in CHADS2. Further, evidence of such possibility is offered by BNP levels ability to discriminate cardioembolic stroke from other sub-types [6-9] including cryptogenic stroke. Also, BNP is associated with poor post stroke prognosis [10] [11].

Second, troponins may be a marker of structural heart disease, reflecting a higher burden of atherosclerosis and thus a higher rate of cardiac apoptosis, and may similarly portend higher stroke risk in those with AF. Troponin I was detectable in about a third of stroke patients[12, 13], and portends poor prognosis in stroke patients[14].

Thirdly, eGFR was found to be a strong, independent predictor of stroke and systemic embolism [15]. Thus, renal dysfunction may be a useful marker for risk stratification in stroke patients. Of note, a model with biomarkers may be able to detect subclinical cardiac or vascular disease in patients with AF prior to developing adverse events or death.

Fourth, hsCRP has been shown to portend poor prognosis in AF patients.

Lastly, a combination of biomarkers reflect different pathologies may improve overall risk prediction. For instance, among those with hypertrophic cardiomyopathy, elevation in both cTnI and BNP values had an 11.7-fold increased risk of major adverse cardiac events (MACE) [16], and stroke than controls [17]. A particular interest may lie in the ability of these biomarkers to identify end-organ damage due to risk factors including in CHADS2 such as from hypertension and diabetes and ability to detect higher propensity of heart failure. Their ability to potentially stratify AF patients for first stroke has strong public health implications as the CHADS2 score puts higher weight on those who already had a stroke.

In this context, there is little information about combined utility of BNP, hsTnT and CrCl in portending risk of stroke, CHD, and death. The utility of combined biomarker panel in AF patients to predict these events have not been studied either. We hypothesize that
these biomarkers will add to the prediction of stroke and other CVD outcomes in AF patients.

5. **Main Hypothesis/Study Questions:**
We hypothesize that a biomarker + demographic based model will provide similar discrimination and fit as clinical risk factor models such as CHADS2 in predicting stroke or recurrent stroke in patients with AF. This model will perform well in those without prevalent stroke as well. Lastly, a combined use of clinical and biomarker model will improve risk prediction as compared to clinical model only.

**Specific aims:**

**In ARIC participants with atrial fibrillation at Visit 4**

To explore the relationship of NT-proBNP, hsTnT and CrCl (using cystatin C) to risk of stroke (esp. cardio-embolic stroke), MACE (includes heart failure, CHD, and CVD mortality), and all cause mortality.

To explore the model discrimination and fit for each of these biomarkers individually and their combination (+hsCRP) to predict stroke, MACE and all cause mortality in models with demographics only vs. CHADS2 vs. other clinical variables.

To develop a parsimonious model to predict ischemic stroke risk using demographics, biomarkers, and clinical variables and to see how this or another modified model predicts MACE or CHD deaths.

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 methodological limitations or challenges if present).**

Study design:
Time to event analysis using ARIC visit 4 as baseline.

Exclusion criteria:
Those without AF by year 2002 or missing information on biomarkers

Variables of interest:

Main outcome of interest: Stroke

Secondary outcome of interest: Cardioembolic stroke, Heart Failure, CHD mortality

Main Exposure: NT-proBNP, hsTnT, eGFR using cystatin C
Other Exposures: hsCRP

Covariates
From visit 4, other measured covariates to be included in the analysis are age, gender, race, heart rate, diabetes mellitus, smoking status, hypertension, use of antihypertensive medications, aspirin, warfarin, steroids, and a history of HF, myocardial infarction (MI), or stroke, medications such as anti-arrhythmics, beta-blockers, calcium channel blockers, digoxin.

Statistical analysis:
Cox proportional hazards models for aim 1 with appropriate transformation of biomarkers.

For aim 2, and 3, using Cox proportional hazards models, we will estimate measures of discrimination (Area Under Receiver Operating Curve and Integrated Discrimination Index, and Net Reclassification Improvement), and model fit will be visualized using Arjas plot. For the incremental value of a biomarker we will look at change in AUC and NRI when adding a biomarker or a combination of them to the base model with CHADS2/CHADSVaSC. Given that some participants will be on oral anticoagulants/anti-platelet therapy, we will recalibrate the base model with CHADS2/CHADVaSC to get beta coefficients within our study sample.

Strengths and limitations:
Uniform measurement of biomarkers from stored sample in a well characterized cohort with adjudicated outcome.
Major limitation is power – though we expect a higher rate of stroke in AF group – the total numbers may not be sufficient for stroke (particularly cardioembolic stroke as outcome).

Sample size:
Approx. 300 AF patients with 35 stroke events (will try to supplement by Medicare data or including those without stroke prior to AF or by including Cardiovascular Health Study cohort)

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 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  ___ No
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

   ____X Yes, no overlap found.  ______ 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)?

   #1665: CRP in AF – relation to stroke and CHD deaths

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

   b. If yes, is the proposal
      _  A. primarily the result of an ancillary study (list number*)
      ____X B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2008.12)

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