ARIC Manuscript Proposal #2105

PC Reviewed: 4/9/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Risk factors for incident atrial fibrillation in patients with normal left atrial size: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Normal left atrial size and AF

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. WQ

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3. Timeline: Analysis to begin after Publication Committee approval.
Manuscript anticipated for initial P&P review in Fall 2013

4. Rationale:

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia that currently affects 2.3 million individuals in the United States. [1] This prevalence is projected to increase to 16

million by 2050.[2,3]The total health expenditures incurred by patients with atrial fibrillation are almost 5 times that of patients without AF and range from $6 – $26 billion.[4] These patients suffer from considerable morbidity and mortality.[5]

In preparation for this 'epidemic' of AF, The National Heart, Lung, and Blood Institute convened an expert panel that has stressed the need for further epidemiological studies to further elucidate the pathophysiology of AF.[6] Based on these recommendations, the Framingham Study investigators developed a risk score derived for predicting incidence of AF.[7]
Increased left atrial (LA) size, or factors that contribute to an increase in LA size, are the most frequently cited risk factors for AF. [8-10] However, a sizable minority of patients with new onset atrial fibrillation have normal atrial sizes.[11]A recent study in women showed that the traditional risk factors of AF might differ in patients with large atrium and normal atrium.[12] Other studies have also shown that there are many other non-traditional risk factors for AF development including biomarkers, genetic, structural and clinical risk factors. However, there are few data regarding the risk factors for developing atrial fibrillation in patients with normal atrial size.Clarifying the etiologic factors that contribute to AF in the setting of normal LA size could emphasize pathogenic mechanisms or suggest novel targets for therapeutic intervention or prevention designed to reduce the clinical and financial burden of AF in our rapidly aging population.[13]

Accordingly, the aims of this study are to investigate traditional and novel risk factors in the patients with AF and to compare them between patients with and without a dilated LA.

5. Specific Aims:

The goal is to identify factors that may be uniquely associated with AF in participants with normal left atrial size. Therefore,among ARIC participants in exam 5, we will:

1) Examine the cross-sectional association between traditional and novel risk factors and prevalent AF, stratified according to the presence or absence of a dilated left atrium.

   –forthe purpose of stratification we will use clinically accepted definitions of LA enlargement (>40mm in women, and >45mm in men) as well as empirically derived cut-points based on the distribution of LA dimensions in the ARIC cohort (>= vs< 75thand 90thsex-specific %tiles)

   - To account for the potential for AF itself to lead to increases in atrial dimensions we will also perform sensitivity analyses to determine the need to adjust for AF duration prior to performing the stratification.

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 population:
Participants with available echocardiographic and electrocardiographic data in ARIC exam 5.

Key variables:

- **Atrial fibrillation:** Cases of atrial fibrillationwill be defined as ECG evidence of AF during exam 5, or previously documented AF during past ARIC visits (i.e. AF cases detected from ECG data in previous ARIC visits, and hospital discharge ICD codes and death certificates)
- LA size and volume as measured by echocardiography.
- Demographics, traditional CVD risk factors, prevalent CVD, chronic kidney disease, relevant medications, exercise, alcohol use, anemia, thyroid disease, and pulmonary disease.
- Additional novel risk factors including:

Novel risk factors:

Echocardiographic measures:

Left ventricular diastolic dysfunction parameters (mitral valve inflow early E and late A diastolic filling waves, E – wave deceleration time, E/A ratio, LV septal thickness, LV posterior wall thickness, IVRT, tissue Doppler mitral valve E', LA volume), tissue Doppler A'.

Biomarkers:

N – terminal pro BNP, C – reactive protein, urine albumin creatinine ratio.

Genetic:

AF related SNPs:

rs3903239, rs3807989, rs1152591, rs1082141, rs7164883, rs10821415, rs2040862, rs10824026, rs12570126, rs3812629, rs2634073, rs7514452, rs6817105, rs6666258 and rs2106261

PR related SNPs:

rs3891585, rs267567, rs3922844, rs11732231, rs11773845, rs1895585, rs6763048, rs6801957, rs11047543, rs4944092, rs251253

Analysis Plan:

Basic exploratory data analysis will be performed to determine the distribution of LA dimensions with and without adjustment for age, race, and sex. In the subset of subjects with prevalent AF, the impact of AF duration on LA size will also be determined. In a similar fashion the distributional characteristics of the other traditional and novel risk factors for AF will be examined and normalizing transformations, imputations and other standard data cleaning efforts will be considered as needed to address highly skewed or missing data.

Subjects will be stratified based on several different cut points including:

- clinically accepted cut-points (>40 mm in women, >45mm in men)

- empirically defined cut-points (50^{th}, 75^{th}, or 90^{th}%tile cur point of the age- and sex-adjusted LA size.

In each stratum, multivariable logistic regression will be performed to determine the association of each of the individual candidate risk factors after adjustment for age, race and sex. For the purpose of the genetic association analysis, an additive genetic model will be assumed. In a second step factors that are individually associated with AF will be selected using a stepwise procedure for inclusion in a final model. If there are variables whose association with AF appears to be substantially different according to LA size, formal interaction analyses will be performed. Sensitivity analyses will also be performed to determine the impact of adjustment for AF duration prior to stratification.

7.a. Will the data be used for non-CVD analysis in this manuscript?
No

8.a. Will the DNA data be used in this manuscript?
Yes

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.
Yes

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 ARIC manuscript proposals looked specifically at AF risk factors in the setting of normal LA size. However, ARIC authors involved in AF-related proposals are included as coauthors (Alvaro Alonso and Elsayed Soliman).

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?

Yes. The PI and investigators from the AF ancillary study are included as coauthors (Alvaro Alonso and Elsayed Soliman)

References:

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