ARIC Manuscript Proposal # 1397

PC Reviewed: 07/30/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: CHARGE GWAS for lone atrial fibrillation

b. Abbreviated Title (Length 26 characters): Lone Afib GWAS

2. Writing Group: CHARGE-AF working group

ARIC writing group members: Dan Arking, Alvaro Alonso, Eric Boerwinkle (and/or other Houston personnel), Georg Ehret, Elsayed Soliman, others welcome. Other authors from additional CHARGE cohorts. The plan is to maintain symmetry across cohorts.

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

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3. Timeline: Summer 2008: analyze and share ARIC data with Charge by July 25, meta-analysis results August 6, manuscript to respective P&P committees August 20.

4. Rationale: Atrial fibrillation (AF) is a major cardiovascular health problem, associated with higher stroke and additional cardiovascular complications. With prevalence of >2 million people in the US alone, identifying genetic factors contributing to susceptibility takes on high priority. The label of lone AF is restricted to those case of AF occurring in young patients (usually <60) in which there is no cardiac or systemic disease that could explain the onset of AF. Although patients with lone AF have a

favorable prognosis with respect to thromboembolism and mortality, over time, those patients move out of the lone AF category and the risks of thromboembolism and mortality rise (Kopecky et al NEJM 1987). Moreover, it is thought that the risk factors for lone AF would be different than risk factors for the most frequent cases of AF occurring in the elderly and those associated to cardiac valve disease and other predisposing disorders. Therefore, specific genetic variants could be associated with the risk of lone AF but not with other forms of this cardiac arrhythmia. To date, there have been no genome wide association studies (GWAS) of lone AF.

CHARGE (ARIC, CHS, Rotterdam, Framingham, and selected other cohorts) is doing a meta analysis of GWAS findings related to AF. The analysis is focusing on a) prevalent AF (which we will not examine due to limited cases), b) incident AF, c) lone AF, and d) PR interval.

5. Main Hypothesis/Study Questions:

Gene variants can be identified that associate with lone AF.

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).

Design: meta-analysis of GWAS studies

Participating groups:

AGES
Framingham Study
Rotterdam Study
ARIC
CHS (2400)
MONICA/KORA
GHS

Phenotypes: lone AF, defined as AF present at baseline or during the follow-up occurring in individuals aged ≤65 y and without heart disease (while according to the ACC/AHA/ESC 2006 Guidelines for the management of patients with Afib, lone AF applies to individuals <60 y, CHARGE has decided upon a 65 y cut-off). AF was identified through ECGs performed at study visits or through hospitalization records (ICD9 code 427.31, 427.32)

1. Model: Logistic regression for cross-sectional analysis. Lone AF patients will be compared with individuals younger than 65 at baseline, without heart disease.

Main analysis will include only whites. The primary analyses will use logistic regression, adjusting for age at DNA draw, sex, HTN, and study site. Secondary

analyses may adjust for important AF risk factors that are available across cohorts including body mass index, and diabetes status at baseline.

Genetic model: additive.

2. Transformation: no transformation, no re-scaling.

3. Covariates: age, sex, study site, HTN, DM

4. Exclusions: history of MI, CHF, valve disease prior to onset of AF

5. Control for multiple comparisons: Bonferroni adjustment based on the number of markers

6. Imputation
Imputation to Hapmap 2.5 M using MACHv1.0.16.

7. Meta-analysis:
Fixed effects meta-analysis based on 2.5 M observed and imputed SNPs

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? ___x_ 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 ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
_x___ Yes ____ No

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
__x__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

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)?

None

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* 2008.09)
_x__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2006.03, 2007.02

*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.