ARIC Manuscript Proposal # 1396

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

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

b. Abbreviated Title (Length 26 characters): 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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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).
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3. Timeline: Summer 2008: analyze and share ARIC data with Charge by July 25, meta-analysis results Aug 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. To date, there have been no genome wide association studies (GWAS) of incident AF (a previous GWAS study conducted in an Icelandic population, and replicated in Chinese and European samples, found a strong

association between two sequence variants on chromosome 4q25 and prevalent AF. Gudbjartsson DF et al. Nature 2007).

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. This manuscript proposal will focus on incident AF.

5. Main Hypothesis/Study Questions:

Gene variants can be identified that associate with incidence of 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: a) incident AF, defined as initial, paroxysmal, persistent, permanent atrial fibrillation or atrial flutter, identified from ECGs conducted at study visits or from hospital discharge summaries (ICD-9 codes 427.31, 427.32).

1. Model: Cox proportional hazards

Main analysis will include only whites.

Genetic model: additive.

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

3. Covariates: primary analysis-age, sex, study site; secondary for top hits-age, sex, study site, HTN (140/90 mm Hg, or treatment), heart failure, MI, BMI, DM

4. Exclusions: Prevalent AF, CABG (censor at time of CABG or valve surgery)

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.