ARIC Manuscript Proposal # 1398

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

1.a. Full Title: CHARGE GWAS for PR interval

b. Abbreviated Title (Length 26 characters): PR 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]**

First author: Dan E. Arking
Address: Johns Hopkins University School of Medicine
733 N. Broadway, BRB 453
Baltimore, MD 21205
Phone: 410-502-4867 Fax: 410-502-7544
E-mail: arking@jhmi.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: Alvaro Alonso
Address: Div. Epidemiology & Community Health
Sch Public Health, U of Minnesota
1300 S 2nd St, Suite 300, Minneapolis, MN 55416
Phone: 612-626-8597 Fax: 612-624-0315
E-mail: alonso@umn.edu

3. Timeline: Summer 2008: analyze and share ARIC data with Charge by July 25, meta-analysis results July 30, manuscript to respective P&P committees August 6

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. However, power is limited by the number of available cases with DNA, therefore plan to look for association with PR interval, which

serves as an endophenotype for AF. Indeed, Soliman et al (manuscript submitted) have demonstrated a 1.46 (1.25, 1.70) hazard ratio associated with Afib for each 1 S.D. change in PR interval, after adjusting for age, sex, and ethnicity in the ARIC cohort. To date, there have been no genome wide association studies (GWAS) of PR interval.

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, b) incident AF, c) lone AF, and d) PR interval. Separate manuscript proposals for AF and lone AF will be submitted.

5. Main Hypothesis/Study Questions:

Gene variants can be identified that associate with levels PR interval.

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: PR interval, which is the time from the beginning of the P wave (onset of atrial fibrillation) to the beginning of the QRS complex (onset of ventricular depolarization), and is measured from a surface ECG. This information was obtained from ECGs conducted during the ARIC first visit.

1. Model: Linear regression for cross-sectional analysis

Main analysis will include only whites.

Genetic model: additive.

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

3. Covariates: age, sex, RR interval, BMI, height, SBP, HTN, diuretics

4. Exclusions: prevalent AF, pacemaker, WPW syndrome, AV Block III-total heart block, CHF, MI, CABG, extreme PR (<80, >320), use of beta-blockers, use of non DHP Ca_Antagonists, use of digoxin, use of Type I and III antiarrhythmic drugs

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-effect 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
___ 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)* 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.