1.a. Full Title: Genome-wide association study of stroke risk in patients with atrial fibrillation: the CHARGE consortium

b. Abbreviated Title (Length 26 characters): GWAS of stroke in AF

2. Writing Group:
Alvaro Alonso, Dan Arking, Thomas Mosley, Lin Y Chen, other ARIC investigators are welcome, CHARGE investigators

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

First author:  Alvaro Alonso
Address:  1300 S 2nd St, Suite 300
University of Minnesota
Minneapolis, MN 55454
Phone:  612-626-8597
E-mail:  alonso@umn.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:  Dan Arking
Address:  733 N Broadway, BRB 453
Johns Hopkins University School of Medicine
Baltimore, MD 21205
Phone:  410-502-4867
E-mail:  arking@jhmi.edu

3. Timeline:
Analysis will be done as soon as the manuscript is approved. A manuscript will be written over the next 6 months

4. Rationale:
Atrial fibrillation (AF) is the most common sustained arrhythmia in the United States and other developed countries and is associated with a significant increase in mortality and morbidity, including a 4-5 fold increase in the risk of stroke(1,2). Stroke is a principle morbidity associated
with AF, and AF is one of the most potent risk factors for stroke in the elderly. Overall this arrhythmia is implicated in greater than 75,000 strokes per year and is a major cause of cardioembolic stroke (3).

The risk of stroke appears to be independent of whether or not the AF is paroxysmal or persistent. The annualized stroke risk is 3-4% in the absence of antithrombotic therapy (4). Meta-analyses of large stroke prevention/treatment trials have identified history of prior transient ischemic attack/stroke, hypertension, increasing age, congestive heart failure and diabetes mellitus as independent risk factors that increase the risk of stroke/TIA in patients with AF (5). There is now an evolving consensus on the use of risk stratification schemes to identify patients with AF who are at higher risk of stroke and therefore warrant anticoagulation (6). The most widely used risk stratification algorithms are the CHADS2 score (7), ACC/AHA/ESC Guidelines (2006) (8) and the ACCP guidelines (2008) (9).

Recently published genome wide association studies have identified genetic variants on chromosome 4q25 to be strongly associated with AF(10,11). Moreover, two of these single nucleotide polymorphisms (SNPs), rs2200733 and rs10033464, were also found to be significantly associated with ischemic stroke and particularly cardioembolic stroke (12). These studies suggest that AF is a more significant factor in ischemic stroke than previously recognized and/or that common genetic factors may underlie ischemic stroke and AF.

Identification of genetic factors predictive of high risk for thromboembolism in patients with AF may provide insight into new therapeutic or diagnostic targets. Markers that are associated with stroke/TIA may help to stratify stroke risk and determine patients in whom anticoagulation would be indicated or contraindicated. The aim of this proposal is to perform a GWAS meta-analysis of stroke/TIA within AF cases.

5. Main Hypothesis/Study Questions:

This study aims to identify genomic regions associated with stroke risk in AF patients

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 design

Analysis will be restricted to white ARIC participants with GWAS data. Further, participants will be selected if they had prevalent AF at baseline or incident AF during follow-up. The outcome of interest is ischemic stroke incidence during the follow-up. The general approach will consist of a stroke case control analysis in patients with history of AF. The primary analysis will define ischemic stroke as all strokes, including cardioembolic stroke and thrombotic stroke due to fixed cerebral atherosclerosis, but excluding hemorrhagic stroke. A secondary analysis will use an additional stroke definition: Ischemic Stroke (see above) after or within 2 years of AF diagnosis. Controls will be all ARIC participants with AF who did not experience stroke during the follow-up.

The reason to analyse the data as a case-control study, rather than survival data, is that the date of AF onset is not well defined in ARIC. In some cases, stroke might be the first manifestation of AF. In others, AF could be initially diagnosed in an outpatient setting, not being identified in ARIC until a hospitalization occurs.

Statistical analysis
1) General analysis guidelines
   a. Logistic regression
   b. Additive genetic model
   c. Analyses adjusted for age, sex, population stratification, cohort or site, and hypertension.

2) Primary Analysis
   Ischemic stroke (includes all strokes, including cardioembolic, thrombotic, and undefined stroke, but excluding known hemorrhagic stroke) cases vs. No Stroke/TIA controls - adjusted for age at DNA blood draw, sex, site (CHS), and hypertension.

3) Secondary Analysis
   Ischemic Strokes (includes all strokes, including cardioembolic, thrombotic, and undefined stroke, but excluding known hemorrhagic stroke) after or within 2 years of AF diagnosis - vs. No Stroke/TIA controls - adjusted for age at DNA blood draw, sex, site, and hypertension.

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.cscu.unc.edu/ARIC/search.php
   ____ 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)?
   - MS #1390: ARIC Stroke GWAS (Fornage)
   - MS #1396: CHARGE GWAS for atrial fibrillation (Arking)
   - MS #1397: CHARGE GWAS for lone atrial fibrillation (Arking)
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* 2008.12)
   ____ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________ __________ __________)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

REFERENCES


