ARIC Manuscript Proposal #2472

PC Reviewed: 12/9/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: "Impact of Genetic Variants on the Upstream Efficacy of Renin Angiotensin System Inhibitors for the Prevention of Atrial Fibrillation"

b. Abbreviated Title (Length 26 characters): **"**Atrial Fibrillation Genetics"

2. Writing Group:
Writing group members:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __JR__ **[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: This ancillary study involving the ARIC cohort is now completed and the manuscript is ready for submission for publication.

4. Rationale: The goal of this study was to examine for genetic variants that may impact the efficacy of ACE inhibitors (ACEi) and/or Angiotensin-II receptor blockers (ARBs) for preventing incident atrial fibrillation. This study was motivated by the observation that two common genetic variants identified through genome wide association studies were in close proximity to genes involved in the renin-angiotensin-system pathway.

5. Main Hypothesis/Study Questions: Examine for an interaction between the use ACEi and/or ARBs and genetic carrier status on the risk of incident atrial fibrillation. Genetic carrier status was with respect to the 9 single nucleotide polymorphisms identified to be associated with atrial fibrillation through genome wide association studies.

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: Cohort study utilizing the Cardiovascular Health Study as the discovery cohort and the ARIC study as a replication cohort. Utilizing these population-based cohorts, we examined for SNP-drug interactions on the risk of incident atrial fibrillation.

Inclusion Criteria:
1. Individuals of European ancestry
2. Documentation of use ACEi and ARBs was not missing
3. Had undergone genotyping

Exclusion Criteria: 1. Prevalent atrial fibrillation

Outcome: Incident atrial fibrillation

Other Covariates included in Cox regression models: Baseline age, gender, hypertension, body mass index, diabetes, coronary artery disease, congestive heart failure.

Summary of Data Analysis: Time-to-event analyses using Cox proportional hazards models were employed to evaluate for associations between SNPs, medication use, and incident AF. An additive genetic model was employed for the SNP analyses. ACEi and ARB medication usage were each treated as time dependent covariates as the majority of study participants were initiated on these medications after their initial enrollment into the study. Multivariable Cox proportional hazards models were performed to adjust for potential confounding. Effect modification of the association between incident AF and ACEi and/or ARB use by genotype was evaluated through use of an interaction term in the Cox models. The SNP-drug interaction analyses were performed using both dominant and additive genetic models

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 ICTDER 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

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)?

No relevant closely related manuscripts.

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* 2012.20)
___ 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.