ARIC Manuscript Proposal #1870

PC Reviewed: 12/13/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1a. Full Title: Antihypertensive drug-gene interactions and cardiovascular events

b. Abbreviated Title: CHARGE antihypertensive-Gene GWAS of CVD events

2. Writing Group: Christy L. Avery, Eric A. Whitsel, Til Stürmer, Eric Boerwinkle, (and attempting to maintain symmetry across contributing cohorts), other members of the CHARGE Drug-Gene GWAS Consortium, as well as other interested members of the ARIC CHD, stroke, or blood pressure working groups

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal.

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3. Timeline:

Statistical analyses: November 2011 – February, 2012
Manuscript preparation: March, 2012 – April, 2012
Manuscript revision: May, 2012 – July, 2012

Manuscript submission: August, 2012

4. Rationale:

In the United States, coronary heart disease (CHD) and stroke are leading causes of mortality and account for approximately 630,000 deaths annually [1]. Hypertension is a major CHD and stroke risk factor; previous reports suggest that every 1 mm Hg decrease in mean systolic BP could prevent approximately 10,000 annual CHD deaths in the United States [2]. Yet, the prevalence of hypertension is high (~33%), while the proportion of Americans with hypertension who are treated to guidelines remains a dismal 34% [3].

Numerous genome wide association (GWA) studies have identified common genetic variants influencing blood pressure [4-6], stroke [7,8], and CHD [9-11] across global populations. Reports have also suggested that common genetic variants may modulate the therapeutic efficacy of antihypertensive medications [12,13]. Interactions between antihypertensive treatment and CHD and stroke incidence have also been described [14-16], although such efforts have generally been unreplicated and limited to a small number of SNPs in a handful of candidate genes.

The goal of the proposed analysis is to systematically examine within a common working group whether common genetic variants modify the association between anti-hypertensive treatment and cardiovascular events, here defined as a composite outcome of incident MI, fatal CHD, or incident stroke. This manuscript proposal is part of a larger effort examining gene-drug associations in the CHARGE consortium. Briefly, CHARGE was formed to facilitate GWAS meta-analyses and replication opportunities among multiple large population-based prospective cohort studies, including the Age, Gene/Environment Susceptibility (AGES) -- Reykjavik Study, the Atherosclerosis Risk in Communities Study (ARIC), the Cardiovascular Health Study (CHS), the Framingham Heart Study (FHS), Rotterdam Study (RS), HealthABC (HABC), and the Multi-Ethnic Study of Atherosclerosis (MESA). With genome-wide data on more than 40,000 participants, this collaboration represents a unique resource for evaluating drug-gene interactions in the "real world" of community-based studies. For this effort, the Cardiovascular Health Research Unit at the University of Washington will also contribute data from a case-control study of myocardial infarction and stroke in patients (n=3,900) with treated hypertension.

5. Main Hypotheses/Study Questions:

To examine whether common genetic variants modify the association between specific antihypertensive treatments and CVD, defined as a composite outcome of incident MI, fatal CHD, or incident stroke. *As we are contrasting associations with specific hypertensive treatments, only participants with treated hypertension will be considered in this analysis.*

6. Design and Analysis:

The approach is first to conduct within-study analyses of the association between phenotype and genotype for each of the 2.5 imputed autosomal SNPs and then to combine the findings from the within-study analyses by the method of inverse-variance meta-analysis. Replication will be provided by the Genetics of Hypertension Associated Treatments study

(GenHAT, Donna Arnett, PI), which includes 11,602 events of all types (including MI, stroke, and fatal CHD) among subjects randomized to doxazosin, chlorthalidone, amlodipine, and lisinopril [17]. Our replication goal is to examine associations between the top 1,000 SNPs per antihypertensive group in the GenHAT study

Outcome. The proposed work focuses a composite outcome of incident MI, fatal CHD, or incident stroke. Participants with a prior history of stroke, CHD, or heart failure are ineligible. We will also exclude all participants without treated hypertension.

Exposure. Drug use is assessed by medication inventory at each visit and includes the following categories: diuretics (thiazides, not loops), beta-blockers, calcium channel blockers, and ace inhibitors. Drug use is categorized according to the use at each visit (i.e. time dependent use). For example, beta-blocker use treatment categorization (1 = report beta-blocker treatment at visit j; 0 = report antihypertensive treatment that does NOT include a beta-blocker at visit j; missing for participants not on an anti-hypertensive at visit j) is updated at each visit (j= 1-4). Although we cannot currently estimate total number of ARIC participants for this analysis (we have yet to create these datasets), it is likely large considering that there are approximately n=1,600 beta blocker and n=2,800 thiazide users at visit 1 alone. Of note, the prevalence of use for these drugs, as well as calcium channel blockers and ace inhibitors, will likely increase in later ARIC visits. SNPs are evaluated using an additive model of inheritance.

Model. We propose a proportional hazards model extended to allow time-dependent exposure effects. Participants enter the analysis cohort when they first have treated hypertension, typically defined in CHARGE cohorts as those who have a history of hypertension and who are using drugs that may be used to treat hypertension. Participants are censored at a visit when they are no longer treated, when they die, when they have an event, or when follow-up ends. Participants may re-enter the treated hypertension cohort analysis at a later visit if they restart treatment and are still without a prior history of MI or stroke. Adjustment factors will include age, sex, study site, and ancestry principal components. The interaction term will be drug use (0, 1) by SNP (0-2).

Genome-Wide Significance Level. Second stage (i.e. GenHAT) *P*-value: 1 ÷ number of tests

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 ICTDER04 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 ICTDER04 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 ICTDER04 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)? Manuscript proposal #1513 ("Genome-wide association study of blood pressure using genotype-by smoking and genotype-by-alcohol intake interactions: the ARIC Study", Franceschini), #1484 ("A Gene-Environment Interaction Approach to Genome-Wide Association Analysis of Blood Pressure in the ARIC Study: Gene-Age Interactions in European Americans", Shi), and #1406 (Genome-wide Association Study of Coronary Heart Disease in White Adults of European ancestry: the CHARGE Consortium", Boerwinkle).However, none of the above-referenced manuscripts evaluate interactions with anti-hypertensive agents. Dr. Boerwinkle is also a co-author on this manuscript.

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 (AS #2009.10)
___ 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/

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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.

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