ARIC Manuscript Proposal #2426

PC Reviewed: 9/9/14  
Status: A  
Priority: 2

SC Reviewed: _________  
Status: _____  
Priority: ____

1a. Full Title: Statin drug-gene interactions and MI

b. Abbreviated Title: CHARGE statin-gene GWAS of CHD

2. Writing Group: Christy L. Avery, Eric A. Whitsel, Til Stürmer, Eric Boerwinkle, Jay Stewart (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 working groups

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

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3. Timeline:
Statistical analyses: November 2014 – February, 2015
Manuscript preparation: March, 2015 – April, 2015
Manuscript submission: August, 2014
4. Rationale:

In the United States, coronary heart disease (CHD) is a leading cause of morbidity and mortality, accounting for approximately 425,000 deaths\(^1\) and 1,958,000 years lost to disability or early mortality annually.\(^2\) The 3-hydroxymethyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, also known as statins, are widely prescribed and are highly effective in the management and prevention of cardiovascular disease, including CHD.\(^3,4\) Statin therapy results in lowering of low-density lipoprotein cholesterol (LDL-C) levels by up to 55%, which usually translates into a 20-30% reduction of cardiovascular events.\(^5\) Despite the clinical efficacy of statins in a wide range of populations, inter-individual variability exists with regard to LDL-C lowering response as well as efficacy in reducing major cardiovascular events.\(^6\)

We previously reported two novel genome-wide significant loci associated with LDL-C response in the CHARGE consortium (Postmus et al., in press). The goal of the proposed analysis is to build upon our previous effort to systematically examine within a common working group whether common genetic variants modify the association between statin use and incident CHD. 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). We also have established collaborations with several randomized clinical trials (RCTs), including the Prospective Study of Pravastatin in the Elderly (PROSPER), Anglo Scandinavian Cardiac Outcomes Trial (ASCOT), Collaborative Atorvastatin Diabetes Study (CARDS), Treating to New Targets (TNT), and Justification for Use of Statins in Primary Prevention (JUPITER).

5. Main Hypotheses/Study Questions:

Using an incident case-only design (definite or probable MI or definite fatal CHD), to examine the association between statin use (1,0) and SNP dosage. The case-only design was chosen to facilitate harmonization between the RCTs and observational studies, as a formal interaction analysis was not possible for the former.

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. We will only examine incident MI or fatal CHD events that occur within three years of ARIC study visits 1-4, reflecting the lack of medication inventory outside ARIC study visits.

**Outcome.** Statin use among incident cases of definite or probable MI or definite fatal CHD. Statin use is assessed by medication inventory at each visit. For this analysis, we will assign statin exposure using the medication inventory preceding the event. Events occurring >3 years after the
preceding medication inventory will be excluded.

**Exposure.** SNP_dose

**Model.** We propose a case-only logistic model as shown below:

Statin use $\sim$ SNP_dose + age + sex +... where "+..." denotes additional study specific covariates (e.g. ancestry PCs).

**Genome-Wide Significance Level.** $5 \times 10^{-8}$

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 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 #1406 (Genome-wide Association Study of Coronary Heart Disease in White Adults of European ancestry: the CHARGE Consortium”, Boerwinkle). Dr. Boerwinkle is a co-author on this manuscript proposal.

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.csc.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.
REFERENCES


