ARIC Manuscript Proposal # 1476

PC Reviewed: 2/10/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Genomic variation associated with total mortality among heart failure patients of European and African ancestry: the CHARGE Consortium

b. Abbreviated Title (Length 26 characters): Heart failure mortality GWAS

2. Writing Group: CHARGE heart failure working group

ARIC writing group members: Alanna Morrison (co-lead author of manuscript), Laura Loehr, Wayne Rosamond, Aaron Folsom, David Couper, Patty Chang, Ervin Fox, Eric Boerwinkle

Please note that other authors from additional consortium cohorts will be included. The ARIC authors listed above are those that also chose to participate as writing group members for the GWAS for incident heart failure. This CHARGE manuscript is lead by the ARIC study. Alanna Morrison is the lead first author on the manuscript and Eric Boerwinkle is a starred last author.

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

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3. Timeline: Manuscript drafted by the end of March 2009, plan for journal submission by May 2009.

4. Rationale:

Heart failure (HF) is a common chronic disease characterized by the inability of the heart to efficiently pump blood. HF represents a significant public health burden and prognosis and survival is a significant concern for HF patients. The public health burden of HF and its associated mortality is likely to increase due to the shift in the distribution of the aging population in the United States and an increase in the prevalence of risk factors for HF, such as coronary artery disease, hypertension and diabetes. Thus, it is increasingly important to understand the etiology of HF in order to prevent, diagnose and treat this disease.

In order to investigate the genetic etiology of HF, the first large-scale, high-density genome-wide association study (GWAS) for incident HF in adults of European and African ancestry was conducted as a part of the Cohorts for Heart and Aging Research in Genome Epidemiology (CHARGE) consortium of population-based prospective cohorts that include the ARIC Study, the Cardiovascular Health Study, the Framingham Heart Study and the Rotterdam Study (ARIC MS# 1392). As a part of the CHARGE consortium, 2,277 participants of European ancestry developed incident HF from ARIC, CHS and RS. In addition, 466 participants of African ancestry from ARIC and CHS were identified as having incident HF events. This cohort of participants with HF will be investigated for an association between approximately 2.5 million single nucleotide polymorphisms (SNPs) and total mortality.

5. Main Hypothesis/Study Questions:

Gene variants can be identified that are associated with total mortality among participants with incident HF.

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: Eligible participants for these analyses are of European or African ancestry and free of clinical HF at baseline. In the ARIC study, a GWAS for incident HF was conducted among 691 HF patients of European ancestry and 331 HF patients of African ancestry (MS# 1392). For this study, survival and case fatality will be computed among the 691 participants with HF of European ancestry and the 331 participants with incident HF of African ancestry. In this analysis we will not include incident HF deaths that were not previously hospitalized. Deaths were ascertained through annual phone calls or through ongoing surveillance of health department death certificate files. The association between genome-wide genetic variation and total mortality will be assessed using time-to-event analyses conducted independently in each cohort and meta-analyzed across the four CHARGE cohorts.

Participating groups: the Framingham Heart Study, the Rotterdam Study, the ARIC Study and the Cardiovascular Health Study.

Phenotype: Death (DEAD04), follow-up time (FUTIMED)

Analysis: The association between genomic variation and total mortality among HF patients will be assessed by Cox proportional hazards models evaluated independently in each cohort and the within-study associations will be meta-analyzed across studies. The follow-up time interval is defined as the time between the date of HF diagnosis and the date of all-cause death, the date of last contact if lost to follow-up, or the end of follow-up, whichever came first. Each model will be evaluated separately in participants of European or African ancestry and adjusted for gender and age at HF event. The primary analysis includes only adults of European ancestry.

African-Americans will be evaluated in ARIC and CHS. Only measured genotypes (~830,000) will be analyzed in ARIC African-Americans. Inclusion of ARIC African-Americans has been approved by the ARIC Steering Committee. Use of GWAS data in African-Americans will follow CARe procedures.

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)?

MS# 1392 "The association of genome-wide variation with the risk of incident heart failure in adults of European and African ancestry: a prospective meta-analysis from the CHARGE Consortium"

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* _2006.03, 2007.02_)

___ 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/

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.