ARIC Manuscript Proposal # 1392r

PC Reviewed: 08/12/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The association of genome-wide genetic variation with incident heart failure in adults of European and African ancestry: the CHARGE Consortium

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

2. Writing Group: CHARGE heart failure working group

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

IF APPLIACABLE: Other authors from additional consortium cohorts will be included. Additional ARIC authors may be invited. The plan is to maintain symmetry across cohorts.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _AM_ **[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: Manuscript drafted by August 2008.

4. Rationale:

Cardiac dysfunction is a major public health burden. The projected direct and indirect cost to society in 2006 due to cardiovascular disease is more than $403 billion, and of this nearly $30 billion is attributed to heart failure. The prevalence of heart failure in the general population is estimated at approximately 2%. In general, progression from cardiac dysfunction to heart failure involves remodeling of the left ventricle with activation of neurohormonal systems, such as the sympathetic nervous system and the renin-angiotensin-aldosterone system. Risk factors for the development of heart failure include coronary heart disease, hypertension, left ventricular hypertrophy, valvular heart disease, diabetes, cigarette smoking, less education, overweight and physical inactivity.

Familial factors contribute to heart failure onset and it is estimated that ~18% of the burden in offspring is attributable to parental heart failure. Identification of genetic variation associated with heart failure risk has primarily relied on candidate genes in the renin-angiotensin-aldosterone system and adrenergic receptors. To date, there has not been a large-scale genome-wide investigation of risk variants published.

The CHARGE cohorts involved in the heart failure working group include ARIC, Cardiovascular Health Study, Rotterdam Study and the Framingham Study. The group is chaired by Nick Smith from CHS. The initial paper will present findings from an investigation of approximately 2.5 million single nucleotide polymorphisms (SNPs) and their association with incident heart failure among adults of European and African ancestry.

5. Main Hypothesis/Study Questions:

Gene variants can be identified that associate with increased risk of heart failure.

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 heart failure at the time DNA was obtained. Participants with prevalent heart failure are excluded. The association between genome-wide genetic variation and heart failure onset is assessed using time-to-event analyses conducted independently in each cohort and meta-analyzed across studies.

Participating groups: Framingham Study, Rotterdam Study, ARIC Study, Cardiovascular Health Study.

Phenotype: Incident heart failure (INCHF04)

Analysis: Within each study, failure-time models were used to test the association between each of the ~2,500,000 variants and heart failure-free survival while adjusting for sex and baseline age. The primary analysis includes only Whites.

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)?

None.

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.