1.a. **Full Title:** Genome-wide Association Study of Coronary Heart Disease in White Adults of European ancestry: the CHARGE Consortium

b. **Abbreviated Title (Length 26 characters):** Genome-wide Study of CHD

2. **Writing Group:**
   Writing group members:
   AGES: Vilmundur Gudnason  
   ARIC: Eric Boerwinkle, Aaron Folsom, Gerardo Heiss, Josef Coresh, Tom Mosley, David Couper, Kelly Volcik, Christie Ballantyne, Maja Barbalic  
   CHS: Bruce Psaty, Jerry Rotter, Susan Heckbert, David Siscovick, Nicholas Smith, Thomas Lumley, Kenneth Rice, Joshua Bis, Nicole Glazer, Kent Taylor, Talin Haritunians, Ida Chen  
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __EB__ [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).  
**Name:** Same as above

3. **Timeline:** All genotyping is complete. Analyses to begin immediately.

4. **Rationale:** Coronary heart disease (CHD) attributable to chronic atherosclerosis and acute myocardial infarction is a leading cause of morbidity and mortality in the United States and other developed and developing countries.\(^1,2\) Family studies have identified a role for genetic variation in determining an individual’s risk of CHD, but biologic candidate gene and family-based linkage approaches have met with only limited success in identifying important genes. Genetic variation also appears to be associated with calcified coronary atherosclerosis, but coronary artery calcification represents a very different phenotype from CHD, with a demonstrably different natural history and likely different genetic architecture. Recent advances in polymorphism discovery, population genetics and genotyping technologies have yielded a genome-wide collection of single nucleotide polymorphisms (SNPs) that span the human genome and predict (or “tag”) other unmeasured SNPs because of linkage disequilibrium.\(^3\) Combined with appropriate population-based samples, good phenotyping and state-of-
the art analysis, it is now possible to use a genome-wide association approach to identify genes influencing CHD, along with other heart, lung and blood phenotypes.

5. Main Hypothesis/Study Questions: Investigate the association of genome-wide genetic variation with incident and prevalent coronary heart disease in adults of European ancestry

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).

General Analysis Approach:
Subjects: European-American with ARIC’s usual exclusions for incident CHD and genetic analyses
Exposure: 2.5 million HapMap genetic variants identified in CEPH trios
Outcome: Coronary heart disease (CHD): Incident fatal or non-fatal MI; Incident fatal or non-fatal hard CHD; prevalent MI (secondary outcome).
Primary statistical approach: Additive model (1 df) with robust variance estimates adjusted for sex, age, and either site (CHS) or cohort (FHS)
Secondary statistical approach: Additive model (1 df) with robust variance estimates adjusted for sex, age, and either site (CHS) or cohort (FHS), as well as other established CHD risk factors (including systolic BP, diastolic BP, HTN rx, total and HDL cholesterol, cholesterol lowering rx, diabetes mellitus, and cigarette smoking). This model will be reserved for SNPs selected from the primary statistical approach.
Meta-analysis: all resulting hazard ratios and p-values
Statistical significance: expected false discovery rate adjustment (1/ number of tests performed) (~10^{-7})
Validation and Replication: Possible validation genotyping for selected findings; correlation of findings with those from existing databases (eg, WTCCC and MIGen)

Major Phenotypes to Analyze: Incident MI or hard CHD (fatal or nonfatal MI or sudden cardiac death).

Cohorts Included in Analysis: CHS, FHS, Rotterdam, and ARIC (AGES to be brought in later). Comparison analyses using data from other completed GWAS (WTCCC and MIGen).

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

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.
____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)?

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__)
   ____  B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________ __________ __________)

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