1.a. Full Title: GWAS for BNP

b. Abbreviated Title (Length 26 characters): GWAS for BNP

2. Writing Group:
   Writing group members: Christie M. Ballantyne, Ron Hoogeveen, Maja Barbalic, et al along with CHARGE investigators

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

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3. Timeline:
   Statistical analysis will be performed as soon as the proposal is approved on those individuals with measured BNP levels (n = 5,000 or greater)

4. Rationale:
   The natriuretic peptides (NP) are a family of cardiac hormones with vasodilatory, natriuretic, and antihypertrophic properties. Because natriuretic peptide release is
governed by atrial and ventricular chamber stretch, circulating concentrations of these molecules provide a sensitive indicator of cardiac wall stress. Both B-type natriuretic peptide (BNP) and N-terminal proBNP (Nt-proBNP) concentrations are used clinically to aid the diagnosis of heart failure. Investigators have shown that modest elevations of NP concentrations in apparently healthy individuals predict the occurrence of future cardiovascular events, heart failure, and mortality (Wang et al, NEJM 2004;350:655-63).

In the Framingham Heart Study, as much as 35 to 45% of the unexplained interindividual variation in NP concentrations was attributable to genetic factors (Wang et al, Circulation 2003;108:13-16). Although NP levels are heritable, their genetic determinants have not been characterized. Variants associated with NP concentrations are likely to fall into two categories: those with a direct effect on NP synthesis, degradation, or release; and those associated with subtle alterations in cardiac wall stress, for which NP serve as a sensitive marker. Identification of both types of variants would be important and potentially clinically relevant, given the critical counter-regulatory role of the endogenous NP and the observation that even small variations in NP concentrations are associated with elevated cardiac risk.

5. Main Hypothesis/Study Questions:
We hypothesize that common genetic variants contribute to interindividual variation in NP concentrations. To discover common variation influencing these biomarker traits, we will perform a GWAS as part of the SHARe project.

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).

Eligible Participants
Offspring participants with SHARe genotype data and phenotype data. All participants with phenotype will be used for creation of residuals.

Exclusions
Missing NP data.
Prevalent heart failure or serum creatinine > 2.0 mg/dl.

Phenotype
NT-proBNP were measured during the 4th exam using the Roche assay

Covariates
Age, sex, BMI, SBP, DBP, anti-hypertensive therapy, DM, serum creatinine, prevalent MI, prevalent AF

Analysis
For population-based analyses of quantitative traits, we will use linear-mixed effects (LME) models that have fixed effects for SNP genotypes, and random effects for individuals correlated within families due to polygenic/familial shared effects. We may also consider a faster two-stage approach for population-based association tests. The first
stage use least-squared regressions or logistic regressions ignoring correlation among family members for all SNPs. The second stage uses LME or GEE that accounts for correlation among family members on a subset of SNPs showing evidence for association based on the first-stage analysis results.

**Secondary analyses**
In secondary analyses, we will perform analyses for a subset of SNPs showing evidence of association, in subgroups according to age, gender, and body mass index.

**Imputation**
In addition to testing for association with genotyped SNPs, we plan to test for association with imputed genotypes for SNPs not genotyped in our 550K scan, using methods such as described by or Abecasis et al. (http://www.sph.umich.edu/csg/abecasis/MACH/).

**Multiple Testing**
We will evaluate our results by using such methods as Bonferroni corrections, false discovery rates, weighted false discovery rates or other approaches as appropriate. Location of a SNP (near or far from a gene), its functionality, and other information will be used in evaluating which results may be real. These are the basic methods that we will apply. Methods for genome-wide association studies are still in flux. As other approaches develop, we will consider their use.

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? ___ x_

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

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* 2008.10________)

_____  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/

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.