**ARIC Manuscript Proposal #2261**

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| **PC Reviewed: 11/12/13** | **Status: A** | **Priority: 2** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1.a. Full Title**: **Differences in natriuretic peptide levels by race**

**b. Abbreviated Title (Length 26 characters)**: **Natriuretic Peptides and Race**

**2. Writing Group**:

Writing group members: Deepak K. Gupta, Thomas J. Wang, Susan Cheng, Brian Claggett, Others Welcome, Kenneth Butler, Thomas Mosley, Suma Konety, Ron Hoogeveen, Eric Boerwinkle, Elizabeth Selvin, Josef Coresh, Wen Hong Linda Kao, Christie M. Ballantyne, Scott D. Solomon.

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


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**3. Timeline**: Analysis will begin following proposal approval with the aim of completing analysis and a manuscript within 6 months.

## 4. Rationale:

Natriuretic peptides (NP) are hormones with cardiovascular and metabolic effects, including the promotion of natriuresis, diuresis, and vasodilation, as well as triggering of lipolysis, weight loss, and improved glucose sensitivity.[1] NP levels have diagnostic and prognostic value across the spectrum of cardiovascular disease,[2, 3] regardless of race and gender.[4] However, African-Americans have a higher prevalence of cardiovascular risk factors, such as hypertension and diabetes mellitus, and are more frequently obese, as compared to Caucasians.[5] It has been suggested that African Americans may have a relative deficiency of NP and there some observations indicate that African-Americans may have lower levels of NP.[4, 6-9] However, NP levels according to race have not been completely characterized and whether the higher prevalence of cardiovascular disease and risk factors is related to a relative deficiency of NP in African-Americans is unknown.

Several factors may be associated with NP levels. Obesity and insulin resistance are associated with lower levels of NP.[10, 11] Despite elevations on left ventricular filling pressures, a known stimulus of NP release, it has previously been demonstrated that obese patients have lower levels of NP.[12] The type of body mass, i.e. lean vs. fat, may also influence NP levels in obesity.[13, 14] While lower NP levels have been observed among those with metabolic syndrome, lower NP levels may also contribute to the risk of diabetes mellitus.[8, 15] In contrast, higher NP levels have been described with lower renal function, lower hematocrit, and higher blood pressures.[16]

Genetic factors may also contribute to NP levels. Polymorphisms in the NP system have been previously described.[17-22] Corin is an enzyme that is partly responsible for the activation of NPs and African-Americans may also have a higher prevalence of a corin allele (T5551/Q568P) which limits the ability to convert proANP to active ANP, leading to increased susceptibility to salt sensitive hypertension and left ventricular hypertrophy.[23, 24] These observations suggest that genetic factors, and possibly the relative contribution of more European vs. more African ancestry may contribute to NP levels.

The Atherosclerosis Risk in Communities Study, which includes a largely bi-racial (Caucasian and African-American) cohort, offers a unique opportunity to characterize NP levels according to race. Furthermore, prior genetic admixture mapping in African-American participants in ARIC will allow for the additional assessment of the relationship between race and NP levels.

## 5. Main Hypothesis/Study Questions:

Primary Objective:

1) To describe NT-proBNP levels according to race.
   *Hypothesis: African-Americans have significantly lower levels of NT-proBNP than Caucasian Americans, independent of age, gender, obesity, insulin resistance, fat*

*mass, renal function, anemia, blood pressure, glucose levels, smoking status, and other traditional risk factors for cardiovascular disease.*

Secondary objectives:

1) To assess the contribution of percentage European genetic ancestry to NT-proBNP levels among African-Americans.
   *Hypothesis: NT-proBNP levels are significantly related to the percentage of European genetic ancestry in African-Americans, independent of "non-genetic" factors.*
2) To assess whether the association between race and NT-proBNP levels is modified by prevalent cardiovascular disease.
   *Hypothesis: Whether or not cardiovascular disease is present, African-Americans have lower levels of NT-proBNP than Caucasian-Americans.*

**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).**

Study design

Cross sectional study of ARIC cohort participants at visit 4.

Study population

To be included in this analysis, participants must have undergone measurement of NT-proBNP levels at visit 4.

Exclusion criteria include:

- Missing NT-proBNP levels at visit 4.
- Missing or self-reported race other than Caucasian or African-American.
- Missing covariates regarding factors related to NT-proBNP levels, including but not limited to: field center, age, gender, height, weight, waist-hip ratio, body mass index, diabetes mellitus, hypertension, prevalent CHD, heart failure, stroke, atrial fibrillation, smoking status, alcohol status, systolic blood pressure, diastolic blood pressure, glucose, creatinine, left ventricular hypertrophy by ECG, and hematocrit.

Exposure and covariates

Primary: Participants will be stratified according to race, defined by self-report as either African-American or White. Clinical characteristics will be compared between races. In particular, clinical variables to be evaluated include: field center, age, gender, socio-economic status, smoking status, alcohol use, height, weight, body mass index, waist-hip ratio, systolic blood pressure, diastolic blood pressure, heart rate, hematocrit, creatinine, estimate glomerular filtration rate, urine protein to creatinine ratio, ECG LVH, and troponin.

Secondary: Percentage European genetic ancestry (PEA) in African-Americans will be quantified from DNA samples obtained at visit 1 as previously described.[25] Briefly, ancestry informative markers will be used to estimate PEA. Ancestry informative markers are single

nucleotide polymorphisms (SNPs) who frequencies significantly differ between persons of Caucasian and African ancestral descent, where the race-specific frequency of each SNP in the ancestry informative markers was estimated from West African and European samples.

Outcome

The primary dependent variable of interest will be NT-proBNP.

Statistical analyses:

Clinical variables will initially be compared according to race. T-tests, Wilcoxon rank sum tests, and Chi squared tests, will be utilized as appropriate to compare clinical characteristics between groups. The distribution of NT-proBNP levels will be assessed according to race and appropriately transformed prior to statistical tests to compare NT-proBNP levels between races.

Multivariate linear regression analysis will be performed to assess the relationship between race (independent variable) and NT-proBNP (dependent variable) when adjusted for the clinical characteristics described above. An interaction term of race x prevalent CVD will then be included in the linear regression models to assess whether the relationship between race and NT-proBNP levels is modified by prevalent CVD status. Prevalent cardiovascular and/or renal disease will be defined as hypertension, coronary heart disease, heart failure, atrial fibrillation, stroke, or chronic kidney disease (defined as eGFR < 60ml/min/1.73m$^2$). If the race x prevalent CVD interaction term is significant ($p < 0.10$), a stratified analysis according to the presence or absence of prevalent CVD will then be presented.

Among African-Americans in whom PEA data is available, NT-proBNP levels will be evaluated across quartiles of PEA using univariate and multivariate linear regression analysis. Covariates in multivariate analysis will include traditional clinical "non-genetic" factors to assess if genetic ancestry contributes to NT-proBNP levels independent of these "non-genetic" factors. Variance in NT-proBNP explained by PEA will be calculated as the square of spearman (unadjusted) and Kendall partial T (adjusted) coefficients.[26]

Limitations

NT-proBNP was only assessed at visit 4. NT-proBNP is the metabolically inactive cleavage product of the prohormone and the active hormone (BNP) was not measured. Detailed measures of cardiac structure and function, such as left ventricular mass and left atrial size, that may contribute to NT-proBNP levels were not measured at visit 4. However, it has been demonstrated that African-Americans tend have higher LV mass then Caucasian Americans and therefore, a finding of lower NT-proBNP levels in African-Americans would likely be strengthened with further inclusion of adjustment for features of cardiac structure and function. This analysis will not include assessments of genetic polymorphisms that may contribute to differences in NT-proBNP levels between races. Furthermore, NT-proBNP will be assessed, but not BNP, ANP, or CNP levels as these were not measured at visit 4. In the estimation of PEA, which is based upon samples from West Africa and Europe, there may be misclassification bias due to inability to account for local ancestry. In addition, results of analyses according to race may not be generalizable to all African-American or Caucasian American populations due to design of ARIC in which participants were enrolled from 4 specific communities.

**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**

**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)?**

ARIC MS Proposal #1309: Genome-wide admixture mapping analyses of cardiovascular and related metabolic traits. Linda Kao, Ching-Yu Cheng, Man Li, David Reich, Jim Wilson, Joe Coresh, Eric Boerwinkle.

- Cheng, C. Y., D. Reich, et al. (2012). "African ancestry and its correlation to type 2 diabetes in African Americans: a genetic admixture analysis in three U.S. population cohorts." PLoS One **7**(3): e32840.
- Maruthur, N. M., W. H. Kao, et al. (2011). "Does genetic ancestry explain higher values of glycated hemoglobin in African Americans?" Diabetes **60**(9): 2434-2438.
- Cheng, C. Y., D. Reich, et al. (2010). "Admixture mapping of obesity-related traits in African Americans: the Atherosclerosis Risk in Communities (ARIC) Study." Obesity (Silver Spring) **18**(3): 563-572.

ARIC MS Proposal #1579: GWAS for BNP. Christie M. Ballantyne, Ron Hoogeveen, Maja Barbalic, et al along with CHARGE investigators

ARIC MS Proposal #1966: The association between NT-proBNP with incident diabetes. Mariana Lazo, Frederick L. Brancati, Seamus Whelton, Josef Coresh, Chiadi E. Ndumele, Ron Hoogeveen, Christie M. Ballantyne, J. Hunter Young, Elizabeth Selvin.

- Lazo, M., J. H. Young, et al. (2013). "NH2-Terminal Pro-Brain Natriuretic Peptide and Risk of Diabetes." Diabetes **62**(9): 3189-3193.

Fox, E. R., S. K. Musani, et al. (2013). "Association of plasma B-type natriuretic peptide concentrations with longitudinal blood pressure tracking in African Americans: findings from the Jackson Heart Study." Hypertension **61**(1): 48-54.

**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-NTProBNP&TropT & 2004.10__)

**___ 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/

**12a. 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.**

**12b. The NIH instituted a Public Access Policy in April, 2008** which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

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