1.a. Full Title: Genetic polymorphisms of the natriuretic peptide system, incident heart failure, and cardiac structure and function in the Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): Natriuretic genetics, HF and Cardiac Function

2. Writing Group:
   Writing group members: Orly Vardeny, Eric Boerwinkle, Christie Ballantyne, Brian Claggett, Scott Solomon, OTHERS WELCOME

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

First author: Orly Vardeny
Address: University of Wisconsin School of Pharmacy
          777 Highland Ave
          Madison, WI 53705-2222

          Phone: 608.265.0591       Fax: 608-265-5421
          E-mail: ovardeny@pharmacy.wisc.edu

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: Scott D. Solomon, MD
   Address: Brigham and Women’s Hospital

          Phone: 857-307-1960
          E-mail: ssolomon@rics.bwh.harvard.edu

3. Timeline: Analysis to begin immediately, First draft by January 2015
4. **Rationale:**

Increases in B-type natriuretic peptide (BNP) levels have been associated with fluid status and neurohormonal activation in patients with heart failure.(1) Variants in the natriuretic peptide receptor (NPR) genes have been associated with altered biologic function and disease. The natriuretic peptide precursor-B (NPPB) -381T/C polymorphism is found in the gene’s promoter region. Carriage of the -381C allele was associated with a 1.8-fold increased expression of BNP levels in cultured cells compared to the T allele.(2) In addition, natriuretic peptide receptor (NPR)-2 variants have also been associated with BNP concentrations, blood pressure, and left ventricular end diastolic pressure.(3-5)

Predisposition for development of heart failure is dependent on many factors, including genetic variations within the pathways that are affect disease progression. We propose to investigate potential genetic factors that may associate with NT-proBNP levels, blood pressure changes, cardiac structure and function, and the development of incident heart failure.

5. **Main Hypothesis/Study Questions:**

*We hypothesize that genetic variants in the natriuretic peptide system are associated with incident heart failure and cardiac structure and function. Further, we hypothesize that these variants will be associated with NT-proBNP levels and blood pressure, and modulate the relationship between BNP, blood pressure, cardiac structure and function, with incident heart failure.*

**Specific Aims:**

1. To assess the relationship between natriuretic peptide system polymorphisms with NT-proBNP levels at visits 4 and 5.
2. To assess the relationship between natriuretic peptide system polymorphisms with presence of hypertension or use of antihypertensive medications at visits 1 through 5
3. To assess whether natriuretic peptide system polymorphisms are associated with cardiac structure and function at visit 5
4. To assess the association between natriuretic peptide system polymorphisms and incident 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).**

Subjects with prevalent heart failure, at visit one will be excluded. Prevalent heart failure will be defined as either participant reported medication use for heart failure or Gothenberg score=3.

**Analysis methods:**
Primary Exposure Variable:

- Natriuretic peptide precursor-A (NPPA) variants: rs5068 and rs198358
- Natriuretic peptide precursor-B (NPPB) variants: rs198388, rs198389, and rs632793
- Natriuretic peptide receptor (NPR)-2 variant: rs10758325

Primary Endpoint: The primary endpoint will be the relationship between NP variants and incident heart failure from visit 1 using ICD-9 codes.

Secondary endpoints will assess the relationship between NP variants:

1. levels of NT-proBNP at visit 4
2. presence of hypertension defined as BP > 140/90 or use of antihypertensive medication.
3. Cardiac structure and Function at Visit 5 by echocardiography - measures include ventricular volumes, atrial volumes, systolic function (ejection fraction and strain), Doppler measures of diastolic function.

Analysis:

1. Subjects with prevalent HF at visit 1 will be excluded.
2. Baseline characteristics will be compared between individuals based on genotype for the variants of interest. Gene frequencies will be compared between white and black participants.
3. We will compare incidence rates of incident heart failure by genotype.
4. NT-proBNP will be compared across genotypes.
5. The following measures of cardiac structure/function will be compared across genotypes:
   a. Left ventricular end-diastolic and end-systolic volume.
   b. Ejection fraction
   c. LV wall thickness and LV mass
   d. Left atrial volume
   e. Global longitudinal Strain
   f. Diastolic function (E’, E/E’)

Limitations

- There are other potential genetic modifiers affecting the risk for incident heart failure; this proposal studies specific candidate genes
- NT-proBNP not available at all visits, limiting ability to perform longitudinal analyses of associations of genetic analyses with changes in NT-pro-BNP levels

References


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.cscd.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)?

There is no overlap with current manuscript proposals. A few relevant proposals include the following:


11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?

Yes  _X_ No

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (list number* __________)

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.