ARIC Manuscript Proposal #3064

PC Reviewed: 2/13/2018 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Endogenous Sex Hormone Levels and Risk for Incident Heart Failure Among Men and Post-Menopausal Women: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Sex hormones and Heart Failure

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

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3. Timeline: Analyses will be performed over Winter/Spring 2018. Abstract is planned for submission to AHA Scientific Sessions 2018 (Fall) and full manuscript draft by end of 2018.

4. Rationale:

Heart failure (HF) is a chronic condition that currently affects about 6.5 million adults in the U.S. and is estimated to increase by 46% by 2030. The Atherosclerosis Risk in Communities (ARIC) study has estimated an annual incidence of 960,000 new HF cases /with age, sex and race based differences.[1] HF is broadly classified into two categories, heart failure with reduced

(HFrEF) or preserved ejection fraction (HFpEF), each accounting for ~50% of disease burden. Sex differences in HF have been described in the past with men and women having a distinct set of risk factors.[2] Men develop HF more frequently as compared to women and at a younger age.[2] However, women are more likely to develop HFpEF and men more likely HFrEF.[2] Independent of these differences in risk factors, women have a unique clinical presentation and better survival.[2 3] The underlying biological mechanisms leading to these sex differences is uncertain but may be related to variations in levels of endogenous sex hormones. Additionally, data from the Women's Health Initiative and ARIC studies showing that early menopause is associated with an increased risk of heart failure, suggesting the role of endogenous sex hormones in the evolution of HF. [4, 5]

Previous studies have looked at the association of sex hormones with cardiovascular risk factors and cardiovascular disease (CVD), and the associations have differed by sex. In men, some studies have found that low testosterone levels were associated with increased risk for cardiovascular mortality and atherosclerosis.[6, 7] However prior work in ARIC evaluating a subset of men (n=1558) did not find any association of testosterone with CVD or HF or mortality.[8]

In women, an opposite pattern is seen, with elevated androgen levels being associated with advanced atherosclerosis and increased CVD risk.[6, 9-12] Specifically, in relation to HF, a recent analysis in the Multi-Ethnic Study of Atherosclerosis (MESA) demonstrated higher levels of androgens were associated with a higher risk of incident HF events among post-menopausal women.[12] Post-menopausal women and women with high testosterone levels were found to have an increase in adiposity and insulin resistance and a decrease in HDL cholesterol, which may be mediating factors in the association between sex hormones and CVD.[9, 13-16] Although in MESA, the association of higher testosterone/estradiol ratio to CVD, coronary heart disease (CHD), and HF was independent of these factors.[12] Sex hormone binding globulin (SHBG) had a mixed pattern on CVD risk, being inversely associated with coronary artery calcium (CAC) in pre-menopausal women, but positively associated with CAC in post-menopausal women.[17, 18] However higher SHBG (and thus lower free testosterone) had favorable associations with left ventricular remodeling in post-menopausal women.[19]

The association of hormone therapy (HT) in post-menopausal women with cardiovascular risk has yielded mixed results, the Heart and Estrogen/progestin Replacement Study (HERS) in women with established CHD showed no reductions in CVD events with use of conjugated estrogens + progestin,[20] while a trial using estradiol/norethindrone acetate found the risk of incident HF was decreased in apparently healthy women in Denmark who were recently post-menopausal.[21] While no clinical trial has assessed the role of testosterone therapy on incident HF in women, testosterone supplementation was associated with improvement of risk profile, clinical symptoms and quality of life, among women with congestive HF and men with HFrEF.[22-24]

Thus, there is presently a lack of clarity on the role of sex hormones in CVD and especially in incident HF. Some of this existing knowledge gap can be attributed to the limitations of studies previously conducted. They have largely been in men with some studies in post-menopausal women. This lack of generalizability has been compounded by a lack of racial diversity as well as varying risk profiles. Other limitations included inadequate sample size, cross-sectional study design, residual confounding and short duration of follow-up. For the most part, the focus of these studies has been on HFrEF with few focusing on differences in HF types or solely HFpEF. The prior ARIC analysis that found no association of testosterone in HF was

only in a subset of men.[8] Therefore there is a need to replicate this in a larger sample size of men with adequate follow-up, and to also study these relationships among women.
We propose to address this gap by examining the associations of sex hormones (testosterone, dehydroepiandrosterone and sex hormone binding globulin (SHBG)) with incident HF among post-menopausal women in the community-based ARIC study. We will also include men as a comparison group. As outlined below and consistent with the prior studies described above, we hypothesize the associations between sex hormones and incident HF will differ by sex.

5. Main Hypothesis/Study Questions:

a. Among post-menopausal women in ARIC, we hypothesize that higher levels of androgens (testosterone and DHEA) at baseline will be associated with an increased risk of incident HF and that associations will be stronger for HFrEF than for HFpEF
b. Among post-menopausal women in ARIC, we hypothesize that higher levels of SHBG at baseline (and thus lower level of free testosterone) will be associated with lower incidence of HF and of HFrEF, specifically.
c. Among men in the ARIC study, we hypothesize that there will be no association between higher levels of androgens and incident HF.

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: Our study will be a longitudinal study and will assess the associations between sex hormone levels measured at ARIC visit 4 (1996-98), and the subsequent risk of incident HF from ARIC visit 4 (1996-1998) through 2015. We will also examine associations with type of HF events (HFpEF vs HFrEF) occurring after 2005, the time at which ARIC began adjudicating HF classification up until the most recent adjudication date. Visit 4 serves as baseline for the present study because plasma total testosterone, DHEA, and SHBG was measured in the whole ARIC cohort at Visit 4 (men and women, N>10,000).

Exclusion/Inclusion criteria: All ARIC visit 4 participants will be included in the study. The main exclusion criteria are prevalent HF before Visit 4, participants with missing sex hormone data at baseline (i.e Exam 4) and missing outcome data.

Main exposure (sex hormones): Morning blood samples were obtained from participants at Visit 4 (1996–1998) and the plasma was stored at -80°C. Plasma total testosterone was measured by liquid chromatography mass spectrometry in 2012. SHBG and DHEA were measured from the same plasma samples. Estradiol has not been measured for the whole cohort. There is also no information at ARIC visit 4 regarding albumin levels to calculate bioavailable testosterone.

Sex hormone levels are known to have a skewed distribution and will be modeled as log transformed continuous variables (per 1 SD) or as a categorical variable (tertiles).

Primary Outcome: Incident (definite or probable) HF hospitalizations or HF death.
Secondary outcomes: Incident HFpEF and HFrEF

Other covariates: Age, sex, race-ARIC field center group, body mass index (BMI) / waist to hip ratio, education, smoking, physical activity (by Baecke score), systolic blood pressure, use of anti-hypertensive medications, diabetes, total cholesterol, HDL cholesterol, use of lipid lowering medications, estimated glomerular filtration rates (eGFR), and prevalent coronary heart disease (CHD). Additionally, for post-menopausal women, the use of hormone therapy (HT).

Statistical analysis:
Primary analysis (all HF): Given that the sex hormone distribution differs by sex and is not overlapping, all analyses will be stratified by sex. Cox proportional hazard regression models will be used to assess the relationship of each sex hormone with incident HF.

Secondary analysis (HF subtypes): Stratified by sex, we will use Cox proportional hazard models to determine the relationship between each sex hormone and incident HFpEF and HFrEF after accounting for the 7-year immortal person time from ARIC visit 4 (1996-98) to 2005, when adjudication for HFpEF and HFrEF was introduced.

The sex-stratified models will be progressively adjusted as follows:
Model 1 (demographics): adjusts for age and race-center groups
Model 2 (+lifestyle factors): model 1 + education, BMI, waist to hip ratio, physical activity, smoking (and in women, use of HT)
Model 3 (+CVD risk factors that are potentially mediating): model 2 + systolic blood pressure, use of antihypertensive medications, total cholesterol, HDL-C, use of lipid lowering medications, diabetes, eGFR, and prevalent CHD

Primary analysis will be performed for testosterone, DHEA, and SHBG separately. We will also analyze testosterone and SHBG together in the same model, as a surrogate measure for free (unbound) testosterone.

In sensitivity analysis, we will exclude those with prevalent and incident CHD during follow-up. Sensitivity analyses will also include restricting to post-menopausal women who are not on HT.

We will also look for interaction by age and race.

Two-sided P values <0.05 will be considered to be statistically significant. All analyses will be performed on Stata version 14.

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 ICTDER 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? ____ Yes X 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"? ____ 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)?

There are a number of proposals related to incident heart failure and some of the most relevant ones are enlisted below:

#2923 Prospective study of the association between endogenous testosterone and incidence of atrial fibrillation

#1883: The association of Insulin Resistance with Incident Heart Failure: The Atherosclerosis Risk in Communities (ARIC) study

2555: Lipoprotein(a) and incident heart failure hospitalization: ARIC study

2224: 25-hydroxyvitamin D and risk of incident heart failure: The Atherosclerosis Risk in Communities Study (ARIC)

#1761: QT subintervals and QRS|T angle as independent predictors of incident heart failure in the ARIC study.

#2022: Peripheral arterial disease and risk of incident heart failure in the Atherosclerosis Risk in Communities Study

#1580: Social Isolation, Psychological Distress, and the Risk of Incident Heart Failure: Findings from the Atherosclerosis Risk in Communities Study

#1893: Serum magnesium, phosphorous, calcium and risk of incident heart failure: The Atherosclerosis Risk in Communities Study

2525: The Association of Age at Menopause and Incident Heart Failure: The Atherosclerosis Risk in Communities (ARIC) Study

2049: Relationship between electrocardiographic QRS duration, cardiac structure and function, and incident heart failure in African-Americans in the Atherosclerosis Risk in Communities Study

1835: Subclinical Atherosclerosis, Glucose Status and Incident Heart Failure: The Atherosclerosis Risk in Communities Study

2233: Depression and incident heart failure: A prospective analysis from the ARIC Study

1352: The association of orthostatic hypotension with incident heart failure

1852: Systolic Blood Pressure Control and incident Heart Failure: The Atherosclerosis Risk in Communities Study

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*)

AS #2013-21. Led by Dr Christie Ballantyne and Dr Ron C. Hoogeveen, includes all ARIC participants at visit 4

___ 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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes _X__No.

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