ARIC Manuscript Proposal #3466

PC Reviewed: 9/10/19 **Status: _____** **Priority: 2**

SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Association of Adiponectin with Risk of Incident Cardiovascular Events and Heart Failure Hospitalization in Older Adults: Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): adiponectin, heart failure and global cardiovascular disease (CVD)

2. Writing Group:

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

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3. Timeline:

Analysis is anticipated to begin as soon as approval is obtained. The manuscript is to be prepared as soon as visit 5 adiponectin measurements (Denka Seiken assay) are available. The analysis and manuscript preparation is anticipated to take place within one year of approval of the proposal.

4. Rationale:

Adiponectin is a 247 amino acid peptide secreted by adipose tissue directly involved with multiple metabolic pathways. Plasma levels are inversely related to body weight, insulin resistance, and type 2 diabetes.[1–3] Adiponectin also has anti-inflammatory and anti-atherogenic properties. [4] Considering these favorable associations with cardiovascular disease (CVD) risk factors, it is surprising that only a few studies in humans found an inverse association between adiponectin and risk of incident CVD in individuals without prior CVD. [5,26] In contrast, multiple other studies found a positive association between adiponectin and several adverse outcomes among individuals with established CVD or at high risk for CVD. Higher adiponectin has been associated with increased mortality in patients with heart failure (HF) [6,7] and with increased overall and CVD mortality [8-11].

Two large prospective studies have investigated the association of adiponectin with new-onset heart failure in older adults. The Cardiovascular Health Study (CHS) recruited 3,228 subjects (mean age of 74±5 years) without prevalent HF or CVD.[12] During the 11.7 years' follow up, it showed that the relationships of total and HMW adiponectin with HF were nonlinear, with significant associations observed only above their medians. Consistent with the HF findings, higher adiponectin tended to be associated with left ventricular systolic dysfunction and left atrial enlargement. However, echocardiographic

data were only available in a subset of the CHS cohort and current state-of-the-art measurements of LA size or LV diastolic functions were not performed. Similarly, NT-proBNP was available only for a subgroup. Meaningful associations with systolic versus diastolic HF were not assessed separately, because such data were unavailable in over half of incident HF cases. In the Copenhagen City Heart Study, 5574 men and women without ischemic heart disease or HF were followed for 8.5 years.[13] Plasma adiponectin and proBNP were strongly associated (P < 0.001). Adiponectin was a predictor of HF: HR1.20 (95%CI 1.06-1.30; P = 0.003]. The association vanished when plasma pro-BNP was included in the analysis, HR 1.08 (95% CI 0.95-1.23; P = 0.26).

With regards to the association of adiponectin and incidence CVD, the data are inconsistent. The Dallas Heart Study (DHS) reported that over median 10.4 years of follow-up increasing adiponectin quartiles were positively associated with MACCE (major adverse cardiovascular and cerebrovascular events, a composite of CVD death, nonfatal MI, nonfatal stroke, or coronary revascularization by percutaneous coronary intervention or coronary artery bypass grafting) Q4 vs. Q1, HR=1.71 (95% CI 1.13, 2.60); and HF Q4 vs. Q1, HR=2.95 (95% CI 1.14, 7.67).[14] A 20 year prospective analyses of the Rancho Bernardo Study in 1513 community-dwelling men and women, aged 50 to 91, showed that higher adiponectin concentrations predicted reduced risk of non-fatal myocardial infarction in men only; adiponectin was not associated with fatal incident CHD events or 20 year CHD mortality (N=215 deaths) in either sex. However, a 20-year time frame may be less relevant for older adults given competing causes of mortality besides ASCVD events.[11]

In two other studies adiponectin exhibits distinct associations with mortality in elders, which shift from U-shaped to flat to direct with greater baseline cardiovascular dysfunction, but become more consistently adverse after accounting for metabolic/inflammatory factors presumed to be favorably regulated by the adipokine.[15,16] Data on the association between adiponectin and stroke are inconsistent.[17-19]

Importantly, insufficient data are available for the predictive value of adiponectin on incidence global CVD including HF in older adults. It's not clear whether high adiponectin levels are associated with structural changes in the heart and are associated with other biomarkers related to pressure overload (NT-proBNP), myocardial changes (hsTnT and hsTnI), fibrosis (galectin 3) and inflammation(hs CRP). The ARIC dataset incorporates quantification of adiponectin and other cardiac biomarkers, detailed echocardiographic measurements as well as rigorous adjudication of outcome events. [20-24] Thus the ARIC study provides us a unique opportunity to investigate the above questions in a larger, older cohort population.

Therefore, we aim to investigate the association of adiponectin with incident CV events and heart failure hospitalization following ARIC visit 5. Furthermore, we aim to use the available echo data and other relevant biomarkers to gain an understanding of the potential mechanism(s) by which adiponectin may be involved in the development of heart failure.

5. Main Hypothesis/Study Questions:

Hypotheses:

1. Adiponectin will predict risk for incident global cardiovascular events (CHD, stroke, HF and specifically HFrEF) in older adults.
2. Adiponectin will predict CVD mortality and overall mortality in older adults.
3. Adiponectin levels are associated with echocardiographic parameters related to heart structural changes and cardiac biomarkers of subclinical CVD.
4. Adiponectin measured by a large unbiased proteomic array at visit 5 (SOMAscan) are highly correlated with adiponectin levels measured by a conventional method (Denka Seiken assay) and associated with incident global CVD.
   4.1. Other proteins measured by a large unbiased proteomic array at visit 5 (SOMAscan) that are highly correlated with adiponectin are associated with incident global CVD.
5. Genetic variants at the ADIPOQ locus and other loci are associated with adiponectin levels and incident global CVD.

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 methodological limitations or challenges if present).

Study Design:

In the primary analysis we will assess the association between adiponectin levels as measured with the Denka Seiken assay at visit 5 and global CVD, CV mortality and overall mortality.

In secondary/exploratory analyses we will assess the correlation between the visit 5 adiponectin levels using the Denka Seiken assay and adiponectin measurements by SOMAscan performed at visit 5 in those ARIC participants who have both measurements available. Subsequently, we will evaluate the association between adiponectin levels as

measured by SOMAscan at visit 5 and global CVD, CV mortality and overall mortality. We will further explore in an unbiased manner the association of 5000 plasma proteins as measured by SOMAscan at visit 5 with incident global CVD using Qiagen Ingenuity Pathway Analysis with Causal Pathway Analysis to elucidate potential upstream regulators associated with circulating adiponectin levels.

Exposures:

The major exposure of interest for this study will be adiponectin levels at visit 5. Adiponectin level will be modeled both as a continuous variable and categorical variable. To test our forth hypothesis we will use proteomic data on 5000 plasma proteins from SOMAscan v.4 obtained at ARIC visit 5.

Outcomes

1. Incident total CHD (fatal CHD, definite/probable MI, cardiovascular revascularization)
2. Incident hard CHD (fatal CHD, definite/probable MI)
3. Incident ischemic stroke
4. Incident HF hospitalization
5. Global CVD (total CHD + stroke+ heart failure)
6. CV mortality and total mortality

Co-variates

Co-variables of interest include age, sex, race, heart rate, body mass index (BMI), systolic (SBP) and diastolic blood pressure (DBP), HDL cholesterol, hypertension status, treatment for hypertension, diabetes status, smoking status, history of coronary heart disease (CHD), estimated glomerular filtration rate (eGFR),

Echocardiographic parameters, cardiac biomarkers of Interest

Left ventricular ejection fraction (LVEF), Left ventricular mass index (LVMI), E/A ratio, left atrial dimension (cm), Left ventricular hypertrophy (LVH) (%), LV wall thickness (mm), LV end diastolic volume /body surface area LVEDV/BSA (ml/m^2), aortic wall thickness, hs- cTnT, hs-TnI, NT-proBNP, galectin 3, hsCRP.

Inclusion/ exclusion criteria:

All eligible ARIC participants will be included in the study. Standard ARIC exclusions (race exclusions for different communities) will apply. The exclusion criteria include

participants without data on exposure, outcome, or covariates and participants with prevalent CHD, prevalent stroke, prevalent HF hospitalization, with a history of HF, with missing information on prevalent HF hospitalization. Specifically for the mortality outcomes, we will not exclude prevalent CVD.

Statistic Analysis plan:

1. Prospective analysis assessing V5 adiponectin levels (Denka Seiken assay) and incident CHD, stroke, HF, global CVD, CV mortality and overall mortality.

Analysis (separately for male and female)

i: Cox proportional hazard models assessing association between V5 adiponectin levels with incident CVD events and mortality.

1) The association of adiponectin as continuous variable with incident CHD, stroke, HF, global CVD, CV mortality and overall mortality.
   Model 1: age and race
   Model 2: PCE model (age, race, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, antihypertensive medication use, current smoking, and diabetes mellitus)
   Model 3: Model 2+BMI+ eGFR.

2) The association and 4-year risk for categories of Adiponectin (tertiles) with incident CHD, stroke, HF, global CVD, CV mortality and overall mortality.
   Model 1: age and race
   Model 2: PCE model
   Model 3: Model 2+BMI+ eGFR.

ii: AUC, NRI, IDI for different models for HF, ASCVD, global CVD, CV mortality and overall mortality

Model 1: basic model: PCE model
Model 2: PCE+ lab 1 (hs-cTnT + NT-pro-BNP + hs CRP)
Model 3: age+race+lab 2 (hs-cTnT + NT-pro-BNP + hs CRP+adiponectin)
Model 4: PCE+ lab 2 (hs-cTnT + NT-pro-BNP + hs CRP+adiponectin)

1) NRI cutpoints for 10 year risk- 5%-10% for ASCVD; 6% and 20% for global CVD.
2) NRI cutpoints for 4-year risk -2% and 4% for ASCVD; 2.4% - 8% for global CVD.

2. Associated of V5 adiponectin levels (Denka Seiken assay) with echocardiographic parameters and cardiac biomarkers of interest. (Separately for male and female).

   i: Echo parameters and cardiac biomarkers based on adiponectin levels tertile.
   ii: Spearman's R: correlations of adiponectin with echo parameters and cardiac biomarkers.
   iii: Linear regression analysis
   Model 1: age and race
   Model 2: PCE model
   Model 3: Model 2+BMI+ eGFR.

3. For the forth aim of the study, we will first investigate the correlation between adiponectin levels measured by a conventional method (Denka Seiken assay) with adiponectin measured by SomaScan at visit 5 as part of an ongoing validation study of visit 5 SomaScan analytes. Secondly, we will perform adjusted linear regression models for each protein of 4931 proteins measured by aptamer-based proteomics versus adiponectin. We will run 3 models accounting for baseline covariates: (1) adjusted for age, sex and race (2) PCE model: adjusted for covariates in model 1 plus total cholesterol level, HDL cholesterol level, systolic blood pressure, use of antihypertensive medications, smoking status and diabetes mellitus (3) adjusted for all covariates in model 2 plus BMI and eGFR. If any strong associations are found, we will then perform additional adjusted Cox regression to examine whether the individual protein is also associated with incident global CVD adjusted using similar models 1, 2 and 3.

4. Genetic analysis of genes associated with adiponectin level and CV health status.
   a) Our primary analysis will investigate the association of genetic variants at the adiponectin locus (ADIPOQ), including single nucleotide polymorphism (SNP) genotypes: -11391 G/A (rs17300539), -11377 C/G (rs266729), -10066 G/A (rs182052), +45 T/G (rs2241766), and +276 G/T (rs1501299), with adiponectin levels and subsequently incident HF hospitalization. [25] In secondary analyses, we will explore the association of genetic variants at other loci that are associated with adiponectin levels and subsequently incident global CVD in a Mendelian randomization study. [27]
   a) Outcome: incident CVD events beyond visit 5 (CHD, ischemic stroke, ASCVD, new HF, HF hospitalization, global CVD)
   b) Analysis: adjusted logistic regression assessing each variant and CVD status stratified by race and gender. Models to be determined.

Limitations / Major Challenges:

- Proteomic assay data from visits 2-4 and 6 are not yet available, therefore we are not able to perform any longitudinal analysis of proteomic data. However, if proteomic assay data from visit 3 becomes available within the timeline of this manuscript preparation we intend to explore the association of adiponectin levels with incident global CVD in younger adults. We realize that the analyses proposed here comprise multiple aims investigating the association of adiponectin with global CVD risk prediction using adiponectin measurements from visit 5 as well as Somascan proteomics and genetic analyses. Depending on our general findings, we may decide to report our findings in more than one manuscript.
- We are aware that certain proteins measured with SomaScan technology at ARIC visit 5 (e.g. troponins) show poor correlations with conventional assay methodologies. Currently there are ongoing efforts in a number of clinical/population studies to validate SomaScan protein data against conventional assays. We plan to validate a number of SomaScan proteins, including the specific proteins listed in this study proposal, either through laboratory validation studies using ARIC visit 5 samples or via communications with other investigators involved in SomaScan validation efforts in other study cohorts.

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? **__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)?

Short-Term Global Cardiovascular Disease Risk Prediction in Older Adults

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PHD, MPH,c Kunihiro Matsushita, MD,c Lynne E. Wagenknecht, DRPH,d Ron

Hoogeveen, PHD,a Josef Coresh, PHD, MPH,c James A. de Lemos, MD,e Christie M. Ballantyne, MDa

High-molecular-weight adiponectin and the risk of type 2 diabetes in the ARIC study.

Zhu N, Pankow JS, Ballantyne CM, Couper D, Hoogeveen RC, Pereira M, Duncan BB, Schmidt MI.

J Clin Endocrinol Metab. 2010 Nov;95(11):5097-104. doi: 10.1210/jc.2010-0716. Epub 2010 Aug 18.

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 * AS#2014.39_and AS#2018.13

___ 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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