ARIC Manuscript Proposal #4046

PC Reviewed: 5/17/22	**Status: _____**	**Priority: 2**
SC Reviewed: ___/___/___	**Status: _____**	**Priority: ____**

1.a. Full Title: Functionally Modifying Variants of ICAM-1 and Incident Heart Failure: The MESA and ARIC Studies

b. Abbreviated Title (Length 26 characters): ICAM-1 Variants an Incident Heart Failure

2. Writing Group:

Writing group members: Jonathan W. Cunningham, Ravi B. Patel, Pedro Giro, Laura Rasmussen-Torvik, Suzette J. Bielinski, Nicholas B. Larson, Xiuqing Guo, Kent Taylor, Wendy Post, Alain Bertoni, Scott D. Solomon, Amil Shah, Brian Claggett, Eric Boerwinkle, Bing Yu, Sanjiv J. Shah, [Others Welcome]

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

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3. Timeline:

Statistical analysis: Summer 2022
Manuscript submission: Fall 2022

4. Rationale:

Coronary microvascular dysfunction (CMD) recently has been postulated to be integral part of the pathogenesis of HFpEF.[1,2] Cellular adhesion molecules (CAMs) including

intercellular adhesion molecule (ICAM)-1, vascular cellular adhesion molecule (VCAM)-1, and E-selectin are biomarkers of endothelial activation that play an important role in initiation of the inflammatory response and the subsequent inflammatory cascade that results in CMD. Their role involves the binding and recruitment of leukocytes into the subendothelial space. Leukocytes then induce a reactive fibrosis through secretion of transforming growth factor-beta (TGF-β) and subsequent conversion of fibroblasts to myofibroblast with enhanced collagen deposition. They also promote oxidative stress and reduced nitric oxide bioavailability all thought to contribute to CMD.[3]

Given their role in endothelial activation, CAMs have been implicated in the pathogenesis of HFpEF.[4–7] Upregulated expression levels of ICAM-1 and E-selectin have been found in myocardial tissue of patients with HFpEF as well as murine mouse models of HFpEF.[4–6] Higher levels of ICAM-1 and E-selectin where independently associated with adverse LV systolic indices as well as mediators between BMI, black race and global longitudinal strain.[4,7] Despite these findings, multiple GWAS using HF as a trait did not find variant associations near genes encoding for these proteins.[8–11] These studies, however, had heterogenous classifications for HF.

Given the plausible causal relationship between CAMs and HFpEF, we hypothesize that polymorphisms affecting gene expression of these proteins would be associated with incident HF. Our criteria for SNP selection includes: (1) Genotyped by Affymetrix Genome-Wide Human SNP Array 6.0 or Infinium HumanExome BeadChip used in MESA SHARe cohort, (2) Have been associated with altered levels of soluble adhesion protein in prior GWAS, (3) reside within the aforementioned candidate genes and have a global minor allele frequency greater than 5%, and (4) are missense variants. Using these criteria, 3 missense SNPs (rs1799969, rs5491, rs5498) were identified in the ICAM1 gene, which have been associated with soluble ICAM (sICAM1) and many cardiovascular phenotypes in variable populations.[12–18]

5. Main Hypothesis/Study Questions:

Aim: Evaluate the association between candidate SNPs with incident HF and its subtypes (HFpEF and HFrEF) in MESA. We aim to validate these associations separately in the ARIC cohort.

Hypothesis: SNPs of candidate genes are associated with incident HF and subtypes (HFpEF and HFrEF)

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: Cohort epidemiology study relating genetic exposure to clinical outcomes

Exposures: 3 SNPs (as genotyped or imputed on the TOPMED panel): rs1799969, rs5491, rs5498

Outcome: Incident HF (HFpEF and HFrEF)

Variables of Interest at baseline: age, sex, race, education, height, weight, body mass index (BMI), systolic blood pressure, resting heart rate, antihypertensive treatment, diabetes, smoking, alcohol, creatinine, estimated glomerular filtration rate (eGFR) by CKD-EPI creatinine based equation, total cholesterol, LDL, HDL, OSA, physical activity level, diet, menopause, family history of HF, genetic ancestry (PCs).

Exclusions: Missing genetic or covariate data; missing f/u data

Statistical Analysis
Adjusted associations of each SNP with incident HF and HF subtypes (HFpEF and HFrEF) will be assessed using Cox proportional hazard models. We will stratify analyses by race/ethnicity group. Covariates will be selected based on known biology or prior associations. The first model will adjust for age, sex, and genetic ancestry (principal components). Fixed effect meta-analysis will be used to combine results across the race groups, as implemented in METAL. All statistical analyses will be performed using R statistical software.

We plan to validate associations of SNPs with incident HF and its subtypes in the ARIC cohort.

Summary/Conclusion
The proposed study will further investigate the relationship between CAMs and heart failure. Finally, it might add support for the importance of coronary microvascular dysfunction in HFpEF.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X_ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 current derived consent file ICTDER05 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/mantrack/maintain/search/dtSearch.html

__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 no overlapping or proposals.

Relevant prior proposals regarding common and rare variant genomic analysis in ARIC include:

MS 3692 (Alkis T & Yu B, 2020) Polygenic risk score and incident heart failure

MS 1392 (Morrison A et al 2008) The association of genome-wide genetic variation with incident heart failure in adults of European and African ancestry: the CHARGE Consortium

MS 1224 (Volcik et al, 2006) ICAM-1 genetic variation, ICAM-1 levels and risk of incident CHD and ischemic stroke: the ARIC study

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* _New Proposal_)
___ 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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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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