ARIC Manuscript Proposal #3540

PC Reviewed: 1/14/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Clonal hematopoiesis and heart failure risk: the ARIC study.

b. Abbreviated Title (Length 26 characters): **CHIP and HF**

2. Writing Group:

Writing group members: Amil Shah MD MPH, Bing Yu PhD, Eric Boerwinkle PhD, Hicham Skali MD, Brian Claggett PhD, Ron Hoogeveen PhD, Pradeep Natarajan MD, Alexander Bick MD PhD, James Pirruccello MD, Gabriel Griffin MD, Christie M. Ballantyne MD [OTHERS WELCOME]

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

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3. Timeline:

Analysis will begin once this manuscript proposal is approved. Anticipate analysis completion within 6 months following proposal approval with final manuscript completion within 9 months of approval.

4. Rationale:

The prevalence of HF increases exponentially with age, disproportionately burdening the elderly who are projected to account for 20% of the U.S. population by 2030.[1] HF with preserved

left ventricular ejection fraction (LVEF; HFpEF), which comprises half of HF cases overall,[2, 3] accounts for up to 80% of prevalent HF in the elderly.[5] Four large trials of inhibitors of the renin-angiotensin-aldosterone system (RAAS) – effective in HFrEF – were neutral in HFpEF.[4-7] Recently, attention has focused on systemic inflammation and associated endothelial dysfunction and myocardial stiffness as underlying cardiac dysfunction and HFpEF development.[8, 9]

Clonal hematopoiesis is an age-related disorder due to the clonal expansion of hematopoietic clones carrying somatic mutations that provide a competitive survival advantage.[10] These mutations have been most commonly observed in the genes *DNMT3A*, *TET2*, *ASXL1*, and *JAK2* and are also associated with myelodysplastic syndrome and acute myeloid leukemia.[11] This has been termed clonal hematopoiesis of indeterminate potential (CHIP) or age-related clonal hematopoiesis [ARCH]. CHIP is rare in persons <40 years of age, but increases in prevalence to >10% in persons >70 years old. CHIP is associated with an increased risk of hematologic cancer, all cause mortality, but also coronary heart disease.[11] Animal studies mimicking CHIP due to *TET2* loss of function suggest this increase in CHD risk is mediated by a proinflammatory state with greater macrophage inflammatory cytokine and chemokine expression, including IL-1β.[12] These findings are supported by recent human studies demonstrating that genetic IL-6 signaling deficiency due to the *IL6R* pAsp358Ala coding mutation attenuated CHIP-associated risk of incident CVD.[13] More recently, using two mouse models of HF (myocardial infarction by LAD banding and afterload excess by aortic banding), clonal hematopoiesis due to *TET2* loss of function was associated greater LV remodeling (LV volumes in infarction model, PW hypertrophy in aortic banding model) and worse LV systolic function.[14] These effects appeared to be mediated by greater inflammatory cytokines and chemokines, and were abrogated by an NLRP3 inflammasome inhibitor which suppresses IL-1β production. Similar findings have been observed in models of the *JAK2 V617F* activating mutation.[15] Furthermore, in at least one single center study of patients with HFrEF, CHIP-associated somatic mutations – particularly in *TET2* and *DNMT3A* – are associated heightened risk for death or HF hospitalization.[16]

These human data suggest a potential role for CHIP in HF, while the animal data provide a mechanism by which CHIP may heighten the risk for incident HF in humans. However, this association has not been tested. This is particularly relevant given recent data linking inflammation to HFpEF, and the availability of canakinumab, a therapeutic monoclonal antibody targeting IL-1β which reduced the occurrence of recurrent myocardial infarction, nonfatal stroke, or CV death in the CANTOS trial.[17]

5. Main Hypothesis/Study Questions:

1. Individuals with CHIP have a higher risk of developing heart failure.
2. Associations of CHIP with incident heart failure will be partially accounted for by associated increases in circulating levels of IL-1β, IL-18, and IL-6 reflecting NLRP3 inflammasome activity.

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 To address hypothesis 1, we will examine the association of CHIP at Visit 2 with incident HF post-Visit 2. We will further assess (a) the association of CHIP with incident HF excluding participants with interim MI; and (b) the association of CHIP with post-MI HF. To address hypothesis 2, we will determine the association of CHIP assessed at Visit 2 with circulating levels of IL-1β, IL-18, and IL-6 measured at Visit 3 using the Somascan platform among participants free of HF at Visits 2 and 3.

Inclusion/exclusion In analyses addressing hypothesis 1, exclusions include: (a) participants without whole exome sequencing to assess CHIP at Visit 2, (b) participants with prevalent HF at Visit 2. In analyses addressing hypothesis 2, exclusions include: (a) participants without whole exome sequencing to assess CHIP at Visit 2, (b) participants without Somascan data at Visit 3, and (c) participants with prevalent HF at Visits 2 or 3.

Primary exposure Primary exposure will be CHIP detected by whole exome sequencing in 10,990 participants at Visit 2 focusing on somatic mutations in 4 candidate genes: *DNMT3A*, *TET2*, *ASXL1*, and *JAK2*. Ascertainment of CHIP at ARIC Visit 2 was performed by Dr Natarajan and colleagues at MGH/Broad as covered by ARIC Ancillary Study Proposal 2017.24 (ARIC PI Ballantyne).

Primary outcomes The primary outcome will be time to first HF hospitalization post-Visit 2. As HF abstraction and adjudication began in 2005, we will use ICD-based HF definite to preserve consistency of HF diagnosis ascertainment throughout the follow-up period.

Covariates Relevant covariates include:

1. Clinical covariates (visit 2): age, gender, race/ethnicity, height, weight, blood pressure, heart rate, history of hypertension, diabetes, dyslipidemia, coronary artery disease, prior MI or revascularization procedure, prior stroke or TIA, PAD, HF, prior hospitalization for HF, prior VTE
2. Laboratory values (visit 2): NT-proBNP, serum albumin and creatinine, hemoglobin, hematocrit, white blood cell count, glucose, hemoglobin A1C, total cholesterol, triglycerides, HDL, LDL

Analytic approach

For hypothesis 1, we will examine whether CHIP carriers have a higher risk of developing incident HF or the composite of death or HF. We will then use a gene-level test to assess the association of mutations in each candidate gene with incident events. We will employ Cox proportional hazard models. Minimally adjusted models with include age, sex, and race. Fully adjusted models will further adjust for hypertension, diabetes, obesity, smoking status, chronic kidney disease, total cholesterol, and high-density lipoprotein cholesterol. We will also perform the following exploratory analyses: (1) We will assess the association of CHIP carrier status with incident events in participants free of interim MI; (2) We will assess the association of CHIP carrier status with incident HF post-MI; (3) We will assess the association of CHIP carrier status with incident HF post-hypertension diagnosis (using longitudinal hypertension assessment from study visits and AFU forms).

For hypothesis 2, we will employ multivariable linear regression to assess the association of CHIP carrier status with circulating levels of IL-1β, IL-18, and IL-6 (measured as part of SomaScan assay at Visit 3). Minimally adjusted models with include age, sex, and race. Fully adjusted models will further adjust for hypertension, diabetes, obesity, smoking status, chronic kidney disease, total cholesterol, and high-density lipoprotein cholesterol. We will then further adjust for IL-1β, IL-18, and IL-6 levels in models relating CHIP carrier status to incident HF or echo measures, to determine the extent to which they account for the CHIP-outcome association.

Anticipated methodologic limitations
Absence of adjudicated HF data consistently post-Visit 2, and of consistent data on incident HF phenotype (HFrEF vs HFpEF) is a limitation of this study. During the period between V2 CHIP assessment and end of follow-up (~25 years), it is likely that CHIP will develop a subset of participants and may lead to underestimation of the association of CHIP with incident HF. Power for the specified exploratory/sensitivity analyses may be low.

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)?
#1504: CRP, WBC, and heart failure incidence (writing group: Aaron Folsom, Wobo Bekwelem, Pam Lutsey, Laura Loehr, Sunil Agarwal, Brad Astor, Christie Ballantyne)
#2907: Exome chip variants associated with Galectin-3 levels and clinical cardiac disease (writing group: Linda Polfus, Carlos Iribarren, David Aguilar, Vijay Nambi, Amil Shah, Ron Hoogeveen, John McEvoy, Elizabeth Selvin, Kunihiro Matsushita, Wensheng Sun, Eric Boerwinkle, Santhi Ganesh, Scott Solomon, Myriam Fornage, Christie Ballantyne)
#2436: Galectin 3 and risk of heart failure and death in a subsample of the Atherosclerosis Risk in Communities (ARIC) study (writing group: John McEnvoy, Yuan Chen, Marc Halushka, Eric Christenson, Christie Ballantyne, Robert Christenson, Elizabeth Selvin)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes ____ No

2017.24: Clonal hematopoiesis and inflammatory and metabolic markers of peripheral artery disease progression in the ARIC study

11.b. If yes, is the proposal

__X_ A. primarily the result of an ancillary study (list number* ___2017.24**_____)**

___ 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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