ARIC Manuscript Proposal #3203

PC Reviewed: 7/10/2018 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:
Metabolomic Profiling and Heart Failure Risk in the Atherosclerosis Risk in Communities (ARIC) Study

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

2.   Writing Group:
   Writing group members:
Amil Shah, Jun Xu, Kunihiro Matsushita, Patty Chang, Laura Loehr, Joseph Rossi, Stuart Russell, Carlos Rodriguez, Sunil Agarwal, David Aguilar, Gerardo Heiss, Eric Boerwinkle and Bing Yu

Others are welcome.

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

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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).
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3.   Timeline:
The data collection of metabolomics and incident heart failure are already accomplished and there is no other data collection work needed. When the proposal is approved, data analysis process will start. The manuscript will be prepared when data analysis is done (~ 3-6 months).

4.   Rationale:

Heart failure (HF) is a major public health problem with an estimated prevalence of 6 million affected individuals in the United States, and this number is increasing with an aging population. With the advent of high-throughput metabolomics, scores of circulating metabolic signatures have been identified to assist clinical management of HF. [1-11] In contrast, little progress has been made to study the metabolic changes that presage the development of HF. We previously reported two metabolites that were related to HF risk in the African Americans among the Atherosclerosis Risk in Communities (ARIC) study.[12] However, the generalizability of identified HF-related metabolites remains unknown. In addition, the etiology of HF is complex, with the distinction between ischemic and non-ischemic etiologies particularly important. The metabolomic predictors of HF with vs. without antecedent myocardial infarction (MI) have not been previously studied. With the recent availability of additional metabolomics data in ARIC and prolonged follow-up (i.e. additional eight years follow-up compared to our early work), we propose to evaluate the association between serum metabolites and HF risk in 2472 AAs and 1551 EAs enrolled in ARIC to explore the consistent and divergent metabolic predictors of HF across two race groups, and evaluate the prognostic relevance of the identified metabolites on HF with and without a preceding MI.

5.   Main Hypothesis/Study Questions:
The overall objective of this proposal is to determine whether metabolomic profiling is associated with HF risk, and whether the identified HF metabolites differentially relate to incident HF with versus without preceding myocardial infarction.

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:
This is a prospective study design using metabolomics information from ARIC visit 1 and incident HF information followed by 2016.

Exclusion criteria:
The individuals will be excluded from this study, whose metabolites data and HF follow-up information are missing, as well as other covariates. Participants with HF history at Visit 1 will also be excluded from the analysis.

Variables:
Outcome variables:

1) Incident HF followed by 2016 (primary);

   Incident HF is defined as the first occurrence of a hospitalization with a HF diagnosis according to the International Classification of Diseases- 9th Revision (ICD-9) code 428

(428.0 to 428.9) in any position, or a death certificate with an ICD-9 code of 428 or with an ICD-10 code of I50 among any of the listed diagnoses or underlying causes of death.

2) Incident HF without preceding myocardial infarction, exclude prevalent MI cases at baseline and censor participants with an incident MI during follow-up at the time of MI (secondary)

MI is defined based on a history of MI at Visit 1 or an incident hospitalized acute myocardial infarction post-Visit 1.

Incident HF without preceding MI is defined as an incident HF event post-Visit 1 occurring in the absence of a history of prior MI at Visit 1 or an incident post-Visit 1 MI event occurring prior to the incident HF event.

3) Incident HF with prior myocardial infarction (secondary).

Incident HF with prior MI is defined as an incident HF event post-Visit 1 occurring in a participant with a history of prior MI at Visit 1 or with an incident MI event occurring post-Visit 1 but before the incident HF event.

Exposure variables: 245 named metabolites detected in both batches;
Metabolites will be excluded if satisfying the following:
  1) The proportion of missing value of the samples is higher than 25% in either batch;
  2) The Pearson correlation coefficient between Batch 1 (2010) and Batch 2(2014) measurements on the same stored sample is less than 0.3.

Covariates:
Age, gender, study center, race, BMI, smoking, alcohol, SBP, blood pressure lowering medication, estimated glomerular filtration rate (eGFR), prevalent CHD, prevalent stroke, prevalent atrial fibrillation, prevalent diabetes and batch effect.

Statistical data analysis:

Statistical analysis will be conducted within AAs and EAs respectively followed by fix-effect inverse variance meta-analysis. Metabolites will be winsorized at 0.5% and standardized (mean = 0. SD = 1) prior to the analyses. We will run Cox proportional hazards regression in each race group for several models to account for potential confounding factors. Model 1 will be adjusted for age, sex, and batch-center. Model 2 will additionally adjust for BMI, SBP and blood pressure lowering medication. Model 3 will further adjust for smoking, alcohol, eGFR, prevalent diabetes and CHD. Model 4 will additionally adjust for prevalent stroke and atrial fibrillation. The Benjamini–Hochberg procedure (BH step-up procedure) will be used to control false discovery rate (FDR) at level of 0.05 to correct for multiple testing. We will evaluate the identified metabolites for their association with HF with and without precedent myocardial infarction. We will also examine the potential effect modification by sex using stratified analysis and interaction term.

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)?

AS#1847 Zheng et al. Role of the Human Metabolome in Incident Heart Failure Etiology among African Americans in the Atherosclerosis Risk in Communities (ARIC) Study

AS#3018 Nambi et al. Evaluation of novel circulating biomarkers in the prediction of adverse cardiovascular events including heart failure

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* _2008.16 and 2014.20_____)
    ___ 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.

Agreed.

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.

Agreed.

Reference

1.	Hunter WG, Kelly JP, McGarrah RW, 3rd, Khouri MG, Craig D, Haynes C, et al. Metabolomic Profiling Identifies Novel Circulating Biomarkers of Mitochondrial Dysfunction Differentially Elevated in Heart Failure With Preserved Versus Reduced Ejection Fraction: Evidence for Shared Metabolic Impairments in Clinical Heart Failure. *J Am Heart Assoc*. 2016;5(8). doi: 10.1161/JAHA.115.003190. PubMed PMID: 27473038; PMCID: PMC5015273.

2.	Zordoky BN, Sung MM, Ezekowitz J, Mandal R, Han B, Bjorndahl TC, et al. Metabolomic fingerprint of heart failure with preserved ejection fraction. *PLoS One*. 2015;10(5):e0124844. doi: 10.1371/journal.pone.0124844. PubMed PMID: 26010610; PMCID: PMC4444296.

3.	Luan H, Chen X, Zhong S, Yuan X, Meng N, Zhang J, et al. Serum metabolomics reveals lipid metabolism variation between coronary artery disease and congestive heart failure: a pilot study. *Biomarkers*. 2013;18(4):314-21. doi: 10.3109/1354750X.2013.781222. PubMed PMID: 23581255.

4.	Cheng ML, Wang CH, Shiao MS, Liu MH, Huang YY, Huang CY, et al. Metabolic disturbances identified in plasma are associated with outcomes in patients with heart failure: diagnostic and prognostic value of metabolomics. *J Am Coll Cardiol*. 2015;65(15):1509-20. doi: 10.1016/j.jacc.2015.02.018. PubMed PMID: 25881932.

5.	Wang J, Li Z, Chen J, Zhao H, Luo L, Chen C, et al. Metabolomic identification of diagnostic plasma biomarkers in humans with chronic heart failure. *Mol Biosyst*. 2013;9(11):2618-26. doi: 10.1039/c3mb70227h. PubMed PMID: 23959290.

6.	Paolillo S, Rengo G, Pellegrino T, Formisano R, Pagano G, Gargiulo P, et al. Insulin resistance is associated with impaired cardiac sympathetic innervation in patients with heart failure. *Eur Heart J Cardiovasc Imaging*. 2015;16(10):1148-53. doi: 10.1093/ehjci/jev061. PubMed PMID: 25845954.

7.	Ahmad T, Kelly JP, McGarrah RW, Hellkamp AS, Fiuzat M, Testani JM, et al. Prognostic Implications of Long-Chain Acylcarnitines in Heart Failure and Reversibility With Mechanical Circulatory Support. *J Am Coll Cardiol*. 2016;67(3):291-9. doi: 10.1016/j.jacc.2015.10.079. PubMed PMID: 26796394; PMCID: PMC5429585.

8.	Sorlie PD, Aviles-Santa LM, Wassertheil-Smoller S, Kaplan RC, Daviglus ML, Giachello AL, et al. Design and implementation of the Hispanic Community Health Study/Study of Latinos. *Ann Epidemiol*. 2010;20(8):629-41. doi: 10.1016/j.annepidem.2010.03.015. PubMed PMID: 20609343; PMCID: PMC2904957.

9.	Tenori L, Hu X, Pantaleo P, Alterini B, Castelli G, Olivotto I, et al. Metabolomic fingerprint of heart failure in humans: a nuclear magnetic resonance spectroscopy analysis. *Int J Cardiol*. 2013;168(4):e113-5. doi: 10.1016/j.ijcard.2013.08.042. PubMed PMID: 24007967.

10.	Deidda M, Piras C, Dessalvi CC, Locci E, Barberini L, Torri F, et al. Metabolomic approach to profile functional and metabolic changes in heart failure. *J Transl Med*. 2015;13:297. doi: 10.1186/s12967-015-0661-3. PubMed PMID: 26364058; PMCID: PMC4567812.

11.	Alexander D, Lombardi R, Rodriguez G, Mitchell MM, Marian AJ. Metabolomic distinction and insights into the pathogenesis of human primary dilated cardiomyopathy. *Eur J Clin Invest*. 2011;41(5):527-38. doi: 10.1111/j.1365-2362.2010.02441.x. PubMed PMID: 21155767; PMCID: PMC3071865.

12.	Zheng Y, Yu B, Alexander D, Manolio TA, Aguilar D, Coresh J, et al. Associations between metabolomic compounds and incident heart failure among African Americans: the ARIC Study. *Am J Epidemiol*. 2013;178(4):534-42. doi: 10.1093/aje/kwt004. PubMed PMID: 23788672; PMCID: PMC3736751.