ARIC Manuscript Proposal # 3258

PC Reviewed: 10/9/18	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Heart Failure Risk Associated with Optimal Levels of Modifiable HF Risk Factors: The Atherosclerosis Risk in Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters): HF and Optimal Risk Factors

2. Writing Group: Carine E. Hamo, Lucia Kwak, Roberta Florido, Justin Echouffo-Tcheugui, Roger Blumenthal, Laura Loehr, Kunihiro Matsushita, Vijay Nambi, Christie M. Ballantyne, Liz Selvin, Aaron Folsom, Gerardo Heiss, Joe Coresh, Chiadi E. Ndumele; others welcome

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

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3. Timeline: We aim to submit this manuscript to the ARIC publications committee <6 months from the date of approval of this manuscript proposal.

4. **Rationale**:

Heart failure (HF) is a growing public health concern with a prevalence of 6.5 million in the United States and an incidence that rises with age.[1,2] Clinically, HF is associated with marked morbidity and mortality.[3] Furthermore, HF hospitalizations are the leading cause of inpatient Medicare spending in the United States.[4] There is therefore growing interest in refining strategies for preventing the development of HF. Several risk factors for HF, both modifiable and non-modifiable, have been well described. However, the degree to which optimization of modifiable risk factors might impact the incidence of HF is not yet fully defined.

Diabetes mellitus (DM) and hypertension (HTN) are potent and modifiable clinical risk factors for HF.[5,6] Chronic hyperglycemia, as reflected by higher hemoglobin A1c (HbA1c), is strongly and independently associated with increased HF risk.[7] Similarly, systolic blood pressure has a graded, direct risk association with incident HF.[6] Obesity is an additional modifiable risk factor that is causally linked to the development of DM and HTN.[8] Furthermore, considerable evidence supports independent effects of excess adiposity on myocardial remodeling and subsequent clinical HF.[9] Physical activity is also strongly linked to the development of DM and HTN, in addition to having an inverse association with HF that is independent of those comorbidities.[10]

Previous studies have demonstrated that the absence of established cardiovascular risk factors, is associated with a lower incidence of HF [11] and total cardiovascular disease.[12] The current study will use clinically utilized cutpoints to focus on risk associations for different levels of risk factor control (optimal, mild to moderately uncontrolled, severely uncontrolled) among those with prevalent risk factors (i.e, HTN, DM). This will allow us to examine the relative and absolute HF risk differences associated with various levels of control of major modifiable risk factors for HF, with a focus on HTN, DM, obesity and physical activity. We will be able to quantify the risk differences associated with incremental differences in risk factor levels, which may provide additional clinical insights regarding the management of those with existing risk factors. We anticipate that this work will extend our current understanding of the incremental benefit achieved by enhanced control of these modifiable HF risk factors. This in turn can assist in informing the focus and prioritization of resources for different HF preventive strategies.

5. **Main Hypothesis/Study Questions**:

Aim:

To estimate the relative and absolute HF risk differences associated with different levels of control of major modifiable risk factors for HF, with a focus on hypertension, diabetes, obesity and physical activity. For obesity and physical activity, we will estimate both the indirect (via mediation through hypertension and diabetes) and direct (after multivariable adjustment in the full regression model) associations of different levels of these variables with 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: This will be a prospective analysis examining the associations of different levels of the modifiable HF risk factors of HTN, DM, obesity and physical activity with HF risk. We will examine the risk associations of different levels of glycemia, systolic blood pressure (SBP) weight and physical activity within the ARIC population. For glycemic and blood pressure control, the principal focus will be on risk associations of optimal levels among those with prevalent diabetes and hypertension. ARIC Visit 2 (1990-1992) will serve as the time point for risk factor assessment and the baseline for follow-up for incident HF events due to the availability of HbA1c at that time point.

Exposures: Prevalent diabetes (defined as either prevalent DM per ARIC, which is fasting blood glucose ≥ 126 mg/dl, non-fasting blood glucose ≥ 200 mg/dl, self-reported physician diagnosis of diabetes, self-reported use of diabetes medications, or measured HbA1c ≥ 6.5%), prevalent hypertension (defined as SBP ≥ 130 mmHg, DBP ≥ 80 mmHg and/or reported use of blood pressure medications), prevalent obesity (defined as a body mass index ≥30 kg/m^2), and poor physical activity (defined as no moderate or vigorous exercise activity). We will use Visit 2 measures to define all of these exposures except for physical activity, which was not assessed at Visit 2 (we will instead use reported physical activity at Visit 1). We will additionally use the following categorization for levels of HbA1c, SBP, BMI and physical activity.

1. HbA1c (%): Among those with diabetes as defined above, HbA1c will be categorized as <7% (reference group), 7-8%, and ≥8%.[13] We will also categorize those without diabetes (no diabetes per ARIC and HbA1c < 6.5%) as <5.7% and 5.7-<6.5%.
2. SBP (mmHg): Among those with hypertension as defined above, SBP will be categorized as <120 mmHg (reference group), 120-<130 mmHg, 130-<140 mmHg, 140-<160 mmHg and ≥160 mmHg.[14] We will additionally categorize those without hypertension (no anti –hypertensive drug use and SBP < 120 mmHg) as <100 mmHg, 100-<110 mmHg and 110-<120 mmHg.
3. BMI (kg/m^2): BMI will be categorized as underweight (<18.5 kg/m^2), normal weight (18.5-25 kg/m$^{2;}$ reference group), overweight (25-29.9 kg/m^2), obese (30-34.9 kg/m^2) and severely obese (≥35 kg/m^2).
4. Physical activity: Measured by a modified Baecke questionnaire and categorized as per AHA guidelines as recommended (≥75 min/week of vigorous intensity or ≥150 min/week of any combination of moderate and vigorous intensity; reference group), intermediate (75-150 min/week of moderate or vigorous intensity), and poor (no moderate or vigorous activity).[15] We will consider further categorization based on a continuous measure of physical activity, calculated in METS*min/week.

Outcomes: Incident HF, defined as HF hospitalization or death using ICD codes (428 for early follow-up and I50 for later follow-up), is the outcome of interest. We will assess risk for HF events occurring after Visit 2 (baseline for prospective analyses) until 12/31/2016 or the most recent follow-up available.

Exclusions: We will exclude participants with HF (self-reported HF at Visit 1; or incident HF events at or prior to Visit 2), those missing data on the primary exposure variables and the small number of individuals not of black or white race.

Covariates: Age, sex, race-center, education, occupation, smoking status, alcohol use, LDL-cholesterol, HDL-cholesterol, triglycerides, estimated glomerular filtration rate (eGFR) and coronary heart disease (defined as prevalent CHD at Visit 1, adjudicated cases of nonfatal MI or fatal CHD at or prior to Visit 2, or silent MI by Visit 2). We may perform analyses considering anti-hypertensive treatment and hypoglycemic therapy as covariates.

Main Analyses:

- We will perform univariate comparisons of covariates among those with 0, 1, 2, 3 and 4 of the major modifiable HF risk factors of prevalent diabetes, hypertension, obesity and poor physical activity. We will use ANOVA for continuous variables and the chi-squared test for categorical variables.
- We will construct Cox regression models, adjusted for the covariates above, and estimate adjusted incidence rates (at mean levels of covariates) and adjusted hazard ratios (with associated 95% confidence intervals) for those with 0, 1, 2, 3 and 4 of the major modifiable HF risk factors. In calculating HRs, those with 0 risk factors will serve as the reference group.
- Using the categorization for major risk factors described above, we will construct Cox regression models that jointly include each of the risk factors and covariates.
    - For estimating associations for obesity and physical activity, we will fit two regression models: Model 1 that includes obesity and physical activity levels and the covariates listed above and Model 2 that includes the Model 1 variables plus HTN and DM categories. Model 2 will be used to assess direct HF associations for categories of obesity and physical activity; The difference between Model 1 and Model 2 estimates (using lincom) will be used to assess indirect HF associations through HTN and DM (mediation). For obesity and physical activity, those with normal weight and recommended physical activity levels, respectively, will serve as the reference groups.
    - For estimating associations for glycemia and blood pressure levels, we will use the output from Model 2 above, which concomitantly includes levels of weight, physical activity, glycemia and blood pressure in addition to covariates. As the focus of this analysis is on the potential benefits of optimal risk factor levels, for HTN and DM, those with the risk factor but with optimal control will serve as the reference group.
    - We will estimate adjusted incidence rates and HRs (with associated 95% CIs) within each category of risk factor control and compare them to the

reference group to determine the absolute and relative risk reduction associated with different levels of risk factor control. While the primary focus will be on risk factor control, we will also define risk associations for those without risk factors (e.g., no HTN or DM) using the categorizations described above.

- We will also construct spline models to estimate the continuous associations of each of the risk factors' levels with incident HF, when included jointly in the same model (a regression model including all of the modifiable HF risk factors), to assess for deviations from linearity.
- We will perform additional analyses categorizing each of the 4 modifiable risk factors as optimal (reference group level), mild to moderately uncontrolled, or severely uncontrolled (e.g., SBP > 160 mmHg, A1c > 8%, BMI ≥ 35 kg/m^2 and poor physical activity [no moderate or vigorous physical activity]). We will then create subgroups based on the number of risk factors and levels of risk factor control (e.g., all optimally controlled risk factors, 1-2 mild to moderately uncontrolled risk factors, 1-2 severely uncontrolled risk factors, etc) and will assess relative and absolute HF risk associations for these subgroups in Cox regression models.
- We will perform analyses stratified by race, sex, and age (>= or <65 years) to assess for demographic differences in the above risk associations

Secondary Analyses:

- In secondary analyses, we will use waist circumference quartiles in place of BMI categories as an alternative measure of adiposity
- We will perform additional analyses excluding those individuals with previously undiagnosed diabetes and hypertension from the definitions of prevalent diabetes and hypertension. We will also perform analyses differentiating those individuals with hypertension and diabetes who are receiving treatment from those individuals who are untreated.

Limitations:

1. Residual confounding due to the observational nature of the study.
2. Limitations in measurement of physical activity due to self-report via a questionnaire.
3. BMI and physical activity are correlated and can be bi-directionally related.
4. Diet, another modifiable risk factor for HF, is not captured well in ARIC and will not be included in this analysis.
5. Risk factor levels may reflect the severity of the comorbidity being assessed, rather than the quality or adequacy of treatment (e.g., anti-HTN therapy) being administered for the condition. As described above, we will perform analyses considering those with prior diagnoses of HTN and DM and those on treatment for these conditions, but this will not fully address this limitation
6. Measurements of risk factors at a single point in time will not reflect the impact of longitudinal changes in those risk factor levels on the observed risk associations
7. Changes in the definitions of DM and HTN over time effect the likelihood of treatment at different risk factor levels. We will assess risk associations at various

levels of glycemia and blood pressure and perform analyses accounting for the use of medical therapies for DM and HTN.

8. The use of ICD-based HF definitions in this analysis, will be associated with some potential for misclassification.

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 ICTDER03 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)?

Shah AM, Claggett B, Folsom AR, et al. Ideal cardiovascular health during adult life and cardiovascular structure and function among the elderly. *Circulation*. 2015;132:1979-1989.

Folsom AR, Yatsuya H, Nettleton JA, et al. Community prevalence of ideal cardiovascular health, by the AHA deficinition, and relation to cardiovascular disease incidence. J Am Coll Cardiol. 2011 April 19; 57(16): 1690–1696.

Avery CL, Loehr LR, Baggett C, et al. The population burden of heart failure attributable to modifiable risk factors: the ARIC (Atherosclerosis Risk in Communities) study. *Journal of the American College of Cardiology.* 2012;60(17):1640-1646.

Florido R, Ndumele CE, Kwak L, Pang Y, Matsushita K, Schrack JA, Lazo M, Nambi V, Blumenthal RS, Folsom AR, Coresh J. Physical activity, obesity, and subclinical myocardial damage. *JACC: Heart Failure*. 2017 May 31;5(5):377-84

Ndumele CE, Coresh J, Lazo M, Hoogeveen RC, Blumenthal RS, Folsom AR, Selvin E, Ballantyne CM, Nambi V. Obesity, Subclinical Myocardial Injury and Incident Heart Failure. *JACC: Heart Failure*. 2014 Dec;2(6):600-7.

Loehr LR, Rosamond WD, Poole C, et al. The potentially modifiable burden of incident heart failure due to obesity: the atherosclerosis risk in communities study. *American journal of epidemiology.* 2010;172(7):781-789.

Matsushita K, Blecker S, Pazin-Filho A, et al. The association of hemoglobin a1c with incident heart failure among people without diabetes: the atherosclerosis risk in communities study. *Diabetes.* 2010;59(8):2020-2026.

Florido R, Kwak L, Lazo M, Nambi V, Ahmed H, Hegde SM, Gerstenblith G, Ballantyne CM, Selvin E, Folsom A, Coresh J, Ndumele CE. Six-Year Changes in Physical Activity and the Risk of Incident Heart Failure: ARIC Study. *Circulation.* 2018 May 15;137(20):2142-2151

Rodriguez CJ, Swett K, Agarwal SK, et al. Systolic blood pressure levels among adults with hypertension and incident cardiovascular events: the atherosclerosis risk in communities study. *JAMA internal medicine.* 2014;174(8):1252-1261.

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* __)
___ 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/

12. 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.

References:

1. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology.* 2013;62(16):e147-239.
2. Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. *Circulation.* 2018;137(12):e67-e492.
3. Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. *Jama.* 2004;292(3):344-350.
4. Kilgore M, Patel HK, Kielhorn A, Maya JF, Sharma P. Economic burden of hospitalizations of Medicare beneficiaries with heart failure. *Risk management and healthcare policy.* 2017;10:63-70.
5. Avery CL, Loehr LR, Baggett C, et al. The population burden of heart failure attributable to modifiable risk factors: the ARIC (Atherosclerosis Risk in Communities) study. *Journal of the American College of Cardiology.* 2012;60(17):1640-1646.
6. Sahle BW, Owen AJ, Krum H, Reid CM. Incidence of heart failure in 6083 elderly hypertensive patients: the Second Australian National Blood Pressure Study (ANBP2). *European journal of heart failure.* 2016;18(1):38-45.
7. Pazin-Filho A, Kottgen A, Bertoni AG, et al. HbA 1c as a risk factor for heart failure in persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetologia.* 2008;51(12):2197-2204.
8. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the Risk of Heart Failure. *New England Journal of Medicine.* 2002;347(5):305-313.
9. Ndumele CE, Coresh J, Lazo M, et al. Obesity, subclinical myocardial injury, and incident heart failure. *JACC Heart failure.* 2014;2(6):600-607.
10. Pandey A, Garg S, Khunger M, et al. Dose-Response Relationship Between Physical Activity and Risk of Heart Failure: A Meta-Analysis. *Circulation.* 2015;132(19):1786-1794.
11. Folsom AR, Yamagishi K, Hozawa A, Chambless LE. Absolute and attributable risks of heart failure incidence in relation to optimal risk factors. *Circulation Heart failure.* 2009;2(1):11-17.
12. Wong ND, Zhao Y, Patel R, et al. Cardiovascular Risk Factor Targets and Cardiovascular Disease Event Risk in Diabetes: A Pooling Project of the Atherosclerosis Risk in Communities Study, Multi-Ethnic Study of Atherosclerosis, and Jackson Heart Study. *Diabetes Care.* 2016;39(5):668-676.
13. 6. Glycemic Targets: Standards of Medical Care in Diabetes—2018. *Diabetes Care.* 2018;41(Supplement 1):S55-S64.
14. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. *A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.* 2018;71(19):e127-e248.
15. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;129(25 Suppl 2):S76-99.