ARIC Manuscript Proposal # 3758

PC Reviewed: 1/12/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Independent and Joint Associations of Diabetes and Galectin-3 and Heart Failure : The Atherosclerosis Risk in Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters): Diabetes, Galectin-3 and Heart Failure

2. Writing Group: Justin Echouffo-Tcheugui, Sui Zhang, Roberta Florido, Vijay Nambi, Gary Gerstenblith, Roger S. Blumenthal, Ron Hoogeveen, Josef Coresh, Christie M. Ballantyne, Elizabeth Selvin, Chiadi E. Ndumele; others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __JBE__ **[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 <one year from the date of approval of this manuscript proposal.

4. Rationale:

Galectin-3 (Gal-3), a β-galactoside–binding lectin expressed in various cell types, has been implicated in several functional pathways including fibrosis and inflammation, and tissue repair.[1] Gal-3 is expressed at low levels in healthy cardiac tissue and at much higher levels during cardiac injury. [2] Mechanistic studies have suggested that Gal-3 may play a critical in the pathogenesis of adverse cardiac remodeling and dysfunction.[3] A number of community-based studies have shown a positive association of circulating levels of Gal-3 with left ventricular hypertrophy, left ventricular dysfunction, and incident heart failure (HF).[4–6] However, these studies included sample that lack racial/ethnic diversity.

Despite the well-recognized associations of gal-3 with HF, the exact underlying pathways from Gal-3 to HF are poorly understood. Metabolic traits such as diabetes may play an important role in the pathways linking Gal-3 and HF. Indeed studies have shown that Gal-3 is associated with impaired glucose regulation/diabetes.[7–9] Furthermore, diabetes is an established risk factor for incident HF,[10] and is independently associated with adverse cardiac remodeling, marked by evidence of fibrosis, which predisposes to HF.[11] However, there is limited clinical or community-based data regarding the associations of diabetes with Gal-3. It is also unclear whether the association of Gal-3 with incident HF differ among subgroups defined by diabetes status, and whether glycemic status and Gal-3 provide complementary prognostic information regarding HF risk.

Using the framework of the community-based Atherosclerosis Risk in Communities Study (ARIC) study, we propose to examine the association of diabetes and myocardial fibrosis, as assessed by Gal-3 levels, as well as a the association of Gal-3 and incident HF among participants with and without diabetes.

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

Aims:

1- To evaluate the association between diabetes and fibrosis, as assessed by Gal-3 levels
2- To assess the influence of the diabetes status on the association of Gal-3 and incident HF, by examining the association of Gal-3 and HF across subgroups defined by glycemic status.
3- To evaluate whether glycemic status and Gal-3 provide complementary prognostic information regarding HF risk

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:

We will perform to set of analyses using ARIC study visit 4 data, which include:

1) A cross-sectional of diabetes and Gal-3 (measured at visit 4).

2) A prospective cohort analysis of the associations of diabetes status and Gal-3 (at visit 4 – baseline) with incident HF occurring after Visit 4, using analyses stratified by diabetes as well as cross-categories of Gal-3 levels and glycemic status

Exposures:
Diabetes assessed at visit 4 will be the exposure of interest in the cross-sectional analyses. Gal-3 measured at visit 4 will be exposure of interest for prospective analyses.

1. Diabetes: It will be defined at Visit 4 as a prior physician diagnosis of diabetes, use of hypoglycemic medications, a fasting blood glucose ≥126 mg/dL or a non-fasting blood glucose ≥ 200 mg/dL. We will also assess the severity of hyperglycemia using HbA_{1C} calculated from glycated albumin at Visit 4.

1. Plasma Gal-3: It was measured in stored blood samples collected at Visit 4. In prospective analyses, Gal-3 will be the exposure of interest, with categorization by diabetes status evaluated as an effect modifier. In these analyses, Gal-3 will be modeled as a continuous (per 1-SD, with log transformation as needed) and categorical (quartiles, or other percentile based categories) variableto incident HF.

Outcomes:
Cross-sectional analyses
Gal-3 will be the main outcome for cross-sectional analyses (visit 4), and will be classified as elevated vs non-elevated. Elevated Gal-3 will be defined as Gal-3 level above the 90^{th} percentile, or Gal-3 level within the highest quartile, which have been shown to be associated with CVD events including HF.
Prospective analyses
Incident HF (from visit 4) will be the outcome for the prospective analyses. HF will be defined as HF hospitalization or death due to HF occurring after Visit 4 (baseline for prospective analyses), through 2019 or most recently available data.

Exclusions: Participants with prevalent coronary heart disease (CHD) or HF (self-reported HF or CHD at Visit 4; or HF events, adjudicated CHD events, or silent MI at or prior to Visit 4) will be excluded from the analyses. We will also exclude those of non-black or non-white race due to small numbers, and those missing data on the exposure variables.

Covariates: Age, sex, race*center, smoking status, alcohol use, systolic blood pressure, anti-hypertensive medications use, LDL-cholesterol, HDL-cholesterol, triglycerides, body mass index, estimated glomerular filtration rate (eGFR), and *rs4644* genotype.

Main Analyses:

1. We will perform bivariate analyses of participant baseline (Visit 4) characteristics according to diabetes status (diabetes vs. no-diabetes). The chi-square test will used for comparison of categorical variables and the appropriate parametric or non-parametric test for continuous variables.
2. We will construct regression models with two levels of adjustment:

a. Model 1: adjusted for age, sex, race*center, smoking status, and alcohol use.
b. Model 2: Adjusted for the variables in Model 1 + systolic blood pressure, anti-hypertensive medications use, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, body mass index, eGFR and *rs4644* genotype.

3. We will use adjusted linear regression to assess the difference in average gal-3 (using log transformation if appropriate) with diabetes status category; we will also use adjusted logistic regression to study the association of the diabetes status with elevated Gal-3 at Visit 4, using those without diabetes as the reference. We will evaluate the continuous associations of estimated glycosylated hemoglobin A_{1C} (HbA_{1C} – estimated from glycated albumin measured at visit 4) and fasting blood glucose with the odds of elevated Gal-3, and of continuous HbA_{1C} (and fasting blood glucose) in restricted cubic spline models.
4. We will evaluate the associations of diabetes status with Gal-3 in analysis stratified by sex, race and age ($\geq$ or <65).
5. In prospective analyses, we will use adjusted Cox proportional hazards models to assess the association of quartiles of Gal-3 and of elevated Gal-3 with incident HF after Visit 4. We will perform this analysis in the overall population, and then in subgroups stratified by diabetes status. If significant differences across the glycemic status groups are identified, we will perform tests for statistical interaction. We will also assess the combined associations of Gal-3 and diabetes with incident HF, using a cross-categorization of exposures that includes Gal-3 quantiles (e.g. quartiles) and diabetes categories (no diabetes with HbA_{1C} <5.7%, no diabetes HbA_{1C} of 5.7-6.4 %, no diabetes with $HbA_{1C}\geq$6.5%, diabetes with HbA_{1C} <7%, diabetes with $HbA_{1C}\geq$7%).

Secondary Analyses:

- We will consider analyses cross-categorizing gal-3 quantiles and glycemic status based on fasting glucose: as normoglycemic (< 100 mg/dl), fasting hyperglycemia (100-125 mg/dl), and overt diabetes (ARIC diagnosis)
- We will perform secondary analyses using glycated albumin, fructosamine, and 1,5-anhydroglucitol markers as alternative measures of glycemia.

Limitations:

2. Residual confounding due to the observational nature of the study.
3. We will not evaluate the changes in Gal-3 or in glycemic status over time in relation to incident HF.

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)?

Manuscript Number 2436: Galectin-3 and Risk of Heart Failure and Death in Blacks and Whites. (resulting paper: McEvoy JW, Chen Y, Halushka MK, Christenson E, Ballantyne CM, Blumenthal RS, Christenson RH and Selvin E. Galectin-3 and Risk of Heart Failure and Death in Blacks and Whites. J Am Heart Assoc. 2016;5(5):e003079)

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:

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2. Suthahar N, Meijers WC, Silljé HHW, Ho JE, Liu FT, de Boer RA. Galectin-3 activation and inhibition in heart failure and cardiovascular disease: An update. *Theranostics*. 2018;8(3):593-609.
3. Yu L, Ruifrok WPT, Meissner M, Bos EM, Van Goor H, Sanjabi B, Van Der Harst P, Pitt B, Goldstein IJ, Koerts JA, Van Veldhuisen DJ, Bank RA, Van Gilst WH, Silljé HHW, De Boer RA. Genetic and pharmacological inhibition of galectin-3 prevents cardiac remodeling by interfering with myocardial fibrogenesis. *Circ Hear Fail*. 2013;6(1):107-17.
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5. Shah R V., Chen-Tournoux AA, Picard MH, Van Kimmenade RRJ, Januzzi JL. Galectin-3, cardiac structure and function, and long-term mortality in patients with acutely decompensated heart failure. *Eur J Heart Fail*. 2010;12(8):826-32.
6. McEvoy JW, Chen Y, Halushka MK, Christenson E, Ballantyne CM, Blumenthal RS, Christenson RH, Selvin E. Galectin-3 and risk of heart failure and death in blacks and whites. *J Am Heart Assoc*. 2016;5(5):e003079.
7. Pang J, Rhodes DH, Pini M, Akasheh RT, Castellanos KJ, Cabay RJ, Cooper D, Perretti M, Fantuzzi G. Increased Adiposity, Dysregulated Glucose Metabolism and Systemic Inflammation in Galectin-3 KO Mice. *PLoS One*. 2013;8(2):e57915.
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9. Vora A, de Lemos JA, Ayers C, Grodin JL, Lingvay I. Association of Galectin-3 with Diabetes Mellitus in the Dallas Heart Study. *J Clin Endocrinol Metab* . 2019;2019;104(10):4449-4458.10. Ohkuma T, Komorita Y, Peters SAE, Woodward M. Diabetes as a risk factor for heart failure in women and men: a systematic review and meta-analysis of 47 cohorts including 12 million individuals. *Diabetologia* . 2019;2019;62(9):1550-1560.
11. Bugger H, Abel ED. Molecular mechanisms of diabetic cardiomyopathy. *Diabetologia*. 2014;57:660–71.