ARIC Manuscript Proposal #3759

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

1.a. Full Title: Independent and Joint Associations of Growth Derived Factor (GDF)-15, Diabetes and Heart Failure : The Atherosclerosis Risk in Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters): GDF-15, Diabetes, and Heart Failure

2. Writing Group: Justin Echouffo-Tcheugui, Natalie Daya, Chiadi E. Ndumele, Ron Hoogeveen, Kunihiro Matsushita, Christie M. Ballantyne, Josef Coresh, Amil M. Shah, Elizabeth Selvin, 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:

Growth differentiation factor 15 (GDF-15) is a protein of the transforming growth factor-β (TGF-β) cytokine superfamily,[1] which is expressed in several human tissues including the adipose tissue.[2] The putative effects of GDF-15 have been described in a mechanistic studies, [3–6] which point to its role in oxidative stress, mitochondrial function, energy

balance, and glucose homeostasis. Community-based studies have described a positive association between GDF-15 and diabetes.[7,8] A number of population-based studies have also shown a robust association between elevated GDF-15 levels and incident HF,[9–13] as well as with HF prognosis.[14–17] Diabetes is an established risk factor for incident HF.[18] While the association of GDF-15 with HF is well-recognized, the exact underlying pathways linking GDF-15 and HF remain poorly understood. Diabetes and GDF-15 may interact to influence the occurrence of HF. It is unclear whether the GDF-15 and incident HF differ among subgroups defined by diabetes status, and whether diabetes and GDF-15 provide complementary prognostic information regarding HF risk. There is limited clinical or population-based data exploring the joint associations of diabetes and GDF-15 with HF.

Using the framework of the community-based Atherosclerosis Risk in Communities Study (ARIC) study, we propose to examine the association of diabetes and GDF-15 levels, as well as the association of GDF-15 and incident HF among participants with and without diabetes.

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

Aims:

1- To assess the evaluate the association between diabetes and GDF-15 levels
2- To assess the influence of diabetes on the association of GDF-15 and incident HF, by examining the association of GDF-15 and HF across subgroups defined by diabetes status.
3- To evaluate whether diabetes status and GDF-15 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 3 data, which include:

1) A cross-sectional analysis of the association of diabetes status and GDF-15 levels (dependent variable) at Visit 3.
2) A prospective cohort analysis of the joint associations of diabetes status and GDF-15 (at Visit 3 – baseline) with incident HF occurring after Visit 3, using analyses stratified by diabetes and cross-categories of GDF-15 levels.

Exposures:

Diabetes assessed at Visit 3 will be the exposure of interest in the cross-sectional analyses.

GDF-15 measured at Visit 3 through the SomaLogic platform will be the exposure for the prospective analyses.

Diabetes will be defined at Visit 3 as a prior physician diagnosis of diabetes, use of hypoglycemic medications, a fasting blood glucose ≥126 mg/dL or non-fasting blood glucose ≥ 200 mg/dL.
Plasma GDF-15: It was measured in blood samples collected at Visit 3 using the SomaLogic proteomics platform. In prospective analyses, GDF-15 will be the exposure of interest, with categorization by diabetes status evaluated as an effect modifier. In these analyses, GDF-15 will be modeled as a continuous (per 1-SD, with log transformation as needed) and categorical (quartiles) variable.

Outcomes:
Cross-sectional analyses
GDF-15 will be the main outcome for cross-sectional analyses (Visit 3), and will be classified as elevated vs non-elevated, with elevated GDF-15 defined as a GDF-15 value within the highest quartile.
Prospective analyses
Incident HF (from Visit 3) will be the outcome for the prospective analyses. HF will be defined as HF hospitalization or death due to HF occurring after Visit 3 (baseline for prospective analyses), through 2018 or most recently available data.

Exclusions: Participants with prevalent HF (self-reported HF or CHD at Visit 3; or HF events, adjudicated CHD events, or silent MI at or prior to Visit 3) 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, systolic blood pressure, anti-hypertensive medications use, LDL-cholesterol, HDL-cholesterol, triglycerides, body mass index, and estimated glomerular filtration rate (eGFR), and metformin use.

Main Analyses:

1. We will present the baseline characteristics of participants at Visit 3 by GDF-15 quartiles (and further by diabetes status). 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.
    b. Model 2: Adjusted for the variables in Model 1 + current smoking, current smoking, systolic blood pressure, use of antihypertensive medications, use of cholesterol lowering medications, total cholesterol, HDL cholesterol, triglycerides, body mass index, and metformin use, as this medication can affect GDF-15 levels.[19].
3. We will use adjusted logistic regression to study the association of diabetes status with elevated GDF-15 at Visit 3, using those without diabetes as the reference.
4. In prospective analyses, we will use adjusted Cox proportional hazards models to assess the association of quartiles of GDF-15 with incident HF after Visit 3. 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 GDF-15 and diabetes with incident HF, using a cross-categorization of exposures that includes GDF-15 quartiles and diabetes categories (no diabetes and diabetes).

Limitations:

1. Residual confounding due to the observational nature of the study.
2. We will not evaluate the changes in GDF-15 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: 3479 - Association of Growth Differentiation Factor (GDF) 15 and Metabolic Outcomes: The Atherosclerosis Risk in Communities (ARIC) Study

Manuscript Number: 3411-The Association of Growth Differentiation Factor-15 and Risk of Incident Atherosclerotic Cardiovascular Disease, Heart Failure Hospitalization, and All-Cause Mortality: The Atherosclerosis Risk in Communities (ARIC) Study

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

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