ARIC Manuscript Proposal #3685

PC Reviewed: 8/11/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The association of growth differentiation factor 15 (GDF-15) with incident atrial fibrillation (AF): The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): GDF-15 & Incident AF

2. Writing Group:

Writing group members: Mengkun Chen, Ning Ding, Lena Mathews, Ron C. Hoogeveen, Christie M. Ballantyne, Lin Yee Chen, Josef Coresh, Kunihiro Matsushita

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _MC___ **[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: Data to be used in this proposal are already available. Analyses and manuscript preparation will be performed over the next 6 months.

4. Rationale:

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder and increases the risk of various adverse cardiovascular events such as stroke, myocardial infarction (MI), heart failure, vascular dementia, and mortality.[1] Most patients with AF are asymptomatic, and thus attempts are made to screen AF among individuals at high

risk of AF based on prediction models including risk factors such as age, sex, race, hypertension, diabetes mellitus, and history of heart failure, myocardial infarction and left ventricular hypertrophy.[2, 3, 4] The c-statistic of those models ranged from 0.70-0.78 but probably can be improved with other biomarkers.

In this context, growth differentiation factor 15 (GDF-15) is a promising predictor of AF. Specifically, GDF-15 is a distant member of the transforming growth factor ß (TGF-ß) superfamily and is involved in various biological processes like cell proliferation, differentiation, and apoptosis.[5] Moreover, some basic studies have shown that GDF-15 plays a role in myocardial fibrosis, hypertrophy, and endothelial dysfunction.[6] Indeed, GDF-15 has been independently associated with several cardiovascular outcomes such as heart failure, myocardial infarction, and left ventricular hypertrophy.[7, 8, 9]

Regarding the association of GDF-15 with incident AF, conflicting results have been reported. Specifically, out of four studies exploring this association, two studies[10, 11] reported positive association (i.e., higher levels of GDF-15 related to higher risk of incident AF), one study[12] null association, and the other[13] an inverse association. Also, only two were community-based studies,[10, 12] and both of them exclusively assessed white individuals.

Therefore, to more comprehensively explore the association of GDF-15 with incident AF, we will analyze data from the ARIC Study, a biracial community-based cohort. The large sample size with a long follow-up over 30 years will allow us to conduct subgroup analysis and investigate the improvement of AF risk prediction using GDF-15.

5. Main Hypothesis/Study Questions:
-GDF-15 will be positively associated with incident AF independently of potential confounders.
-GDF-15 will improve the prediction of incident AF beyond traditional predictors.

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).

Inclusions/exclusions:
- All ARIC participants with GDF-15 data at visit 3 and without prevalent AF (defined by ECG at visits 1-3 or AF hospitalization before visit 3).
- Given the data availability and length of follow-up, we will primarily use visit 3 GDF-15 but will also explore GDF-15 at visits 2 (when available) and 5.

Exposure:
-GDF-15: measured by Soma scan at ARIC visits 2, 3 and 5.

Outcome:

-Incident AF: AF identification[14] will be based on hospital discharge codes (ICD-9 codes 427.31 and 427.32 for atrial fibrillation and flutter, ICD-10 codes I48.x) and death certificates (427.3 or I48) after the relevant visit followed through 2018.

Other variables of interest and covariates:
-Sociodemographics: age from visit 3, race, gender, education level from visit 1
-Physical information: body mass index (height, body weight), waist circumference, heart rate, systolic and diastolic blood pressure (and use of antihypertensive medication), kidney function measures (GFR as estimated by the CKD-EPI equation using serum creatinine and/or cystatin C[16]), lipid profiles (total cholesterol, HDL cholesterol, triglyceride, and the use of cholesterol-lowering medications)
-Lifestyle: smoking status, alcohol consumption, and physical activity
-Medical history: cardiovascular disease (coronary heart disease, stroke, and heart failure), diabetes mellitus
-other biomarkers: inflammatory biomarkers (CRP and white blood cell count) and cardiac biomarkers (high-sensitivity cardiac troponin T and NT-proBNP)

Statistical Analysis Plan:
-GDF-15 will be treated as categorical (e.g., quartiles) and continuous variables.
-Comparing baseline characteristics across quartiles of GDF-15 using chi-square tests and analysis of variance.
-Cumulative incidence of AF across quartiles of GDF-15 over the follow-up.
-Cox proportional hazards models to estimate hazard ratio and 95% confidence intervals of incident AF across quartiles of GDF-15. Models will be adjusted for the above listed covariates. Model 1 will be crude. Model 2 will be adjusted for demographic variables, i.e., age, race, gender and level of education. Model 3 will be adjusted for AF classic risk factors, e.g., systolic blood pressure, antihypertensive medication, smoking, alcohol, total cholesterol, HDL cholesterol, body mass index, diabetes mellitus and a history of cardiovascular disease (coronary heart disease, heart failure). Model 4 will be further adjusted for biomarkers associated with AF, i.e., hs-cTnT and NT-proBNP.[11, 15, 16]
-Prediction statistics: We will compute Hosmer-Lemeshow χ^2, c-statistics, and net reclassification improvement for models with and without GDF-15.
-Sensitivity analyses: subgroup analysis by age (< and ≥ median age), gender (male vs. female), race (black vs. white), BMI, lifestyle (smoking status, alcohol consumption), prevalent cardiovascular disease like coronary heart disease, heart failure, stroke and diabetes mellitus (yes vs. no).

Limitations:
-Soma Scan provides values of GDF-15 in relative fluorescence units but not in absolute concentration.
-The ascertainment of AF is based mostly on hospital discharges codes or death codes. Some cases of AF diagnosed and treated in outpatient settings could be missed and misclassified.
-Paroxysmal AF and subclinical AF could be missed.
-Residual confounding.

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

We could not find any proposals exploring GDF-15 and incident AF.

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)?
No previous proposal in ARIC focus specifically on the association of GDF-15 and incident atrial fibrillation.

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* _2017.27)
___ 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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