ARIC Manuscript Proposal #3430

PC Reviewed: 7/9/19	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The association of growth differentiating factor 15 and risk of bleeding in the community. The Atherosclerosis in Communities (ARIC) Study.

b. Abbreviated Title (Length 26 characters): GDF15 and risk of bleeding.

2. Writing Group: Writing group members: Lena Mathews, Ning Ding, Junichi Ishigami, Mahmoud Al Rifai, Ron C. Hoogeveen, Josef Coresh, Christie M. Ballantyne, Elizabeth Selvin, Kunihiro Matsushita

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

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3. Timeline:

Once the data it obtained, data analysis and manuscript preparation will be done in the next 6 months.

4. Rationale:

Background:

Major bleeding events are associated with substantial morbidity, mortality and medical costs.[1] Factors that are associated with bleeding may elucidate the mechanistic causes of bleeding events, identify individuals at high risk, and potentially guide clinical management (e.g., selecting antithrombotic medications with lower risk of bleeding). In addition to known risk factors of bleeding (e.g., age, female sex, chronic kidney disease, and liver disease[2,3]), there are several emerging biomarkers associated with bleeding. For example, high-sensitivity cardiac

troponin T (hs-cTnT) and N-terminal pro-B type natriuretic peptide (NT-proBNP) have been associated with bleeding in several previous studies. [4-9]

Growth differentiating factor 15 (GDF-15) is another potential predictor of bleeding. GDF-15 is in the family of transforming growth factor ß (TGFß) and involved in cell proliferation and differentiation.[10,11] For example, elevated GDF-15 was strongly associated with bleeding in nearly 15,000 patients with atrial fibrillation on anticoagulation in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial[12] and in nearly 17,000 patients with acute coronary syndrome on dual antiplatelet therapy in the PLATO (PLATelet inhibition and patient Outcomes) trial.[13,14] Accordingly, the ARISTOTLE study authors developed a bleeding risk score known as the "ABC bleeding score", including GDF-15, which was shown to better predict bleeding events in individuals with atrial fibrillation compared to other established bleeding risk scores such as the HAS-BLED.[9] Potential mechanisms for the association of GDF15 with bleeding include platelet activity inhibition,[15] and it may also be expressed during times of cellular stress and tissue vulnerability.[13]

However, no studies have assessed whether GDF-15 is prospectively associated with bleeding in the general population. Therefore, we would like to investigate if elevated GDF-15 levels are independently associated with bleeding risk and can predict future bleeding events in the general population. We will explore the association of GDF15 measured at two time points at Visit 2 and Visit 5/6 with risk of hospitalization with bleeding in asymptomatic individuals in the community in the Atherosclerosis Risk in Communities (ARIC) study.

5. Main Hypothesis/Study Questions:

Does elevated GDF-15 predict increased risk of bleeding complications in asymptomatic individuals?

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 methodological limitations or challenges if present).

Study design:
-Prospective cohort analysis

Inclusion criteria:
-All ARIC study participants who had GDF-15 measured at visit 2, visits 5 and/or 6.

Exclusion criteria:
-Study participants with prevalent bleeding
-Study participants with prevalent cardiovascular disease including prevalent CHD, stroke and heart failure

Exposure:
We will use GDF-15 from Visits 2 and 5 measured by Soma scan and from Visit 6 measured by ELISA. We will model GDF-15 continuously and categorically (e.g., quartiles).

Outcome:
Primary outcome:
-Incidence of all-cause hospitalization for bleeding complications based on ICD-9 discharge codes defined as ICD-9 code:
-578.9 gastrointestinal bleeding
-431.0 intracerebral hemorrhage, 430.0 subarachnoid hemorrhage, 432.1 subdural hematoma

-V58.2 blood transfusion without reported diagnosis
-793.6459.0 retroperitoneal hemorrhage

Secondary outcome:
-Specific bleeding events: Gastrointestinal, intracranial, retroperitoneal

Other variables of interest:
-Age
-Race
-Gender
-Body Mass Index (BMI)
-Blood pressure (systolic and diastolic)
-Smoking status
-Alcohol consumption
-Education level from visit 1
-Kidney function measures:
    -GFR as estimated by CKD-EPI equation using serum creatinine and cystatin C[16]
-Baseline hs-cTnT and NT-proBNP
-Medication use:
    -Aspirin
    -Antiplatelet (non-aspirin)
    -Coumadin
    -Steroids
    -Proton pump inhibitor
    -H_2 blockers
    -Antihypertensive medication
-Medical history:
    -Diabetes mellitus (DM)
    -Hypertension
    -Prior gastrointestinal bleeding (GIB)
    -Prior intracranial bleeding (ICH)
    -Cancer
    -Liver disease
    -Chronic obstructive pulmonary disease (COPD)
    -Prior stroke

Statistical analysis plan:
-Baseline characteristics will be compared across quartiles of GDF-15 (at visit 2 and visit 5/6) using chi-square tests and analysis of variance.
-Estimate incidence rates and 95% confidence intervals with Poisson regression models
-Estimate hazard ratio and 95% confidence intervals with Cox proportional hazard models
-Models will be adjusted for age, sex, race-center, BMI, smoking status, alcohol consumption, educational level, aspirin use, antiplatelet use, history of hypertension, diabetes, prior GIB, prior ICH, eGFR, hs-cTnT, and NT-proBNP
-As a measure of risk discrimination, we will compute c-statistics between models with and without GDF-15.
-Sensitivity analysis: Subgroup analysis by incident CHD (yes vs. no), sex (men vs. women), age (<60 vs ≥60 years), race (black vs. white), DM (yes vs. no), incident stroke (yes vs. no), incident HF (yes vs. no),

Limitations:

-Misclassification of outcome due to reliance of ICD-9 discharge codes
-Mild cases of bleeding not requiring hospitalization may not be captured
-Residual confounding

7.a. Will the data be used for non-CVD analysis in this manuscript? __x__ Yes ____ 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
To our knowledge, there are no proposals exploring GDF-15 in the context of bleeding risk. MP2959 may be potentially relevant but aims to treat hs-cTnT and NT-proBNP as exposures for subsequent risk of bleeding.

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)?
None

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __x__ No

11.b. If yes, is the proposal
___ 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/

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.

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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes ____ No.

References:

1. Redfors B, Watson BM, McAndrew T, et al. Mortality, Length of Stay, and Cost Implications of Procedural Bleeding After Percutaneous Interventions Using Large-Bore Catheters. *JAMA Cardiol.* 2017;2(7):798-802.
2. Widimsky P, Motovska Z, Bolognese L, et al. Predictors of bleeding in patients with acute coronary syndromes treated with prasugrel. *Heart.* 2015;101(15):1219-1224.
3. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest.* 2010;138(5):1093-1100.
4. Iser DM, Thompson AJ, Sia KK, Yeomans ND, Chen RY. Prospective study of cardiac troponin I release in patients with upper gastrointestinal bleeding. *J Gastroenterol Hepatol.* 2008;23(6):938-942.
5. Al-Mallah M, Bazari RN, Jankowski M, Hudson MP. Predictors and outcomes associated with gastrointestinal bleeding in patients with acute coronary syndromes. *J Thromb Thrombolysis.* 2007;23(1):51-55.
6. Hijazi Z, Wallentin L, Siegbahn A, et al. High-sensitivity troponin T and risk stratification in patients with atrial fibrillation during treatment with apixaban or warfarin. *Journal of the American College of Cardiology.* 2014;63(1):52-61.
7. Hijazi Z, Oldgren J, Andersson U, et al. Cardiac biomarkers are associated with an increased risk of stroke and death in patients with atrial fibrillation: a Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) substudy. *Circulation.* 2012;125(13):1605-1616.
8. Hijazi Z, Siegbahn A, Andersson U, et al. High-sensitivity troponin I for risk assessment in patients with atrial fibrillation: insights from the Apixaban for Reduction in Stroke and other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. *Circulation.* 2014;129(6):625-634.
9. Hijazi Z, Oldgren J, Lindback J, et al. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study. *Lancet.* 2016;387(10035):2302-2311.
10. Kempf T, Eden M, Strelau J, et al. The transforming growth factor-beta superfamily member growth-differentiation factor-15 protects the heart from ischemia/reperfusion injury. *Circ Res.* 2006;98(3):351-360.
11. Xu J, Kimball TR, Lorenz JN, et al. GDF15/MIC-1 functions as a protective and antihypertrophic factor released from the myocardium in association with SMAD protein activation. *Circ Res.* 2006;98(3):342-350.

12. Wallentin L, Hijazi Z, Andersson U, et al. Growth differentiation factor 15, a marker of oxidative stress and inflammation, for risk assessment in patients with atrial fibrillation: insights from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. *Circulation.* 2014;130(21):1847-1858.
13. Hagstrom E, James SK, Bertilsson M, et al. Growth differentiation factor-15 level predicts major bleeding and cardiovascular events in patients with acute coronary syndromes: results from the PLATO study. *Eur Heart J.* 2016;37(16):1325-1333.
14. Lindholm D, James SK, Gabrysch K, et al. Association of Multiple Biomarkers With Risk of All-Cause and Cause-Specific Mortality After Acute Coronary Syndromes: A Secondary Analysis of the PLATO Biomarker Study. *JAMA cardiology.* 2018.
15. Rossaint J, Vestweber D, Zarbock A. GDF-15 prevents platelet integrin activation and thrombus formation. *J Thromb Haemost.* 2013;11(2):335-344.
16. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *The New England journal of medicine.* 2012;367(1):20-29.