ARIC Manuscript Proposal #3430

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]

First author: Lena Mathews
Address: Department of Medicine
          Johns Hopkins Bloomberg School of Medicine
          600 N. Wolfe Street, Blalock 524D
          Baltimore, MD, 21218
          Phone: 917-270-8339
          E-mail: lmathew6@jhmi.edu

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).

Name: Kunihiro Matsushita
Address: Department of Epidemiology
          Johns Hopkins Bloomberg School of Public Health,
          2024 E. Monument St., Suite 2-600 (Rm 2-602), Baltimore, MD
          Phone: (443) 287-8766                Fax: (443) 683-8358
          E-mail: kmatsush@jhsph.edu

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 disease2,3), 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) trial12 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
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
  - Baseline hs-cTnT and NT-proBNP
- Medication use:
  - Aspirin
  - Antiplatelet (non-aspirin)
  - Coumadin
  - Steroids
  - Proton pump inhibitor
  - H2 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

   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

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:


