May 4, 2017

Dear Dr. Coresh and the ARIC Publications Committee,

On behalf of our fellow co-authors, we would like to thank you for your prompt review of our ARIC manuscript proposal #2959, "Cardiac biomarkers and subsequent risk of bleeding in the community: The Atherosclerosis in Communities (ARIC) Study." We greatly appreciate the specific feedback you have given in order to make the proposal more scientifically rigorous. We have provided specific responses to your questions on subsequent pages. In addition we have attached 2 copies of the revised proposal with and without the proposed changes highlighted.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Lena Mathews
Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe Street, Baltimore, MD, 21205

Kunihiro Matsushita, MD, PhD
Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
Welch Center for Prevention, Epidemiology, and Clinical Research
2024 E. Monument St., Suite 2-600 (Rm 2-602), Baltimore, MD 21287
Tel (443) 287-8766 Fax (410) 367-2384
kmatsus5@jhmi.edu

Response to questions:

1. The specified outcomes are all hospitalizations. Yet, can bleeding disorders be managed in the outpatient clinic? If so, the authors may want to consider using the claims data to examine evidence of bleeding outside of the hospital setting. This is merely a suggestion to consider.

- Thanks for this important suggestion. Although we briefly described the use of CMS data to capture outpatient bleeding in the original proposal, we realized that that was not clear. Therefore, we have now specified the use of CMS data in the section of "outcomes". (Line 104-105)

2. Also consider if bleeding disorders be assessed on the basis of the use of specific medications such as blood products?

- Our primary outcome now includes report of blood transfusion on the discharge diagnosis (V58.2) (Line 100-101)

3. The study population is very heterogeneous, such that there could be quite a range in terms of recommendations for antiplatelet medications. That could pertain both to the type of medications, their strength, as well as duration of treatment. It seems counterproductive to lump stroke, HF, and CHD exposures together.

- Sorry for not being clear but we are planning to exclude participants who had a history of stroke, HF, and CHD at baseline (namely visits 2 and 4): "Study participants with prevalent cardiovascular disease including prevalent CHD, stroke and heart failure" (Line 80-81). We realized that our rationale beginning with the impact of bleeding in patients with cardiovascular disease might be misleading and thus modified it. In the revised proposal, we further specified that we would exclude those who had a history of atrial fibrillation and venous thrombosis. Moreover, we will deal with incident cases of these cardiovascular diseases in three ways: 1. Adjusting for as a time-varying covariate, 2. Censoring at the time of incident events, and 3. Looking specifically at individuals who developed these cardiovascular diseases. Since antiplatelet and anticoagulation therapy may be difference among these diseases, this sensitivity analysis will be done individually for each of CHD, stroke, heart failure, atrial fibrillation, and venous thromboembolic disease. (Line 160-165 and Figure 1)

4. You may want to also consider long-term trends in that medications changed from V2 to V4 to the present.

- We have amended the proposal to include medications as a covariate measured at baseline and as a time varying covariate until the outcome whenever possible. (Line 151-152)

5. What were the guideline recommendations for antiplatelet therapy, for example post MI, at the time of V2 (or V4)? Most likely not the same as now (as stents were not in as frequent use at that time).

- Thanks for this important comment. For our main analysis using Cox models among all eligible participants at either of visit 2 or 4, we will check the proportionality assumption by plotting -log [-log (survival probability)] against log (survival time). This comment can be more relevant in our sensitivity analysis among those who developed incident cardiovascular disease (e.g., myocardial infarction) during follow-up. To account on this issue, we will adjust for calendar years of incident cardiovascular disease (e.g., before 2000, 2001-2010, and after 2010).

6. Will use of antiplatelet medications be assessed only at baseline or also during follow-up?

- The use of antiplatelet medications will be assessed at the baseline study visit (MSR Form), and by annual follow up (AFU Form), and at hospital discharge from an MI event (HRA Form) as much as we can. (Line 122 and 151)

7. How will aspirin use be ascertained?

- Aspirin use will be ascertained at the baseline visit (MSR Form), at Annual follow up visits (AFU form), and at the time of hospital discharge from an MI event discharge (HRA Form) as much as we can. (Line 122 and 151)

8. Should stroke not be considered as a separate outcome?

- We will include intracranial hemorrhage (431.0 (intracerebral hemorrhage), 430.0 (subarachnoid hemorrhage), 432.1 (subdural hematoma)) in the primary outcome (Line 94-95). In addition, as noted above we will conduct a sensitivity analysis focusing on participants who developed incident stroke during follow-up. (Line 161)

9. Reasons for transfusions can be quite varied and unrelated to use of antiplatelet drugs (e.g. anemia). I would be cautious in using that as one of the outcome measures.

- Related to the Committee comment #2 “Also consider if bleeding disorders be assessed on the basis of the use of specific medications such as blood products”, we think it is better to keep blood transfusions. However, as per this suggestion, we will take into account a blood transfusion diagnosis not related to acquired or congenital hemolytic anemia, hemoglobinopathy, or neoplasm. (Line 100-101). Nonetheless, we will repeat the analysis for bleeding events without accounting for transfusions as well.

ARIC Manuscript Proposal #5/9/2017

PC Reviewed: 5/9/17 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Cardiac biomarkers and subsequent risk of bleeding in the community: The Atherosclerosis in Communities (ARIC) Study.

b. Abbreviated Title (Length 26 characters): Cardiac markers and bleeding

2. Writing Group: Writing group members: Lena Mathews, Junichi Ishigami, Ron C. Hoogeveen, Christie M. Ballantyne, Rebecca Gottesman, Aaron Folsom, Josef Coresh, 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 Epidemiology
Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe Street, Baltimore, MD, 21205
Phone: 917-270-8339 Fax:
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: (410) 367-2384
E-mail: kmatsush@jhsph.edu

3. Timeline:

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

4. Rationale:

Background: Major bleeding requiring hospitalization is associated with excess medical expenditure and poor prognosis.[1] Therefore, factors that can predict bleeding risk may help clinicians to identify persons at high risk of bleeding and guide clinical management. In this context, several predictors of bleeding have been reported including older age, female gender,

chronic kidney disease,[2-5] liver disease, prior stroke, bleeding history, and alcohol use.[6,7] Of interest, a small clinical study reported a positive association between cardiac troponin (cTn) elevation and re-bleeding in patients with upper gastrointestinal bleeding in 2008.[8] Subsequently, a few large trials (e.g., ARISTOTLE and RE-LY) observed that high-sensitivity troponin (hs-cTn) is independently associated with incident major bleeding in individuals with atrial fibrillation on anticoagulation therapy.[7,9-11] However, to the best of our knowledge, no studies have explored whether hs-cTnT is prospectively associated with bleeding events in the general population.

Therefore, we will investigate if baseline levels of hs-cTnT can predict future bleeding events among individuals in the Atherosclerosis Risk in Communities (ARIC) study. We will also evaluate whether this association is unique to hs-cTn or associated with elevations in NT-proBNP, a marker of cardiac overload and thus elevated venous pressure. This comparison is important since both ARISTOTLE and RE-LY reported a significant association of major bleeding with hs-cTn but not NT-proBNP.[7,10]

5. Main Hypothesis/Study Questions:

Do elevated cardiac biomarkers predict increased risk of major bleeding complications in the general population?

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 cTnT and NT-proBNP measured at visits 2 and/or 4

Exclusion criteria:
-Study participants with prior bleeding
-Study participants with prevalent cardiovascular disease including prevalent CHD, stroke, heart failure, atrial fibrillation, and venous thromboembolic disease

Exposure:
-Cardiac biomarkers: hs-cTnT, NT-proBNP

Outcomes:
Primary outcome (as a composite and individual types of gastrointestinal, intracranial, and retroperitoneal):
-Incidence of all-cause hospitalization for spontaneous bleeding defined as ICD-9 code:
-gastrointestinal bleeding (see supplemental table 1): 532.xx, 531.xx, 535.01, 534.xx, 533.xx, 535.31, 537.83, 535.11, 532.xx, 531.xx, 534.xx, 535.61, 533.xx, 537.84, 530.82, 456.0, 456.20,

535.21, 530.7, 578.0, 535.41, 530.21, 535.51, 569.85, 569.86, 562.13, 562.03, 562.12, 562.02, 557.0, 569.3, 578.9, 792.1, 578.1)
-Intracranial hemorrhage: 431.0 (intracerebral hemorrhage), 430.0 (subarachnoid hemorrhage), 432.1 (subdural hematoma)

- To be consistent with other bleeding events, we will primarily analyze ICD-based events, but, as a sensitivity analysis, we will explore adjudicated hemorrhagic stroke events as well.

-retroperitoneal hemorrhage (793.6, 459.0)
-blood transfusion reported diagnosis (V58.2) not related to hemolytic anemia or hemoglobinopathy (282.xx, 283.xx) neoplasm (140.xx -239.xx)

Secondary outcome:
- We will also explore outpatient bleeding diagnosis using the Center for Medicare and Medicaid Services (CMS) data.

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[12]
    -Urinary ACR (visit 4)
-Liver enzymes (only at visit 4)
-Lipids
-Hemoglobin (mainly visit 2 as only two field centers measured hemoglobin at visit 4)
-Medication use at baseline and as a time varying covariate until the primary outcome:
    -Aspirin
    -Antiplatelet (non aspirin)
    -Nonsteroidal anti-inflammatory drugs (NSAIDS)
    -Coumadin
    -Steroids
    -Proton pump inhibitor (PPI)
    -Histamine 2-receptor antagonists (H2 blocker)
    -Antihypertensive medication
    -Antidiabetic medication
    -Lipid lowering therapy
-Medical history:
    -Diabetes mellitus (DM)
    -Hypertension
    -Cancer
    -Liver disease

-Chronic obstructive pulmonary disease (COPD)

Statistical analysis plan: (See Figure 1 showing the design of main analysis and three sensitivity analyses regarding to how to deal with incident CVD cases)

-Baseline characteristics will be compared across categories of hs-cTnT (e.g., <0.005 ng/mL, 0.005-0.013 ng/mL, ≥0.014 ng/mL)[13] using chi-square tests and analysis of variance.

-We will estimate incidence rates of bleeding events and corresponding 95% confidence intervals using Poisson regression models

-We will estimate hazard ratios and corresponding 95% confidence intervals using Cox proportional hazards models

-The models will be adjusted for age, sex, race, BMI, smoking status, alcohol consumption, educational level, lipid levels, aspirin use, antiplatelet use, steroid use, PPI use, H2 blocker use, NSAID use, history of hypertension, diabetes, cancer, liver disease, COPD, eGFR, hemoglobin, and each of cardiac biomarker, as appropriate. Medications will be assessed as time varying covariates at baseline until the occurrence of the outcome.

-We will test that proportional hazards assumption has been met by visualizing the log Nelson-Aalen cumulative hazard plot.

-When we use visit 4 data, we will additionally account for liver enzymes and ACR.

-Sensitivity analyses:

-Subgroup analysis by sex (men vs. women), age (<60 vs. ≥60 years), race (black vs. white), DM (yes vs. no), kidney dysfunction (yes vs. no), obesity (yes vs. no), anticoagulation therapy (yes vs. no), antiplatelet therapy (yes vs. no), PPI and H2 blocker (yes vs. no).

-We will analyze primary discharge diagnosis for bleeding as an outcome.

-We will deal with incident CVD cases (i.e., myocardial infarction, stroke, heart failure, atrial fibrillation venous thromboembolic disease [VTE]) in three ways: 1. Adjusting for these cases as a time-varying covariate, 2. Censoring at the time of incident CVD events, and 3. Looking specifically at individuals who developed these CVDs, clinical populations likely to be on antiplatelet or anticoagulation therapy (see Figure 1 below).

-We will explore whether the analysis of outpatient bleeding diagnosis using CMS data provide different results or not.

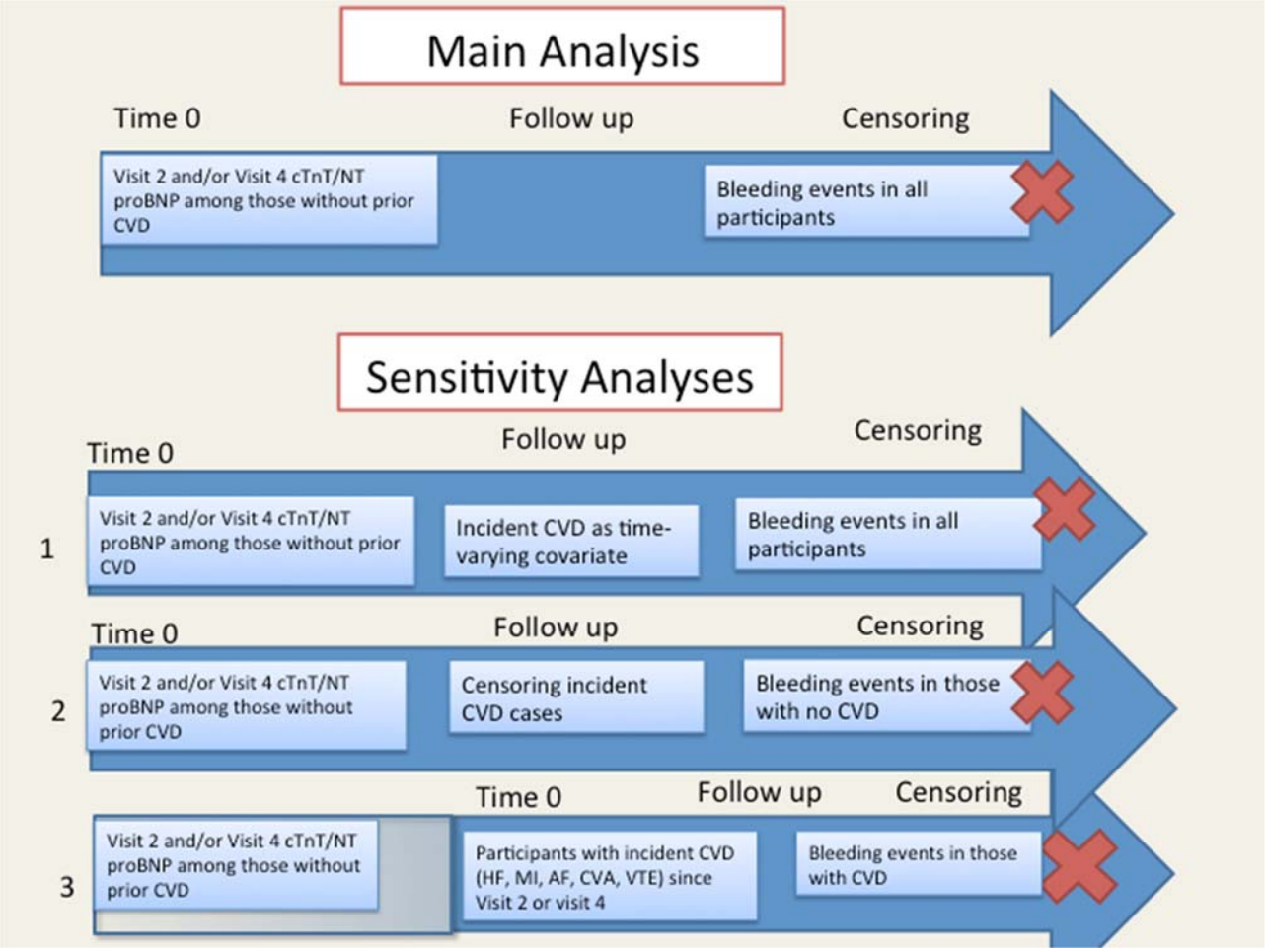

Figure 1: Schematic of the study methods

Limitations:

-Misclassification of the outcome due to reliance of ICD-9 codes
-Mild cases of bleeding not requiring hospitalization may not be captured
-Residual confounding
-Medical conditions associated with bleeding that are not captured at follow up including liver disease
-Anticoagulant and antiplatelet information collected at discrete time points at study visits and doesn't take into account changes in medications or changes in anticoagulation levels

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

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)?

#1856: Cardiac Troponin T Measured by Highly Sensitive Assay and MRI-Defined Small Vessel Disease of the Brain in the Atherosclerosis Risk in Community Study
#1899: Troponin T, NT-proBNP and stroke incidence
#2480: Chronic kidney disease and risk for gastrointestinal bleeding in the community: The Atherosclerosis Risk in Communities (ARIC) Study

These proposals have been published and key authors from each proposal are invited to the current proposal.

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* _ 2013.20 and 2009.16 _____)

___ 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. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation.* 2011;123(23):2736-2747.
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. Wanha W, Kawecki D, Roleder T, et al. Gender differences and bleeding complications after PCI on first and second generation DES. *Scand Cardiovasc J.* 2017;51(1):53-60.
4. Chandrasekhar J, Baber U, Sartori S, et al. Sex-related differences in outcomes among men and women under 55 years of age with acute coronary syndrome undergoing percutaneous coronary intervention: Results from the PROMETHEUS Study. *Catheter Cardiovasc Interv.* 2016.
5. Hochholzer W, Wiviott SD, Antman EM, et al. Predictors of bleeding and time dependence of association of bleeding with mortality: insights from the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel--Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38). *Circulation.* 2011;123(23):2681-2689.
6. 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.
7. 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.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. McEvoy JW, Chen Y, Ndumele CE, et al. Six-Year Change in High-Sensitivity Cardiac Troponin T and Risk of Subsequent Coronary Heart Disease, Heart Failure, and Death. *JAMA cardiology.* 2016;1(5):519-528.

ARIC Manuscript Proposal #2959

PC Reviewed: 5/9/17 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Cardiac biomarkers and subsequent risk of bleeding in the community: The Atherosclerosis in Communities (ARIC) Study.

b. Abbreviated Title (Length 26 characters): Cardiac markers and bleeding

2. Writing Group: Writing group members: Lena Mathews, Junichi Ishigami, Ron C. Hoogeveen, Christie M. Ballantyne, Rebecca Gottesman, Aaron Folsom, Josef Coresh, 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 Epidemiology
Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe Street, Baltimore, MD, 21205
Phone: 917-270-8339 Fax:
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: (410) 367-2384
E-mail: kmatsush@jhsph.edu

3. Timeline:

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

4. Rationale:

Background: ~~Incidence of m~~Major bleeding requiring hospitalization ~~are~~ is associated with excess medical expenditure and poor prognosis~~ particularly in people with cardiovascular disease~~.[1] ~~A cornerstone of cardiovascular disease prevention and treatment is with antiplatelet and anticoagulation therapy, which predisposes individuals to bleeding and precludes~~

~~continuation of evidence-based therapy. For example, in individuals at high risk of atherosclerotic disease or with established ischemic heart disease, bleeding often results in cessation of antiplatelet therapy and a corresponding increased risk of thrombotic events.[1] Similarly, bleeding results in interruption of anticoagulation therapy and increased in risk of thromboembolic events in individuals with atrial fibrillation (AF).~~

Therefore, factors that can predict bleeding risk ~~especially in the context of prevention and management of cardiovascular disease are important and~~ may help clinicians to identify persons at high risk of bleeding and guide clinical management. In this context, several predictors of bleeding have been reported including older age, female gender, chronic kidney disease,[2-5] liver disease, prior stroke, bleeding history, and alcohol use.[6,7] Of interest, a small clinical study reported a positive association between cardiac troponin (cTn) elevation and re-bleeding in patients with upper gastrointestinal bleeding in 2008.[8] Subsequently, a few large trials (e.g., ARISTOTLE and RE-LY) observed that high-sensitivity troponin (hs-cTn) is independently associated with incident major bleeding in individuals with atrial fibrillation on anticoagulation therapy.[7,9-11] However, to the best of our knowledge, no studies have explored whether hs-cTnT is prospectively associated with bleeding events in the general population.

Therefore, we will investigate if baseline ~~elevation in~~levels of hs-cTnT can predict future bleeding events among individuals in the Atherosclerosis Risk in Communities (ARIC) study. We will also evaluate whether this association is unique to hs-cTn or associated with elevations in NT-proBNP, a marker of cardiac overload and thus elevated venous pressure. This comparison is important since both ARISTOTLE and RE-LY reported a significant association of major bleeding with hs-cTn but not NT-proBNP.[7,10]

5. Main Hypothesis/Study Questions:

Do elevated cardiac biomarkers predict increased risk of major bleeding complications in the general population?

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 cTnT and NT-proBNP measured at visits 2 and/or 4

Exclusion criteria:
-Study participants with prior bleeding
-Study participants with prevalent cardiovascular disease including prevalent CHD, stroke, ~~and~~ heart failure, atrial fibrillation, and venous thromboembolic disease

Exposure:

-Cardiac biomarkers: hs-cTnT, NT-proBNP

Outcomes:
Primary outcome (as a composite and individual types of gastrointestinal, intracranial, and retroperitoneal):
-Incidence of all-cause hospitalization for spontaneous bleeding defined as ICD-9 code:
-gastrointestinal bleeding (see supplemental table 1): 532.xx, 531.xx, 535.01, 534.xx, 533.xx, 535.31, 537.83, 535.11, 532.xx, 531.xx, 534.xx, 535.61, 533.xx, 537.84, 530.82, 456.0, 456.20, 535.21, 530.7, 578.0, 535.41, 530.21, 535.51, 569.85, 569.86, 562.13, 562.03, 562.12, 562.02, 557.0, 569.3, 578.9, 792.1, 578.1)
-Intracranial hemorrhage: 431.0 (intracerebral hemorrhage), 430.0 (subarachnoid hemorrhage), 432.1 (subdural hematoma)

- To be consistent with other bleeding events, we will primarily analyze ICD-based events, but, as a sensitivity analysis, we will explore adjudicated hemorrhagic stroke events as well.

-retroperitoneal hemorrhage (793.6, 459.0)
-blood transfusion reported diagnosis (V58.2) not related to hemolytic anemia or hemoglobinopathy (282.xx, 283.xx) neoplasm (140.xx -239.xx)

Secondary outcome:
- We will also explore outpatient bleeding diagnosis using the Center for Medicare and Medicaid Services (CMS) data. ~~Specific bleeding complications: Gastrointestinal, intracranial, and 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[12]
    -Urinary ACR (visit 4)
-Liver enzymes (only at visit 4)
-Lipids
-Hemoglobin (mainly visit 2 as only two field centers measured hemoglobin at visit 4)
-Medication use at baseline and as a time varying covariate until the primary outcome:~~:~~
    -Aspirin
    -Antiplatelet (non aspirin)
    -Nonsteroidal anti-inflammatory drugs (NSAIDS)
    -Coumadin
    -Steroids
    -Proton pump inhibitor (PPI)

-Histamine 2-receptor antagonists (H2 blocker)
-Antihypertensive medication
-Antidiabetic medication
-Lipid lowering therapy

-Medical history:
-Diabetes mellitus (DM)
-Hypertension
-Cancer
-Liver disease
-Chronic obstructive pulmonary disease (COPD)

Statistical analysis plan: (See Figure 1 showing the design of main analysis and three sensitivity analyses regarding to how to deal with incident CVD cases)

-Baseline characteristics will be compared across categories of hs-cTnT (e.g., <0.005 ng/mL, 0.005-0.013 ng/mL, ≥0.014 ng/mL)[13] using chi-square tests and analysis of variance.

-We will estimate incidence rates of bleeding events and corresponding 95% confidence intervals using Poisson regression models

-We will estimate hazard ratios and corresponding 95% confidence intervals using Cox proportional hazards models

-The models will be adjusted for age, sex, race, BMI, smoking status, alcohol consumption, educational level, lipid levels, aspirin use, antiplatelet use, steroid use, PPI use, H2 blocker use, NSAID use, history of hypertension, diabetes, cancer, liver disease, COPD, eGFR, hemoglobin, and each of cardiac biomarker, as appropriate. Medications will be assessed as time varying covariates at baseline until the occurrence of the outcome.

-We will test that proportional hazards assumption has been met by visualizing the log Nelson-Aalen cumulative hazard plot.

-When we use visit 4 data, we will additionally account for liver enzymes and ACR.

-Sensitivity analyses:
-Subgroup analysis by sex (men vs. women), age (<60 vs. ≥60 years), race (black vs. white), DM (yes vs. no), kidney dysfunction (yes vs. no), obesity (yes vs. no), anticoagulation therapy (yes vs. no), antiplatelet therapy (yes vs. no), PPI and H2 blocker (yes vs. no).
-We will analyze primary discharge diagnosis for bleeding as an outcome.
-We will deal with incident CVD cases (i.e., myocardial infarction, stroke, heart failure, atrial fibrillation venous thromboembolic disease [VTE]) in three ways: 1. Adjusting for these cases as a time-varying covariate, 2. Censoring at the time of incident CVD events, and 3. Looking specifically at individuals who developed these CVDs~~We will also repeat the analysis among those who developed myocardial infarction, stroke, heart failure and venous thromboembolic disease (VTE) during follow-up~~, clinical populations likely to be on antiplatelet or anticoagulation therapy (see Figure 1 below).
-We will explore whether the ~~addition~~ analysis of outpatient bleeding diagnosis using CMS data provide different results or not.

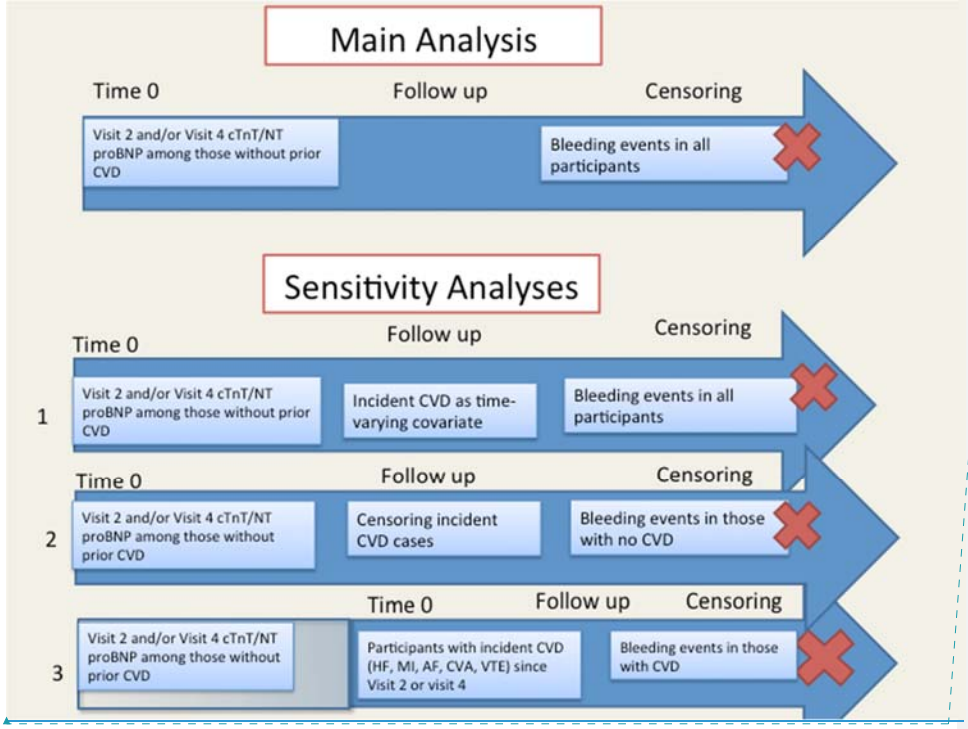

Figure 1: Schematic of the study methods

Limitations:

-Misclassification of the outcome due to reliance of ICD-9 codes
-Mild cases of bleeding not requiring hospitalization may not be captured
-Residual confounding
-Medical conditions associated with bleeding that are not captured at follow up including liver disease
-Anticoagulant and antiplatelet information collected at discrete time points at study visits and doesn't take into account changes in medications or changes in anticoagulation levels

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.)

Formatted: Font: 12 pt

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)?

#1856: Cardiac Troponin T Measured by Highly Sensitive Assay and MRI-Defined Small Vessel Disease of the Brain in the Atherosclerosis Risk in Community Study
#1899: Troponin T, NT-proBNP and stroke incidence
#2480: Chronic kidney disease and risk for gastrointestinal bleeding in the community: The Atherosclerosis Risk in Communities (ARIC) Study

These proposals have been published and key authors from each proposal are invited to the current proposal.

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* _ 2013.20 and 2009.16 _____)

___ 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. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation.* 2011;123(23):2736-2747.
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. Wanha W, Kawecki D, Roleder T, et al. Gender differences and bleeding complications after PCI on first and second generation DES. *Scand Cardiovasc J.* 2017;51(1):53-60.
4. Chandrasekhar J, Baber U, Sartori S, et al. Sex-related differences in outcomes among men and women under 55 years of age with acute coronary syndrome undergoing percutaneous coronary intervention: Results from the PROMETHEUS Study. *Catheter Cardiovasc Interv.* 2016.
5. Hochholzer W, Wiviott SD, Antman EM, et al. Predictors of bleeding and time dependence of association of bleeding with mortality: insights from the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel--Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38). *Circulation.* 2011;123(23):2681-2689.
6. 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.
7. 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.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. McEvoy JW, Chen Y, Ndumele CE, et al. Six-Year Change in High-Sensitivity Cardiac Troponin T and Risk of Subsequent Coronary Heart Disease, Heart Failure, and Death. *JAMA cardiology.* 2016;1(5):519-528.