

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,

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## 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  $-\log [-\log (\text{survival probability})]$  against  $\log (\text{survival time})$ . 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.



1 **ARIC Manuscript Proposal #5/9/2017**

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4 **PC Reviewed: 5/9/17**                      **Status: \_\_\_\_\_**                      **Priority: 2**  
5 **SC Reviewed: \_\_\_\_\_**                      **Status: \_\_\_\_\_**                      **Priority: \_\_\_\_\_**  
6

7 **1.a. Full Title:** Cardiac biomarkers and subsequent risk of bleeding in the community: The  
8 Atherosclerosis in Communities (ARIC) Study.  
9

10 **b. Abbreviated Title (Length 26 characters):** Cardiac markers and bleeding  
11

12 **2. Writing Group:** Writing group members: Lena Mathews, Junichi Ishigami, Ron C.  
13 Hoogeveen, Christie M. Ballantyne, Rebecca Gottesman, Aaron Folsom, Josef Coresh,  
14 Elizabeth Selvin, Kunihiro Matsushita  
15

16 I, the first author, confirm that all the coauthors have given their approval for this manuscript  
17 proposal. **\_LM\_[please confirm with your initials electronically or in writing]**  
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35

36 **3. Timeline:**  
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38 Once the data is obtained, data analysis and manuscript preparation will be done in the next 6  
39 months.  
40

41 **4. Rationale:**  
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43 **Background:** Major bleeding requiring hospitalization is associated with excess medical  
44 expenditure and poor prognosis.<sup>1</sup> Therefore, factors that can predict bleeding risk may help  
45 clinicians to identify persons at high risk of bleeding and guide clinical management. In this  
46 context, several predictors of bleeding have been reported including older age, female gender,

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

55  
56 Therefore, we will investigate if baseline levels of hs-cTnT can predict future bleeding events  
57 among individuals in the Atherosclerosis Risk in Communities (ARIC) study. We will also  
58 evaluate whether this association is unique to hs-cTn or associated with elevations in NT-  
59 proBNP, a marker of cardiac overload and thus elevated venous pressure. This comparison is  
60 important since both ARISTOTLE and RE-LY reported a significant association of major  
61 bleeding with hs-cTn but not NT-proBNP.<sup>7,10</sup>

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

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

## 67 **6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of 68 interest with specific reference to the time of their collection, summary of data analysis, 69 and any anticipated methodological limitations or challenges if present).**

### 70 Study design:

71  
72 -Prospective cohort analysis

### 73 Inclusion criteria:

74  
75 -All ARIC study participants who had cTnT and NT-proBNP measured at visits 2 and/or 4

### 76 Exclusion criteria:

77  
78 -Study participants with prior bleeding  
79 -Study participants with prevalent cardiovascular disease including prevalent CHD, stroke, heart  
80 failure, atrial fibrillation, and venous thromboembolic disease

### 81 Exposure:

82  
83 -Cardiac biomarkers: hs-cTnT, NT-proBNP

### 84 Outcomes:

85  
86 Primary outcome (as a composite and individual types of gastrointestinal, intracranial, and  
87 retroperitoneal):

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89 -Incidence of all-cause hospitalization for spontaneous bleeding defined as ICD-9 code:  
90 -gastrointestinal bleeding (see supplemental table 1): 532.xx, 531.xx, 535.01, 534.xx, 533.xx,  
91 535.31, 537.83, 535.11, 532.xx, 531.xx, 534.xx, 535.61, 533.xx, 537.84, 530.82, 456.0, 456.20,

92 535.21, 530.7, 578.0, 535.41, 530.21, 535.51, 569.85, 569.86, 562.13, 562.03, 562.12, 562.02,  
93 557.0, 569.3, 578.9, 792.1, 578.1)  
94 -Intracranial hemorrhage: 431.0 (intracerebral hemorrhage), 430.0 (subarachnoid hemorrhage),  
95 432.1 (subdural hematoma)  
96 • To be consistent with other bleeding events, we will primarily analyze ICD-based events,  
97 but, as a sensitivity analysis, we will explore adjudicated hemorrhagic stroke events as  
98 well.  
99 -retroperitoneal hemorrhage (793.6, 459.0)  
100 -blood transfusion reported diagnosis (V58.2) not related to hemolytic anemia or  
101 hemoglobinopathy (282.xx, 283.xx ) neoplasm (140.xx -239.xx)

102  
103 Secondary outcome:

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

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107 Other variables of interest:

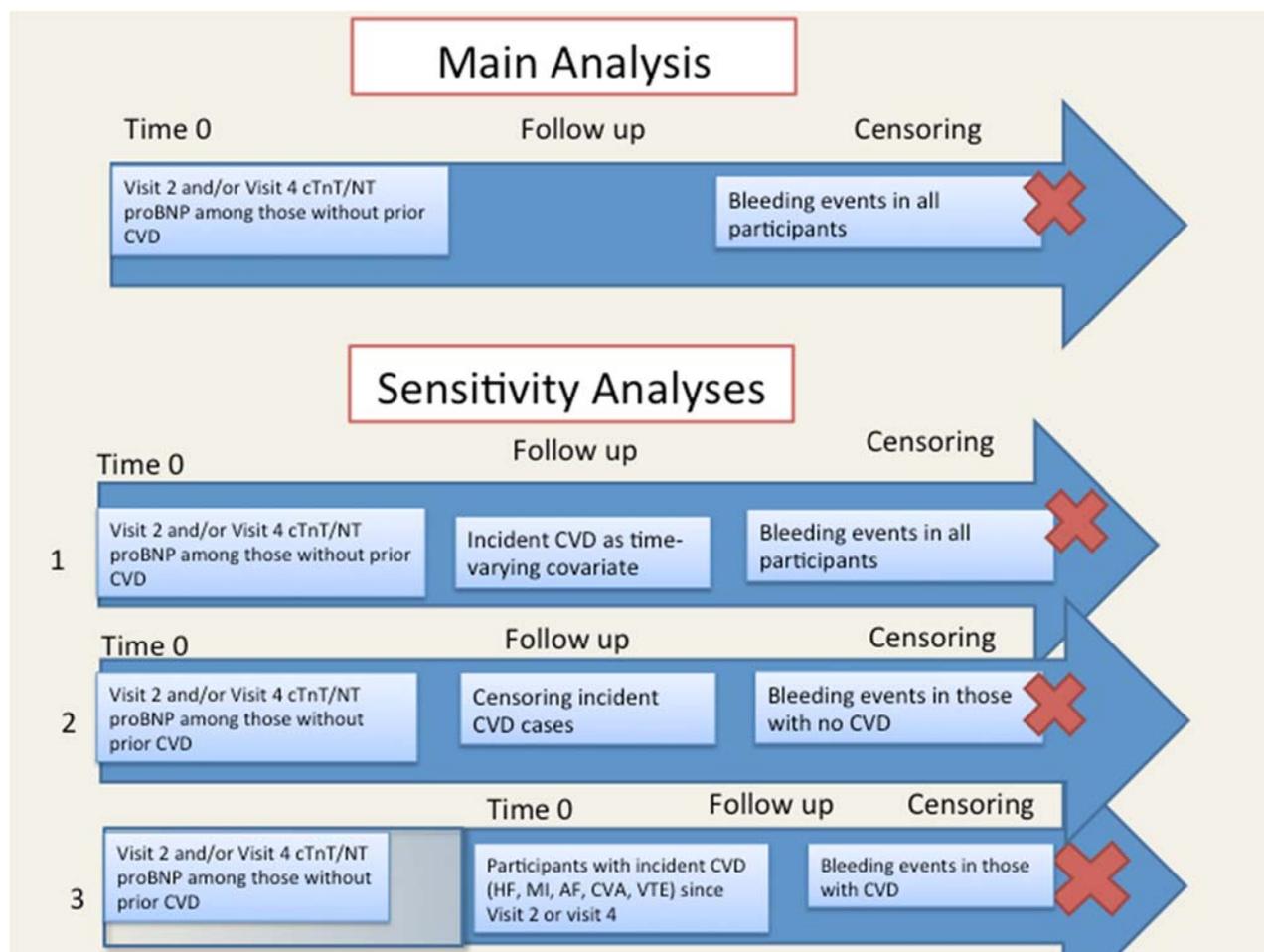
108 -Age  
109 -Race  
110 -Gender  
111 -Body mass index (BMI)  
112 -Blood pressure (systolic and diastolic)  
113 -Smoking status  
114 -Alcohol consumption  
115 -Education level from visit 1  
116 -Kidney function measures:  
117 -GFR as estimated by CKD-EPI equation using serum creatinine<sup>12</sup>  
118 -Urinary ACR (visit 4)  
119 -Liver enzymes (only at visit 4)  
120 -Lipids  
121 -Hemoglobin (mainly visit 2 as only two field centers measured hemoglobin at visit 4)  
122 -Medication use at baseline and as a time varying covariate until the primary outcome:  
123 -Aspirin  
124 -Antiplatelet (non aspirin)  
125 -Nonsteroidal anti-inflammatory drugs (NSAIDS)  
126 -Coumadin  
127 -Steroids  
128 -Proton pump inhibitor (PPI)  
129 -Histamine 2-receptor antagonists (H2 blocker)  
130 -Antihypertensive medication  
131 -Antidiabetic medication  
132 -Lipid lowering therapy  
133 -Medical history:  
134 -Diabetes mellitus (DM)  
135 -Hypertension  
136 -Cancer  
137 -Liver disease

138 -Chronic obstructive pulmonary disease (COPD)

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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,  $\geq 0.014$  ng/mL)<sup>13</sup> 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.  $\geq 60$  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.



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171 Figure 1: Schematic of the study methods

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173 Limitations:

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174 -Misclassification of the outcome due to reliance of ICD-9 codes

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175 -Mild cases of bleeding not requiring hospitalization may not be captured

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176 -Residual confounding

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177 -Medical conditions associated with bleeding that are not captured at follow up including liver disease

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179 -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

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182 **7.a. Will the data be used for non-CVD analysis in this manuscript?  Yes  No**

183

184 **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**

185

186 (This file ICTDER has been distributed to ARIC PIs, and contains

187

188 the responses to consent updates related to stored sample use for research.)

189

190 **8.a. Will the DNA data be used in this manuscript?** \_\_\_ Yes \_\_\_x\_\_\_ No

191  
192 **8.b. If yes, is the author aware that either DNA data distributed by the Coordinating**  
193 **Center must be used, or the file ICTDER03 must be used to exclude those with value**  
194 **RES\_DNA = “No use/storage DNA”?** \_\_\_ Yes \_\_\_ No

195  
196 **9. The lead author of this manuscript proposal has reviewed the list of existing ARIC**  
197 **Study manuscript proposals and has found no overlap between this proposal and**  
198 **previously approved manuscript proposals either published or still in active status.**  
199 ARIC Investigators have access to the publications lists under the Study Members Area of  
200 the web site at: <http://www.csc.unc.edu/ARIC/search.php>

201  
202 \_\_\_x\_\_\_ Yes \_\_\_\_\_ No

203  
204 **10. What are the most related manuscript proposals in ARIC (authors are encouraged to**  
205 **contact lead authors of these proposals for comments on the new proposal or**  
206 **collaboration)?**

207 #1856: Cardiac Troponin T Measured by Highly Sensitive Assay and MRI-Defined Small Vessel  
208 Disease of the Brain in the Atherosclerosis Risk in Community Study

209 #1899: Troponin T, NT-proBNP and stroke incidence

210 #2480: Chronic kidney disease and risk for gastrointestinal bleeding in the community: The  
211 Atherosclerosis Risk in Communities (ARIC) Study

212  
213 These proposals have been published and key authors from each proposal are invited to the  
214 current proposal.

215  
216 **11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any**  
217 **ancillary study data?** \_\_X\_\_ Yes \_\_\_ No

218  
219 **11.b. If yes, is the proposal**

220 \_\_\_X\_\_\_ **A. primarily the result of an ancillary study (list number\* \_2013.20 and**  
221 **2009.16 \_\_\_\_\_)**

222 \_\_\_ **B. primarily based on ARIC data with ancillary data playing a minor role**  
223 **(usually control variables; list number(s)\* \_\_\_\_\_)**

224

225 \*ancillary studies are listed by number at <http://www.csc.unc.edu/aric/forms/>

226

227 **12a. Manuscript preparation is expected to be completed in one to three years. If a**  
228 **manuscript is not submitted for ARIC review at the end of the 3-years from the date of the**  
229 **approval, the manuscript proposal will expire.**

230

231 **12b. The NIH instituted a Public Access Policy in April, 2008** which ensures that the public  
232 has access to the published results of NIH funded research. It is **your responsibility to upload**  
233 **manuscripts to PubMed Central** whenever the journal does not and be in compliance with this  
234 policy. Four files about the public access policy from <http://publicaccess.nih.gov/> are posted in  
235 <http://www.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms.

236 [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals  
237 automatically upload articles to PubMed central.

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239 **13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be**  
240 **submitted by the Coordinating Center to CMS for informational purposes prior to**  
241 **publication.** Approved manuscripts should be sent to Pingping Wu at CC, at  
242 [pingping\\_wu@unc.edu](mailto:pingping_wu@unc.edu). I will be using CMS data in my manuscript \_\_\_\_ Yes \_\_\_\_ No.

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245 References:

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262 BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey.  
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270 atrial fibrillation during treatment with apixaban or warfarin. *Journal of the American College of*  
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273 and death in patients with atrial fibrillation: a Randomized Evaluation of Long-term Anticoagulation  
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281 Risk of Subsequent Coronary Heart Disease, Heart Failure, and Death. *JAMA cardiology*. 2016;1(5):519-  
282 528.

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1 **ARIC Manuscript Proposal #2959**

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4 **PC Reviewed: 5/9/17**                      **Status: \_\_\_\_\_**                      **Priority: 2**  
5 **SC Reviewed: \_\_\_\_\_**                      **Status: \_\_\_\_\_**                      **Priority: \_\_\_\_\_**  
6

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

9  
10 **b. Abbreviated Title (Length 26 characters):** Cardiac markers and bleeding

11  
12 **2. Writing Group:** Writing group members: Lena Mathews, Junichi Ishigami, Ron C.  
13 Hoogeveen, Christie M. Ballantyne, Rebecca Gottesman, Aaron Folsom, Josef Coresh,  
14 Elizabeth Selvin, Kunihiro Matsushita

15  
16 I, the first author, confirm that all the coauthors have given their approval for this manuscript  
17 proposal. LM **[please confirm with your initials electronically or in writing]**  
18

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26 **ARIC author** to be contacted if there are questions about the manuscript and the first author  
27 does not respond or cannot be located (this must be an ARIC investigator).  
28

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33 Phone: (443) 287-8766                      Fax: (410) 367-2384  
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35

36 **3. Timeline:**

37  
38 Once the data is obtained, data analysis and manuscript preparation will be done in the next 6  
39 months.  
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41 **4. Rationale:**

42  
43 **Background:** ~~Incidence of m~~Major bleeding requiring hospitalization ~~are is~~ associated with  
44 ~~excess medical expenditure and poor prognosis particularly in people with cardiovascular~~  
45 ~~disease.<sup>1</sup> A cornerstone of cardiovascular disease prevention and treatment is with antiplatelet~~  
46 ~~and anticoagulation therapy, which predisposes individuals to bleeding and precludes~~

47 ~~continuation of evidence-based therapy. For example, in individuals at high risk of~~  
48 ~~atherosclerotic disease or with established ischemic heart disease, bleeding often results in~~  
49 ~~cessation of antiplatelet therapy and a corresponding increased risk of thrombotic events.<sup>4</sup>~~  
50 ~~Similarly, bleeding results in interruption of anticoagulation therapy and increased in risk of~~  
51 ~~thromboembolic events in individuals with atrial fibrillation (AF).~~

52  
53 Therefore, factors that can predict bleeding risk ~~especially in the context of prevention and~~  
54 ~~management of cardiovascular disease are important and~~ may help clinicians to identify persons  
55 at high risk of bleeding ~~and guide clinical management~~. In this context, several predictors of  
56 bleeding have been reported including older age, female gender, chronic kidney disease,<sup>2-5</sup> liver  
57 disease, prior stroke, bleeding history, and alcohol use.<sup>6,7</sup> Of interest, a small clinical study  
58 reported a positive association between cardiac troponin (cTn) elevation and re-bleeding in  
59 patients with upper gastrointestinal bleeding in 2008.<sup>8</sup> Subsequently, a few large trials (e.g.,  
60 ARISTOTLE and RE-LY) observed that high-sensitivity troponin (hs-cTn) is independently  
61 associated with incident major bleeding in individuals with atrial fibrillation on anticoagulation  
62 therapy.<sup>7,9-11</sup> However, to the best of our knowledge, no studies have explored whether hs-cTnT  
63 is prospectively associated with bleeding events in the general population.

64  
65 Therefore, we will investigate if baseline ~~elevation in levels of~~ hs-cTnT can predict future  
66 bleeding events among individuals in the Atherosclerosis Risk in Communities (ARIC) study.  
67 We will also evaluate whether this association is unique to hs-cTn or associated with elevations  
68 in NT-proBNP, a marker of cardiac overload and thus elevated venous pressure. This  
69 comparison is important since both ARISTOTLE and RE-LY reported a significant association  
70 of major bleeding with hs-cTn but not NT-proBNP.<sup>7,10</sup>

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

72  
73  
74 Do elevated cardiac biomarkers predict increased risk of major bleeding complications in the  
75 general population?

## 76 **6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of** 77 **interest with specific reference to the time of their collection, summary of data analysis,** 78 **and any anticipated methodological limitations or challenges if present).**

### 79 Study design:

80 -Prospective cohort analysis

### 81 Inclusion criteria:

82 -All ARIC study participants who had cTnT and NT-proBNP measured at visits 2 and/or 4

### 83 Exclusion criteria:

84 -Study participants with prior bleeding

85 -Study participants with prevalent cardiovascular disease including prevalent CHD, stroke, ~~and~~  
86 heart failure, atrial fibrillation, and venous thromboembolic disease

### 87 Exposure:

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

94

95 Outcomes:

96 Primary outcome (as a composite and individual types of gastrointestinal, intracranial, and

97 retroperitoneal):

98 -Incidence of all-cause hospitalization for spontaneous bleeding defined as ICD-9 code:

99 -gastrointestinal bleeding (see supplemental table 1): 532.xx, 531.xx, 535.01, 534.xx, 533.xx,  
100 535.31, 537.83, 535.11, 532.xx, 531.xx, 534.xx, 535.61, 533.xx, 537.84, 530.82, 456.0, 456.20,  
101 535.21, 530.7, 578.0, 535.41, 530.21, 535.51, 569.85, 569.86, 562.13, 562.03, 562.12, 562.02,  
102 557.0, 569.3, 578.9, 792.1, 578.1)

103 -Intracranial hemorrhage: 431.0 (intracerebral hemorrhage), 430.0 (subarachnoid hemorrhage),  
104 432.1 (subdural hematoma)

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

108 -retroperitoneal hemorrhage (793.6, 459.0)

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

111

112 Secondary outcome:

113 - We will also explore outpatient bleeding diagnosis using the Center for Medicare and Medicaid  
114 Services (CMS) data. Specific bleeding complications: Gastrointestinal, intracranial, and  
115 retroperitoneal

116

117 Other variables of interest:

118 -Age

119 -Race

120 -Gender

121 -Body mass index (BMI)

122 -Blood pressure (systolic and diastolic)

123 -Smoking status

124 -Alcohol consumption

125 -Education level from visit 1

126 -Kidney function measures:

127 -GFR as estimated by CKD-EPI equation using serum creatinine<sup>12</sup>

128 -Urinary ACR (visit 4)

129 -Liver enzymes (only at visit 4)

130 -Lipids

131 -Hemoglobin (mainly visit 2 as only two field centers measured hemoglobin at visit 4)

132 -Medication use at baseline and as a time varying covariate until the primary outcome:±

133 -Aspirin

134 -Antiplatelet (non aspirin)

135 -Nonsteroidal anti-inflammatory drugs (NSAIDS)

136 -Coumadin

137 -Steroids

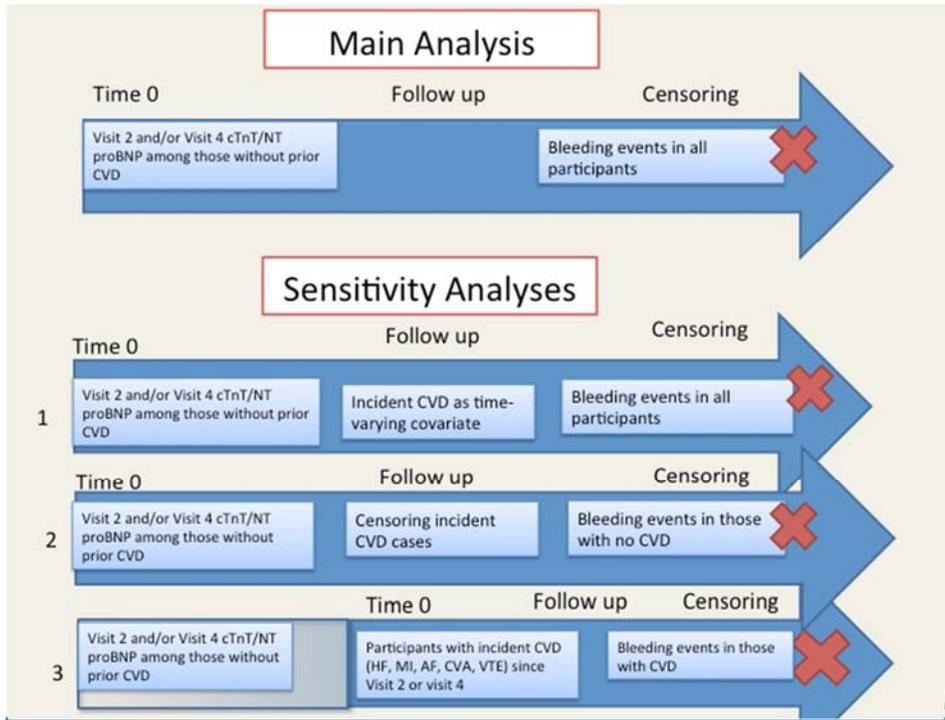
138 -Proton pump inhibitor (PPI)

- 139 -Histamine 2-receptor antagonists (H2 blocker)
- 140 -Antihypertensive medication
- 141 -Antidiabetic medication
- 142 -Lipid lowering therapy
- 143 -Medical history:
- 144 -Diabetes mellitus (DM)
- 145 -Hypertension
- 146 -Cancer
- 147 -Liver disease
- 148 -Chronic obstructive pulmonary disease (COPD)

149  
150 Statistical analysis plan: (See Figure 1 showing the design of main analysis and three sensitivity  
151 analyses regarding to how to deal with incident CVD cases)

- 152 -Baseline characteristics will be compared across categories of hs-cTnT (e.g., <0.005 ng/mL,
- 153 0.005-0.013 ng/mL,  $\geq 0.014$  ng/mL)<sup>13</sup> using chi-square tests and analysis of variance.
- 154 -We will estimate incidence rates of bleeding events and corresponding 95% confidence intervals
- 155 using Poisson regression models
- 156 -We will estimate hazard ratios and corresponding 95% confidence intervals using Cox
- 157 proportional hazards models
- 158 -The models will be adjusted for age, sex, race, BMI, smoking status, alcohol consumption,
- 159 educational level, lipid levels, aspirin use, antiplatelet use, steroid use, PPI use, H2 blocker use,
- 160 [NSAID use](#), history of hypertension, diabetes, cancer, liver disease, COPD, eGFR, hemoglobin,
- 161 and each of cardiac biomarker, as appropriate. [Medications will be assessed as time varying](#)
- 162 [covariates at baseline until the occurrence of the outcome.](#)
- 163 [-We will test that proportional hazards assumption has been met by visualizing the log Nelson-](#)
- 164 [Aalen cumulative hazard plot.](#)
- 165 -When we use visit 4 data, we will additionally account for liver enzymes and ACR.
- 166 -Sensitivity analyses:
- 167 -Subgroup analysis by sex (men vs. women), age (<60 vs.  $\geq 60$  years), race (black vs. white),
- 168 DM (yes vs. no), kidney dysfunction (yes vs. no), obesity (yes vs. no), anticoagulation
- 169 therapy (yes vs. no), antiplatelet therapy (yes vs. no), PPI and H2 blocker (yes vs. no).
- 170 -We will analyze primary discharge diagnosis for bleeding as an outcome.
- 171 [-We will deal with incident CVD cases \(i.e., myocardial infarction, stroke, heart failure,](#)
- 172 [atrial fibrillation venous thromboembolic disease \[VTE\]\) in three ways: 1. Adjusting for](#)
- 173 [these cases as a time-varying covariate, 2. Censoring at the time of incident CVD events,](#)
- 174 [and 3. Looking specifically at individuals who developed these CVDs](#)~~We will also repeat~~
- 175 ~~the analysis among those who developed myocardial infarction, stroke, heart failure and~~
- 176 ~~venous thromboembolic disease (VTE) during follow-up~~, clinical populations likely to be on
- 177 antiplatelet or anticoagulation therapy (see Figure 1 below).
- 178 -We will explore whether the [addition analysis](#) of outpatient bleeding diagnosis using CMS
- 179 data provide different results or not.

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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?  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.)

202 **8.a. Will the DNA data be used in this manuscript?** \_\_\_ Yes \_\_\_x\_\_\_ No  
203  
204 **8.b. If yes, is the author aware that either DNA data distributed by the Coordinating**  
205 **Center must be used, or the file ICTDER03 must be used to exclude those with value**  
206 **RES\_DNA = “No use/storage DNA”?** \_\_\_ Yes \_\_\_ No  
207

208 **9. The lead author of this manuscript proposal has reviewed the list of existing ARIC**  
209 **Study manuscript proposals and has found no overlap between this proposal and**  
210 **previously approved manuscript proposals either published or still in active status.**  
211 **ARIC Investigators have access to the publications lists under the Study Members Area of**  
212 **the web site at: <http://www.csc.unc.edu/ARIC/search.php>**  
213  
214 \_\_\_x\_\_\_ Yes \_\_\_ No  
215

216 **10. What are the most related manuscript proposals in ARIC (authors are encouraged to**  
217 **contact lead authors of these proposals for comments on the new proposal or**  
218 **collaboration)?**  
219 #1856: Cardiac Troponin T Measured by Highly Sensitive Assay and MRI-Defined Small Vessel  
220 Disease of the Brain in the Atherosclerosis Risk in Community Study  
221 #1899: Troponin T, NT-proBNP and stroke incidence  
222 #2480: Chronic kidney disease and risk for gastrointestinal bleeding in the community: The  
223 Atherosclerosis Risk in Communities (ARIC) Study  
224  
225 These proposals have been published and key authors from each proposal are invited to the  
226 current proposal.  
227

228 **11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any**  
229 **ancillary study data?** \_\_\_X\_\_\_ Yes \_\_\_ No  
230

231 **11.b. If yes, is the proposal**  
232 **\_\_\_X\_\_\_ A. primarily the result of an ancillary study (list number\* \_2013.20 and**  
233 **2009.16 \_\_\_\_\_)**  
234 **\_\_\_ B. primarily based on ARIC data with ancillary data playing a minor role**  
235 **(usually control variables; list number(s)\* \_\_\_\_\_)**  
236

237 \*ancillary studies are listed by number at <http://www.csc.unc.edu/atic/forms/>  
238

239 **12a. Manuscript preparation is expected to be completed in one to three years. If a**  
240 **manuscript is not submitted for ARIC review at the end of the 3-years from the date of the**  
241 **approval, the manuscript proposal will expire.**  
242

243 **12b. The NIH instituted a Public Access Policy in April, 2008** which ensures that the public  
244 has access to the published results of NIH funded research. It is **your responsibility to upload**  
245 **manuscripts to PubMed Central** whenever the journal does not and be in compliance with this  
246 policy. Four files about the public access policy from <http://publicaccess.nih.gov/> are posted in  
247 <http://www.csc.unc.edu/atic/index.php>, under Publications, Policies & Forms.

248 [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals  
249 automatically upload articles to PubMed central.

250

251 **13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be**  
252 **submitted by the Coordinating Center to CMS for informational purposes prior to**  
253 **publication.** Approved manuscripts should be sent to Pingping Wu at CC, at  
254 [pingping\\_wu@unc.edu](mailto:pingping_wu@unc.edu). I will be using CMS data in my manuscript \_\_\_\_ Yes \_\_\_\_ No.

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