ORIGINAL RESEARCH

Cardiac Biomarkers and Subsequent Risk of Hospitalization With Bleeding in the Community: Atherosclerosis Risk in Communities Study

Lena Mathews, MD, MHS; Junichi Ishigami, MD, MPH; Ning Ding, MD, ScM; Ron C. Hoogeveen, PhD; Anna Kucharska-Newton, PhD, MPH; Christie M. Ballantyne, MD; Rebecca Gottesman, MD, PhD; Elizabeth Selvin, PhD, MPH; Kunihiro Matsushita, MD, PhD

***Background*—**hs-cTnT (high-sensitivity cardiac troponin T), but not NT-proBNP (N-terminal pro–B natriuretic peptide), has been shown to predict bleeding in patients with atrial fibrillation. Whether these biomarkers are independently associated with bleeding in the general population is unknown.

***Methods and Results*—**We used Cox proportional hazards models to examine the association of hs-cTnT and NT-proBNP with incident bleeding (defined by *International Classification of Diseases, Ninth Revision* [*ICD-9*] codes) among 9550 middle-aged men and women without a history of cardiovascular disease or bleeding. There were 847 hospitalizations with bleeding (92% from gastrointestinal bleeding) during a median follow-up of 9.0 years. Serum levels of hs-cTnT were associated with bleeding in a graded fashion, with a hazard ratio of 1.28 (95% CI, 1.06–1.59) for 6 to <9 ng/L, 1.52 (1.21–1.91) for 9 to <14, and 2.05 (1.56–2.69) for ≥14 versus <3 ng/L. For NT-proBNP, the highest category (≥264 versus <42 pg/mL) showed a hazard ratio of 2.00 (1.59–2.61), and the remaining 3 categories had hazard ratios ranging from 1.2 to 1.3. Individuals in the highest category of both hs-cTnT and NT-proBNP had a hazard ratio of 3.03 (1.97–4.68) compared with those in the lowest categories.

***Conclusions*—**In a community-based population, elevated hs-cTnT and NT-proBNP were associated with bleeding-related hospitalizations. These biomarkers may have a high utility in identifying people at high risk for bleeding. There is a need for research on the underlying mechanisms linking subclinical cardiac abnormalities and bleeding. **(*J Am Heart Assoc*. 2020;9: e013560. DOI: 10.1161/JAHA.119.013560.)**

Key Words: bleeding • cardiac troponin T • gastrointestinal bleeding • natriuretic peptide

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 (eg, select antithrombotic medications with lower risk of bleeding). Several predictors of bleeding have been reported, including age, female sex, chronic kidney disease, liver disease, prior stroke, bleeding history, and excessive alcohol use.[2,3]

A few studies have shown that hs-cTnT (high-sensitivity cardiac troponin T), a biomarker associated with myocardial injury,[4] is a potent predictor of bleeding. For example, hs-cTnT predicted recurrences of bleeding in an observational study of patients with gastrointestinal bleeding.[5] In addition, peak troponin levels were associated with an increased risk of bleeding in patients with acute coronary syndrome.[6] Furthermore, 2 large clinical trials: ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) and RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) showed an independent association of hs-cTnT with incident major bleeding in individuals with atrial fibrillation on anticoagulation therapy.[7-10] A bleeding risk score that included age, biomarkers (hemoglobin, growth differentiating factor-15, and hs-cTnT), and history of bleeding, known as the "ABC bleeding score,"

From the Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (L.M., J.I., N.D., E.S., K.M.); Division of Cardiology (L.M.) and Department of Neurology (R.G.), Johns Hopkins School of Medicine, Baltimore, MD; Department of Medicine, Baylor College of Medicine, Houston, TX (R.C.H., C.M.B.); Gillings School of Global Public Health, University of North Carolina at Chapel Hill, NC (A.K.-N.); College of Public Health, University of Kentucky, Lexington, KY (A.K.-N.).

Accompanying Tables S1 through S5 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013560

Correspondence to: Kunihiro Matsushita, MD, PhD, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 2024 E Monument St, Suite 2-600, Baltimore, MD. E-mail: kmatsush@jhsph.edu

Received July 17, 2019; accepted January 31, 2020.

Clinical Perspective

What Is New?

- In this long-term prospective study of 9550 individuals in the Atherosclerosis Risk in Communities study without known cardiovascular disease or bleeding history, subclinical elevations of high-sensitivity cardiac troponin T, a marker of myocardial injury, and N-terminal pro–B natriuretic peptide, a marker of myocardial wall stress, were associated with an increased risk of hospitalization with bleeding.
- Both high-sensitivity cardiac troponin T and N-terminal pro–B natriuretic peptide significantly improved the risk discrimination of bleeding beyond established clinical predictors of bleeding.

What Are the Clinical Implications?

- For those individuals with elevated high-sensitivity cardiac troponin T and/or N-terminal pro–B natriuretic peptide at risk of both cardiovascular disease events and bleeding, primary prevention should prioritize therapies that do not increase the risk for bleeding such as statins, blood pressure control, and diabetes mellitus control.
- For people at high cardiovascular risk due to traditional risk factors but at lower risk of bleeding represented by low levels of high-sensitivity cardiac troponin T and N-terminal pro–B natriuretic peptide, preventive antiplatelet therapy may be a reasonable option when indicated.
- Future studies may be necessary to confirm the risk prediction improvement of bleeding with these cardiac biomarkers in other settings.

was derived and validated in these large studies and was shown to better predict bleeding events in individuals with atrial fibrillation compared with other bleeding risk scores such as the HAS-BLED (Hypertension, Abnormal Renal or Liver Function, Stroke, Bleeding, Labile INR, Elderly, Prior Drug or Alcohol Usage) or ORBIT (Outcomes Registry for Better Informed Treatment) scores that are based on clinical characteristics.[10]

There are a few plausible mechanisms underlying the association of hs-cTnT with bleeding. Elevated hs-cTnT and bleeding may share some risk factors such as diabetes mellitus and hypertension.[11,12] In addition, hs-cTnT may reflect subclinical cardiac abnormalities resulting in elevated venous pressure and increased bleeding risk.[13] Moreover, there is growing literature on the association of hs-cTnT with markers of subclinical microvascular disease in a variety of organs including the brain and kidney.[4,14] Thus hs-cTnT may reflect systemic and subclinical small-vessel disease including in the gastrointestinal tract and may be associated with an elevated risk of bleeding.[15]

No studies have assessed whether hs-cTnT is prospectively associated with bleeding in the general population. Because some investigators propose using hs-cTnT for predicting incident cardiovascular events,[16,17] it would be important to quantify the value of hs-cTnT for predicting bleeding events as well. Although the benefit and harm of antiplatelet therapy for cardiovascular disease prevention are controversial,[18-20] and some expert organizations such as the US Preventive Services Task Force recommend aspirin for some individuals,[21] such quantification will have clinical implications. Therefore, we investigated whether elevations of hs-cTnT were prospectively associated with bleeding events among individuals without a history of cardiovascular disease in the ARIC (Atherosclerosis Risk in Communities) study. We also evaluated whether this association was also present for NT-proBNP (N-terminal pro–B-type natriuretic peptide), a marker of myocardial wall stress and volume overload. In ARISTOTLE and RE-LY, NT-proBNP was not a predictor of bleeding among atrial fibrillation patients.[8,10]

Methods

The study data will not be made available to other researchers for the purposes of reproducing the results or replicating the procedure because of human subject restrictions. However, interested investigators can request access to the ARIC study data by contacting the ARIC Study Coordinating Center at the University of North Carolina–Chapel Hill.[22]

Study Population

We used data from the ARIC Study, a prospective cohort study of 15 792 individuals aged 45 to 64 years from 4 communities in the United States (Forsyth County, NC; Jackson, MS; suburban Minneapolis, MN; Washington County, MD) enrolled between 1987 and 1989.[23] Three follow-up visits (visits 2 to 4) took place approximately every 3 years, and subsequent visits 5 and 6 during 2011 to 2013 and 2016 to 2017, respectively. Phone interviews were conducted annually and semiannually from 2012. We used visit 4 (1996-1998) as our baseline because of the availability of albuminuria, a predictor of bleeding,[24] a higher prevalence of elevated hs-cTnT and NT-proBNP, and bleeding events. Out of 11 656 participants in visit 4, we excluded individuals with a prior history of bleeding (n=235), prevalent coronary heart disease (CHD) or stroke (n=1148), nonwhite and nonblack individuals (n=28), those who received blood transfusions (n=2), and those missing baseline covariates, hs-cTnT, and NT-proBNP (n=693), leaving 9550 individuals in the study who participated in visit 4 (Figure 1). A history of CHD was defined as a self-reported history of myocardial infarction or prior coronary

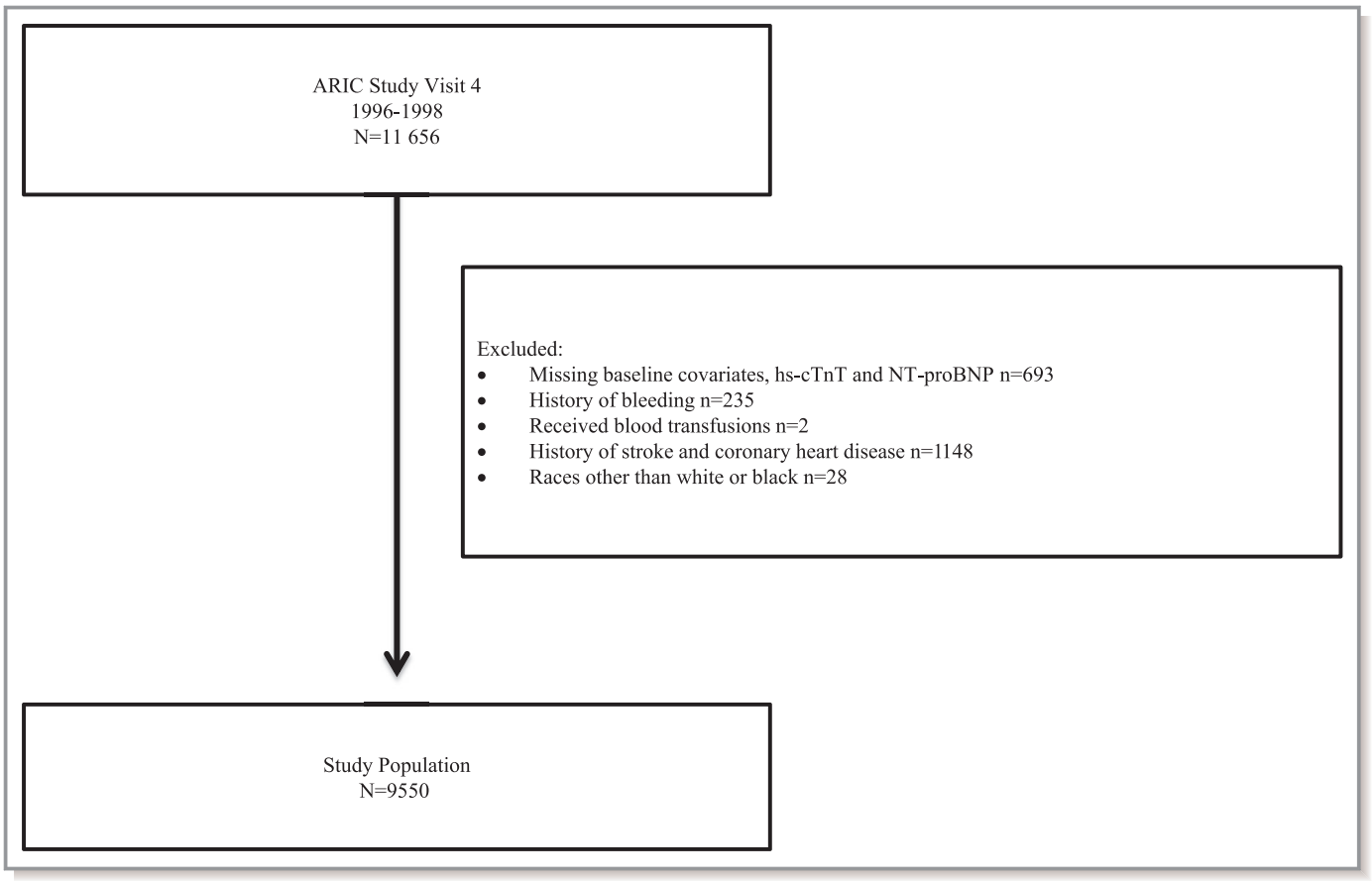

Figure 1. Derivation of the study population, the ARIC Study (N=9550). ARIC indicates Atherosclerosis Risk in Communities; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

revascularization at visit 1, evidence of silent myocardial infarction on electrocardiogram, or an adjudicated CHD event between visits 1 and 4.[25] A history of stroke was defined as a self-reported history of stroke at visit 1 or an adjudicated ischemic stroke event between visits 1 and 4.[26] The institutional review boards of all participating centers approved the research protocol, and all participants provided written informed consent. The study complied with the Declaration of Helsinki.

Cardiac Biomarkers

Hs-cTnT was measured in 2010-2011 from plasma samples collected at Visit 4 using a Cobas e411 analyzer (Roche Diagnostics, Indianapolis, IN) and stored at −70°C. The limit of blank was 3 ng/L, the limit of detection was 5 ng/L, and the upper reference limit of ≥14 ng/L corresponded to the 99th percentile in healthy individuals.[27] For participants with hs-cTnT below the detectable threshold, we assigned a value of 1.5 ng/L.[28] The coefficient of variation was 10% at 13 ng/L.[29]

NT-proBNP was also measured from plasma samples on the Cobas e411 analyzer (Roche Diagnostics, Basel, Switzerland) using the Elecsys NT-proBNP assay. The lower limit of detection was 5 pg/mL.[30] For participants with NT-proBNP below the detectable threshold, we assigned a value of 2.5 pg/mL.[30,31]

Definition of the Outcome

The outcome of hospitalization with bleeding was identified from hospital *International Classification of Disease, Ninth Revision* (*ICD-9*) discharge codes at any position through December 31, 2013 and was defined as cases with a hospital discharge diagnosis of gastrointestinal, intracranial, or retroperitoneal bleeding and blood transfusions (Table S1).[24,32] Participants were followed until incident bleeding hospitalization, death, loss to follow up, or the end of follow-up.

Covariates

Baseline demographics, lifestyle factors, and clinical characteristics were obtained at visit 4, except education, which was obtained at visit 1. Education was categorized as basic

education (<high school), intermediate education (high school graduate or vocational school), and advanced education (college, graduate, or professional school).[27] Participants reported their use of medications over the previous 2 weeks, and medication bottles were inspected at the study visit. Aspirin, NSAIDs, and anticoagulants were also examined at visit 5 and during phone interviews. Self-reported cigarette use was categorized as current, former, or never smoker. Self-reported alcohol use was categorized as current drinker (presently consuming alcoholic beverages), former drinker (previously but not currently consuming alcoholic beverages), and never drinker. Body mass index was defined as weight in kilograms divided by height in meters squared. Sitting blood pressure was measured twice using a sphygmomanometer, and the mean of the 2 measurements was recorded. Hypertension was defined as a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of blood pressure–lowering medications. Diabetes mellitus was defined as having a fasting glucose ≥126 mg/dL, random glucose ≥200 mg/dL, self-reported physician diagnosis of diabetes mellitus, or antidiabetic medication use. History of bleeding or cancer was obtained from hospital records based on *ICD-9* discharge codes. Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.[33] Urine albumin-creatinine ratio was used as a measure of albuminuria.[34] Total cholesterol was measured by enzymatic methods, and high-density lipoprotein cholesterol was measured after dextran-magnesium precipitation of non–high-density lipoprotein particles.[35] Alanine aminotransferase and aspartate aminotransferase were measured at visit 4. History of hepatic failure was defined as 3 times the upper limit of normal of alanine aminotransferase or aspartate aminotransferase or an *ICD-9* diagnosis of liver cirrhosis.[24] Incident CHD and stroke events were adjudicated by physician panels.

Statistical Analysis

Hs-cTnT levels were divided into 5 categories[27]: <3 (reference), 3 to <6, 6 to <9, 9 to <14, and ≥14 ng/L (corresponding to the 99th percentile in healthy individuals). NT-proBNP levels were also divided into 5 categories based on the same percentiles as hs-cTnT: <42 (reference), 42 to <81, 81 to <140, 140 to <264, and ≥264 pg/mL. Baseline characteristics were summarized across the 5 categories of hs-cTnT and NT-proBNP separately and were compared using ANOVA for continuous variables and a chi-squared test for categorical variables.

We used Poisson regression models to estimate the incidence rate of bleeding adjusted for age, sex, and race according to natural log–transformed hs-cTnT and NT-proBNP values. We used linear splines with 4 knots corresponding to the thresholds for the 5 biomarker categories and, trimmed at the 99.5th percentile for data presentation. We used multivariable Cox proportional hazards models to evaluate the association of hs-cTnT and NT-proBNP with incident hospitalization with bleeding. The cardiac biomarkers were modeled categorically and continuously (after log transformation). Model 1 was adjusted for age, race, sex, education, body mass index, diabetes mellitus, systolic blood pressure, cigarette use, alcohol use, total cholesterol, high-density lipoprotein cholesterol, aspirin use, anticoagulation use, NSAID use, antihypertensive use, statin use, estimated glomerular filtration rate, albumin-creatinine ratio, and liver function markers (alanine aminotransferase and aspartate aminotransferase). Aspirin, anticoagulants, and NSAIDs were modeled as time-varying covariates. Model 2 was adjusted for all variables in model 1 plus cardiac biomarkers (hs-cTnT in the NT-proBNP analysis and vice versa). Model 3 was adjusted for all variables in model 2 plus incident atherosclerotic cardiovascular disease (CHD and stroke) events occurring during follow-up modeled as time-varying covariates. Specifically, participants who developed CHD or stroke before bleeding had 2 rows in the data set. The first row was for the status of no CHD or stroke and the follow-up time until the development of atherosclerotic cardiovascular disease, and the second row was for the status of prevalent CHD or stroke and the follow-up time after atherosclerotic cardiovascular disease through censoring or bleeding. We used log Nelson-Aalen cumulative hazard plots and confirmed that the proportional hazard assumptions were met.

We performed several sensitivity analyses. First, we restricted our analysis to bleeding events as the primary discharge diagnosis. Second, we evaluated a joint association of hs-cTnT and NT-proBNP by analyzing their cross-categories. Third, we performed subgroup analysis by stratifying by age (<60 versus ≥60 years), sex, race (black versus white), current smoker, hypertension (yes versus no), diabetes mellitus (yes versus no), use of aspirin (yes versus no), and anticoagulation (yes versus no). Fourth, we performed analysis including participants with a prior history of bleeding at baseline. Lastly, we assessed the improvement in risk prediction beyond established predictors of bleeding using a base model consisting of predictors of bleeding in the HAS-BLED score (hypertension, abnormal liver/kidney function, age >65 years, drugs associated with bleeding, excess alcohol use defined as >8 drinks per week, and incident stroke).[3] Prior stroke and bleeding were included in the HAS-BLED score but were not taken into account in our analysis because individuals with a history of these conditions had been excluded from the baseline characteristics. However, we accounted for incident stroke during follow-up. We used the Harrell *c* statistic to measure the discrimination and estimated its change with the addition of log-transformed hs-cTnT and/or NT-proBNP to the base model.

A 2-sided $P<0.05$ was considered statistically significant. All statistical analyses were performed using Stata 15.1 (StataCorp, College Station, TX).

Results

Baseline Characteristics

Compared with individuals with undetectable hs-cTnT, those with progressively higher hs-cTnT levels were older, were more likely to be black, male, have a more basic or lower education level, a higher body mass index, were more likely to be former smokers (current smoking had a J-shaped association), more likely to be former drinkers (current drinking was inversely associated), more likely to have diabetes mellitus, hypertension, worse kidney function, higher alanine aminotransferase, aspartate aminotransferase, and NT-proBNP, and to use anticoagulants (Table 1). The baseline characteristics of the study participants according to NT-proBNP levels showed similar patterns to those for hs-cTnT except for the following: progressively higher NT-proBNP was more likely associated with female sex, white race, higher hs-cTnT, lower body mass index, current smoking, and never having used alcohol (Table S2).

Association of Cardiac Biomarkers With Bleeding

Among the study participants, 847 experienced hospitalized bleeding events during a median of 9.0 years of follow-up (maximum 17.7 years). Of those events, 433 (51%) had a primary diagnosis of bleeding. Gastrointestinal was the predominant type of bleeding (781 events [92%]), followed by intracranial (49 events [5.8%]) and retroperitoneal (31 events [3.7%]). The association of continuous hs-cTnT and NT-proBNP with the incidence rate for bleeding adjusted for age, sex, and race are shown in Figures 2A and 2B, respectively. The incidence rate for bleeding increased largely linearly with higher levels of log-transformed biomarkers, with an approximately 3-fold risk gradient in the range below their 99.5th percentile.

In multivariable adjusted models, compared with individuals with hs-cTnT <3 ng/L, there was an increasing risk of bleeding in a graded fashion with a hazard ratio (HR) of 1.28 (95% CI, 1.06–1.59) for 6 to <9 ng/L, 1.52 (1.21–1.91) for 9 to <14 ng/L, and 2.05 (1.56–2.69) for ≥14 ng/L (model 1, Table 2). Further accounting for NT-proBNP (model 2) or incident stroke and CHD during follow-up as a time-varying covariate (model 3) did not substantially alter the results. Continous log-transformed hs-cTnT was associated with an increased hazard for bleeding in the fully adjusted model.

Similarly, higher NT-proBNP was associated with increasing risk of bleeding (model 1, Table 2). The highest category of NT-proBNP demonstrated a similar HR as the highest category of hs-cTnT with HR 2.14 (1.65–2.79). The lower NT-proBNP categories showed HRs of 1.2 to 1.3. The results remained consistent even after adjustment for hs-cTnT (model 2) or incident cardiovascular disease during follow-up (model 3). Continuous log-transformed NT-proBNP was associated with an increased hazard for bleeding in the fully adjusted model.

The results were generally consistent in cases in which bleeding was the primary discharge diagnosis (Table S3) and when we examined the association by type of bleeding diagnosis (Table S4). We found similar results when we included individuals who had a prior history of bleeding and further adjusted for a history of bleeding (Table S5). There were no significant interactions between bleeding and a 2-fold increase in both biomarkers by race, sex, and different clinical risk factors. The association was similar among those with and without treatment with aspirin and anticoagulation (Figure 3A and 3B).

When cross-categories of hs-cTnT and NT-proBNP were studied, we found that individuals with both the highest hs-cTnT (≥14 ng/L) and NT-proBNP (≥264 pg/mL) categories had a HR of 3.03 (1.97–4.68) for bleeding compared with the lowest category with hs-cTnT (<6 ng/L) and NT-proBNP (<80 pg/mL) (Table 3). In addition, subclinical elevation of both hs-cTnT (6 to <14 ng/L) and NT-proBNP (80 to <264 pg/mL) had a HR 1.62 (1.28–2.05). Subclinical elevation of hs-cTnT alone (with NT-proBNP <80 pg/mL) demonstrated a significant HR of 1.48 (1.20–1.83), but subclinical elevation of NT-proBNP alone (80 to <264 pg/mL with hs-cTnT <6 ng/L) did not evidently confer an increased bleeding risk (HR 1.06).

Risk Discrimination by Adding Cardiac Biomarkers

The base model with predictors in the HAS-BLED score showed a *c*-statistic of 0.640 for bleeding (Table 4). The addition of hs-cTnT alone improved the *c*-statistic by 0.011 (0.006–0.016), and the addition of NT-proBNP alone improved the *c*-statistic by 0.009 (0.004–0.013). When both cardiac biomarkers were included, the improvement of the *c*-statistic was 0.015 (0.009–0.020).

Discussion

In this community-based study, higher baseline levels of hs-cTnT and NT-proBNP were independently and robustly associated with the risk of hospitalizations with bleeding. Each of the highest biomarker categories (hs-cTnT ≥14 ng/L and NT-proBNP ≥264 pg/mL) conferred a nearly 2-fold increase in

Table 1. Baseline Characteristics According to Categories of hs-cTnT in the ARIC Study (1996-1998) (N=9550)

Baseline Characteristics	hs-cTnT <3 ng/L	hs-cTnT 3 to <6 ng/L	hs-cTnT 6 to <9 ng/L	hs-cTnT 9 to <14 ng/L	hs-cTnT ≥14 ng/L	*P* Value
No. of participants	3240	2456	1947	1233	674	
Age, y	60.6 (5.0)	62.4 (5.5)	63.6 (5.5)	65.0 (5.6)	65.3 (5.7)	<0.001
Female	78.7%	61.9%	46.9%	35.0%	26.0%	<0.001
Black	21.4%	18.6%	21.7%	23.2%	28.5%	<0.001
Body mass index, kg/m^2	28.2 (5.5)	28.5 (5.5)	29.0 (5.6)	29.4 (5.4)	29.7 (5.5)	<0.001
Education level						
Basic	15.1%	17.2%	17.6%	22.5%	24.9%	<0.001
Intermediate	45.3%	43.0%	41.2%	37.2%	36.9%	
Advanced	39.6%	39.9%	41.2%	40.3%	38.1%	
Family history of CAD	54.5%	57.2%	58.9%	57.1%	55.0%	0.028
Smoking status						
Current smokers	20.7%	12.7%	9.7%	9.9%	12.9%	<0.001
Former smokers	36.4%	41.6%	45.6%	49.1%	50.0%	
Never smokers	42.9%	45.7%	44.6%	40.9%	37.1%	
Drinking status						
Current drinkers	52.4%	53.1%	49.2%	46.6%	45.1%	<0.001
Former drinkers	27.0%	26.5%	29.2%	30.3%	35.8%	
Never drinkers	20.6%	20.4%	21.6%	23.1%	19.1%	
NT-proBNP, pg/mL, median (IQR)	59.2 (29.6, 106.8)	61.9 (31.6, 113.5)	61.9 (30.7, 122.4)	71.7 (36.1, 147.1)	96.0 (44.2, 263.6)	<0.001
Systolic blood pressure, mm Hg	124.3 (17.8)	126.3 (18.1)	128.3 (18.6)	131.6 (19.9)	132.7 (20.7)	<0.001
Total cholesterol, mmol/L	5.3 (0.9)	5.2 (0.9)	5.2 (1.0)	5.1 (1.0)	5.0 (1.0)	<0.001
HDL cholesterol, mmol/L	1.4 (0.4)	1.3 (0.4)	1.3 (0.4)	1.2 (0.4)	1.2 (0.4)	<0.001
eGFR categories in mL/min per 1.73 m^2						
<30	0.03%	0.04%	0.10%	0.32%	2.4%	<0.001
30 to 60	2.6%	4.1%	6.5%	10.1%	18.0%	
>60	97.4%	95.9%	93.4%	89.6%	79.7%	
AST, U/L, median (IQR)	17.0 (15.0-21.0)	18.0 (15.0-21.0)	18.0 (16.0-22.0)	19.0 (16.0-22.0)	20 (16.0-24.0)	<0.001
ALT, U/L, median (IQR)	12.0 (9.0-16.0)	13.0 (10.0-17.0)	14.0 (10.0-18.0)	14.0 (10.0-18.0)	14.0 (10.0-20.0)	<0.001
Medication use						
Hypertension medications	27.7%	30.0%	36.7%	40.4%	49.6%	<0.001
Aspirin	53.6%	54.3%	53.9%	55.8%	57.1%	0.4
Statin	8.7%	8.4%	8.6%	10.5%	11.4%	0.04
Anticoagulant	0.5%	0.7%	1.2%	2.2%	5.2%	<0.001
Diabetes mellitus	9.8%	11.9%	16.7%	20.8%	34.4%	<0.001
History of hepatic failure	0.2%	0.3%	0.5%	0.2%	0.3%	0.4
History of cancer	7.6%	8.2%	7.5%	8.8%	8.9%	0.5

Values are mean (SD) or percentage, unless otherwise indicated. ALT indicates alanine aminotransferase; ARIC, Atherosclerosis Risk in Communities; AST, aspartate aminotransferase; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hs-cTnT, high-sensitivity cardiac troponin T; IQR, interquartile range; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

the hazard for bleeding. Even subclinical elevation of hs-cTnT of 9 to <14 ng/L contributed an approximately 1.5 times higher risk of bleeding. The associations were consistent after accounting for incident atherosclerotic cardiovascular disease during follow-up and across demographic and clinical subgroups. Importantly, both hs-cTnT and NT-proBNP significantly improved risk discrimination of bleeding beyond its established predictors.

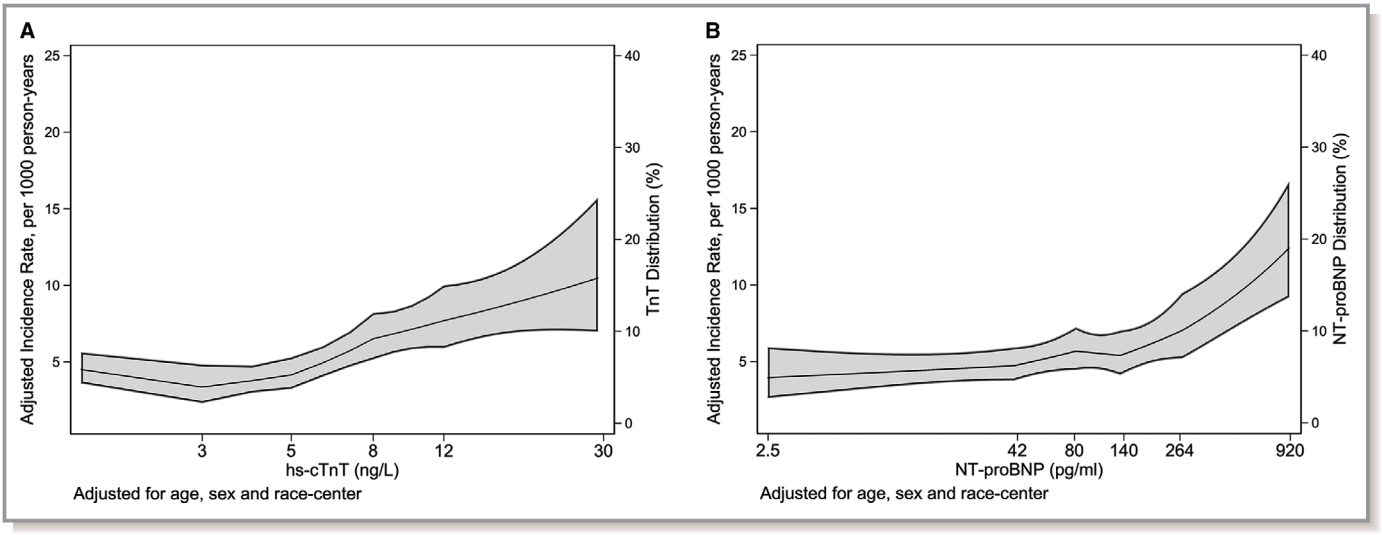

Figure 2. Incidence rates (95% CI) for the association of baseline categories of natural log–transformed (**A**) hs-cTnT (ng/L) and (**B**) NT-proBNP (pg/mL) with incident hospitalizations for bleeding in the ARIC study (N=9550). The solid line indicates the point estimate, the shaded area is 95% CI. The results are adjusted for age, sex, and race. The knots correspond to the thresholds for the 5 biomarker categories, trimmed at the 99.5th percentile. ARIC indicates Atherosclerosis Risk in Communities; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

Our results for hs-cTnT are consistent with previous findings in populations with a history of atrial fibrillation on oral anticoagulation in the RE-LY and ARISTOTLE studies.[8-10] However, our study is unique in several aspects. First, we confirmed hs-cTnT was a predictor of bleeding in the general population. Second, we had follow-up over 17 years (<2 years in RE-LY and ARISTOTLE).[10] Third, we confirmed that the association of hs-cTnT with bleeding was consistent across several demographic and clinical subgroups. Importantly, significant association between hs-cTnT and bleeding was seen among those with or without aspirin and those who did not take anticoagulants. Finally, unlike the results from RE-LY and ARISTOTLE, in addition to hs-cTnT, we found an association between elevated NT-proBNP and a subsequent risk of bleeding, with a slightly weaker or similar magnitude as hs-cTnT particularly in the clinically elevated range.

Although we are not sure about the exact mechanism for the association of elevated hs-cTnT with bleeding, there are some potential mechanisms to consider. First, this may be due to imbalance in the use of aspirin or anticoagulation

Table 2. Adjusted HRs (95% CIs) for the Association of Baseline Categories and Log-Transformed hs-cTnT and NT-proBNP With Incident Hospitalizations for Bleeding, from the ARIC Study

	hs-cTnT (ng/L)					
	<3	3 to <6	6 to <9	9 to <14	≥14	log hs-cTnT
Model 1	Reference	0.80 (0.64–0.98)	1.28 (1.06–1.59)	1.52 (1.21–1.91)	2.05 (1.56–2.69)	1.28 (1.17–1.41)
Model 2	Reference	0.79 (0.64–0.98)	1.29 (1.05–1.59)	1.52 (1.21–1.91)	1.99 (1.51–2.61)	1.26 (1.14–1.38)
Model 3	Reference	0.78 (0.63–0.96)	1.30 (1.06–1.59)	1.50 (1.19–1.89)	1.95 (1.48–2.56)	1.25 (1.14–1.38)
	NT-proBNP (pg/mL)					
	<42	42 to <81	81 to <140	140 to <264	≥264	log NT-proBNP
Model 1	Reference	1.23 (1.02–1.55)	1.27 (1.02–1.57)	1.29 (1.01–1.65)	2.14 (1.65–2.79)	1.18 (1.10–1.27)
Model 2	Reference	1.28 (1.02–1.55)	1.26 (1.02–1.57)	1.29 (1.01–1.64)	2.12 (1.62–2.76)	1.18 (1.10–1.27)
Model 3	Reference	1.26 (1.01–1.53)	1.24 (1.00–1.54)	1.27 (0.99–1.62)	2.00 (1.59–2.61)	1.16 (1.08–1.25)

Model 1 adjusted for age, sex, race, education, BMI, diabetes mellitus, family history of coronary artery disease, systolic blood pressure, cigarette use, alcohol use, total cholesterol, HDL cholesterol, statin use, aspirin, anticoagulation, NSAID, antihypertensive, eGFR, ACR, AST, ALT. Model 2 adjusted for variables in model 1 and for hs-cTnT or NT-proBNP. Model 3 adjusted for variables in model 2 and incident stroke and coronary heart disease. ACR indicates albumin-creatinine ratio; ALT, alanine aminotransferase; ARIC, Atherosclerosis Risk in Communities; AST, aspartate aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HR, hazard ratio; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

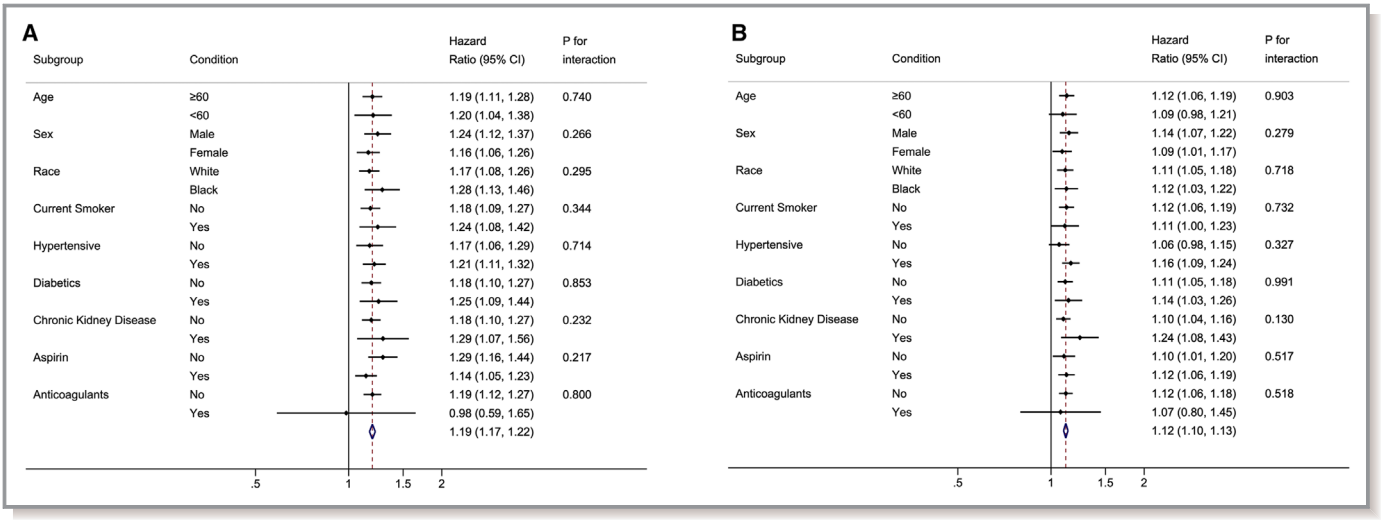

Figure 3. Adjusted HRs (95% CIs) for bleeding according to a 2-fold increase in (**A**) hs-cTnT (ng/L) and (**B**) NT-proBNP (pg/mL). The models are adjusted for age, sex, race, education, BMI, diabetes mellitus, systolic blood pressure, cigarette use, alcohol use, total cholesterol, HDL cholesterol, aspirin, anticoagulation, NSAID, antihypertensive medication, eGFR, ACR, AST, ALT, hs-cTnT, and NT pro-BNP. ACR indicates albumin-creatinine ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HR, hazard ratio; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

across hs-cTnT categories. However, we excluded those with prevalent CHD, and this significant association between hs-cTnT and bleeding persisted after adjustment for incident CHD and time-varying aspirin, NSAID, and anticoagulant use. Second, both subclinical myocardial damage and gastrointestinal bleeding have multiple shared risk factors including smoking,[36] age,[36] hypertension,[11] and diabetes mellitus.[12] However, again, the association was independent of these potential confounders. Third, hs-cTnT has been associated with incident heart failure,[37] and may be a marker of subclinical elevation of venous filling pressure that may lead to gastrointestinal mucosal congestion and bleeding.[13] Finally, another possibility may be related to recent findings indicating that hs-cTnT is a marker of microvascular disease in several organs including the brain and kidneys.[4,15,38] Microvascular disease may result in fragile vessels in the gastrointestinal tract that make them more prone to bleeding

Table 3. Adjusted HRs (95% CIs) for the Association of Baseline Cross-Categories of hs-cTnT and NT-proBNP With Incident Hospitalizations for Bleeding, From the ARIC Study

	hs-cTnT		
	<6 ng/L	6-<14 ng/L	≥14 ng/L
NT-proBNP			
<80 pg/mL	Reference	1.48 (1.20–1.83)	2.19 (1.52–3.16)
80 to <264 pg/mL	1.06 (0.85–1.33)	1.62 (1.28–2.05)	1.99 (1.33–2.98)
≥264 pg/mL	1.37 (0.90–2.09)	2.31 (1.64–3.25)	3.03 (1.97–4.68)

Model adjusted for age, sex, race, education, BMI, diabetes mellitus, family history of coronary artery disease, systolic blood pressure, cigarette use, alcohol use, total cholesterol, HDL cholesterol, aspirin, anticoagulation, NSAID, antihypertensive, eGFR, ACR, AST, ALT, incident stroke, coronary heart disease. ACR indicates albumin-creatinine ratio; ALT, alanine aminotransferase; ARIC, Atherosclerosis Risk in Communities; AST, aspartate aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HR, hazard ratio; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide.

Table 4. *c*-Statistic Improvement by Adding hs-cTnT and/or NT-proBNP to Established Bleeding Score HAS-BLED Score

	Harrell *c* (95% CI)	*c*-Statistic Difference From Base Model (95% CI)	*P* Value for Difference
Base model	0.640 (0.617–0.663)	. . .	. . .
+Log hs-cTnT	0.651 (0.629–0.674)	0.011 (0.006–0.016)	<0.001
+Log NT-proBNP	0.649 (0.626–0.671)	0.009 (0.004–0.013)	<0.001
+Log hs-cTnT +log NT-proBNP	0.654 (0.632–0.677)	0.015 (0.009–0.020)	<0.001

The base model includes predictors of bleeding based on the HAS-BLED Score and the improvement in risk prediction of bleeding with cardiac biomarkers added to the HAS-BLED score. Uncontrolled hypertension defined as systolic blood pressure >160 mm Hg; severe kidney disease defined as eGFR <30 mL/min per 1.73 m^2; liver disease defined as the presence of liver cirrhosis and esophageal varices without bleeding from *ICD-9* discharge codes; excess alcohol use defined as greater than 8 drinks per week, naturally log-transformed hs-cTnT in ng/L and NT-proBNP per 1000 pg/mL (prior bleeding, labile INR excluded). eGFR indicates estimated glomerular filtration rate; hs-cTnT, high-sensitivity cardiac troponin T; *ICD-9*, *International Classification of Diseases, Ninth Revision*; INR, international normalized ratio; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

and decrease healing of mucosal injuries.[11,39,40] Nonetheless, given consistent observations about the TnT-bleeding relationship in different settings, future research is needed to understand potential mechanisms.

As noted above, the association of NT-proBNP with bleeding was contrary to prior null findings in RE-LY and ARISTOTLE.[8,10] This discrepancy may be due to the difference in study populations. Specifically, RE-LY and ARISTOTLE enrolled patients with atrial fibrillation on anticoagulation, whereas our study was community based. However, in subgroup analyses, our results similarly did not show an association of NT-proBNP with bleeding in patients on anticoagulation. In addition, it is possible that many patients in RE-LY and ARISTOTLE had more comorbidities including heart failure (30% to 40% of patients in these 2 trials had heart failure), and thus, NT-proBNP might not efficiently discriminate the bleeding risk in this population with higher comorbidities. Thus, the risk of bleeding associated with NT-proBNP may be more relevant in individuals expected to have lower NT-proBNP, specifically those without cardiovascular disease. In terms of a potential mechanism, elevated NT-proBNP also reflects elevated filling pressures that lead to changes in the gastrointestinal vasculature including angiodysplasia,[41] mucosal congestion,[42] activated fibrinolytic pathways, and then potentially to increased gastrointestinal bleeding. Nevertheless, studies are needed to replicate the association between natriuretic peptides and a subsequent risk of bleeding in the general population.

The addition of both cardiac biomarkers to established bleeding predictors significantly improved the prediction of bleeding. Although the range in the change of the c-statistic with the addition of hs-cTnT, NT-proBNP, or both biomarkers was modest (0.009 to 0.015) and may look small, this level of discrimination improvement was actually higher than those of established bleeding predictors such as uncontrolled hypertension (Δc-statistic 0.006), estimated glomerular filtration rate <30 mL/min per 1.73 m^2 (0.006), and the use of aspirin or anticoagulation (0.008). Of note, there may be clinical scenarios where data on hs-cTnT and NT-proBNP are already available, and in such circumstances, our results suggest that taking into account these cardiac biomarkers would lead to improved prediction of bleeding risk. Nonetheless, future studies may be necessary to confirm the improvement in risk prediction of bleeding with these cardiac biomarkers in other settings.

There are a few potential implications of our study. First, our results suggest that these 2 cardiac biomarkers may be helpful in classifying the risk of bleeding. Aspirin use for primary cardiovascular disease prevention in select patients with high risk is associated with substantial reduction in adverse cardiovascular outcomes but with an increased risk of major bleeding events.[20] Balancing the benefits and harm of cardiovascular disease with primary preventive therapies is crucial and often challenging. In this context our observation of high bleeding risk in individuals with elevated hs-cTnT and/or NT-proBNP indicates complexity in the decision to use antiplatelet therapy for primary cardiovascular prevention because those individuals are known to be at high risk of cardiovascular disease events as well. Nonetheless, for those individuals at risk of both cardiovascular disease events and bleeding, an option is to prioritize cardiovascular disease prevention that does not further increase the risk for bleeding, such as statins, blood pressure control, and diabetes mellitus control as appropriate. On the other hand, for those at high cardiovascular risk due to traditional risk factors but at lower risk of bleeding represented by low levels of hs-cTnT and NT-proBNP, preventive antiplatelet therapy may remain a reasonable option when indicated. In this context it is important that these cardiac biomarkers attract attention for guiding risk-centered preventive therapy.[43,44] Nonetheless, whether the use of these cardiac markers would actually guide better risk-benefit discussions should be tested in future studies.

Our study has several limitations that should be considered in the interpretation of our findings. First, we used *ICD-9* hospitalization discharge codes for the diagnosis of bleeding events, which are prone to misclassification. However, when we used *ICD-9* hospitalization codes with bleeding as the primary reason for hospitalization, our findings were largely consistent. Also, a recent landmark study quantified bleeding events among populations without cardiovascular disease using discharge *ICD* codes.[32] Second, we did not capture mild bleeding events that were managed only in the outpatient setting. However, the majority of clinically significant bleeding events are managed in the hospital.[45] Also, our investigation of more severe bleeding cases is important because they are the major contributor to poor prognosis and increased costs.[1] Third, our study is a community-based cohort of white and black men and women aged 53 to 75 years, and thus our results may not directly extrapolate to other age or racial/ethnic groups or to specific clinical populations (eg, severely reduced kidney function). Fourth, even though we adjusted for the major predictors of bleeding, our study was observational, and residual confounding could have still played a role in our findings. For example, information on medications such as aspirin, antiplatelet agents, and NSAIDs was based on the clinical visits and annual phone follow-up, and thus we could not capture intermittently used medications or medications initiated just before bleeding if any.

Conclusions

Elevations of hs-cTnT and NT-proBNP in a community-based population without prevalent cardiovascular disease at

baseline were associated with future risks of major bleeding events. These cardiac markers improved the prediction of bleeding risk beyond conventional predictors, suggesting their utility in identifying individuals at high bleeding risk. Research into the underlying pathophysiological mechanisms behind our observation may elucidate abnormal hemostatic mechanisms in individuals with subclinical cardiac abnormalities and may further guide prevention of bleeding.

Acknowledgments

The authors thank the staff and participants of the ARIC study for their important contributions. All authors materially participated in the research and/or preparation of the article and have approved the final article.

Sources of Funding

The Atherosclerosis Risk in Communities study has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under Contract nos. (HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700005I, HHSN26820 1700004I). Dr. Mathews is supported by a training grant (grant Number T32 HL007024) from the National Heart, Lung, and Blood Institute, National Institutes of Health. Dr. Selvin was supported by National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Health grants (grant numbers K24DK 106414, R01DK089174). Roche Diagnostics provided a grant to Baylor College of Medicine for supplies to perform all the assays.

Disclosures

Dr. Ballantyne reports receiving grants and personal fees from Roche Diagnostics during the conduct of the study. Dr. Hoogeveen reports receiving grants from Roche Diagnostics during the conduct of the study and reports grants and personal fees from Denka Seiken outside the submitted work. Drs. Ballantyne and Hoogeveen report that a provisional patent (patent no. 61721475) entitled “Biomarkers to Improve Prediction of Heart Failure Risk” has been filed by Baylor College of Medicine and Roche Diagnostics. Dr. Matsushita reports nonfinancial support from Roche Diagnostics outside the submitted work. The remaining authors have no disclosures to report.

References

1. Redfors B, Watson BM, McAndrew T, Palisaitis E, Francese DP, Razavi M, Safirstein J, Mehran R, Kirtane AJ, Genereux P. Mortality, length of stay, and cost implications of procedural bleeding after percutaneous interventions using large-bore catheters. *JAMA Cardiol*. 2017;2:798–802.
2. Widimsky P, Motovska Z, Bolognese L, Dudek D, Hamm C, Tanguay JF, Ten Berg J, Brown E, LeNarz L, Miller DL, Montalescot G; ACCOAST Investigators. Predictors of bleeding in patients with acute coronary syndromes treated with prasugrel. *Heart*. 2015;101:1219–1224.
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;138:1093–1100.
4. McEvoy JW, Chen Y, Nambi V, Ballantyne CM, Sharrett AR, Appel LJ, Post WS, Blumenthal RS, Matsushita K, Selvin E. High-sensitivity cardiac troponin T and risk of hypertension. *Circulation*. 2015;132:825–833.
5. 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;23:938–942.
6. 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;23:51–55.
7. Hijazi Z, Wallentin L, Siegbahn A, Andersson U, Alexander JH, Atar D, Gersh BJ, Hanna M, Harjola VP, Horowitz JD, Husted S, Hylek EM, Lopes RD, McMurray JJ, Granger CB; ARISTOTLE Investigators. High-sensitivity troponin T and risk stratification in patients with atrial fibrillation during treatment with apixaban or warfarin. *J Am Coll Cardiol*. 2014;63:52–61.
8. Hijazi Z, Oldgren J, Andersson U, Connolly SJ, Ezekowitz MD, Hohnloser SH, Reilly PA, Vinereanu D, Siegbahn A, Yusuf S, Wallentin L. 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;125:1605–1616.
9. Hijazi Z, Siegbahn A, Andersson U, Granger CB, Alexander JH, Atar D, Gersh BJ, Mohan P, Harjola VP, Horowitz J, Husted S, Hylek EM, Lopes RD, McMurray JJ, Wallentin L; ARISTOTLE Investigators. 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;129:625–634.
10. Hijazi Z, Oldgren J, Lindback J, Alexander JH, Connolly SJ, Eikelboom JW, Ezekowitz MD, Held C, Hylek EM, Lopes RD, Siegbahn A, Yusuf S, Granger CB, Wallentin L; ARISTOTLE and RE-LY Investigators. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study. *Lancet*. 2016;387:2302–2311.
11. Niikura R, Nagata N, Akiyama J, Shimbo T, Uemura N. Hypertension and concomitant arteriosclerotic diseases are risk factors for colonic diverticular bleeding: a case-control study. *Int J Colorectal Dis*. 2012;27:1137–1143.
12. Peng YL, Leu HB, Luo JC, Huang CC, Hou MC, Lin HC, Lee FY. Diabetes is an independent risk factor for peptic ulcer bleeding: a nationwide population-based cohort study. *J Gastroenterol Hepatol*. 2013;28:1295–1299.
13. Sparrow CT, Nassif ME, Raymer DS, Novak E, LaRue SJ, Schilling JD. Preoperative right ventricular dysfunction is associated with gastrointestinal bleeding in patients supported with continuous-flow left ventricular assist devices. *JACC. Heart Failure*. 2015;3:956–964.
14. Dadu RT, Fornage M, Virani SS, Nambi V, Hoogeveen RC, Boerwinkle E, Alonso A, Gottesman RF, Mosley TH, Ballantyne CM. Cardiovascular biomarkers and subclinical brain disease in the Atherosclerosis Risk in Communities study. *Stroke*. 2013;44:1803–1808.
15. von Rennenberg R, Siegerink B, Ganeshan R, Villringer K, Doehner W, Audebert HJ, Endres M, Nolte CH, Scheitz JF. High-sensitivity cardiac troponin T and severity of cerebral white matter lesions in patients with acute ischemic stroke. *J Neurol*. 2019;266:37–45.
16. Biener M, Giannitsis E, Kuhner M, Zelniker T, Mueller-Hennessen M, Vafaie M, Trenk D, Neumann FJ, Hochholzer W, Katus HA. Prognostic value of high-sensitivity cardiac troponin T compared with risk scores in stable cardiovascular disease. *Am J Med*. 2017;130:572–582.
17. de Lemos JA, Ayers CR, Levine BD, deFilippi CR, Wang TJ, Hundley WG, Berry JD, Seliger SL, McGuire DK, Ouyang P, Drazner MH, Budoff M, Greenland P, Ballantyne CM, Khera A. Multimodality strategy for cardiovascular risk assessment: performance in 2 population-based cohorts. *Circulation*. 2017;135:2119–2132.
18. ASCEND Study Collaborative Group , Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, Barton J, Murphy K, Aung T, Haynes R, Cox J, Murawska A, Young A, Lay M, Chen F, Sammons E, Waters E, Adler A, Bodansky J, Farmer A, McPherson R, Neil A, Simpson D, Peto R, Baigent C, Collins R, Parish S, Armitage J. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med*. 2018;379:1529–1539.
19. McNeil JJ, Wolfe R, Woods RL, Tonkin AM, Donnan GA, Nelson MR, Reid CM, Lockery JE, Kirpach B, Storey E, Shah RC, Williamson JD, Margolis KL, Ernst ME, Abhayaratna WP, Stocks N, Fitzgerald SM, Orchard SG, Trevaks RE, Beilin

LJ, Johnston CI, Ryan J, Radziszewska B, Jelinek M, Malik M, Eaton CB, Brauer D, Cloud G, Wood EM, Mahady SE, Satterfield S, Grimm R, Murray AM; ASPREE Investigator Group. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. *N Engl J Med*. 2018;379:1509–1518.

20. Zheng SL, Roddick AJ. Association of aspirin use for primary prevention with cardiovascular events and bleeding events: a systematic review and meta-analysis. *JAMA*. 2019;321:277–287.
21. Bibbins-Domingo K; US Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: US preventive services task force recommendation statement. *Ann Intern Med*. 2016;164:836–845.
22. ARIC Investigators. Collaborative studies coordinating center. 2019.
23. ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) study: design and objectives. *Am J Epidemiol*. 1989;129:687–702.
24. Ishigami J, Grams ME, Naik RP, Coresh J, Matsushita K. Chronic kidney disease and risk for gastrointestinal bleeding in the community: the Atherosclerosis Risk in Communities (ARIC) study. *Clin J Am Soc Nephrol*. 2016;11:1735–1743.
25. White AD, Folsom AR, Chambless LE, Sharret AR, Yang K, Conwill D, Higgins M, Williams OD, Tyroler HA. Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) study: methods and initial two years' experience. *J Clin Epidemiol*. 1996;49:223–233.
26. Rosamond WD, Folsom AR, Chambless LE, Wang CH, McGovern PG, Howard G, Copper LS, Shahar E. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. *Stroke*. 1999;30:736–743.
27. Matsushita K, Kwak L, Yang C, Pang Y, Ballew SH, Sang Y, Hoogeveen RC, Jaar BG, Selvin E, Ballantyne CM, Sharrett AR, Folsom AR, Heiss G, Coresh J, Hirsch AT. High-sensitivity cardiac troponin and natriuretic peptide with risk of lower-extremity peripheral artery disease: the Atherosclerosis Risk in Communities (ARIC) study. *Eur Heart J*. 2018;39:2412–2419.
28. McEvoy JW, Chen Y, Ndumele CE, Solomon SD, Nambi V, Ballantyne CM, Blumenthal RS, Coresh J, Selvin E. Six-year change in high-sensitivity cardiac troponin T and risk of subsequent coronary heart disease, heart failure, and death. *JAMA Cardiol*. 2016;1:519–528.
29. Limited RDI. Elecsys troponin T high sensitive package insert. 2018.
30. Lazo M, Young JH, Brancati FL, Coresh J, Whelton S, Ndumele CE, Hoogeveen R, Ballantyne CM, Selvin E. NH_2-terminal pro–brain natriuretic peptide and risk of diabetes. *Diabetes*. 2013;62:3189–3193.
31. Nambi V, Liu X, Chambless LE, de Lemos JA, Virani SS, Agarwal S, Boerwinkle E, Hoogeveen RC, Aguilar D, Astor BC, Srinivas PR, Deswal A, Mosley TH, Coresh J, Folsom AR, Heiss G, Ballantyne CM. Troponin T and N-terminal pro-B-type natriuretic peptide: a biomarker approach to predict heart failure risk—the Atherosclerosis Risk in Communities study. *Clin Chem*. 2013;59:1802–1810.
32. Selak V, Kerr A, Poppe K, Wu B, Harwood M, Grey C, Jackson R, Wells S. Annual risk of major bleeding among persons without cardiovascular disease not receiving antiplatelet therapy. *JAMA*. 2018;319:2507–2520.
33. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF III, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
34. Kim Y, Matsushita K, Sang Y, Grams ME, Skali H, Shah AM, Hoogeveen RC, Solomon SD, Ballantyne CM, Coresh J. Association of high-sensitivity cardiac troponin T and natriuretic peptide with incident ESRD: the Atherosclerosis Risk in Communities (ARIC) study. *Am J Kidney Dis*. 2015;65:550–558.
35. Sharrett AR, Patsch W, Sorlie PD, Heiss G, Bond MG, Davis CE. Associations of lipoprotein cholesterols, apolipoproteins A-I and B, and triglycerides with carotid atherosclerosis and coronary heart disease. The Atherosclerosis Risk in Communities (ARIC) study. *Arterioscler Thromb*. 1994;14:1098–1104.
36. Garrow D, Delegge MH. Risk factors for gastrointestinal ulcer disease in the US population. *Dig Dis Sci*. 2010;55:66–72.
37. Evans JDW, Dobbin SJH, Pettit SJ, Di Angelantonio E, Willeit P. High-sensitivity cardiac troponin and new-onset heart failure: a systematic review and meta-analysis of 67,063 patients with 4,165 incident heart failure events. *JACC Heart Fail*. 2018;6:187–197.
38. Hilal S, Chai YL, van Veluw S, Shaik MA, Ikram MK, Venketasubramanian N, Richards AM, Biessels GJ, Chen C. Association between subclinical cardiac biomarkers and clinically manifest cardiac diseases with cortical cerebral microinfarcts. *JAMA Neurol*. 2017;74:403–410.
39. Tsuruoka N, Iwakiri R, Hara M, Shirahama N, Sakata Y, Miyahara K, Eguchi Y, Shimoda R, Ogata S, Tsunada S, Sakata H, Fujimoto K. NSAIDs are a significant risk factor for colonic diverticular hemorrhage in elder patients: evaluation by a case-control study. *J Gastroenterol Hepatol*. 2011;26:1047–1052.
40. Aoyama T, Fukumoto A, Shigita K, Asayama N, Mukai S, Nagata S. Arteriosclerosis is a major predictor of small bowel vascular lesions. *Dig Dis Sci*. 2018;63:723–730.
41. Warkentin TE, Moore JC, Morgan DG. Gastrointestinal angiodysplasia and aortic stenosis. *N Engl J Med*. 2002;347:858–859.
42. Raja K, Kochhar R, Sethy PK, Dutta U, Bali HK, Varma JS. An endoscopic study of upper-GI mucosal changes in patients with congestive heart failure. *Gastrointest Endosc*. 2004;60:887–893.
43. Melloni C, Roe MT. Cardiac troponin and risk stratification in ischemic heart disease. *N Engl J Med*. 2015;373:672–674.
44. Welsh P, Doolin O, Willeit P, Packard C, Macfarlane P, Cobbe S, Gudnason V, Di Angelantonio E, Ford I, Sattar N. N-terminal pro-B-type natriuretic peptide and the prediction of primary cardiovascular events: results from 15-year follow-up of WOSCOPS. *Eur Heart J*. 2013;34:443–450.
45. Gralnek IM. Outpatient management of "low-risk" nonvariceal upper GI hemorrhage. Are we ready to put evidence into practice? *Gastrointest Endosc*. 2002;55:131–134.

SUPPLEMENTAL MATERIAL

Table S1. Summary of ICD-9 hospital discharge codes used in the derivation of the outcome, hospitalization with bleeding.

Outcome	ICD-9 Code	Specific diagnosis
Upper gastrointestinal bleeding	532.xx	Acute or chronic duodenal ulcer with hemorrhage
	531.xx	Acute or chronic gastric ulcer with hemorrhage
	535.01, 535.31	Acute gastritis with hemorrhage
	535.41	Other specified gastritis with hemorrhage
	535.51	Unspecified gastritis and gastroduodenitis with hemorrhage
	534.xx	Acute or chronic gastrojejunal ulcer with hemorrhage
	533.xx	Acute or chronic peptic ulcer with hemorrhage
	537.83	Angiodysplasia of stomach and duodenum with hemorrhage
	537.84	Dieulafoy lesion (hemorrhagic) of stomach and duodenum
	535.11	Atrophic gastritis with hemorrhage
	535.61	Duodenitis with hemorrhage
	530.21	Ulcer of the esophagus with bleeding
	530.82	Esophageal hemorrhage
	456.xx	Esophageal varices with bleeding
	456.2	Esophageal varices with bleeding diseases classified elsewhere
	535.21	Gastric mucosal hypertrophy with hemorrhage (hypertrophic gastritis)

	530.7	Gastroesophageal laceration-hemorrhage syndrome (Mallory Weiss syndrome)
	578.xx	Hematemesis
Lower gastrointestinal bleeding	569.85	Angiodysplasia of intestine with hemorrhage
	569.86	Dieulafoy lesion (hemorrhagic) of intestine
	562.13	Diverticulitis of colon with hemorrhage
	562.03	Diverticulitis of small intestine with hemorrhage
	562.12	Diverticulosis of colon with hemorrhage
	562.02	Diverticulosis of small intestine with hemorrhage
	569.3	Hemorrhage of rectum and anus
Unspecified source	578.9	Hemorrhage of gastrointestinal tract, unspecified
	578.1	Blood in stool
Intracranial hemorrhage	430.0	Subarachnoid hemorrhage
	431.0	Intracerebral hemorrhage
	432.1	Subdural hemorrhage
Retroperitoneal bleeding	459.0	Hemorrhage unspecified
	793.6	Abnormal finding on imaging of the abdomen

Table S2. Baseline characteristics according to categories of NT-proBNP, the ARIC Study (1996-1998)（N=9,550).

Baseline characteristics	NT-proBNP <42 pg/mL	NT-proBNP 42-81 pg/mL	NT-proBNP 81-140 pg/mL	NT-proBNP 140-264 pg/mL	NT-proBNP ≥264 pg/mL	p-values
No. of participants	3,229	2,474	1,937	1,236	674	
Age, years	60.9 (5.2)	62.5 (5.5)	63.3 (5.5)	64.4 (5.8)	65.7 (5.4)	<0.001
Female	42.9%	61.3%	69.5%	72.3%	66.2%	<0.001
Black	30.7%	19.3%	15.7%	13.6%	16.2%	<0.001
Body mass index, kg/m^2	29.4 (5.1)	28.7 (5.6)	28.2 (5.7)	28.0 (5.8)	28.2 (5.9)	<0.001
Family History of CAD	52.5%	56.8%	58.9%	60.4%	60.2%	<0.001
Education level						<0.001
Basic	17.7%	16.7%	16.5%	18.5%	24.3%	
Intermediate	38.9%	43.7%	45.4%	43.3%	41.7%	
Advanced	43.3%	39.5%	38.2%	38.2%	34.0%	
Smoking status						<0.001
Current smokers	13.9%	13.8%	14.1%	15.2%	19.3%	
Former smokers	44.6%	41.0%	40.0%	41.9%	42.0%	
Never smokers	41.5%	45.1%	45.8%	42.9%	38.7%	
Drinking status						<0.001
Current drinkers	50.4%	52.4%	50.4%	49.7%	47.5%	

Former drinkers	30.5%	26.0%	28.1%	26.9%	30.1%	
Never drinkers	19.0%	21.5%	21.5%	23.4%	22.4%	
Hs-cTnT, ng/L, median (IQR)	4.0 (1.5, 7.0)	1.5, 7.0	4.0 (1.5, 7.0)	5.0 (1.5, 8.0)	8.0 (4.0, 13.0)	<0.001
Systolic blood pressure, mmHg	123.2 (15.8)	126.2 (18.3)	128.6 (18.9)	131.5 (20.1)	137.5 (23.8)	<0.001
Total cholesterol, mmol/l	5.3 (1.0)	5.2 (0.9)	5.2 (0.9)	5.2 (0.9)	5.1 (1.0)	<0.001
HDL cholesterol, mmol/l	1.2 (0.4)	1.3 (0.4)	1.4 (0.5)	1.4 (0.5)	1.4 (0.5)	<0.001
eGFR categories in ml/min per 1.73m^2						<0.001
< 30	0.1%	0.1%	0.0%	0.2%	2.5%	
30 - 60	3.0%	4.9%	6.2%	8.0%	17.7%	
>60	97.0%	95.0%	93.8%	91.7%	79.8%	
AST, U/L, median (IQR)	18.0 (16.0, 22.0)	18.0 (15.0, 21.0)	18.0 (15.0, 21.0)	18.0 (15.0, 21.0)	18.0 (15.0, 21.0)	<0.001
ALT, U/L, median (IQR)	15.0 (11.0, 20.0)	13.0 (10.0, 18.0)	12.0 (9.0, 16.0)	12.0 (9.0, 15.0)	11.0 (9.0, 15.0)	<0.001
Medication use						
Hypertension medications	30.4%	30.0%	32.5%	38.5%	52.1%	<0.001
Aspirin	52.4%	53.6%	55.9%	55.0%	61.4%	<0.001
Statin	9.4%	8.5%	8.5%	8.3%	12.2%	0.03
Anticoagulant	0.5%	0.8%	0.7%	1.2%	7.4%	<0.001
Diabetes mellitus	17.5%	14.5%	12.3%	11.7%	17.8%	<0.001

History of hepatic failure	0.2%	0.1%	0.3%	0.2%	1.0%	0.002
History of cancer	6.4%	8.9%	8.2%	9.4%	8.9%	0.001

Values are mean ± SD or percentage, unless otherwise indicated.

eGFR (estimated glomerular filtration rate), AST (aspartate aminotransferase), ALT (alanine aminotransferase), CAD (coronary artery disease), HDL (high density lipoprotein), hs-cTnT (high sensitivity cardiac troponin T), NT-proBNP (N-terminal pro B-type natriuretic peptide).

Table S3. Hazard ratios (95% confidence intervals) for the association of baseline categories and log-transformed hs-cTnT (ng/L) and NT-proBNP (pg/ml) with incident hospitalizations for bleeding as the primary discharge diagnosis, the ARIC Study.

hs-cTnT	**<3**	**3-6**	**6- <9**	**9- <14**	**≥14**	**log hs-cTnT**
Model 1	Reference	0.82 (0.60 - 1.11)	1.26 (0.60 - 1.70)	1.68 (1.21 - 2.32)	2.20 (1.48 - 3.22)	1.32 (1.16 – 1.51)
Model 2	Reference	0.81 (0.60 - 1.10)	1.25 (0.60 - 1.69)	1.67 (1.21 - 2.32)	2.13 (1.44 - 3.15)	1.30 (1.14 – 1.49)
Model 3	Reference	0.81 (0.59 - 1.09)	1.25 (0.59 - 1.69)	1.66 (1.20 - 2.30)	2.08 (1.41 - 3.07)	1.29 (1.13 – 1.48)
NT-pro BNP	**<42**	**42- <81**	**81- <140**	**140- <264**	**≥ 264**	**log NT-proBNP**
Model 1	Reference	1.31 (0.99 - 1.74)	1.34 (0.98 - 1.82)	1.40 (0.99 - 1.98)	1.97 (1.33 - 2.91)	1.20 (1.08 – 1.33)
Model 2	Reference	1.31 (0.99 - 1.73)	1.33 (0.98 - 1.81)	1.39 (0.99 - 1.97)	1.93 (1.30 - 2.87)	1.19 (1.08 -1.32)
Model 3	Reference	1.29 (0.98 - 1.72)	1.31 (0.96 - 1.78)	1.36 (0.96 - 1.93)	1.82 (1.22 - 2.71)	1.18 (1.06 – 1.30)

Model 1 adjusted for age, sex, race-center, education, BMI, diabetes, family history of coronary artery disease, systolic blood pressure, cigarette use, alcohol use, total cholesterol, HDL cholesterol, statin use, aspirin, anticoagulation, NSAID, antihypertensive, eGFR, ACR, AST, ALT.

Model 2 adjusted for variables in Model 1 and for hs-cTnT or NT-proBNP

Model 3 adjusted for variables in Model 2 and incident stroke and coronary heart disease

eGFR (estimated glomerular filtration rate), ACR (albumin creatinine ratio), AST (aspartate aminotransferase), ALT (alanine aminotransferase), HDL (high density lipoprotein), hs-cTnT (high sensitivity cardiac troponin T), HR (hazard ratio), NT-proBNP (N-terminal pro B-type natriuretic peptide).

Table S4. Hazard ratios and 95 % confidence intervals for the association of baseline categories and log-transformed hs-cTnT (ng/L) and NT-proBNP (pg/ml) with incident hospitalizations for (a) gastrointestinal bleeding, (b) intracranial bleeding, (c) retroperitoneal bleeding in the ARIC Study.

(a)

hs-cTnT	**<3**	**3-6**	**6- <9**	**9- <14**	**≥14**	**log hs-cTnT**
Model 1	Reference	0.84 (0.67 - 1.04)	1.33 (1.06 - 1.65)	1.50 (1.18-1.90)	1.96 (1.47-2.60)	1.28 (1.16 – 1.41)
Model 2	Reference	0.83 (0.67 - 1.04)	1.33 (1.08 - 1.64)	1.50 (1.18 - 1.90)	1.89 (1.43 - 2.53)	1.25 (1.13 – 1.38)
Model 3	Reference	0.82 (0.66 - 1.02)	1.33 (1.07 - 1.64)	1.48 (1.16 - 1.88)	1.86 (1.39 - 2.47)	1.24 (1.13 – 1.37)
NT-pro BNP	**<42**	**42- <81**	**81- <140**	**140- <264**	**≥ 264**	**log NT-proBNP**
Model 1	Reference	1.28 (1.05 - 1.57)	1.27 (1.01 - 1.57)	1.29 (0.99 - 1.65)	2.17 (1.65 - 2.86)	1.19 (1.11 – 1.28)
Model 2	Reference	1.28 (1.05 - 1.57)	1.26 (1.01 - 1.58)	1.28 (0.99 - 1.65)	2.14 (1.63 - 2.83)	1.19 (1.10 – 1.28)
Model 3	Reference	1.26 (1.03 - 1.56)	1.24 (0.99 - 1.55)	1.27 (0.99 - 1.64)	2.01 (1.53 - 2.66)	1.16 (1.08 – 1.26)

(b)

hs-cTnT	**<3**	**3-6**	**6- <9**	**9- <14**	**≥14**	**log hs-cTnT**
Model 1	Reference	0.47 (0.16 - 1.38)	1.14 (0.47 - 2.78)	1.94 (0.79 - 4.74)	1.94 (0.65 - 5.80)	1.42 (0.95 – 2.11)
Model 2	Reference	0.47 (0.16 - 1.38)	1.14 (0.47 - 2.75)	1.94 (0.79 - 4.74)	1.89 (0.63 - 5.70)	1.40 (0.93 – 2.10)
Model 3	Reference	0.46 (0.16 - 1.36)	1.14 (0.47 - 2.76)	1.92 (0.78 - 4.70)	1.93 (0.64 - 5.81)	1.41 (0.93 – 2.13)
NT-pro BNP	**<42**	**42- <81**	**81- <140**	**140- <264**	**≥ 264**	**Log NT-proBNP**
Model 1	Reference	1.13 (0.52 - 2.43)	0.99 (0.41 - 2.41)	0.95 (0.34 - 2.62)	1.49 (0.48 - 4.65)	1.06 (0.80 – 1.41)

Model 2	Reference	1.13 (0.52 - 2.43)	0.99 (0.41 - 2.41)	0.95 (0.34 - 2.61)	1.48 (0.47 - 4.64)	1.06 (0.80 – 1.41)
Model 3	Reference	1.11 (0.51 - 2.34)	0.97 (0.40 - 2.34)	0.95 (0.35 - 2.63)	1.44 (0.46 - 4.57)	1.05 (0.79 – 1.40)

(c)

hs-cTnT	**<3**	**3-6**	**6- <9**	**9- <14**	**≥14**	**Continuous hs-cTnT**
Model 1	Reference	0.91(0.34 - 2.42)	0.38 (0.08 - 1.80)	2.38 (0.80 - 7.03)	4.23 (1.21 - 14.84)	1.33 (0.83 – 2.14)
Model 2	Reference	0.91 (0.34 - 2.41)	0.38 (0.08 - 1.79)	2.37 (0.80 - 7.00)	4.16 (1.17 - 14.84)	1.32 (0.82 – 2.13)
Model 3	Reference	0.91 (0.34 - 2.42)	0.38 (0.08 - 1.81)	2.42 (0.82 - 7.15)	4.30 (1.20 - 15.35)	1.34 (0.82 – 2.19)
NT-pro BNP	**<42**	**42- <81**	**81- <140**	**140- <264**	**≥ 264**	**Continuous NT-proBNP**
Model 1	Reference	1.49 (0.50 - 4.46)	1.59 (0.50 - 5.10)	2.24 (0.68 - 7.40)	2.58 (0.62 - 10.67)	1.36 (0.93 – 2.00)
Model 2	Reference	1.49 (0.50 - 4.45)	1.59 (0.50 - 5.09)	2.23 (0.68 - 7.38)	2.55 (0.61 - 10.59)	1.36 (0.92 – 2.00)
Model 3	Reference	1.49 (0.50 - 4.45)	1.58 (0.49 - 5.07)	2.23 (0.67 - 7.39)	2.58 (0.62 - 10.75)	1.36 (0.93 – 2.01)

Model 1 adjusted for age, sex, race-center, education, BMI, diabetes, family history of coronary artery disease, systolic blood pressure, cigarette use, alcohol use, total cholesterol, HDL cholesterol, statin use, aspirin, anticoagulation, NSAID, antihypertensive, eGFR, ACR, AST, ALT.

Model 2 adjusted for variables in Model 1 and for hs-cTnT or NT-proBNP

Model 3 adjusted for variables in Model 2 and incident stroke and coronary heart disease

Abbreviations: eGFR (estimated glomerular filtration rate), ACR (albumin creatinine ratio), AST (aspartate aminotransferase), ALT (alanine aminotransferase), HDL (high density lipoprotein), hs-cTnT (high sensitivity cardiac troponin T), HR (hazard ratio), NT-proBNP (N-terminal pro B-type natriuretic peptide).

Table S5. Hazard ratios (95% confidence intervals) for the association of baseline categories and log-transformed hs-cTnT (ng/L) and NT-proBNP (pg/ml) with incident hospitalizations for bleeding, the ARIC Study. Patients with prevalent bleeding at visit 4 included.

hs-cTnT	**<3**	**3-6**	**6- <9**	**9- <14**	**≥14**	**log hs-cTnT**
Model 1	Reference	0.80 (0.65 - 0.99)	1.29 (1.05 - 1.59)	1.52 (1.21 - 1.91)	2.05 (1.57 - 2.69)	1.35 (1.23 – 1.48)
Model 2	Reference	0.80 (0.64 - 0.98)	1.29 (1.05 - 1.58)	1.52 (1.21 - 1.91)	1.99 (1.52 - 2.62)	1.28 (1.17 – 1.41)
Model 3	Reference	0.78 (0.64 - 0.97)	1.29 (1.05 - 1.58)	1.51 (1.20 - 1.89)	1.95 (1.49 - 2.56)	1.26 (1.14 – 1.38)
Model 4	Reference	0.78 (0.64 - 0.97)	1.29 (1.05 - 1.58)	1.50 (1.20 - 1.89)	1.95 (1.48 - 2.60)	1.25 (1.14 – 1.36)
NT-pro BNP	**<42**	**42- <81**	**81- <140**	**140- <264**	**≥ 264**	**log NT-proBNP**
Model 1	Reference	1.29 (1.06 - 1.57)	1.26 (1.02 - 1.57)	1.28 (1.01 - 1.64)	2.14 (1.64 - 2.79)	1.22 (1.14 – 1.31)
Model 2	Reference	1.29 (1.06 - 1.56)	1.26 (1.02 – 1.56)	1.28 (1.00 - 1.63)	2.12 (1.62 - 2.76)	1.18 (1.10 – 1.27)
Model 3	Reference	1.27 (1.05 - 1.55)	1.24 (1.00 - 1.54)	1.26 (0.99 - 1.60)	2.00 (1.53 - 2.61)	1.18 (1.10 – 1.27)
Model 4	Reference	1.27 (1.05 - 1.55)	1.24 (1.00 - 1.53)	1.25 (0.98 – 1.60)	2.00 (1.53 - 2.61)	1.16 (1.08 – 1.25)

Model 1 adjusted for age, sex, race-center, education, BMI, diabetes, family history of coronary artery disease, systolic blood pressure, cigarette use, alcohol use, total cholesterol, HDL cholesterol, statin use, aspirin, anticoagulation, NSAID, antihypertensive, eGFR, ACR, AST, ALT.

Model 2 adjusted for variables in Model 1 and for hs-cTnT or NT-proBNP

Model 3 adjusted for variables in Model 2 and incident stroke and coronary heart disease

Model 4 adjusted for variables in Model 3 and history of prevalent bleeding

eGFR (estimated glomerular filtration rate), ACR (albumin creatinine ratio), AST (aspartate aminotransferase), ALT (alanine aminotransferase), HDL (high density lipoprotein), hs-cTnT (high sensitivity cardiac troponin T), HR (hazard ratio), NT-proBNP (N-terminal pro B-type natriuretic peptide).