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).