

Supplemental Material Figure Legend

Supplemental Table 1: Disease classes corresponding to the *ICD-9* codes

Supplemental Table 2: Modified definition of HAS-BLED

Supplemental Table 3: Baseline characteristics stratified by eGFR categories

Supplemental Table 4: Baseline characteristics stratified by ACR categories

Supplemental Table 5: Hazard ratios of GI bleeding events according to cross-category of eGFR and ACR

Supplemental Table 6: Cox proportional hazard models according to the site of GI bleeding

Supplemental Table 7: Cox proportional hazard model including a covariate of incident cardiovascular disease as time varying exposure

Supplemental Table 8: Cox proportional hazard model including a covariate of incident end-stage renal disease as time varying exposure

Supplemental Table 9: Hazard ratio of GI bleeding as the primary discharge diagnosis

Supplemental Table 10: Hazard ratio of mortality from GI bleeding

Supplemental Table 11: Relative risk for GI bleeding including outpatient events among individuals aged 65+ years

Supplemental Table 12: Hazard ratio of GI bleed-related and non-GI bleed-related hospitalization

Supplemental Figure 1: Cohort diagram of the study population

Supplemental Table 1: Disease classes corresponding to the ICD-9 codes

Upper GI bleeding	Acute duodenal ulcer with hemorrhage	532.xx
	Acute gastric ulcer with hemorrhage	531.xx
	Acute gastritis with hemorrhage	535.01
	Acute gastrojejunal ulcer with hemorrhage	534.xx
	Acute peptic ulcer with hemorrhage	533.xx
	Alcoholic gastritis with hemorrhage	535.31
	Angiodysplasia of stomach and duodenum with hemorrhage	537.83
	Atrophic gastritis with hemorrhage	535.11
	Chronic duodenal ulcer with hemorrhage	532.xx
	Chronic gastric ulcer with hemorrhage	531.xx
	Chronic or unspecified gastrojejunal ulcer with hemorrhage	534.xx
	Duodenitis, with hemorrhage	535.61
	Chronic peptic ulcer with hemorrhage	533.xx
	Dieulafoy lesion (hemorrhagic) of stomach and duodenum	537.84
	Esophageal hemorrhage	530.82
	Esophageal varices with bleeding	456
	Esophageal varices with bleeding in diseases classified elsewhere	456.2
	Gastric mucosal hypertrophy with hemorrhage (hypertrophic gastritis)	535.21
	Gastroesophageal laceration-hemorrhage syndrome (Mallory-Weiss syndrome)	530.7
Lower GI bleeding	Hematemesis	578
	Other specified gastritis with hemorrhage	535.41
	Ulcer of the esophagus with bleeding	530.21
	Unspecified gastritis and gastroduodenitis with hemorrhage	535.51
	Angiodysplasia of intestine with hemorrhage	569.85
	Dieulafoy lesion (hemorrhagic) of intestine	569.86

	Diverticulitis of colon with hemorrhage	562.13
	Diverticulitis of small intestine with hemorrhage	562.03
	Diverticulosis of colon with hemorrhage	562.12
	Diverticulosis of small intestine with hemorrhage	562.02
	Hemorrhage of rectum and anus	569.3
Unspecified source	Hemorrhage of gastrointestinal tract, unspecified Blood in stool	578.9 578.1

Abbreviation: *ICD*, International Classification of Diseases; GI, gastrointestinal.

Supplemental Table 2: Modified definition of HAS-BLED

	Original definition	Modified definition
H	hypertension (uncontrolled, ≥ 160 mmHg systolic)	systolic blood pressure ≥ 160 mmHg regardless of treatment status
A	abnormal renal function (presence of chronic dialysis, renal transplantation, serum creatinine ≥ 200 $\mu\text{mol/L}$), abnormal liver function (chronic hepatic disease [e.g., cirrhosis] or biochemical evidence of significant hepatic derangement [e.g., bilirubin >2 times greater than upper limit of normal, in association with aspartate aminotransferase {AST}, alanine aminotransferase {ALT}, or alkaline phosphatase 3 times greater than upper limit normal])	abnormal renal function (eGFR <30 ml/min/1.73m ²), abnormal liver function (AST/ALT >3 times greater than upper limit), history of liver cirrhosis or esophageal varices without bleeding
S	previous history of stroke	previous history of stroke at visit 4
B	prior bleeding or presence of anemia	(Not included)
L	labile international normalized ratio (INR)	the use of anticoagulant agents
E	older age (≥ 65 years)	older age (≥ 65 years)
D	alcohol excess , or the use of antiplatelet agents or nonsteroidal anti-inflammatory drugs	the use of aspirin

Supplemental Table 3: Baseline characteristics stratified by eGFR categories

Characteristic	eGFR ≥90 ml/min/1.73m ² (n=4684)	eGFR 60-89 ml/min/1.73m ² (n=5629)	eGFR 30-59 ml/min/1.73m ² (n=733)	eGFR <30 ml/min/1.73m ² (n=42)
Age, mean(SD), y	60.6 (5.1)	64.1 (5.5)	66.4 (5.3)	64.2 (5.7)
Female, No. (%)	2672 (57)	3123 (55)	405 (55)	17 (40)
Black race, No. (%)	1412 (30)	916 (16)	130 (18)	17 (40)
Body mass index, mean(SD), kg/m ²	28.3 (5.5)	29.1 (5.6)	29.7 (6.0)	29.6 (5.9)
Blood pressure, mean(SD), mmHg				
Systolic	126.7 (18.6)	127.7 (18.8)	131.5 (22.2)	133.7 (22.1)
Diastolic	71.9 (10.0)	70.6 (10.4)	68.8 (12.0)	71.3 (10.1)
Current/Former smoker, No. (%)	2729 (59)	3233 (58)	451 (62)	27 (64)
Current/Former alcohol consumer, No. (%)	3731 (80)	4436 (79)	532 (73)	31 (74)
12 years or more of education, No. (%)	3840 (82)	4534 (81)	531 (73)	29 (73)
Medication use, No. (%)				
Aspirin	2546 (55)	3243 (58)	468 (64)	26 (62)
Anticoagulant	52 (1)	120 (2)	40 (5)	4 (10)
NSAIDs	1387 (30)	1527 (27)	227 (31)	12 (29)
H ₂ blocker	363 (8)	585 (10)	100 (14)	7 (17)
Proton pump inhibitor	124 (3)	176 (3)	43 (6)	2 (5)
Medical history, No. (%)				
Hypertension	1535 (33)	2163 (39)	467 (64)	37 (88)
Diabetes	804 (17)	836 (15)	179 (24)	19 (45)
Liver failure	20 (0)	41 (1)	11 (2)	0 (0)
Prior cardiovascular disease	335 (7)	605 (11)	152 (21)	18 (43)
Prior neoplasm	318 (7)	508 (9)	82 (11)	3 (7)

Prior GERD/peptic ulcer	60 (1)	100 (2)	26 (4)	1 (2)
-------------------------	--------	---------	--------	-------

eGFR indicates estimated glomerular filtration rate; GI, gastrointestinal; NSIADs, non-steroid anti-inflammatory drugs; GERD, gastroesophageal reflux disease.

^a Complete-case analysis was performed for the following variables with missing data: body mass index (n=22), systolic blood pressure (n=2), diastolic blood pressure (n=2), smoking status (n=70), alcohol consumption (n=68), years of education (n=17), liver failure (n=63), hypertension (n=63), diabetes (n=55), use of aspirin (n=32), and use of anticoagulant agents (n=31).

Supplemental Table 4: Baseline characteristics stratified by ACR categories

Characteristic	ACR <10 mg/g (n=8766)	ACR 10-29 mg/g (n=1300)	ACR 30-299 mg/g (n=728)	ACR ≥300 mg/g (n=190)
Age, mean(SD), y	62.5 (5.6)	63.8 (5.8)	64.2 (5.7)	64.6 (6.2)
Female, No. (%)	4889 (56)	792 (61)	384 (53)	92 (48)
Black race, No. (%)	1854 (21)	244 (19)	263 (36)	79 (42)
Body mass index, mean(SD), kg/m ²	28.7 (5.5)	28.7 (5.9)	29.6 (6.4)	30.7 (6.2)
Blood pressure, mean(SD), mmHg				
Systolic	125.3 (17.7)	133.5 (20.0)	139.5 (22.2)	143.6 (23.6)
Diastolic	70.5 (9.9)	72.5 (11.2)	74.1 (12.4)	74.1 (13.1)
Current/Former smoker, No. (%)	5035 (58)	773 (60)	455 (63)	124 (66)
Current/Former alcohol consumer, No. (%)	6957 (80)	1027 (79)	545 (76)	137 (72)
12 years or more of education, No. (%)	7193 (82)	1024 (79)	508 (70)	129 (69)
Medication use, No. (%)				
Aspirin	4876 (56)	790 (61)	438 (60)	122 (65)
Anticoagulant	130 (1)	44 (3)	30 (4)	9 (5)
NSAIDs	2531 (29)	350 (27)	203 (28)	47 (25)
H ₂ blocker	847 (10)	106 (8)	67 (9)	25 (13)
Proton pump inhibitor	274 (3)	35 (3)	24 (3)	8 (4)
Medical history, No. (%)				
Hypertension	2955 (34)	590 (46)	439 (61)	161 (85)
Diabetes	1121 (13)	292 (23)	278 (39)	120 (64)
Liver failure	53 (1)	11 (1)	6 (1)	2 (1)
Prior cardiovascular disease	735 (8)	151 (12)	146 (20)	61 (32)
Prior neoplasm	697 (8)	126 (10)	62 (9)	15 (8)
Prior GERD/peptic ulcer	152 (2)	19 (1)	7 (1)	8 (4)

ACR indicates albumin-to-creatinine ratio; GI, gastrointestinal; NSIADs, non-steroid anti-inflammatory drugs; GERD, gastroesophageal reflux disease.

^a Complete-case analysis was performed for the following variables with missing data: body mass index (n=22), systolic blood pressure (n=2), diastolic blood pressure (n=2), smoking status (n=70), alcohol consumption (n=68), years of education (n=17), liver failure (n=63), hypertension (n=63), diabetes (n=55), use of aspirin (n=32), and use of anticoagulant agents (n=31).

Supplemental Table 5: Hazard ratios of GI bleeding events according to cross-category of eGFR and ACR

	ACR <10 mg/g		ACR 10-29 mg/g		ACR 30-299 mg/g		ACR ≥300 mg/g	
	HR (95%CI)	Events/N	HR (95%CI)	Events/N	HR (95%CI)	Events/N	HR (95%CI)	Events/N
eGFR ≥90 ml/min/1.73m ²	1 [Reference]	155/3791	1.36 (0.93-1.98)	35/560	1.95 (1.24-3.08)	24/252	2.82 (1.14-6.97)	6/42
eGFR 60-89 ml/min/1.73m ²	1.21 (0.98-1.49)	271/4520	1.55 (1.12-2.16)	50/631	2.49 (1.77-3.51)	46/351	0.78 (0.25-2.45)	4/69
eGFR 30-59 ml/min/1.73m ²	1.22 (0.82-1.83)	31/448	2.36 (1.34-4.15)	15/108	3.19 (1.95-5.23)	20/119	2.20 (0.96-5.06)	6/53
eGFR <30 ml/min/1.73m ²	6.99 (1.71-28.60)	2/7	-	0/1	5.16 (0.72-37.16)	1/6	10.06 (4.85-20.86)	8/26

Abbreviations: HR, hazard ratio; CI, confidence interval; GI, gastrointestinal; eGFR, estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio.
The model was adjusted for age, race, sex, body mass index, smoking status, alcohol consumption, education level, use of aspirin, anticoagulant, non-steroid anti-inflammatory agents, H₂ blocker, proton pump inhibitor, and history of hypertension, diabetes, liver failure, prior cardiovascular disease, prior neoplasm, and prior GERD/peptic ulcer.

Supplemental Table 6: Cox proportional hazard models according to the site of GI bleeding

	Hazard Ratio (95% CI)		
	Upper GI bleeding (n=422)	Lower GI bleeding (n= 177)	GI bleeding, site unknown (n= 363)
eGFR ≥90+ ml/min/1.73m ²	1 [Reference]	1 [Reference]	1 [Reference]
eGFR 60-89 ml/min/1.73m ²	1.20 (0.90-1.59)	1.47 (1.03-2.11)	1.07 (0.83-1.38)
eGFR 30-59 ml/min/1.73m ²	1.18 (0.72-1.93)	2.32 (1.35-4.02)	1.96 (1.36-2.81)
eGFR <30 ml/min/1.73m ²	5.33 (1.92-14.79)	10.81 (3.83-30.53)	6.02 (2.61-13.91)
ACR <10 mg/g	1 [Reference]	1 [Reference]	1 [Reference]
ACR 10-29 mg/g	1.31 (0.91-1.88)	0.94 (0.56-1.57)	1.66 (1.25-2.22)
ACR 30-299 mg/g	2.15 (1.48-3.13)	2.41 (1.54-3.76)	2.27 (1.64-3.15)
ACR ≥300 mg/g	2.41 (1.24-4.69)	2.55 (1.15-5.65)	2.43 (1.36-4.34)

Abbreviations: GI, gastrointestinal; CI, confidence interval; eGFR, estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio. The model was adjusted for age, race, sex, body mass index, smoking status, alcohol consumption, education level, use of aspirin, anticoagulant, non-steroid anti-inflammatory agents, H2 blocker, proton pump inhibitor, and history of hypertension, diabetes, liver failure, prior cardiovascular disease, prior neoplasm, and prior GERD/peptic ulcer.

^a Hazard ratios were estimated independently according to each site of GI bleeding. Therefore, sum of the number of gastrointestinal bleeding events in three categories (n=962) is greater than the number of events in overall analyses (n=686).

Supplemental Table 7: Cox proportional hazard model including a covariate of incident cardiovascular disease as time varying exposure

	HR (95%CI)
eGFR ≥90+ ml/min/1.73m ²	1 [Reference]
eGFR 60-89 ml/min/1.73m ²	1.18 (0.98-1.41)
eGFR 30-59 ml/min/1.73m ²	1.46 (1.09-1.95)
eGFR <30 ml/min/1.73m ²	6.89 (3.81-12.44)
ACR <10 mg/g	1 [Reference]
ACR 10-29 mg/g	1.33 (1.06-1.66)
ACR 30-299 mg/g	2.01 (1.58-2.55)
ACR ≥300 mg/g	1.94 (1.24-3.02)

Abbreviations: HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio. The model was adjusted for age, race, sex, body mass index, smoking status, alcohol consumption, education level, use of aspirin, anticoagulant, non-steroid anti-inflammatory agents, H2 blocker, proton pump inhibitor, and history of hypertension, diabetes, liver failure, prior cardiovascular disease, prior neoplasm, and prior GERD/peptic ulcer. A variable for cardiovascular disease was treated as categorical values of either without cardiovascular disease, incident cardiovascular disease, or prevalent cardiovascular disease.

Supplemental Table 8: Cox proportional hazard model including a covariate of incident end-stage renal disease as time varying exposure

	HR (95%CI)
eGFR ≥90+ ml/min/1.73m ²	1 [Reference]
eGFR 60-89 ml/min/1.73m ²	1.16 (0.96-1.38)
eGFR 30-59 ml/min/1.73m ²	1.30 (0.96-1.75)
eGFR <30 ml/min/1.73m ²	3.03 (1.55-5.95)
ACR <10 mg/g	1 [Reference]
ACR 10-29 mg/g	1.32 (1.05-1.65)
ACR 30-299 mg/g	1.97 (1.55-2.52)
ACR ≥300 mg/g	1.43 (0.89-2.29)

Abbreviations: HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio. The model was adjusted for age, race, sex, body mass index, smoking status, alcohol consumption, education level, use of aspirin, anticoagulant, non-steroid anti-inflammatory agents, H2 blocker, proton pump inhibitor, and history of hypertension, diabetes, liver failure, prior cardiovascular disease, prior neoplasm, and prior GERD/peptic ulcer, and incident end stage renal disease (yes or no).

Supplemental Table 9: Hazard ratio of GI bleeding as the primary discharge diagnosis

	HR (95%CI)
eGFR ≥90+ ml/min/1.73m ²	1 [Reference]
eGFR 60-89 ml/min/1.73m ²	1.27 (0.99-1.64)
eGFR 30-59 ml/min/1.73m ²	1.59 (1.05-2.41)
eGFR <30 ml/min/1.73m ²	9.75 (4.47-21.27)
ACR <10 mg/g	1 [Reference]
ACR 10-29 mg/g	1.31 (0.95-1.80)
ACR 30-299 mg/g	1.97 (1.39-2.78)
ACR ≥300 mg/g	2.36 (1.29-4.32)

Abbreviations: HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio. The model was adjusted for age, race, sex, body mass index, smoking status, alcohol consumption, education level, use of aspirin, anticoagulant, non-steroid anti-inflammatory agents, H2 blocker, proton pump inhibitor, and history of hypertension, diabetes, liver failure, prior cardiovascular disease, prior neoplasm, and prior GERD/peptic ulcer.

Supplemental Table 10: Hazard ratio of mortality from GI bleeding

	Total No.	No. of deaths	HR (95%CI)
eGFR ≥90+ ml/min/1.73m ²	4684	10	1 [Reference]
eGFR 60-89 ml/min/1.73m ²	5629	13	0.87 (0.35-2.12)
eGFR 30-59 ml/min/1.73m ²	733	4	1.96 (0.55-7.01)
eGFR <30 ml/min/1.73m ²	42	3	30.44 (7.30-127.01)
ACR <10 mg/g	8766	17	1 [Reference]
ACR 10-29 mg/g	1300	3	1.03 (0.30-3.61)
ACR 30-299 mg/g	728	6	3.56 (1.32-9.60)
ACR ≥300 mg/g	190	4	9.26 (2.71-31.71)

Abbreviations: HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio. There were 79 deaths observed during or within 30 days after discharge of GI bleeding related hospitalization. The model was adjusted for age, race, sex, body mass index, smoking status, alcohol consumption, education level, use of aspirin, anticoagulant, non-steroid anti-inflammatory agents, H2 blocker, proton pump inhibitor, and history of hypertension, diabetes, liver failure, prior cardiovascular disease, prior neoplasm, and prior GERD/peptic ulcer.

Supplemental Table 11: Relative risk for GI bleeding including outpatient events among individuals aged 65+ years

Total No.	Inpatient events only			Outpatient and inpatients events		
	No. of events	Hazard Ratio (95% CI)		No. of events	Hazard Ratio (95% CI)	
		Model1	Model2		Model1	Model2
(A) eGFR						
≥90 ml/min/1.73m ²	1017	81	1 [Reference]	1 [Reference]	305	1 [Reference]
60-89 ml/min/1.73m ²	2441	193	0.99 (0.75-1.30)	0.99 (0.75-1.31)	747	0.97 (0.85-1.12)
30-59 ml/min/1.73m ²	429	49	1.40 (0.95-2.05)	1.32 (0.89-1.94)	147	1.12 (0.90-1.38)
<30 ml/min/1.73m ²	19	5	6.03 (2.39-15.20)	5.38 (2.06-14.06)	7	2.21 (1.04-4.70)
(B) ACR						
<10 mg/g	2894	212	1 [Reference]	1 [Reference]	888	1 [Reference]
10-29 mg/g	557	54	1.39 (1.02-1.89)	1.37 (1.01-1.87)	163	1.00 (0.84-1.18)
30-299 mg/g	331	48	2.21 (1.58-3.09)	2.09 (1.49-2.93)	114	1.30 (1.06-1.60)
≥300 mg/g	84	9	1.74 (0.88-3.46)	1.39 (0.68-2.83)	26	1.29 (0.86-1.92)
						1.18 (0.78-1.78)

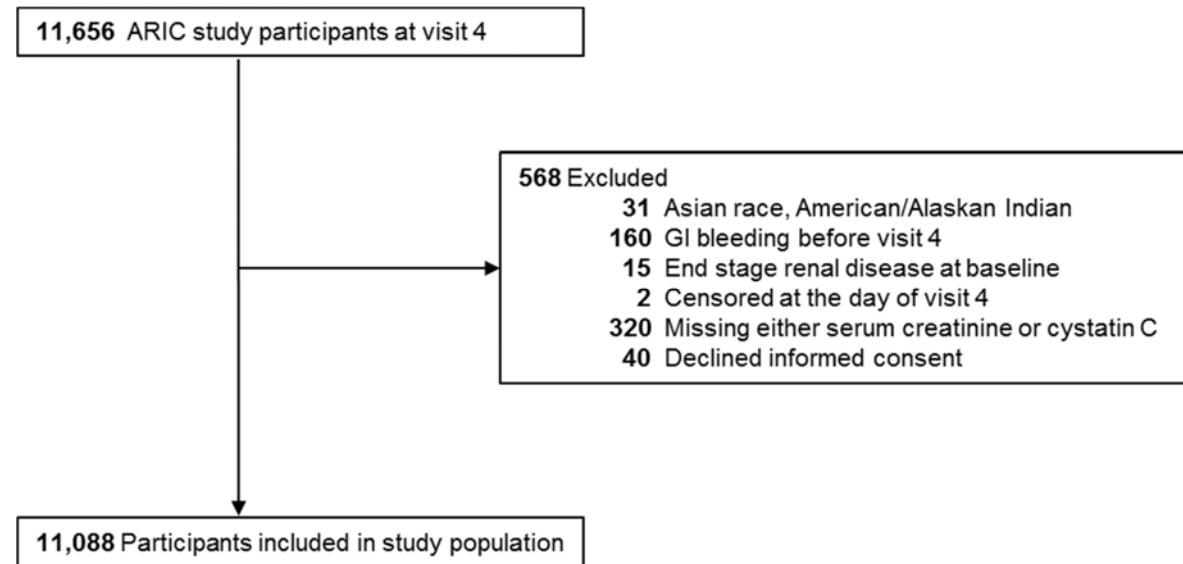
Abbreviations: CI, confidence interval; GI, gastrointestinal; eGFR, estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio. The model 1 was adjusted for age, sex, race, body mass index, alcohol consumption, smoking status, education level, aspirin, anticoagulant agents, NSIADs, H2 blocker, proton pump inhibitor, hypertension, diabetes, liver failure, cardiovascular disease, neoplasm, and GERD/peptic ulcer. The model 2 was adjusted for ACR/eGFR in addition to the model

Supplemental Table 12: Hazard ratio of GI bleed-related and non-GI bleed-related hospitalization

	HR (95%CI)	
	GI-bleeding	No GI-bleeding
eGFR ≥90+ ml/min/1.73m ²	1 [Reference]	1 [Reference]
eGFR 60-89 ml/min/1.73m ²	1.19 (1.00-1.43)	1.04 (0.99-1.10)
eGFR 30-59 ml/min/1.73m ²	1.51 (1.13-2.02)	1.28 (1.17-1.40)
eGFR <30 ml/min/1.73m ²	7.06 (3.91-12.76)	2.97 (2.16-4.09)
ACR <10 mg/g	1 [Reference]	1 [Reference]
ACR 10-29 mg/g	1.35 (1.08-1.69)	1.12 (1.05-1.20)
ACR 30-299 mg/g	2.13 (1.68-2.71)	1.41 (1.29-1.53)
ACR ≥300 mg/g	2.07 (1.33-3.22)	2.03 (1.74-2.37)

Abbreviations: HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio. The model was adjusted for age, race, sex, body mass index, smoking status, alcohol consumption, education level, use of aspirin, anticoagulant, non-steroid anti-inflammatory agents, H₂ blockers, proton pump inhibitors, and history of hypertension, diabetes, liver failure, prior cardiovascular disease, prior neoplasm, and prior GERD/peptic ulcer.

Supplemental Figure 1: Cohort diagram of the study population



ARIC indicates Atherosclerosis Risk in Communities; GI, gastrointestinal