

Long-Term Incidence of Gastrointestinal Bleeding Following Ischemic Stroke

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Background and Purpose Previous research on patients with acute ischemic stroke (AIS) has shown a 0.5% incidence of major gastrointestinal bleeding (GIB) requiring blood transfusion during hospitalization. The existing literature has insufficiently explored the long-term incidence in this population despite the decremental impact of GIB on stroke outcomes.

Methods We analyzed the data from a cohort of patients with AIS admitted to 14 hospitals as part of a nationwide multicenter prospective stroke registry between 2011 and 2013. These patients were followed up for up to 6 years. The occurrence of major GIB events, defined as GIB necessitating at least two units of blood transfusion, was tracked using the National Health Insurance Service claims data.

Results Among 10,818 patients with AIS (male, 59%; mean age, 68±13 years), 947 (8.8%) experienced 1,224 episodes of major GIB over a median follow-up duration of 3.1 years. Remarkably, 20% of 947 patients experienced multiple episodes of major GIB. The incidence peaked in the first month after AIS, reaching 19.2 per 100 person-years, and gradually decreased to approximately one-sixth of this rate by the 2nd year with subsequent stabilization. Multivariable analysis identified the following

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predictors of major GIB: anemia, estimated glomerular filtration rate <60 mL/min/1.73 m², and a 3-month modified Rankin Scale score of ≥ 4 .

Conclusion Patients with AIS are susceptible to major GIB, particularly in the first month after the onset of AIS, with the risk decreasing thereafter. Implementing preventive strategies may be important, especially for patients with anemia and impaired renal function at stroke onset and those with a disabling stroke.

Keywords Gastrointestinal bleeding; Ischemic stroke; Medical complications

Introduction

The administration of antithrombotics following acute coronary syndrome (ACS) and acute ischemic stroke (AIS) is recommended to reduce the risk of subsequent major cardiovascular events but concurrently heightens the risk of bleeding complications.^{1,2} Major bleeding is a significant predictor of all-cause mortality,³⁻⁵ as well as cardiovascular mortality in patients receiving antithrombotic medications.⁶

Gastrointestinal bleeding (GIB) is the most common type of bleeding complication,⁷ accounting for 76% of cases.⁸ In patients with ACS, the incidence has been reported as 0.7% during hospitalization⁹ and 1.4% during the first year.¹⁰ In the case of AIS, the incidence of GIB has been observed to be 1.5% during hospitalization, with one-third of the cases requiring blood transfusion.¹¹ However, information regarding the long-term incidence of GIB after AIS is limited.

The Oxford Vascular Study (OXVASC) reported an annual major bleeding risk of 1.46% among patients with transient ischemic attack (TIA), ischemic stroke, or myocardial infarction, with 40% of the cases attributed to upper GIB.⁸ However, the OXVASC did not explicitly report GIB after AIS, and the findings were restricted to the Oxfordshire region. Another single-center study from Scotland showed a 3% GIB incidence over 3 years among 613 patients with acute stroke but did not specify GIB after AIS.¹² Furthermore, information on how incidence rates of and risk factors for major GIB evolve in AIS is lacking.

Our study aimed to investigate the long-term incidence rates of and identify risk factors for major GIB following AIS and examine how these may vary according to the time elapsed since the onset of stroke. We employed a robust methodology, leveraging a large-scale, prospective, multicenter stroke registry database from South Korea and linking it to national claims data to ensure the reliability and completeness of our analysis and accurately capture and scrutinize the incidence of major GIB in this population.

Methods

Study population

Our study included participants with AIS who were admitted to 14 university hospitals or regional stroke centers between January 2011 and November 2013 and registered in the Clinical Research Collaboration for Stroke in Korea–National Institute of Health (CRCS–K–NIH) registry database. We tracked GIB occurrences after AIS for a period ranging from a minimum of 3 years to a maximum of 6 years by linking the CRCS–K–NIH database with the National Health Insurance Service (NHIS) claims data.^{13,14}

The NHIS, a compulsory health insurance service providing extensive medical care coverage since 1989, covers 97.1% of the Korean population.¹⁵ Its claims database comprises information regarding beneficiaries' demographics, diagnostic codes, procedures, and medication prescriptions for inpatient and outpatient care.^{16,17}

We included patients with AIS, aged ≥ 18 years, admitted within 7 days of symptom onset, and with corresponding stroke lesions on brain imaging (Supplementary Figure 1). Patients who died during hospitalization were excluded from the study.

Ethics statements

The collection of clinical information for the CRCS–K–NIH registry and its linkage with secondary databases for stroke research was conducted following informed consent and approval from the local ethics committees of all participating centers. The Institutional Review Board of Seoul National University Bundang Hospital approved this study's utilization of the CRCS–K–NIH database and its linkage with the NHIS claims data under approval number B-1511/322-106. This study was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.¹⁸

Data collection and definitions

Data on baseline demographics, medical histories, risk factors, laboratory findings, stroke characteristics, medications prescribed

at discharge, reperfusion therapies, 3-month functional outcomes, and post-stroke cardiovascular events were obtained from the registry database. The CRCS-K-NIH registry prospectively captured vascular events during hospitalization and up to 1 year after the index stroke through medical record review and telephone interviews conducted by experienced stroke coordinators at each participating center.¹⁴ Additional information regarding histories of gastroduodenal ulcer and gastrointestinal (GI) hemorrhage, the prescription of antithrombotic drugs at 1 year after stroke, and post-index stroke GIB was obtained from the claims database.

Age was dichotomized, with a threshold of 75 years serving as the demarcation. Stroke severity at admission was determined using National Institutes of Health Stroke Scale (NIHSS) scores. Disability at 3 months was evaluated using the modified Rankin Scale (mRS). Estimated glomerular filtration rates (eGFR) were calculated using the Modification of Diet in Renal Disease equation ($\text{eGFR} [\text{mL/min/1.73 m}^2] = 175 \times [\text{serum creatinine}]^{-1.154} \times [\text{age}]^{0.203} [\times 0.742, \text{ if female}]$)¹⁹ and were subsequently segmented into four categories: 90 or above, 60–89, 30–59, and below 30 mL/min/1.73 m². The severity of anemia was categorized into two groups according to the World Health Organization criteria. Mild anemia was defined as follows: for men, hemoglobin levels between 11 and 13 g/dL, and for women, hemoglobin levels between 11 and 12 g/dL. Moderate to severe anemia was defined as hemoglobin levels below 11 g/dL for both sexes.²⁰ Long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) was defined as a history of being prescribed NSAIDs at least four times within 1 year prior to being hospitalized for a stroke (Supplementary Table 1).²¹ Chronic alcohol use was defined as the presence of the International Classification of Disease, 10th Revision (ICD-10), diagnostic codes (Supplementary Table 2) for chronic diseases and conditions related to alcohol use within 1 year prior to being hospitalized for a stroke.²²

The primary outcome was the incidence of major GIB following the index stroke. GIB was detected from the claims database using the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM), coding system. Major GIB was defined as the occurrence of specific diagnostic codes (I85, K22.6, K22.7, K22.8, K25, K26, K27, K28, K29, K62.5, K66.1, or K92.2) coupled with the administration of two or more units of transfusion. The follow-up period spanned up to 6 years after the index stroke, segmented into seven distinct intervals: ≤ 1 month, 2–3 months, 4–6 months, 7–12 months, the 2nd year, the 3rd year, and > 3 years.

Statistical analysis

Baseline characteristics were presented as frequencies and per-

centages for categorical variables and as mean $\pm$ standard deviation or median (interquartile range) for continuous variables. For each participant, the elapsed time in days from the index stroke to the occurrence of GIB, end of the follow-up period, or death was calculated. The incidence rates of GIB and their corresponding 95% confidence intervals (CIs) were computed for each of the seven intervals and predetermined subgroups. In the subgroup analysis, an absence of overlap between two CIs indicated a statistically significant difference.²³ Variables for the subgroup analysis were selected based on our understanding and knowledge of risk factors for GIB after AIS.^{24–26} Adjusted incidence rate ratios (IRRs) with 95% CIs were also estimated for these variables. To facilitate comparisons with previous studies, we computed cumulative incidence functions (CIFs) to represent the probability of GIB after the index stroke, considering mortality as a competing risk, using subdivision hazard models.^{8,11} Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). A two-sided *P* value of < 0.01 was deemed statistically significant.

Data availability

The data used in this study originated from the link between the CRCS-K-NIH registry database and the NHIS claims data, which are stored on a separate server managed by the NHIS. Access to these data is restricted to pre-approved researchers and is slated for deletion from the server after a predetermined study duration. Consequently, the data availability cannot be guaranteed.

Results

Of the 10,818 patients with AIS included in the study, 59% were male with an average age of 68 ± 13 years. The median NIHSS score was 3. Six percent of patients had a history of GI hemorrhage (Table 1). Upon discharge, approximately 44% of the patients were receiving a single antiplatelet therapy, with aspirin being the most common choice (83%), followed by clopidogrel (12%) and other agents (5%) (Supplementary Table 3). Dual antiplatelet therapy was administered to 31% of patients, while 20% were on anticoagulants.

During a median follow-up period of 3.1 years, 947 patients (8.8%) experienced major GIB, resulting in 1,224 episodes over 31,208 person-years. Among the 947 patients, 20% had recurrent episodes, with a second episode mostly occurring within a month of the first (Figure 1). The CIFs for major GIB were 0.7% at 1 week, 1.6% at 1 month, 5.0% at 1 year, and 8.3% at 3 years (Figure 2 and Supplementary Table 4).

The incidence of major GIB varies depending on the time elapsed since the index stroke. During the first month, the incidence rates

Table 1. Baseline characteristics of the patients with acute ischemic stroke included in the study

Characteristic	Value (n=10,818)
Male sex	6,381 (59.0)
Age (yr), mean±SD	67.5±12.9
<75	7,272 (67.2)
≥75	3,546 (32.8)
Premorbid mRS	
0	8,851 (81.8)
1	572 (5.3)
2	435 (4.0)
3	539 (5.0)
4	265 (2.4)
5	156 (1.4)
Smoker	2,874 (26.6)
Previous medical history	
Hypertension	7,358 (68.0)
Diabetes	3,571 (33.0)
Dyslipidemia	3,544 (32.8)
Atrial fibrillation	2,220 (20.5)
History of gastroduodenal ulcer	7,562 (69.9)
History of gastrointestinal hemorrhage	672 (6.2)
Long-term NSAID use*	3,758 (34.7)
Chronic alcohol use†	368 (3.4)
TOAST	
LAA	4,029 (37.2)
SVO	1,964 (18.2)
Cardioembolism	2,291 (21.2)
Other determined	238 (2.2)
Undetermined	2,296 (21.2)
Initial NIHSS	
Median (IQR)	3 (1–8)
0–4	6,484 (59.9)
5–14	3,225 (29.8)
≥15	1,109 (10.3)
Anemia on admission	
None	8,369 (77.4)
Mild (11≤Hb<13 g/dL in male, 11≤Hb<12 g/dL in female)	1,539 (14.2)
Moderate to severe (Hb <11 g/dL)	910 (8.4)
eGFR (mL/min/1.73 m ²)	
≥90	4,144 (38.3)
60–89	4,490 (41.5)
30–59	1,867 (17.3)
<30	317 (2.9)
Reperfusion therapy	
IV thrombolysis	1,445 (13.4)
Endovascular treatment	650 (6.0)

Table 1. Continued

Characteristic	Value (n=10,818)
Antithrombotics at discharge	
No treatment	552 (5.1)
Aspirin mono	3,942 (36.4)
Other antiplatelets mono	797 (7.4)
Dual Antiplatelets or more	3,341 (30.9)
Anticoagulants without antiplatelets	1,662 (15.4)
Anticoagulants with antiplatelets	524 (4.8)
3-Month mRS‡	
0	2,931 (27.1)
1	2,492 (23.0)
2	1,785 (16.5)
3	1,330 (12.3)
4	1,081 (10.0)
5	713 (6.6)
6	455 (4.2)

Values presented are number of patients (%) if not indicated.

SD, standard deviation; mRS, modified Rankin Scale; NSAID, nonsteroidal anti-inflammatory drug; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; LAA, large artery atherosclerosis; SVO, small vessel occlusion; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; Hb, hemoglobin; eGFR, estimated glomerular filtration rate; IV, intravenous; ICD-10, International Classification of Disease, 10th Revision.

*Long-term NSAID use was defined as a history of being prescribed NSAIDs at least four more times within 1 year prior to hospitalization for stroke;

†Chronic alcohol use was defined as the presence of ICD-10 diagnostic codes for chronic diseases and conditions related to alcohol use within 1 year prior to hospitalization for stroke; ‡Thirty-one patients (0.3%) with missing information on 3-month mRS were excluded from the analysis of 3-month mRS.

peaked at 19.2 per 100 person-years, gradually decreasing to approximately one-sixth of this rate in the 2nd year and then stabilizing (Table 2).

Incidence rates were further examined within the subgroups for each interval (Table 2). In the first month, patients with AIS and moderate-to-severe anemia exhibited the highest incidence rate (116 per 100 person-years), followed by those with a 3-month mRS score of 6, a 3-month mRS score of 5, and an eGFR <30 mL/min/1.73 m². From the 2nd to 3rd month after stroke, patients with a 3-month mRS score of 6 had the highest incidence, followed by those with an eGFR of <30 and moderate-to-severe anemia. From the 4th month to the 3rd year, individuals with an eGFR < 30 had the highest incidence rate, followed by those with moderate-to-severe anemia and a 3-month mRS score of 5.

Throughout most of the observation periods, patients aged ≥75 years and with a history of GI hemorrhage, anemia, and an eGFR <60 had higher incidence rates than those without these characteristics, respectively. During the first year following the index stroke, patients with an initial NIHSS score of 5–14 and

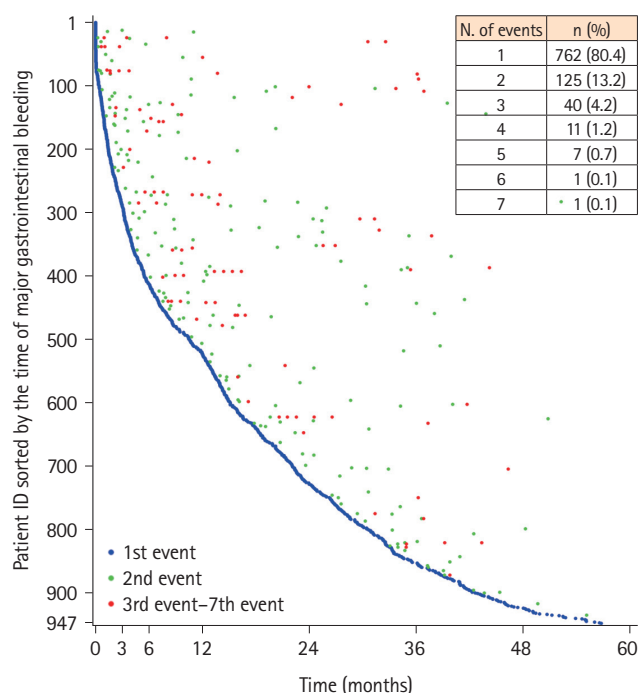


Figure 1. Time distribution of major gastrointestinal bleeding events following acute ischemic stroke. Major gastrointestinal bleeding was defined as bleeding leading to the transfusion of two or more units of whole blood or red blood cells.

≥15 had higher incidence rates than those with an initial NIHSS score of 0–4. History of long-term NSAID use and chronic alcohol use showed relatively high major GIB incidence rates within the first month post-stroke, but no significant difference thereafter.

Regarding the antithrombotics prescribed at discharge, patients who received anticoagulants without antiplatelet agents had the lowest GIB rates within the first month (Supplementary Table 5). By contrast, patients who did not receive antithrombotics had the highest rates. Patients on other antiplatelet monotherapies, excluding aspirin, had rates approximately three times higher than those on aspirin monotherapy within the first month. However, no significant differences in GIB were observed according to the antithrombotic medications prescribed at discharge after the initial period.

We also assessed changes in the prescription of antithrombotic drugs from discharge to the end of the first year after the index stroke. Of the patients prescribed antithrombotic medications at discharge, 68.4% were on different antithrombotic medications 1 year later (Supplementary Table 6). More than 70% of the patients initially receiving dual antiplatelet therapy or more at discharge transitioned to antiplatelet monotherapy at the end of the first year. Approximately 45% of patients initially on anticoagulants at discharge discontinued their use within 1 year.

Multivariable analysis demonstrated that advanced age (≥75 years), anemia, low eGFR, and high 3-month mRS scores were

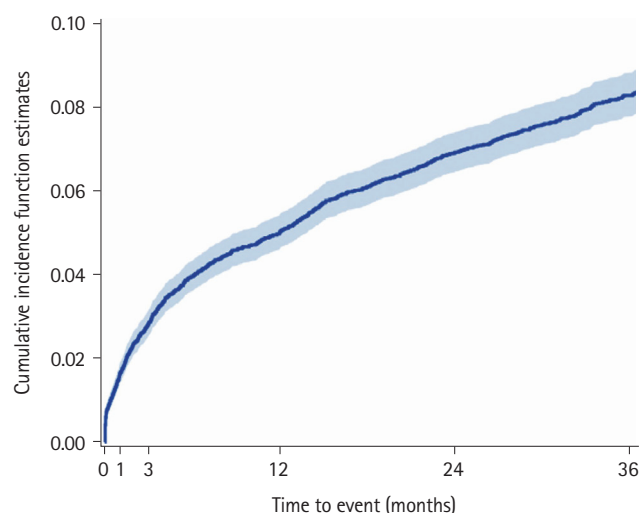


Figure 2. Cumulative incidence function for major gastrointestinal bleeding following acute ischemic stroke.

independently associated with major GIB during most of the observational period after AIS (Figure 3 and Supplementary Table 7). Unlike the unadjusted analyses (Table 2), initial NIHSS scores and history of GI hemorrhage were not associated with major GIB. A history of long-term NSAID and chronic alcohol use showed no significant differences throughout the observation period.

Regarding variations of risk depending on the elapsed time since the time of stroke onset, among patients aged ≥75 years compared to those aged <75 years, the risk of major GIB gradually increased over time; the IRR for those aged ≥75 years was more than twice as high after 3 years compared to within the first month (Figure 3). As for moderate-to-severe anemia, the IRR was >7 in the first month but almost halved in the 2nd and 3rd months and stabilized thereafter. On the contrary, compared to patients with an eGFR ≥90, those with an eGFR <30 had a threefold higher risk of GIB after the first month, and the risk remained elevated until the 3rd year.

Discussion

In our study, 8.8% of the patients with AIS experienced major GIB during a median follow-up period of 3.1 years. The incidence rate of major GIB was highest in the first month, at a rate of 19.2 per 100 person-years, which is more than 7 times that observed after 3 years (2.6 per 100 person-years). Throughout the observation period, we found that anemia, lower eGFR, and disability at 3 months were consistently associated with an increased risk of major GIB.

We observed that the incidence rate of major GIB was highest immediately after AIS, followed by a gradual decrease and stabilizing after 2 years. Although this higher incidence rate in

Table 2. Incidence rates of major GI bleeding in patients with acute ischemic stroke according to the elapsed time since stroke onset and predefined subgroups

	N	Intervals after the onset of index stroke					
		≤1 month	2–3 months	4–6 months	7–12 months	2nd year	3rd year
Overall	10,818	19.2 (16.5–22.3)	9.0 (7.7–10.6)	6.2 (5.3–7.3)	3.5 (3.0–4.0)	3.0 (2.7–3.4)	2.5 (2.1–2.9)
Sex							
Male	6,381	17.8 (14.5–21.8)	9.0 (7.3–11.0)	6.0 (4.9–7.4)	3.1 (2.5–3.8)	2.6 (2.2–3.1)	2.2 (1.8–2.7)
Female	4,437	21.3 (17.0–26.7)	9.1 (7.1–11.7)	6.4 (5.0–8.2)	4.1 (3.3–5.1)	3.6 (3.0–4.3)	2.8 (2.3–3.5)
Age (yr)							
<75	7,272	15.9 (13.0–19.5)	6.7 (5.4–8.4)	4.8 (3.9–6.0)	2.4 (2.0–3.0)	2.3 (1.9–2.7)	1.7 (1.4–2.1)
≥75	3,546	26.1 (20.8–32.7)	14.0 (11.2–17.6)	9.3 (7.4–11.7)	6.0 (4.9–7.4)	5.0 (4.2–5.9)	4.8 (3.9–5.9)
Smoking							
No	7,944	20.6 (17.4–24.4)	9.9 (8.3–11.9)	6.5 (5.5–7.8)	3.7 (3.1–4.4)	3.3 (2.9–3.8)	2.6 (2.2–3.1)
Yes	2,874	15.4 (11.1–21.4)	6.6 (4.6–9.4)	5.2 (3.7–7.3)	2.9 (2.1–4.0)	2.3 (1.8–3.0)	2.1 (1.5–2.8)
Initial NIHSS							
0–4	6,484	13.6 (10.8–17.2)	5.8 (4.5–7.4)	4.2 (3.3–5.4)	2.5 (2.0–3.1)	2.6 (2.2–3.0)	2.0 (1.6–2.4)
5–14	3,225	22.7 (17.6–29.3)	12.0 (9.3–15.5)	8.8 (6.9–11.3)	4.9 (3.9–6.2)	3.3 (2.7–4.1)	3.5 (2.7–4.4)
≥15	1,109	43.0 (31.2–59.4)	21.4 (15.2–30.0)	11.5 (7.7–17.1)	6.3 (4.2–9.4)	5.7 (4.1–7.8)	3.4 (2.1–5.5)
IV tPA							
No	9,373	18.7 (15.9–22.1)	8.9 (7.5–10.6)	6.1 (5.1–7.2)	3.4 (2.9–4.0)	3.0 (2.6–3.4)	2.5 (2.2–2.9)
Yes	1,445	22.5 (15.3–33.0)	9.9 (6.5–15.0)	6.9 (4.5–10.4)	4.0 (2.7–6.0)	3.4 (2.5–4.7)	2.1 (1.3–3.3)
History of gastroduodenal ulcer							
No	3,256	17.0 (12.7–22.8)	7.9 (5.8–10.8)	4.3 (3.0–6.0)	1.9 (1.3–2.7)	2.3 (1.8–2.9)	1.6 (1.2–2.3)
Yes	7,562	20.2 (16.9–24.1)	9.5 (7.9–11.4)	7.0 (5.9–8.4)	4.2 (3.6–5.0)	3.4 (2.9–3.8)	2.9 (2.4–3.4)
History of gastrointestinal hemorrhage							
No	10,146	18.0 (15.4–21.2)	8.5 (7.2–10.1)	5.8 (4.9–6.9)	3.3 (2.9–3.9)	2.8 (2.4–3.1)	2.4 (2.0–2.7)
Yes	672	37.1 (23.9–57.5)	16.6 (10.3–26.7)	12.3 (7.8–19.6)	5.7 (3.4–9.3)	7.3 (5.3–10.0)	4.4 (2.7–7.1)
Long-term NSAID use							
None	7,060	17.0 (13.9–20.7)	9.0 (7.4–11.0)	5.3 (4.3–6.6)	3.1 (2.5–3.8)	2.9 (2.5–3.4)	1.8 (1.5–2.2)
Yes	3,758	23.5 (18.6–29.6)	9.0 (6.9–11.8)	7.8 (6.1–9.9)	4.2 (3.3–5.3)	3.2 (2.6–3.9)	3.7 (3.0–4.5)
Chronic alcohol use							
None	10,450	18.9 (16.2–22.1)	9.0 (7.7–10.6)	6.3 (5.4–7.4)	3.5 (3.0–4.0)	3.0 (2.7–3.4)	2.4 (2.1–2.8)
Yes	368	26.9 (13.4–53.8)	8.7 (3.6–20.9)	2.4 (0.6–9.6)	3.6 (1.6–8.0)	2.6 (1.3–5.2)	2.8 (1.4–5.9)

Table 2. Continued

	N	Intervals after the onset of index stroke						
		≤1 month	2–3 months	4–6 months	7–12 months	2nd year	3rd year	>3 years
Anemia								
None	8,369	8.4 (6.5–10.9)	5.6 (4.4–7.0)	4.1 (3.3–5.1)	2.1 (1.7–2.6)	2.0 (1.7–2.4)	1.8 (1.5–2.1)	1.8 (1.4–2.2)
Mild	1,539	24.3 (17.0–34.7)	13.1 (9.2–18.6)	11.3 (8.2–15.5)	7.3 (5.5–9.7)	4.9 (3.8–6.4)	4.8 (3.5–6.4)	5.7 (4.1–7.9)
Moderate to severe	910	115.7 (93.1–143.9)	38.5 (29.0–51.1)	20.4 (14.6–28.5)	13.1 (9.6–17.9)	13.1 (10.3–16.7)	8.2 (5.7–11.8)	10.3 (6.9–15.4)
eGFR (mL/min/1.73 m ²)								
≥90	4,144	14.6 (11.0–19.3)	5.0 (3.6–7.0)	3.9 (2.9–5.4)	2.5 (1.9–3.3)	1.7 (1.3–2.2)	1.6 (1.2–2.1)	1.7 (1.4–2.2)
60–89	4,490	17.0 (13.3–21.9)	7.1 (5.3–9.3)	5.9 (4.6–7.6)	3.2 (2.5–4.1)	2.8 (2.3–3.3)	2.0 (1.6–2.6)	2.6 (2.0–3.3)
30–59	1,867	30.9 (23.1–41.2)	17.8 (13.5–23.5)	8.0 (5.7–11.3)	4.6 (3.3–6.4)	5.9 (4.7–7.3)	5.2 (4.0–6.8)	5.3 (3.8–7.4)
<30	317	44.0 (24.4–79.5)	43.6 (28.1–67.5)	34.9 (22.7–53.5)	18.3 (11.8–28.4)	14.2 (9.6–21.0)	12.0 (7.1–20.3)	7.0 (2.9–16.8)
Antithrombotics at discharge								
ASA mono	3,942	12.2 (8.9–16.7)	5.7 (4.1–8.0)	5.0 (3.8–7.0)	2.0 (1.5–2.8)	2.2 (1.7–2.7)	1.8 (1.4–2.4)	1.5 (1.0–2.1)
Other AP mono	797	42.5 (29.2–62.0)	8.9 (4.9–16.1)	10.1 (6.3–16.0)	3.1 (1.7–5.6)	4.5 (3.2–6.5)	1.9 (1.0–3.5)	4.1 (2.6–6.6)
Dual AP or more	3,341	17.3 (13.0–23.0)	9.1 (6.8–12.0)	4.3 (3.0–6.0)	3.7 (2.8–4.8)	2.8 (2.2–3.5)	2.5 (2.0–3.3)	2.5 (1.9–3.4)
AC without AP	1,662	9.6 (5.6–16.6)	11.2 (7.8–16.1)	9.1 (6.5–12.7)	4.9 (3.5–6.8)	3.5 (2.6–4.7)	4.4 (3.3–5.9)	4.9 (3.5–6.8)
AC with AP	524	18.9 (9.4–37.7)	13.6 (7.5–24.6)	10.6 (6.0–18.6)	6.9 (4.2–11.5)	5.7 (3.7–8.6)	2.6 (1.3–5.2)	3.8 (1.9–7.7)
No treatment	552	83.0 (59.3–116.2)	24.7 (15.6–39.3)	9.0 (4.7–17.4)	7.5 (4.5–12.7)	6.0 (3.8–9.3)	2.3 (1.0–5.2)	2.2 (0.8–6.0)
3-Month mRS								
0	2,931	9.6 (6.4–14.5)	2.3 (1.3–4.2)	3.6 (2.4–5.3)	2.3 (1.6–3.2)	2.0 (1.5–2.6)	1.4 (1.0–2.0)	2.1 (1.5–2.9)
1	2,492	6.9 (4.1–11.6)	3.2 (1.9–5.5)	3.0 (1.9–4.7)	1.3 (0.8–2.1)	1.7 (1.3–2.3)	1.7 (1.2–2.4)	2.0 (1.4–2.8)
2	1,785	15.1 (9.9–22.9)	6.2 (3.9–9.9)	4.7 (3.0–7.2)	3.5 (2.4–5.0)	2.9 (2.2–3.8)	3.1 (2.2–4.2)	3.0 (2.0–4.5)
3	1,330	13.8 (8.3–22.9)	6.9 (4.2–11.6)	7.3 (4.9–11.0)	4.0 (2.7–6.0)	5.1 (3.9–6.6)	2.7 (1.8–4.0)	3.0 (1.9–4.7)
4	1,081	35.4 (24.9–50.3)	19.3 (13.7–27.2)	11.1 (7.6–16.1)	6.9 (4.9–9.8)	5.3 (3.9–7.1)	4.4 (3.0–6.5)	4.5 (2.8–7.4)
5	713	54.1 (38.0–76.9)	33.5 (24.3–46.2)	24.0 (17.3–33.2)	13.7 (9.8–19.1)	8.5 (6.0–12.0)	10.0 (6.7–14.9)	7.3 (3.9–13.6)
6	455	109.2 (77.3–154.5)	108.0 (73.5–158.6)	0	0	0	0	0

Values presented are incidence rates (95% confidence intervals) if not indicated.

GI, gastrointestinal; NIHSS, National Institutes of Health Stroke Scale; IV tPA, intravenous tissue plasminogen activator; NSAID, nonsteroidal anti-inflammatory drug; eGFR, estimated glomerular filtration rate; ASA, aspirin; AP, antiplatelet; AC, anticoagulant; mRS, modified Rankin Scale.

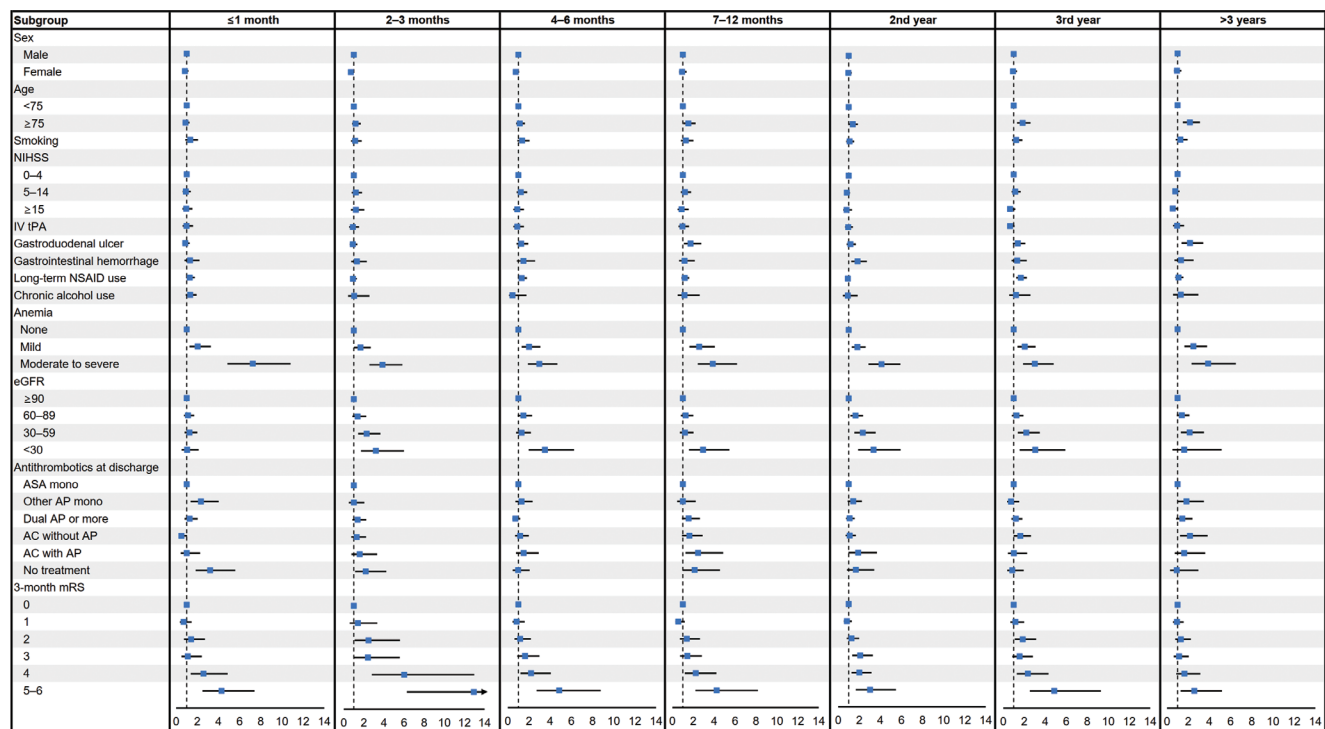


Figure 3. Adjusted IRR (95% CI) of selected variables for major GI bleeding following acute ischemic stroke. GI, gastrointestinal; NIHSS, National Institutes of Health Stroke Scale; IV tPA, intravenous tissue plasminogen activator; NSAID, nonsteroidal anti-inflammatory drug; eGFR, estimated glomerular filtration rate; ASA, aspirin; AP, antiplatelet; AC, anticoagulant; mRS, modified Rankin Scale; IRR, incidence rate ratio; CI, confidence interval.

the early period than in the later periods has not been previously reported, it aligns with our knowledge of the occurrence of stress ulcers, gastroesophageal erosions, and hemorrhagic gastritis in patients hospitalized for acute stroke.²⁷ One study reported that 44% of patients admitted to intensive care units with AIS had GI ulcers.²⁸ Therefore, unsurprisingly, the CIF of major GIB was 0.7% 7 days after AIS in our study. A previous study from the Registry of the Canadian Stroke Network reported an in-hospital incidence of major GIB of 0.5%.¹¹

Combination antiplatelet therapy may contribute to an early increase in the incidence of major GIB after AIS. Despite clinical trial data suggesting an increased risk of bleeding with dual antiplatelets,²⁹⁻³¹ there is insufficient evidence to indicate that the increased risk is independent and consistent over the long term, particularly for major GIB. In our study, the incidence of major GIB within the first month was approximately 1.4 times higher in individuals receiving combination antiplatelet therapy than in those receiving aspirin monotherapy. However, this difference in the point estimates of the incidence rate was not statistically significant, as there were overlapping 95% CIs. Furthermore, the difference in incidence rates diminished over time, although most of the differences might be explained by the diminished use of combination therapy, as almost two-thirds of the patients on combination therapy at discharge were on monotherapy 1 year later.

The long-term incidence of major GIB in patients with AIS has not been extensively reported. However, based on a report from the OXVASC in a mixed cohort of patients with AIS, TIA, and myocardial infarction,⁸ the cumulative incidence of major GIB was anticipated to be approximately 2% at 1 year. In our AIS population, the CIF of major GIB at 1 year was 5.03% (95% CI, 4.63%–5.45%). The higher incidence observed in our study may be partially attributed to the higher prevalence of peptic ulcer disease in Asian populations.³² The long-term use of multiple antithrombotic agents may be another contributing factor. However, the proportion of patients using more than one type of antithrombotic drug decreased from one-third at discharge to <4% at 1 year. The impact of direct oral anticoagulants on GIB rates is not likely to be a key factor in the reimbursement for this class of medications by the Korean government, which began in 2015, and enrollment in the current study occurred between 2011 and 2013.

The temporal pattern in the incidence rates of major GIB in our study was similar to that observed in a pooled analysis of six clinical trials involving patients with TIA or ischemic stroke. However, the absolute incidence rates were lower in the pooled analysis than in our study.³³ Notably, the observation of major GIB in these six trials commenced after the acute period of stroke.

During the first month following AIS, the IRR for moderate-to-severe anemia (hemoglobin level <11 g/dL) in major GIB was

the highest at 7.25. The ratio then decreased to 3.85 in the 2nd and 3rd months and remained in the range of 3–4 thereafter. Anemia is a well-known risk factor for GIB,³⁴ as well as mortality,³⁵ and has been regarded as a significant predictor of bleeding complications.^{36,37} However, anemia may be due to previous GIB or chronic kidney disease. The potential for reverse causation is demonstrated in Supplementary Table 8, which shows that increasing severity of anemia was associated with a higher proportion of individuals with a history of gastroduodenal ulcers, a history of GI hemorrhage, and lower eGFR. A history of long-term NSAID and chronic alcohol use was associated with an increase in major GIB within the first month post-stroke, without statistically significant differences throughout the study period. This could be due to the absence of an evaluation of the continuation of NSAID prescriptions and ongoing alcohol consumption after stroke onset.

Recurrent GIB not only increases mortality but also increases the risk of ischemic events by disrupting the administration of antithrombotics.^{38,39} In our study, 20% of patients who experienced a major GIB had a recurrence of GIB, with most recurrences occurring within a month after the first episode. Further research is needed to investigate the impact of major GIB on outcomes such as mortality and stroke recurrence. Specifically, it is crucial to elucidate whether recurrent GIB has more detrimental effects on multiple relevant outcomes than a single occurrence. Our analysis emphasizes the need for immediate prevention of GIB recurrence following the first episode of GIB.

Generally, the incidence of major GIB after an AIS decreased over time. However, this decline was slower in individuals aged 75 years than in those aged <75 years. This observation might help explain the increasing trend of adjusted IRR of being aged ≥75 as time progressed. Age is widely recognized as a risk factor for GIB,⁸ and the effects of aging may have a more pronounced effect in patients with AIS.

Our study had several limitations. First, the observed incidence of major GIB was notably high compared to that in previous studies.^{7,8,11,12} This discrepancy might be attributed to the high prevalence of peptic ulcer disease in the Asian population.³² Remarkably, the prevalence of gastroduodenal ulcers in our study was approximately 70%, which is considerably higher than the 18.0%–20.2% reported in the general Korean population.⁴⁰ This significant difference might stem from the common practice of prescribing antithrombotic drugs and proton pump inhibitors (PPIs) in patients with stroke during hospitalization. The Korean reimbursement policy, which requires the diagnosis of gastroduodenal ulcer for PPI prescription coverage, might have contributed to the higher prevalence observed in our study. Another possible cause of the relatively high GIB incidence rates could be a

selection bias related to the use of the registry database. Data were collected from 14 hospitals participating in the CRCS-K-NIH registry, which are primarily tertiary hospitals to which more severe cases are admitted. This may have resulted in the higher incidence of GIB in our study.

Furthermore, our analysis of antithrombotic drugs was limited to those prescribed at discharge. Given the complexity of drug types at discharge and medication changes after discharge, we acknowledge that a comprehensive analysis of antithrombotic drugs after discharge may be beyond the scope of this study and should be explored in future studies.

Our study did not include variables related to GI-protective drugs. The role of post-stroke GI protectors in the prevention of GIB has not yet been fully elucidated. A meta-analysis of randomized trials of PPIs in patients taking antiplatelets showed that PPI use reduced upper GIB by 74%.⁴¹ However, the OXVASC indicated that the use of GI protectors had a minimal effect on the crude incidence rates of GIB.⁸ Further research is needed to clarify the role of GI protectors after stroke.

Conclusions

Major GIB requiring transfusion appears to be common after AIS, although the risk gradually decreases over time. Implementing preventive measures to mitigate the occurrence of GIB, particularly in patients with anemia, impaired renal function, or disabling stroke, is crucial.

Supplementary materials

Supplementary materials related to this article can be found online at <https://doi.org/10.5853/jos.2024.00661>.

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Conflicts of interest

H-J Bae reports grants from AstraZeneca, Bayer Korea, Bristol Myers Squibb Korea, Chong Gun Dang Pharmaceutical Corp., Dong-A ST, Jeil Pharmaceutical Co., Ltd., Korean Drug Co., Ltd., Samjin Pharm, Takeda Pharmaceuticals Korea Co., Ltd., and Yuhon Corporation; roles as a principal investigator or co-investigator of clinical trials sponsored by Bayer, Bristol Myers Squibb, GNT Pharma, Korean Drug Co., Ltd., and Shinpoong Pharm. Co.,

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Author contribution

Conceptualization: JYK, HJB. Study design: JYK, HJB. Methodology: JYK, SEK, JSL, JL, HJB. Data collection: JYK, SEK, JSL. Investigation: JYK. Statistical analysis: SEK, JSL. Writing—original draft: JYK. Writing—review & editing: JYK, BJK, JK, DYK, MKH, HL, JMP, KK, SJL, JGK, JKC, DHK, THP, JL, HKP, YJC, KSH, KHC, JTK, DEK, JCC, MSO, KHY, BCL, KYP, SJ, JEC, JL, MSK, PBG, HJB. Funding acquisition: HJB. Approval of final manuscript: all authors.

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Supplementary Table 1. Medication claims code of NSAID

347701ACH, 347701ATB, 347702ACH, 347702ATB, 347703ATB, 636901ATB, 636401ATB, 233201ATB, 143402ATB, 143504ATB, 143506ATB, 143534BIJ, 143536BIJ, 143536BLP, 143538BLP, 186732ASY, 186733ASY, 186734ASY, 233201ATB, 233202ATB, 233202ATR, 233203ATB, 156602ACH, 156602ATB, 156603ATB, 156603ATR, 156604ATB, 156605ATB, 186801ATB, 186801ATC, 186802ATB, 186803ATB, 186804ATB, 186804ATD, 218602ATB, 180001ATB, 180033BIJ, 100901ACH, 100901ACS, 100901ATB, 100903ATR, 214001ACH, 214001ATB, 214004ACH, 214004ATB, 214201ACH, 214201ATB, 214202ACH, 214202ATB, 214203ACH, 214203ATB, 189701ACH, 189701ATB, 189701ATD, 189702ACH, 189702ATB, 189702ATD, 189703ACH, 189703ATB, 189704ACH, 189704ATB, 186101ATB, 186102ATR, 249901ATB, 493401ATB, 493402ATB, 172833ASY, 172834ASY, 172835ASY, 172836ASY, 172837ASY, 249901ATB, 249902ATB, 249903ATB, 199401ATR, 199402ACS, 199404ATB, 199501ATB, 179731BIJ, 238901ATB, 142331ASY, 142332ASY, 142333ASY, 142334ASY, 142335ASY, 233701ATB, 233702ATB, 518000ATB, 523500ATB, 527400ATB, 189001ACH, 189003ATB, 234401ATB, 416601ATB, 618201ATB, 198102ATB, 201801ATB, 458402ATB

NSAID, nonsteroidal anti-inflammatory drug.

Supplementary Table 2. ICD-10 codes of chronic diseases and conditions related to alcohol use

ICD-10 codes	Diseases
F10.0	Acute intoxication
F10.1	Harmful use
F10.2	Dependence syndrome
F10.3	Withdrawal state
F10.4	Withdrawal state with delirium
F10.5	Psychotic disorder
F10.6	Amnesic syndrome
F10.7	Residual and late-onset psychotic disorder
F10.8	Other mental and behavioral disorders
F10.9	Unspecified mental and behavioral disorder
G31.2	Degeneration of nervous system attributed to alcohol
G62.1	Alcoholic polyneuropathy
G72.1	Alcoholic myopathy
I42.6	Alcoholic cardiomyopathy
K29.2	Alcoholic gastritis
K70	Alcoholic liver disease
K70.0	Alcoholic fatty liver
K70.1	Alcoholic hepatitis
K70.2	Alcoholic fibrosis and sclerosis of liver
K70.3	Alcoholic cirrhosis of liver
K70.4	Alcoholic hepatic failure
K70.9	Alcoholic liver disease, unspecified
K85.2	Alcohol-induced acute pancreatitis
K86.0	Alcohol-induced chronic pancreatitis
P04.3	Fetus and newborn affected by maternal use of alcohol
Q86.0	Fetal alcohol syndrome (dysmorphic)

ICD-10, International Classification of Disease, 10th Revision.

Supplementary Table 3. Profiles of antithrombotics at discharge

Antithrombotics at discharge	Value (n=10,818)
No treatment	552 (5.1)
Aspirin mono	3,942 (36.4)
Other antiplatelet mono	797 (7.4)
Clopidogrel	549 (5.1)
Cilostazol	157 (1.5)
Triflusal	56 (0.5)
Ticlopidine	9 (0.1)
Other	26 (0.2)
Antiplatelet agents dual or above	3,341 (30.9)
Aspirin+clopidogrel	2,617 (24.2)
Aspirin+cilostazol	515 (4.8)
Clopidogrel+cilostazol	54 (0.5)
Other combination of dual	74 (0.7)
Other combination of triple or above	81 (0.7)
Anticoagulation without antiplatelet	1,662 (15.4)
Warfarin	1,491 (13.8)
Apixaban	0
Dabigatran	38 (0.4)
Rivaroxaban	12 (0.1)
Other	121 (1.1)
Anticoagulation with antiplatelet	524 (4.8)
Aspirin+warfarin	362 (3.3)
Aspirin+NOAC	12 (0.1)
Other combination	150 (1.4)

Values presented are number of patients (%).

NOAC, non-vitamin K antagonist oral anticoagulants.

Supplementary Table 4. Cumulative incidence function for major gastrointestinal bleeding after stroke (n=10,818)

Intervals after the onset of index stroke	Cumulative incidence function (95% CI), %
1 Week	0.70 (0.62–1.02)
1 Month	1.56 (1.35–1.81)
3 Months	2.83 (2.53–3.15)
1 Year	5.03 (4.63–5.45)
2 Years	6.93 (6.47–7.41)
3 Years	8.30 (7.78–8.83)

Cumulative incidence function was estimated for competing risk data. Death was a competing event for major gastrointestinal bleeding event. CI, confidence interval.

Supplementary Table 5. Incidence rates of major GI bleeding in patients with acute ischemic stroke according to the elapsed time since stroke onset and predefined subgroups of antithrombotics at discharge

Antithrombotics at discharge	Intervals after the onset of index stroke						
	≤1 month	2–3 months	4–6 months	7–12 months	2nd year	3rd year	>3 years
ASA mono	12.2 (8.9–16.7)	5.7 (4.1–8.0)	5.0 (3.8–7.0)	2.0 (1.5–2.8)	2.2 (1.7–2.7)	1.8 (1.4–2.4)	1.5 (1.0–2.1)
Other AP mono	42.5 (29.2–62.0)	8.9 (4.9–16.1)	10.1 (6.3–16.0)	3.1 (1.7–5.6)	4.5 (3.2–6.5)	1.9 (1.0–3.5)	4.1 (2.6–6.6)
Clopidogrel	31.8 (18.8–53.6)	5.8 (2.4–13.9)	7.9 (4.3–14.7)	2.0 (0.8–4.8)	4.6 (3.0–7.0)	2.4 (1.2–4.6)	3.3 (1.8–6.1)
Cilostazol	81.8 (44.0–152.1)	21.8 (9.1–52.4)	24.8 (12.4–49.5)	6.5 (2.4–17.3)	4.5 (1.9–10.8)	1.1 (0.2–7.7)	4.2 (1.4–13.2)
Others	41.4 (13.4–128.4)	7.2 (1.0–51.2)	0	5.1 (1.3–20.5)	4.3 (1.4–13.3)	0	8.4 (3.5–20.1)
Dual AP or more	17.3 (13.0–23.0)	9.1 (6.8–12.0)	4.3 (3.0–6.0)	3.7 (2.8–4.8)	2.8 (2.2–3.5)	2.5 (2.0–3.3)	2.5 (1.9–3.4)
Aspirin+clopidogrel	17.3 (12.6–23.8)	8.9 (6.5–12.2)	4.6 (3.2–6.7)	4.0 (3.0–5.3)	2.7 (2.1–3.5)	2.9 (2.2–3.8)	2.8 (2.1–3.9)
Aspirin+cilostazol	16.6 (7.9–34.7)	9.6 (4.8–19.3)	2.5 (0.8–7.6)	2.4 (1.1–5.4)	3.1 (1.8–5.2)	1.1 (0.4–3.0)	1.2 (0.4–3.8)
Others	19.3 (4.8–77.0)	9.9 (2.5–39.8)	3.5 (0.5–24.6)	1.7 (0.2–12.4)	2.8 (0.9–8.5)	1.1 (0.2–7.7)	1.1 (0.2–7.7)
AC without AP	9.6 (5.6–16.6)	11.2 (7.8–16.1)	9.1 (6.5–12.7)	4.9 (3.5–6.8)	3.5 (2.6–4.7)	4.4 (3.3–5.9)	4.9 (3.5–6.8)
Warfarin	7.9 (4.3–14.8)	10.3 (6.9–15.2)	8.8 (6.2–12.5)	4.8 (3.4–6.8)	3.4 (2.5–4.5)	4.4 (3.3–6.0)	4.9 (3.5–6.8)
NOAC	0	14.6 (2.1–103.4)	10.0 (1.4–71.1)	5.3 (0.8–37.8)	3.0 (0.4–21.2)	6.6 (0.9–46.6)	0
Others	44.6 (14.4–138.1)	34.5 (12.9–91.8)	19.1 (6.2–59.3)	7.5 (1.9–29.9)	6.7 (2.2–20.7)	0	9.6 (1.4–68.2)
AC with AP	18.9 (9.4–37.7)	13.6 (7.5–24.6)	10.6 (6.0–18.6)	6.9 (4.2–11.5)	5.7 (3.7–8.6)	2.6 (1.3–5.2)	3.8 (1.9–7.7)
No treatment	83.0 (59.3–116.2)	24.7 (15.6–39.3)	9.0 (4.7–17.4)	7.5 (4.5–12.7)	6.0 (3.8–9.3)	2.3 (1.0–5.2)	2.2 (0.8–6.0)

Values presented are incidence rates (95% confidence intervals).

GI, gastrointestinal; ASA, aspirin; AP, antiplatelets; AC, anticoagulants; NOAC, non-vitamin K antagonist oral anticoagulants.

Supplementary Table 6. Antithrombotics at one year after discharge by proportion of days covered

Antithrombotics	Value
Overall (n=9,540)	
No treatment	2,565 (26.9)
ASA mono	1,872 (19.6)
Other AP mono	3,762 (39.4)
AP dual or above	132 (1.4)
AC without AP	991 (10.4)
AC with AP	218 (2.3)
No treatment at discharge (n=350)	
No treatment	131 (37.4)
ASA mono	62 (17.7)
Other AP mono	112 (32.0)
AP dual or above	2 (0.6)
AC without AP	39 (11.1)
AC with AP	4 (1.1)
ASA mono at discharge (n=3,632)	
No treatment	921 (25.4)
ASA mono	1,485 (40.9)
Other AP mono	1,119 (30.8)
AP dual or above	18 (0.5)
AC without AP	60 (1.7)
AC with AP	29 (0.8)
Other AP mono at discharge (n=694)	
No treatment	194 (28.0)
ASA mono	35 (5.0)
Other AP mono	445 (64.1)
AP dual or above	2 (0.3)
AC without AP	13 (1.9)
AC with AP	5 (0.7)
AP dual or above at discharge (n=3,034)	
No treatment	758 (25.0)
ASA mono	207 (6.8)
Other AP mono	1,921 (63.3)
AP dual or above	102 (3.4)
AC without AP	39 (1.3)
AC with AP	7 (0.2)
AC without AP at discharge (n=1,405)	
No treatment	436 (31.0)
ASA mono	43 (3.1)
Other AP mono	97 (6.9)
AP dual or above	6 (0.4)
AC without AP	753 (53.6)
AC with AP	70 (5.0)

Supplementary Table 6. Continued

Antithrombotics	Value
AC with AP at discharge (n=425)	
No treatment	125 (29.4)
ASA mono	40 (9.4)
Other AP mono	68 (16.0)
AP dual or above	2 (0.5)
AC without AP	87 (20.5)
AC with AP	103 (24.2)

ASA, aspirin; AP, antiplatelets; AC, anticoagulants.

Supplementary Table 7. Adjusted IRRs (95% CIs) of selected factors for major GI bleeding following AIS

	Time intervals elapsed since the onset of index stroke					
	≤1 month	2–3 months	4–6 months	7–12 months	2nd year	3rd year
Female sex	0.83 (0.59–1.17)	0.71 (0.49–1.02)	0.75 (0.52–1.07)	0.93 (0.64–1.36)	0.97 (0.72–1.29)	0.93 (0.67–1.31)
Age, ≥75	0.89 (0.62–1.26)	1.18 (0.83–1.69)	1.13 (0.79–1.62)	1.53 (1.06–2.22)	1.39 (1.03–1.87)	1.85 (1.32–2.60)
Smoking	1.34 (0.87–2.07)	1.13 (0.72–1.78)	1.35 (0.90–2.05)	1.29 (0.82–2.01)	1.09 (0.77–1.52)	1.23 (0.84–1.82)
Initial NIHSS						
5–14	0.92 (0.61–1.38)	1.20 (0.79–1.82)	1.23 (0.84–1.83)	1.20 (0.80–1.79)	0.82 (0.59–1.13)	1.15 (0.80–1.66)
≥15	0.96 (0.60–1.54)	1.21 (0.71–2.05)	0.90 (0.53–1.52)	0.88 (0.50–1.56)	0.80 (0.48–1.32)	0.65 (0.37–1.15)
IV tPA	0.99 (0.61–1.60)	0.91 (0.54–1.52)	0.90 (0.53–1.52)	0.97 (0.59–1.59)	0.96 (0.65–1.40)	0.65 (0.39–1.08)
History of gastroduodenal ulcer	0.87 (0.59–1.28)	0.90 (0.60–1.35)	1.27 (0.83–1.93)	1.74 (1.10–2.76)	1.17 (0.81–1.68)	1.39 (0.92–2.10)
History of gastrointestinal hemorrhage	1.32 (0.79–2.21)	1.31 (0.74–2.29)	1.48 (0.85–2.58)	1.17 (0.64–2.14)	1.84 (1.24–2.72)	1.33 (0.79–2.24)
Long-term NSAID use	1.29 (0.95–1.76)	0.92 (0.66–1.29)	1.31 (0.95–1.81)	1.18 (0.87–1.61)	0.92 (0.71–1.18)	1.67 (1.24–2.25)
Chronic alcohol use	1.50 (0.74–3.07)	1.04 (0.43–2.55)	0.44 (0.11–1.76)	1.16 (0.51–2.61)	0.92 (0.45–1.85)	1.22 (0.57–2.59)
Anemia						
Mild	2.04 (1.26–3.28)	1.67 (1.04–2.68)	2.01 (1.31–3.07)	2.57 (1.63–4.06)	1.83 (1.29–2.60)	2.05 (1.36–3.08)
Moderate to severe	7.25 (4.85–10.82)	3.85 (2.55–5.83)	2.98 (1.90–4.68)	3.87 (2.43–6.18)	4.12 (2.88–5.90)	3.01 (1.89–4.80)
eGFR (mL/min/1.73 m ²)						
60–89	1.12 (0.74–1.71)	1.38 (0.86–2.23)	1.47 (0.94–2.29)	1.27 (0.81–2.00)	1.65 (1.16–2.36)	1.26 (0.82–1.92)
30–59	1.27 (0.80–2.00)	2.28 (1.43–3.64)	1.30 (0.78–2.18)	1.20 (0.72–2.02)	2.34 (1.54–3.56)	2.20 (1.39–3.48)
<30	1.04 (0.52–2.12)	3.20 (1.71–5.98)	3.51 (1.97–6.25)	2.94 (1.59–5.45)	3.36 (1.90–5.92)	3.05 (1.57–5.91)
Antithrombotics at discharge						
Other AP mono	2.35 (1.37–4.02)	1.01 (0.50–2.05)	1.30 (0.72–2.34)	1.00 (0.45–2.23)	1.43 (0.90–2.25)	0.74 (0.37–1.52)
Dual AP or more	1.28 (0.80–2.04)	1.38 (0.86–2.23)	0.72 (0.44–1.17)	1.55 (0.92–2.63)	1.09 (0.75–1.57)	1.20 (0.78–1.82)
AC without AP	0.50 (0.25–1.03)	1.29 (0.75–2.22)	1.17 (0.69–1.98)	1.63 (0.92–2.89)	1.10 (0.71–1.68)	1.63 (1.00–2.64)
AC with AP	1.00 (0.44–2.27)	1.59 (0.76–3.32)	1.50 (0.77–2.92)	2.46 (1.25–4.86)	1.90 (0.98–3.68)	1.01 (0.45–2.27)
No treatment	3.22 (1.85–5.59)	2.19 (1.13–4.23)	0.98 (0.46–2.06)	2.13 (0.99–4.55)	1.68 (0.83–3.42)	0.86 (0.38–1.94)
3-month mRS						
1	0.71 (0.35–1.46)	1.41 (0.59–3.33)	0.84 (0.45–1.59)	0.57 (0.28–1.18)	0.83 (0.53–1.30)	1.16 (0.68–1.99)
2	1.42 (0.74–2.72)	2.46 (1.08–5.59)	1.17 (0.63–2.18)	1.38 (0.72–2.64)	1.27 (0.81–1.99)	1.86 (1.10–3.13)
3	1.11 (0.51–2.43)	2.40 (1.03–5.57)	1.63 (0.89–2.99)	1.43 (0.73–2.82)	2.09 (1.33–3.29)	1.56 (0.86–2.82)
4	2.59 (1.38–4.87)	6.01 (2.79–12.98)	2.20 (1.20–4.06)	2.24 (1.19–4.21)	2.01 (1.27–3.16)	2.35 (1.29–4.31)
5–6	4.30 (2.49–7.41)	12.94 (6.28–26.63)	4.88 (2.72–8.77)	4.24 (2.20–8.18)	3.03 (1.67–5.48)	4.86 (2.54–9.30)

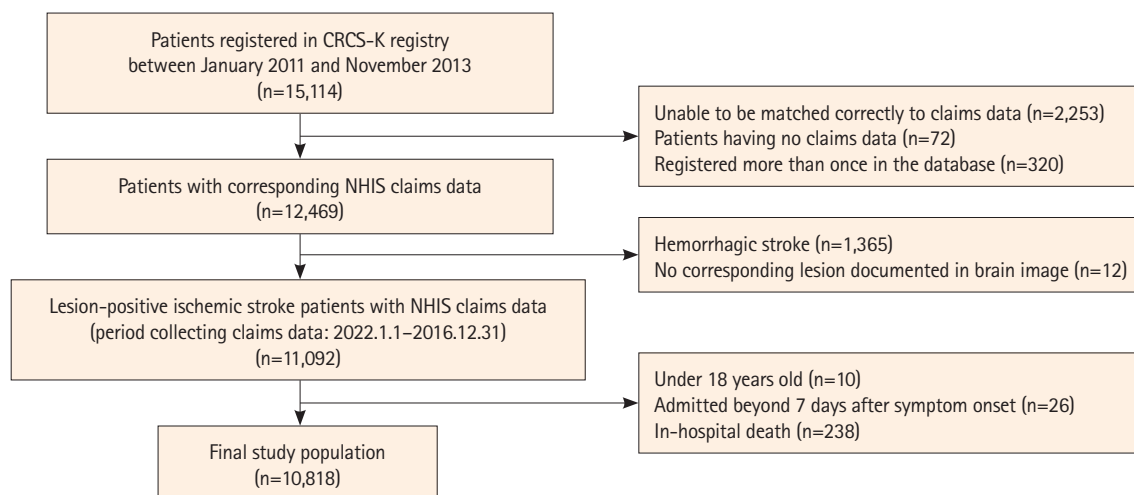
Adjusted IRR (95% CI) of major GI bleeding were calculated using the Fine-Gray competing risk model for sub-distribution hazard with death as a competing risk. Reference group: sex (male), age (<75 years), smoking (no), initial NIHSS (0–4), IV tPA (no), histories of gastroduodenal ulcer (no), gastrointestinal hemorrhage (no), long-term NSAID use (no), chronic alcohol use (no), anemia (none), eGFR (≥90 mL/min/1.73 m²), antithrombotics at discharge (ASA mono), and 3-month mRS (0).

IRR, incidence rate ratio; CI, confidence interval; GI, gastrointestinal; AIS, acute ischemic stroke; NIHSS, National Institutes of Health Stroke Scale; IV tPA, intravenous tissue plasminogen activator; NSAID, nonsteroidal anti-inflammatory drug; eGFR, estimated glomerular filtration rate; ASA, aspirin; AP, antiplatelets; AC, anticoagulants; mRS, modified Rankin Scale.

Supplementary Table 8. Medical history and kidney function according to the status of anemia

Anemia on admission	Value (n=10,818)
None (n=8,369)	
Gastroduodenal ulcer	5,687 (68.0)
Hemorrhage of GI tract	448 (5.4)
eGFR (mL/min/1.73 m ²)	
≥90	3,452 (41.2)
60–89	3,659 (43.7)
30–59	1,172 (14.0)
<30	86 (1.0)
Mild (n=1,539)	
Gastroduodenal ulcer	1,157 (75.2)
Hemorrhage of GI tract	107 (7.0)
eGFR (mL/min/1.73 m ²)	
≥90	443 (28.8)
60–89	582 (37.8)
30–59	427 (27.7)
<30	87 (5.7)
Moderate to severe (n=910)	
Gastroduodenal ulcer	718 (78.9)
Hemorrhage of GI tract	117 (12.9)
eGFR (mL/min/1.73 m ²)	
≥90	249 (27.4)
60–89	249 (27.4)
30–59	268 (29.5)
<30	144 (15.8)

GI, gastrointestinal; eGFR, estimated glomerular filtration rate.

**Supplementary Figure 1.** Study population. CRCS-K, Clinical Research Collaboration for Stroke in Korea; NHIS, National Health Insurance Service.