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Antithrombotic Resumption After Gastrointestinal Bleeding: 30-Day Outcomes

Yavuz Özden[1*], Serdar Durak[2]

[1]*Department of Gastroenterology, Kayseri City Hospital, University of Health Sciences, Kayseri, Turkey*
[2]*Department of Gastroenterology, Faculty of Medicine, Istanbul Beykent University, Istanbul, Turkey*

ABSTRACT

The optimal timing of antithrombotic resumption after acute gastrointestinal bleeding remains uncertain, as delayed resumption may increase ischemic risk whereas early resumption may precipitate recurrent bleeding. This study evaluated 30-day ischemic and bleeding risks according to antithrombotic resumption timing after gastrointestinal bleeding.

This retrospective single-center cohort study included 1,448 adults hospitalized with acute gastrointestinal bleeding while receiving antithrombotic therapy between January 2021 and December 2025. Patients were categorized as early (≤7 days), intermediate (8–15 days), late (>15 days), or not resumed within 30 days. The primary outcome was 30-day ischemic cardiovascular events; secondary outcomes included recurrent gastrointestinal bleeding, all-cause mortality, and hospital readmission. Cox regression, landmark analysis at day 7, and continuous-time analysis were performed.

Early resumption occurred in 486 patients (33.6%), intermediate resumption in 412 (28.5%), late resumption in 298 (20.6%), and no resumption within 30 days in 252 (17.4%). Compared with intermediate resumption, early resumption was associated with lower ischemic risk (adjusted HR 0.61; 95% CI 0.42–0.89) but higher recurrent bleeding risk (adjusted HR 2.18; 95% CI 1.47–3.24). Non-resumption was associated with higher ischemic risk (adjusted HR 2.84; 95% CI 1.92–4.21) and all-cause mortality (adjusted HR 2.67; 95% CI 1.71–4.16).

Antithrombotic resumption timing was associated with competing 30-day ischemic and bleeding risks. An intermediate window of 8–15 days showed the most favorable short-term balance, supporting individualized, risk-adapted decision-making.

Keywords: Gastrointestinal bleeding, anticoagulants, antiplatelet therapy, thromboembolism, risk assessment

Introduction

Acute gastrointestinal bleeding in patients receiving antithrombotic therapy is a frequent clinical problem and often creates a difficult treatment decision. Antiplatelet agents and oral anticoagulants are used to prevent stroke, myocardial infarction, stent thrombosis, and systemic embolism in patients with cardiovascular disease. However, these benefits are accompanied by an increased risk of both upper and lower gastrointestinal bleeding (1-5). After a bleeding episode, clinicians must decide when to restart treatment, balancing the risk of recurrent hemorrhage against the risk of ischemic complications related to prolonged interruption (6-8).

This issue has become increasingly relevant as the use of long-term antithrombotic therapy has expanded. Patients receiving these drugs are often older and have multiple comorbidities, which may further complicate the balance between bleeding and thrombotic risk. In addition, gastrointestinal bleeding risk differs across antithrombotic regimens, and recent studies have shown clinically important differences among oral anticoagulants, particularly in patients at high risk for gastrointestinal bleeding (4,5).

Current guidelines provide general recommendations for the management of antithrombotic therapy after gastrointestinal bleeding, but the optimal timing of resumption remains uncertain. The 2021 BSG/ESGE guideline update recommends individualized decision-making based on thrombotic and hemorrhagic risk rather than a fixed time interval (6). Similarly, ESGE guidelines on upper and lower gastrointestinal bleeding emphasize the role of endoscopic findings, comorbidity burden, and the underlying cardiovascular indication when interruption and resumption of treatment are considered (7,8). Nevertheless, available evidence remains largely observational, and data specifically addressing the timing of antithrombotic resumption after gastrointestinal bleeding remain limited (3,6-8).

Several clinically relevant questions therefore remain unresolved. Most studies have focused primarily on recurrent bleeding, while ischemic cardiovascular

*Corresponding Author: Yavuz Özden, Department of Gastroenterology, Kayseri City Hospital, University of Health Sciences, Kayseri, Turkey
E-mail: yavuzozden@gmail.com
ORCID ID: Yavuz Özden: 0000-0002-5760-3529, **Serdar Durak:** 0000-0002-8175-9611
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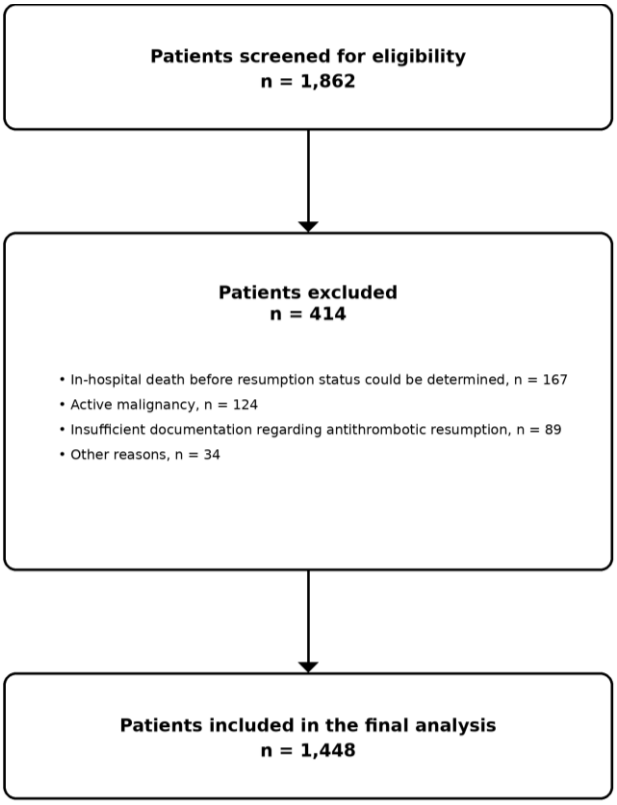

Fig. 1. Flow diagram of patient screening, exclusion, and inclusion in the final study cohort. A total of 1,862 patients hospitalized with acute gastrointestinal bleeding while receiving antithrombotic therapy were screened. After application of the exclusion criteria, 1,448 patients were included in the final analysis. The most common reasons for exclusion were in-hospital mortality before resumption status could be determined (n=167), active malignancy (n=124), insufficient documentation regarding antithrombotic resumption (n=89), and other reasons (n=34)

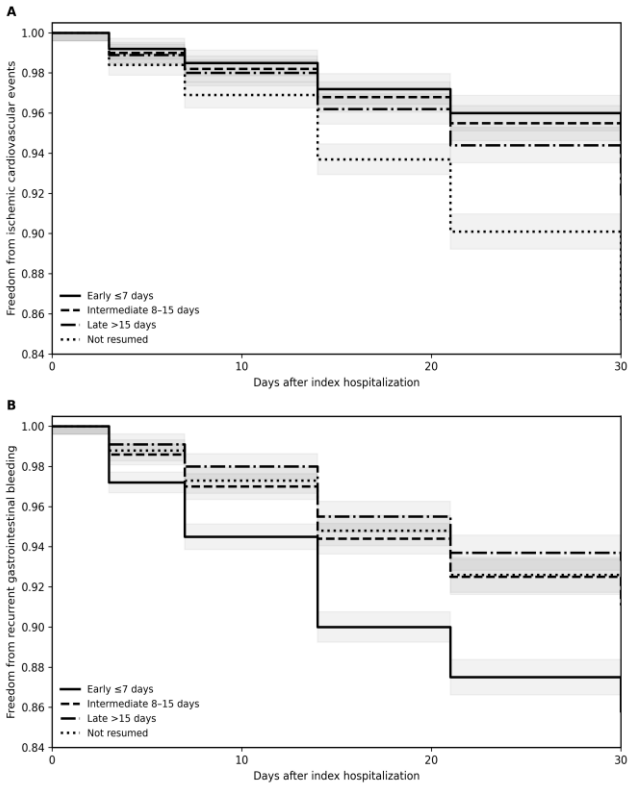

Fig. 2. Kaplan-Meier curves for freedom from (A) ischemic cardiovascular events and (B) recurrent gastrointestinal bleeding over 30 days according to timing of antithrombotic resumption. Shaded areas represent 95% confidence intervals

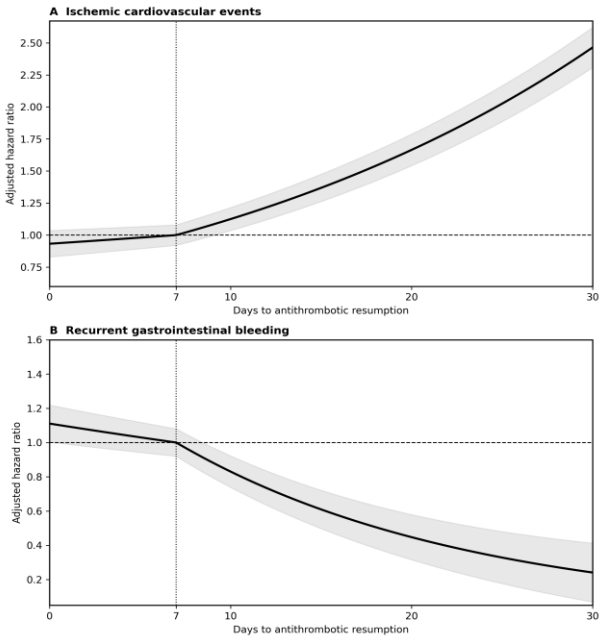

Fig. 3. Adjusted hazard ratios for ischemic cardiovascular events and recurrent gastrointestinal bleeding according to resumption timing modeled as a continuous variable using restricted cubic splines. The reference point was set at day 7. Solid lines indicate adjusted hazard ratios, and shaded areas represent 95% confidence intervals

outcomes are often evaluated as secondary endpoints. In addition, upper and lower gastrointestinal bleeding are frequently assessed together, despite differences in etiology, management, and recurrence patterns. The first 30 days after the index bleeding episode are particularly important because both recurrent bleeding and thromboembolic events tend to occur during this early period. This time window also corresponds to the period in which resumption decisions are most commonly made in daily practice (9,10).

To address these gaps, we evaluated the association between antithrombotic resumption timing after acute gastrointestinal bleeding and 30-day clinical outcomes. Specifically, we aimed to determine whether different resumption intervals were associated with ischemic cardiovascular events and recurrent gastrointestinal bleeding within 30 days. We hypothesized that ischemic and bleeding risks would vary in opposite

directions across resumption intervals, supporting the need for individualized decision-making.

Materials and Methods

Study Design and Setting: This retrospective cohort study was conducted at a tertiary referral center between January 2021 and December 2025. The aim was to evaluate whether the timing of antithrombotic resumption after acute gastrointestinal bleeding was associated with 30-day clinical outcomes. The study complied with the Declaration of Helsinki and was approved by the local institutional ethics committee prior to data analysis (approval no: 836; date: 02.04.2026). Because of the retrospective design, informed consent was waived. Reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (11).

Study Population: We screened consecutive adults aged 18 years or older who were hospitalized with acute gastrointestinal bleeding while receiving antithrombotic therapy for at least 30 days before admission. Antithrombotic therapy included antiplatelet agents, oral anticoagulants, or both. Acute gastrointestinal bleeding was defined as hematemesis, melena, hematochezia, or clinically significant blood loss leading to hospital admission and supported by endoscopic, radiologic, or clinical evaluation.

Patients with clinically suspected bleeding but without a definitively identified source on endoscopy or imaging were also eligible if the treating team considered the presentation highly consistent with acute gastrointestinal bleeding based on clinical features, laboratory findings, and follow-up data. These patients represented a small proportion of the cohort and were retained to reflect real-world clinical practice.

We excluded patients who underwent elective surgery for the bleeding source during the index hospitalization, had trauma-related bleeding, were pregnant, had active malignancy, or had unavailable follow-up data or insufficient documentation regarding antithrombotic resumption. Patients who died before resumption status could be determined or documented (n=167) were also excluded because the primary exposure could not be classified in these cases.

Exposure Definition: The primary exposure variable was the timing of antithrombotic resumption after the index bleeding event. Resumption timing was defined as the number of days between hospital admission for the index bleed and reinitiation of antithrombotic therapy, determined from clinical records, discharge prescriptions, and medication records.

Patients were categorized as early (≤7 days), intermediate (8–15 days), late (>15 days), or not resumed within 30 days. These cutoffs were informed by prior literature suggesting a clinically relevant trade-off between recurrent bleeding and thromboembolic risk after anticoagulation resumption following gastrointestinal bleeding (12). To address potential immortal time bias, we performed a landmark analysis at day 7.

Antithrombotic regimens were classified as single antiplatelet therapy, dual antiplatelet therapy, vitamin K antagonist therapy, direct oral anticoagulant therapy, or combination therapy. We also recorded regimen modification after the index bleed, including de-escalation from dual to single antiplatelet therapy. Proton pump inhibitor prescription at discharge, whether newly initiated or continued, was documented.

Outcome Measures: The primary outcome was a composite of 30-day ischemic cardiovascular events: nonfatal myocardial infarction, nonfatal ischemic stroke, cardiovascular death, urgent revascularization for stent thrombosis, or objectively documented systemic thromboembolism occurring within 30 days after the index bleed. Myocardial infarction was defined according to the Fourth Universal Definition of Myocardial Infarction (13), and stroke as a new focal neurological deficit lasting more than 24 hours with confirmatory imaging. Individual components of the composite outcome were also examined in secondary analyses.

The secondary outcome was recurrent gastrointestinal bleeding within 30 days. Recurrent bleeding was defined as new overt gastrointestinal bleeding after initial stabilization, accompanied by repeat hospital presentation, a hemoglobin decreases of at least 2 g/dL, blood transfusion, repeat endoscopy, repeat hemostatic intervention, or clinician-documented recurrent bleeding. In a sensitivity analysis, we applied a more restrictive definition requiring overt bleeding with objective confirmation by endoscopy, imaging, repeat intervention, or transfusion.

Additional secondary outcomes were 30-day all-cause mortality and all-cause hospital readmission.

Covariates: We collected data on age, sex, hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation, heart failure, chronic kidney disease, previous stroke, and concomitant use of nonsteroidal anti-inflammatory drugs, corticosteroids, and selective serotonin reuptake

inhibitors. Admission variables included systolic blood pressure, heart rate, hemoglobin, platelet count, and international normalized ratio. Endoscopic variables included bleeding location, endoscopic diagnosis, high-risk stigmata of recent hemorrhage (Forrest class Ia–IIb in upper gastrointestinal bleeding, where applicable), endoscopic hemostatic treatment modality, and successful endoscopic hemostasis.

Statistical Analysis: Continuous variables were expressed as mean ± standard deviation or median [interquartile range], depending on distribution. Categorical variables were presented as numbers and percentages. Group comparisons were performed using one-way analysis of variance or the Kruskal-Wallis test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate.

We used Cox proportional hazards regression to assess the association between resumption timing and 30-day outcomes. Time-to-event analyses were calculated from the date of index hospital admission. Hazard ratios with 95% confidence intervals were reported. Multiple adjustment was based on a prespecified covariate set including age, sex, cardiovascular comorbidities, bleeding severity, and proton pump inhibitor use; variables associated with the outcome at $p<0.10$ in univariable analyses were additionally considered. The intermediate resumption group (8–15 days) served as the reference category.

To address potential immortal time bias, we performed a landmark analysis at day 7, excluding patients who experienced the primary outcome or were censored before that time point. We also performed subgroup analyses according to antithrombotic class and bleeding location (upper vs. lower gastrointestinal bleeding); interaction was assessed using likelihood ratio testing.

The proportional hazards assumption was tested using Schoenfeld residuals and was satisfied for the primary analyses. Missing data were handled by complete-case analysis because the proportion of missing values was low (<5%) for all modeled variables. A two-sided p value <0.05 was considered statistically significant. Analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study Population and Baseline Characteristics: Of 1,862 patients screened for eligibility, 1,448 were included in the final analysis. The main reasons for exclusion were in-hospital death before resumption status could be determined (n=167), active malignancy (n=124), and insufficient documentation regarding antithrombotic resumption (n=89); 34 patients were excluded for other reasons (Figure 1).

The median age was 74 years [IQR 66–81], and 844 patients (58.3%) were male. Baseline demographic and clinical characteristics according to resumption timing are shown in Table 1. Patients in the early resumption group (≤7 days) had higher rates of coronary artery disease and lower CHA_2DS_2-VASc scores, whereas patients who did not resume therapy had higher rates of chronic kidney disease, prior stroke, and lower admission hemoglobin. Upper gastrointestinal bleeding accounted for 991 index events (68.4%), with peptic ulcer disease as the most common etiology (44.2%). Endoscopic hemostasis was performed in 1,044 patients (72.1%) and was successful in 93.8%.

Antithrombotic Regimens and Resumption Patterns: At index bleeding, 903 patients (62.4%) were receiving antiplatelet therapy, 504 (34.8%) anticoagulant therapy alone, and 41 (2.8%) combination therapy (Table 2).

Overall, 1,196 patients (82.6%) resumed antithrombotic therapy within 30 days, with a median time to resumption of 9 days [IQR 5–18]. Early resumption occurred in 486 patients (33.6%), intermediate resumption in 412 (28.5%), and late resumption in 298 (20.6%); 252 patients (17.4%) did not resume therapy within 30 days.

Patients receiving single antiplatelet therapy, particularly aspirin, were more likely to resume treatment early, whereas patients receiving dual antiplatelet therapy or warfarin more often resumed in the intermediate or late windows. Among anticoagulated patients, direct oral anticoagulant users resumed earlier than warfarin users (8 days [IQR 4–14] vs. 14 days [IQR 8–22]; $p<0.001$). Regimen modification occurred in 264 patients (18.2%), including de-escalation from dual to single antiplatelet therapy (n=142) and switching from warfarin to a direct oral anticoagulant (n=68). In exploratory analyses, ischemic event rates were similar in patients with and without regimen modification (7.4% vs. 7.8%; p=0.82), whereas recurrent bleeding was numerically lower in the modification group (8.7% vs. 10.6%; p=0.21).

Thirty-Day Outcomes: Within 30 days, 112 patients (7.7%) experienced an ischemic cardiovascular event, 148 (10.2%) had recurrent gastrointestinal bleeding, 75 (5.2%) died, and 266 (18.4%) were readmitted. Outcome distributions

Table 1: Baseline Characteristics According to Timing of Antithrombotic Resumption

Characteristic	Overall (n=1448)	Early ≤7 days (n=486)	Intermediate 8–15 days (n=412)	Late >15 days (n=298)	Not resumed within 30 days (n=252)	p-value
Age, years, median [IQR]	74 [66–81]	72 [64–79]	74 [67–82]	76 [15]	75 [15]	0.120
Male sex, n (%)	844 (58.3)	291 (59.9)	240 (58.3)	171 (57.4)	142 (56.3)	0.780
Hypertension, n (%)	1122 (77.5)	377 (77.6)	319 (77.4)	231 (77.5)	195 (77.4)	0.990
Diabetes mellitus, n (%)	612 (42.3)	208 (42.8)	174 (42.2)	124 (41.6)	106 (42.1)	0.960
Coronary artery disease, n (%)	698 (48.2)	272 (56.0)	198 (48.1)	129 (43.3)	99 (39.3)	0.001
Atrial fibrillation, n (%)	814 (56.2)	243 (50.0)	236 (57.3)	177 (59.4)	158 (62.7)	0.002
Chronic kidney disease, n (%)	352 (24.3)	102 (21.0)	97 (23.5)	80 (26.8)	73 (29.0)	0.040
Prior stroke/TIA, n (%)	276 (19.1)	78 (16.0)	79 (19.2)	62 (20.8)	57 (22.6)	0.090
CHA_2DS_2-VASc score, median [IQR]	4 [2]	3 [3]	4 [2]	4 [3]	4 [3]	0.020
HAS-BLED score, median [IQR]	3 [2]	3 [2]	3 [2]	3 [2]	3 [1]	0.450
Admission hemoglobin, g/dL, mean ± SD	9.8 ± 2.4	10.1 ± 2.3	9.8 ± 2.4	9.6 ± 2.5	9.4 ± 2.6	0.001
Upper gastrointestinal bleeding, n (%)	991 (68.4)	348 (71.6)	283 (68.7)	197 (66.1)	163 (64.7)	0.120
Endoscopic hemostasis performed, n (%)	1044 (72.1)	361 (74.3)	298 (72.3)	211 (70.8)	174 (69.0)	0.380
Proton pump inhibitor prescribed at discharge, n (%)	1128 (77.9)	398 (81.9)	324 (78.6)	226 (75.8)	180 (71.4)	0.007

Abbreviations: IQR, interquartile range; SD, standard deviation; TIA, transient ischemic attack

according to resumption timing are shown in Table 3.

Ischemic event incidence was lowest in the early resumption group (5.3%) and highest in the non-resumption group (14.3%) ($p<0.001$). In contrast, recurrent gastrointestinal bleeding was most frequent in the early resumption group (14.2%) and least frequent in the late resumption group (6.7%) ($p<0.001$). The corresponding ischemic and recurrent bleeding rates in the intermediate group were 6.6% and 8.7%, respectively. Cardiovascular death occurred in 24 patients (1.7%) and was more common in the non-resumption group (3.6% vs. 1.0%–1.7%; $p=0.04$). All-cause mortality was highest with non-resumption (10.3%, $p<0.001$), whereas readmission rates did not differ across groups ($p=0.64$).

Association Between Resumption Timing and Clinical Outcomes: In Cox regression, using the intermediate group (8–15 days) as the reference, early resumption was associated with lower ischemic risk (adjusted HR 0.61; 95% CI 0.42–0.89; $p=0.009$) but higher recurrent bleeding risk (adjusted HR 2.18; 95% CI 1.47–3.24; $p<0.001$). Late resumption was associated with a nonsignificant increase in ischemic risk (adjusted HR 1.42; 95% CI 0.94–2.13; $p=0.09$) and a nonsignificant decrease in bleeding risk (adjusted HR 0.68; 95% CI 0.43–1.08; $p=0.10$). Non-resumption was associated with increased risks of ischemic events (adjusted HR 2.84; 95% CI 1.92–4.21; $p<0.001$) and all-cause mortality (adjusted HR 2.67; 95% CI 1.71–4.16; $p<0.001$). Kaplan-Meier curves are shown in Figure 2.

Subgroup Analyses: Exploratory subgroup analyses by antithrombotic class showed that

Table 2: Antithrombotic Regimens According to Timing of Antithrombotic Resumption

Antithrombotic regimen	Overall (n=1448)	Early ≤7 days (n=486)	Intermediate 8–15 days (n=412)	Late >15 days (n=298)	Not resumed within 30 days (n=252)
Single antiplatelet therapy, n (%)	622 (43.0)	246 (50.6)	181 (43.9)	112 (37.6)	83 (32.9)
∟ Aspirin	498 (34.4)	204 (42.0)	144 (35.0)	86 (28.9)	64 (25.4)
∟ $P2Y_{12}$ inhibitor	124 (8.6)	42 (8.6)	37 (9.0)	26 (8.7)	19 (7.5)
Dual antiplatelet therapy, n (%)	281 (19.4)	78 (16.0)	82 (19.9)	67 (22.5)	54 (21.4)
Vitamin K antagonist, n (%)	268 (18.5)	67 (13.8)	76 (18.4)	64 (21.5)	61 (24.2)
Direct oral anticoagulant, n (%)	236 (16.3)	82 (16.9)	65 (15.8)	51 (17.1)	38 (15.1)
Combination therapy, n (%)	41 (2.8)	13 (2.7)	8 (1.9)	4 (1.3)	16 (6.3)

Abbreviation: $P2Y_{12}$ inhibitor, clopidogrel, ticagrelor, or prasugrel

Table 3: Thirty-Day Clinical Outcomes According to Timing of Antithrombotic Resumption

Outcome	Overall (n=1448)	Early ≤7 days (n=486)	Intermediate 8–15 days (n=412)	Late >15 days (n=298)	Not resumed within 30 days (n=252)	p-value
Primary outcome						
30-day ischemic cardiovascular events, n (%)	112 (7.7)	26 (5.3)	27 (6.6)	24 (8.1)	35 (13.9)	<0.001
∟ Nonfatal myocardial infarction	48 (3.3)	12 (2.5)	12 (2.9)	10 (3.4)	14 (5.6)	0.12
∟ Nonfatal ischemic stroke	31 (2.1)	7 (1.4)	8 (1.9)	7 (2.3)	9 (3.6)	0.24
∟ Cardiovascular death	24 (1.7)	5 (1.0)	5 (1.2)	5 (1.7)	9 (3.6)	0.04
∟ Stent thrombosis	9 (0.6)	2 (0.4)	2 (0.5)	2 (0.7)	3 (1.2)	0.67
∟ Systemic thromboembolic event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	—
Secondary outcomes						
Recurrent gastrointestinal bleeding within 30 days, n (%)	148 (10.2)	69 (14.2)	36 (8.7)	20 (6.7)	23 (9.1)	<0.001
All-cause mortality within 30 days, n (%)	75 (5.2)	16 (3.3)	18 (4.4)	15 (5.0)	26 (10.3)	<0.001
All-cause hospital readmission within 30 days, n (%)	266 (18.4)	88 (18.1)	73 (17.7)	52 (17.4)	53 (21.0)	0.64

Abbreviation: GI, gastrointestinal

Table 4: Exploratory Interaction Analyses According to Bleeding Location

Outcome	p for interaction
Ischemic cardiovascular events	0.34
Recurrent gastrointestinal bleeding	0.21

Note: No statistically significant interaction was observed between bleeding location, upper versus lower gastrointestinal bleeding, and resumption timing for either ischemic cardiovascular events or recurrent gastrointestinal bleeding. Associations were directionally similar across subgroups

Table 5: Sensitivity Analyses

Analysis	Adjusted HR	95% CI	p-value
Endoscopically confirmed hemostasis, ischemic events: early vs intermediate resumption	0.58	0.38–0.88	—
Endoscopically confirmed hemostasis, recurrent bleeding: early vs intermediate resumption	2.24	1.43–3.51	—
Restrictive recurrent bleeding definition: early vs intermediate resumption	2.05	1.36–3.10	0.001
Landmark analysis at day 7, ischemic events: early vs intermediate resumption	0.58	0.40–0.85	0.002
Landmark analysis at day 7, recurrent bleeding: early vs intermediate resumption	2.21	1.45–3.37	0.001

Population for endoscopically confirmed hemostasis analysis: patients with endoscopically confirmed hemostasis, n=979.
Population for landmark analysis: patients' event-free at day 7, n=1,281.
Exact p-values for the endoscopically confirmed hemostasis sensitivity analyses were not reported in the current text and are therefore shown as "—".

among patients receiving antiplatelet therapy alone (n=903), early resumption was associated with lower ischemic risk (HR 0.48; 95% CI 0.29–0.79; p=0.003) but higher recurrent bleeding (HR 2.31; 95% CI 1.42–3.76; p<0.001). Among anticoagulant-only patients (n=504), early resumption was associated with a nonsignificant reduction in ischemic events (HR 0.74; 95% CI 0.44–1.24; p=0.25) but increased recurrent bleeding (HR 2.04; 95% CI 1.18–3.52; p=0.01). In the direct oral anticoagulant subgroup (n=236), the bleeding increase with early resumption was attenuated compared with warfarin users (HR 1.68; 95% CI 0.92–3.07 vs. 2.46; 95% CI 1.33–4.55), with no significant interaction (p=0.18).

Analyses by bleeding location showed no significant interaction for ischemic events (p=0.34) or recurrent bleeding (p=0.21) (Table 4). Proton pump inhibitor prescription at discharge was associated with lower recurrent upper gastrointestinal bleeding (HR 0.62; 95% CI 0.48–0.80; p<0.001), most strongly in those resuming antiplatelet therapy early (HR 0.54; 95% CI 0.37–0.79).

Sensitivity Analyses: Sensitivity analyses restricted to patients with endoscopically confirmed hemostasis (n=979) showed similar associations: early resumption remained associated with lower ischemic risk (HR 0.58; 95% CI 0.38–0.88) and higher recurrent bleeding (HR 2.24; 95% CI 1.43–3.51). Excluding patients receiving combination therapy did not alter the findings.

Using a restrictive recurrent bleeding definition requiring objective confirmation, early resumption remained associated with recurrent bleeding (HR 2.05; 95% CI 1.36–3.10; p<0.001). In landmark analyses restricted to 1,281 patients who were event-free at day 7, early resumption remained associated with lower ischemic risk (HR 0.58; 95% CI 0.40–0.85) and higher recurrent bleeding (HR 2.21; 95% CI 1.45–3.37) (Table 5). As a continuous variable, each 1-day delay beyond day 7 increased ischemic hazard by 4% (HR 1.04; 95% CI 1.01–1.07; p=0.008) and reduced bleeding hazard by 6% (HR 0.94; 95% CI 0.91–0.97; p<0.001). Figure 3 shows the adjusted associations between resumption timing and outcomes modeled with restricted cubic splines.

Discussion

In this retrospective single-center cohort of 1,448 patients hospitalized with acute gastrointestinal bleeding while receiving antithrombotic therapy, the timing of treatment resumption was associated with different patterns of 30-day ischemic and bleeding

risk. Early resumption (≤7 days) was associated with a lower risk of ischemic events but a higher risk of recurrent bleeding. In contrast, patients who did not resume antithrombotic therapy within 30 days had the highest rates of ischemic events and all-cause mortality. No systemic thromboembolic events occurred in this cohort; therefore, this component did not contribute to the composite ischemic outcome.

The lower ischemic risk observed with earlier resumption is consistent with the clinical concern that prolonged interruption of antithrombotic therapy may expose high-risk patients to preventable cardiovascular events. Current guidelines (6-8) and contemporary reviews (14) recommend individualized resumption decisions based on the balance between thrombotic and bleeding risk. This approach is also supported by previous studies showing cardiovascular benefit after early continuation or reintroduction of antithrombotic therapy (12,15,16).

The higher rate of recurrent bleeding in the early resumption group reflects the main clinical dilemma in this setting. Prior observational studies and meta-analyses have similarly reported that earlier resumption may reduce thromboembolic complications and mortality, although at the cost of increased recurrent bleeding (10,12,17). In the present cohort, patients who resumed treatment between 8 and 15 days had the most favorable short-term balance between ischemic and bleeding outcomes. This interval should not be viewed as a fixed rule, but it may help guide clinical judgment after stabilization and hemostasis.

Non-resumption within 30 days was associated with higher ischemic and mortality risks, in line with earlier reports (10,15). In clinical practice, permanent discontinuation may be appropriate in selected patients with persistent or prohibitive bleeding risk, but the decision should be made carefully, particularly in patients with clear cardiovascular indications for antithrombotic therapy.

The continuous analysis also supported a time-dependent risk pattern. Each additional day of delay beyond day 7 was associated with a higher ischemic risk and a lower bleeding risk. This finding suggests that the optimal timing of resumption is unlikely to be the same for all patients and should be adapted to the individual clinical context.

These findings may be relevant to daily clinical practice. Decisions about restarting antithrombotic therapy after gastrointestinal bleeding are often made under uncertainty, especially in older patients with multiple comorbidities. Bleeding severity, cardiovascular indication, endoscopic findings, hemostasis status, and comorbidity burden should all be considered when deciding whether to resume treatment early or delay reinitiation.

Subgroup analyses provided additional clinical information. Among patients receiving antiplatelet therapy, early resumption was associated with a clearer reduction in ischemic events, but recurrent bleeding was more frequent. Among anticoagulant users, the ischemic benefit was less evident, while the increase in bleeding risk persisted. The smaller increase in bleeding among direct oral anticoagulant users compared with warfarin users is consistent with previous comparative data showing differences in gastrointestinal bleeding risk across anticoagulant classes and agents (5,17,18).

Proton pump inhibitor prescription at discharge was associated with lower recurrent upper gastrointestinal bleeding. This finding is consistent with the role of gastroprotection, especially in patients who resume antiplatelet therapy early (19).

Further prospective multicenter studies are needed to clarify optimal resumption strategies across different antithrombotic regimens and bleeding etiologies. Future studies incorporating clinical risk scores, endoscopic findings, and treatment indication may help refine individualized decision-making after gastrointestinal bleeding.

Strengths of this study include its focus on the early 30-day period, simultaneous evaluation of ischemic and bleeding outcomes, real-world cohort design, and use of subgroup and sensitivity analyses. The landmark analysis at day 7 yielded findings consistent with the primary analysis (Table 5).

Limitations: Several limitations should be acknowledged. Despite multiple adjustment, residual confounding by indication cannot be excluded, as the timing of antithrombotic resumption was determined by clinician judgment and may have been influenced by unmeasured differences in thrombotic and bleeding risk across patient groups. The single-center design may limit generalizability. The inclusion of both upper and lower gastrointestinal bleeding improves real-world relevance but also introduces clinical heterogeneity. Exclusion of patients who died before resumption status could be determined (n=167) may have biased the cohort toward healthier survivors. Patients with active malignancy were also excluded. Finally, although the 8–15-day interval was associated with the most favorable balance in this cohort, this finding should be regarded as hypothesis-generating rather than definitive.

In this cohort, antithrombotic resumption timing after acute gastrointestinal bleeding was associated with competing 30-day ischemic and bleeding risks. Early resumption was associated with fewer ischemic

events but more recurrent bleeding, whereas non-resumption was associated with the highest risks. Resumption between 8 and 15 days showed the most favorable short-term balance. These findings support individualized decision-making and highlight the importance of weighing ischemic and recurrent bleeding risks during the early post-bleeding period.

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