Major gastrointestinal bleeding in patients receiving anticoagulant therapy for venous thromboembolism

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Data in brief

- The gastrointestinal (GI) tract is a frequent site of bleeding in patients receiving anticoagulant therapy for venous thromboembolism (VTE).
- At-risk patients have not been consistently identified yet.
- We used the RIETE registry to assess the incidence and severity of major GI bleeding during anticoagulation for VTE.
- Among 87,431 patients with VTE, 778 (0.9%) suffered major GI bleeding. Of these, 33% died within the first 30 days after bleeding.
- We built a predictive score to predict the risk of major GI bleeding, c-statistics: 0.771 (95%CI. 0.755-0.786).

Abstract:

Introduction: The gastrointestinal (GI) tract is a frequent site of bleeding in patients receiving anticoagulant therapy for venous thromboembolism (VTE). At-risk patients have not been consistently identified yet.

Methods: We used the RIETE registry to assess the clinical characteristics of patients developing major GI bleeding during the course of anticoagulation. Then, we built a predictive score based on multivariable analysis, aiming to identify patients at increased risk for major GI bleeding.

Results: We included 87,431 patients with acute VTE. During the course of anticoagulation, 778 (0.89%) suffered major GI bleeding, 815 (0.93%) non-major GI bleeding and 1,462 (1.67%) had major bleeding outside the GI tract. During the first 30 days after major GI bleeding, 7.6% of patients re-bled, 3.9% had VTE recurrences and 33% died. On multivariable analysis, male sex, age ≥70 years, initial VTE presentation as pulmonary embolism, active cancer, prior VTE, recent major bleeding in the GI tract, esophageal varicosities, anemia, abnormal prothrombin time, renal insufficiency and use of corticosteroids were associated to an increased risk for major GI bleeding. Using the predictive score, 39,591 patients (45%) were at low risk; 36,602 (42%) at intermediate-risk; 9,315 (11%) at high-risk; and 1,923 (2.2%) at very high risk. Their rates of major GI bleeding were: 0.21%, 0.96%, 2.41% and 6.08%, respectively. The c-statistics was 0.771 (95%CI. 0.755-0.786).

Conclusions: We have developed a score which has the potential to identify patients at increased risk for GI bleeding, but needs to be externally validated."

Keywords: Anticoagulants, Venous thromboembolism, Gastrointestinal bleeding.

Introduction

Bleeding is the most feared complication in patients receiving anticoagulant therapy for venous thromboembolism (VTE). The most common site of major bleeding in most reported series is the gastrointestinal (GI) tract, accounting for around 40% of all major bleeds and a mortality rate around 30%.[1–3] Early identification of at risk patients may help to better individualize the management of VTE in order to decrease the risk of GI bleeding. Measures could include the use of safer anticoagulant drugs, avoidance of unnecessary corticosteroids, antiplatelets or anti-inflammatory drugs, close monitoring of patients, or even the use of preventive strategies, such as proton pump inhibitors or endoscopic procedures. However, the amount of variables that may influence the risk for GI bleeding includes demographics (age, sex, body weight), concomitant diseases in the GI tract (cancer, peptic ulcer, hiatal hernia, oesophageal varicosities), concomitant diseases outside the GI tract (non-GI cancer, anaemia, renal insufficiency) or concomitant therapies (corticosteroids, non-steroidal anti-inflammatory drugs, antiplatelets), among others.[4,5] Prior studies did not specifically focus on GI bleeding, most likely because they were underpowered to evaluate the influence of all these variables on the risk for GI bleeding, because of small patient populations or because of the absence of information on some of these variables.[4,6]

The RIETE (Registro Informatizado Enfermedad TromboEmbólica) database is an ongoing, multicenter, international, prospective registry of consecutive patients with objectively confirmed acute deep vein thrombosis (DVT) or pulmonary embolism (PE). Data from this registry have been used to evaluate outcomes after VTE, such as the frequency of recurrent VTE, major bleeding or mortality, and risk factors for such outcomes.[7] The aim of the current analysis was to assess the clinical characteristics of patients that developed major GI bleeding during the course of anticoagulant therapy. We compared them versus those in patients developing non-major GI bleeding, major bleeding outside the GI tract, and those who did not bleed. We built a prognostic score to try to identify patients at increased risk for major GI bleeding.

Methods

Data source

We used the data from the RIETE registry, which prospectively collects information on patients with symptomatic, objectively confirmed acute VTE (ClinicalTrials.gov identifier, NCT02832245). Previous publications have described the design and conduct of the RIETE registry.[7] All patients (or their relatives) provided written or oral informed consent for participation in the registry, in accordance with the local ethics committee requirements.

Inclusion criteria

Consecutive patients with acute, symptomatic VTE confirmed by objective tests (ventilation-perfusion lung scan, helical CT-scan or contrast angiography for patients with clinically suspected PE; compression ultrasonography or contrast venography for those with suspected DVT) were considered for this analysis. Patients were excluded if they were currently participating in a blind therapeutic clinical trial. We did not exclude patients with isolated distal DVT at baseline, nor those with isolated subsegmental PE.

Study design

First, we compared the clinical characteristics of patients developing major GI bleeding during the course of anticoagulant therapy vs. those with: 1) non-major GI bleeding; 2) major bleeding outside the GI tract; or 3) no bleeding. Only the first bleeding was analysed. Then, we performed a multivariable analysis through a logistic regression model trying to identify independent predictors for major bleeding in the GI tract. Finally, we built a predictive score assigning points to each independent variable according to regression coefficients β. Major bleeding was defined as any bleeding event that was overt and required a transfusion of two units or more of blood, or was retroperitoneal, spinal, intracranial or was fatal. Non-major bleeding was defined as any overt bleeding not meeting criteria for major bleeding but requiring medical assistance. Fatal bleeding was defined as any death occurring within 10 days of a major bleeding episode, in the absence of an alternative cause of death.

Study variables

The following variables were recorded in RIETE: patient's characteristics; VTE signs and symptoms at baseline; clinical status including any coexisting or

underlying conditions such as chronic heart or lung disease, recent (<30 days before) major bleeding, anemia or renal insufficiency; concomitant disorders including a number of anatomical GI lesions (peptic ulcer, hiatal hernia, gastritis, esophageal varicosities, Crohn's disease, ulcerative colitis and angiodysplasia); risk factors for VTE; blood tests at baseline (including anemia, platelet count, prothrombin time and creatinine clearance levels), the treatment received upon VTE diagnosis (drugs, doses and duration); concomitant drugs (including corticosteroids, non-steroidal anti-inflammatory drugs [NSAIDs] or antiplatelets) and the outcomes at least during the first 30 days after bleeding. Immobilized patients were defined as non-surgical patients who had been immobilized (i.e., total bed rest with or without bathroom privileges) for ≥4 days in the 2-month period prior to PE diagnosis. Surgical patients were defined as those who had undergone an operation in the 2 months prior to PE. Active cancer was defined as newly diagnosed cancer (<3 months before) or when receiving anti-neoplastic treatment of any type (i.e., surgery, chemotherapy, radiotherapy, hormonal, support therapy or combined therapies). Anemia was defined as hemoglobin levels <13 g/dL for men and <12 g/dL for women. The RIETE registry restricted all values of these variables to the nearest recorded to the time of PE diagnosis. We imputed missing values where necessary.

Treatment and follow-up

Patients were managed according to the clinical practice of the attending physicians and participating hospitals (i.e., there was no standardization of treatment). The type, dose and duration of therapy were recorded. After hospital discharge, all patients were followed-up in the outpatient clinic. During each visit, any signs or symptoms suggesting VTE recurrences or bleeding were noted. All episodes of clinically suspected VTE recurrences were investigated by repeat compression ultrasonography, helical CT pulmonary scan, ventilation–perfusion lung scintigraphy or pulmonary angiography. Fatal PE was defined as any death occurring within 10 days of a PE episode (either the index event or recurrent PE) in the absence of an alternative cause of death.

Statistical analysis

Categorical variables were reported as frequency counts (percentages) and compared using the chi-square test (two-sided) and Fisher´s Exact Test (two-sided). Continuous variables were reported as mean and standard error of the mean (or median with interquartile range, if not normally distributed), and compared using Student t test. Odds ratios (ORs) and corresponding 95% confidence intervals (CI) were calculated. The risk for major bleeding was assessed using logistic regression models. Covariates entering into the model were selected by a significance level of $P < 0.10$ on univariable analysis or by a well-known association reported in the literature. The doses of anticoagulant drugs were not included because its choice might have been influenced by the physician's assessment of a patient's risk of bleeding or recurrent VTE.

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We built a prognostic score assigning points to each independent variable according to regression coefficients β, rounding to the nearest integer. We assigned a risk score to each patient by adding up points for each independent variable. Performance was quantified in terms of calibration, using the Hosmer-Lemeshow test. Internal validity of the score was confirmed using bootstrap analysis. Then, we tried to identify patients at low-, intermediate-, high- or very-high risk for major GI bleeding during the course of anticoagulation. Discrimination was quantified calculating the sensitivity, specificity, and area under the receiver operating characteristic curve.Statistical analyses were conducted with IBM SPSS Statistics (version 25).

Results

From March 2001 to March 2021 we included 87,431 patients with acute VTE. During the course of anticoagulation (median: 182 days; inter-quartile range: 101-315 days), 778 patients (0.89%) developed major GI bleeding, 815 (0.93%) had non-major GI bleeding and 1,462 (1.67%) had major bleeding outside the GI tract.

Clinical characteristics at baseline

Patients developing bleeding complications (wherever the site or intensity) were older, weighed less, and were more likely to initially present as symptomatic PE (versus DVT alone), to have recent immobility or active cancer, and were less likely to use hormonal therapy or to be pregnant than those who did not bleed (Table I). Moreover, patients who bled were more likely to have anemia, thrombocytopenia, abnormal prothrombin time or renal insufficiency at baseline, or to use antiplatelets or corticosteroids than those who did not bleed

Patients developing major bleeding in the GI tract were more likely to have cancer or recent (<30 days before) major GI bleeding at baseline, or to have non-cancer lesions in the GI tract (such as hiatal hernia, gastroduodenal ulcer, cirrhosis, esophagitis, esophageal varicosities or angiodysplasia) than patients that developed non-major GI bleeding, major non-GI bleeding or no bleeding at all. Patients developing major bleeding in the GI tract were more likely to be treated by unfractionated heparin while DAOCs and fondaparinux were less frequent, as initial therapy. (Table I)

Time course, current therapies and 30-day outcomes

One in every 3 patients with major GI bleeding (30%) bled during the first 10 days, one in every 3 (37%) bled from Day 11 to Day 90 and one in every 3 (33%) bled beyond the first 3 months. Similar figures were found for patients with non-major GI bleeding or those with major non-GI bleeding (Table II). There were no major differences on the INR levels in those who bled during the course of therapy with vitamin K antagonists (VKAs), as shown in Table II. During the first 30 days, patients with major GI bleeding had a two-fold higher rate of major re-bleeding than VTE recurrences (7.6% vs. 3.9%, respectively)

and a mortality rate of 33%. Patients with non-major GI bleeding had more VTE recurrences than major re-bleeds (1.7% vs. 0.7%, respectively) and 11% died. Patients with major non-GI bleeding suffered as many major re-bleeds as VTE recurrences (3.7% vs. 3.8%, respectively), and had a similar mortality rate than those with major GI bleeding (30%).

Almost half of the major GI bleeds (367 of 778, 47%) appeared during the first 30 days of therapy, as compared to 36% of non-major GI bleeds and 55% of major bleeds outside the GI tract (Figure 1). The rates of major re-bleeding, fatal bleeding or all-cause mortality were highest in patients that bled during the first 7 days, and then progressively decreased over time (Table III). There were no differences in the severity of bleeding according to the existence of cancer in the GI tract, cancer outside the GI tract or non-cancer lesions in the GI tract (Table III).

On multivariable analysis, male sex, age ≥70 years, initial presentation as PE (compared to isolated DVT), active cancer, prior VTE, recent major bleeding in the GI tract, esophageal varicosities, anemia, abnormal prothrombin time, renal insufficiency and concomitant therapy with corticosteroids independently predicted the risk for major GI bleeding (Table IV). These variables were used to build a predictive score assigning different points according to the β coefficients. There were 39,591 patients (45%) at low risk (≤1.0 points); 36,602 (42%) at intermediate risk (1.0 to <2.0 points); 9,315 (11%) at high risk (2.0 to <3.0 points) and 1,923 (2.2%) at very high risk (≥3 points). Their rates of major GI bleeding during the course of anticoagulation were: 0.21%, 0.96%, 2.41% and 6.08%, respectively (Table V and Figure 2). The c-statistics was 0.771 (95%CI: 0.755-0.786). The rates of fatal GI bleeding were: 0.002%, 0.15%, 0.63% and 1.66%, respectively (Table V and Figure 3). The c-statistics for fatal GI bleeding was 0.864 (95%CI: 0.841-0.886). The c-statistics for non-major GI bleeding was 0.656 (95%CI: 0.637-0.674), and for major bleeding outside the GI tract: 0.657 (95%CI: 0.645-0.669). We observed that the prognostic score applied similarly well in the subgroup of patients receiving Direct Oral Anticoagulants (DOACs).

Discussion

Our findings, obtained from a large cohort of unselected patients with objectively proven VTE, reveal that one in every 112 such patients (0.89%) suffered major GI bleeding, one in every 107 (0.93%) had non-major GI bleeding and one in every 60 (1.67%) had major bleeding outside the GI tract. One in every 3 patients suffering major bleeding (in the GI tract or outside the GI tract) died within the first 30 days, as also reported in other series. [8] Thus, the potential severity of major GI bleeding should not be underestimated. We built a predictive score that reliably identifies which patients at baseline are at increased risk for major GI bleeding. This is important since these patients might theoretically benefit from use of safer anticoagulant drugs, avoidance of unnecessary corticosteroids, close monitoring of early signs of bleeding, or even the use of proton pump inhibitors.

We found a number of variables at baseline (patient's age, initial presentation as PE, active cancer, anemia, thrombocytopenia, abnormal prothrombin time, renal failure or concomitant use of corticosteroids) to be significantly more common in patients that subsequently developed major bleeding in- or outside the GI tract. We also found some additional variables (gastroduodenal ulcer, hiatal hernia, esophageal varicosities, Crohn's disease, ulcerative colitis, other non-cancer GI lesions) to be more common in patients that subsequently bleed in the GI tract, but not outside the GI tract. On multivariable analysis however, only few of these GI lesions (recent major bleeding in the GI tract and esophageal varicosities) independently predicted the risk for major bleeding in the GI tract. Similar findings were found for some concomitant therapies: on univariable analysis, both antiplatelets and corticosteroids were associated with a higher rate of GI bleeding, but on multivariable analysis only concomitant use of corticosteroids independently predicted the risk for bleeding in the GI tract.

Characteristics of patients are different depending on the site of bleeding. Using our predictive score focused on GI bleeding, there were 39,591 patients (45%) at low risk, 42% at intermediate risk, 11% at high risk, and 2.2% at very high risk. Their rates of major GI bleeding during anticoagulation were: 0.21%, 0.96%, 2.41% and 6.08%, respectively. The c-statistics was 0.771 (95%CI:

0.755-0.786). Thus, our score was reasonably good at identifying patients at increased risk for major GI bleeding. It was also good to identify patients at risk for fatal GI bleeding (c-statistics: 0.864 (95%CI: 0.841-0.886), but performed worse in patients with non-major GI bleeding or in patients with major bleeding outside the GI tract.

A number of predictive scores have been developed during the last years, including HEMOR2RHAGES[9], ATRIA[10] or HAS-BLED[11], but focused only on patients with atrial fibrillation. The OBRI score [12] is limited to patients receiving VKAs. The RIETE score[13] did not distinguish the site of major bleeding. Finally, the Qbleed score estimates the risk of bleeding before or after starting anticoagulant therapy, but only in the upper GI tract.[4] At variance with previous scores, the RIETE database contains information on a number of GI disorders (peptic ulcer, hiatal hernia, esophageal varicosities, Crohn's disease, ulcerative colitis, etc.), that improve the likelihood to identify patients at increased risk for bleeding.

Our study suffers from a number of limitations that should be reported. First, the analysis was a post-hoc analysis of prospectively collected data, in unselected patients with acute VTE. Despite it was not a-priori calibrated to assess the hypothesis, and may be underpowered, the RIETE registry is the largest ongoing database on patients with VTE. Second, the management of patients (for the acute VTE and for the bleeding event) was let to investigators and local usual care. Third, we assessed the major bleeding events according to the RIETE definition, rather than the Thrombolysis in Myocardial Infarction (TIMI), International Society of Thrombosis and Hemostasis (ISTH), or Bleeding Academic Research Consortium (BARC).[14,15] In fact, the RIETE registry was designed before the ISTH definition for bleeding was developed. However, the RIETE major bleeding definition closely resembles to the ISTH definition.Fourth, the proportion of patients on LMWH who had major GI bleeding is very high. It is probably because lots of patients with major GI bleeding are cancer patients, who have been likely treated with LMWH during the first months. Plus, there is low proportion of patients treated with DOACs. It may also be explained by the long period of the RIETE registry running since 2001. Differences concerning

initial choice of anticoagulant therapy may have been guided by the clinical perception of the risk of the bleeding. This may have provided some heterogeneity in the management of patients, but it also increases the application of our findings in real-life setting. Finally, we did not externally validate the score using another cohort of patients, but hope that other researchers will be able to do it.

In conclusion, our findings confirm that major GI bleeding is an early severe complication in patients receiving anticoagulant therapy for VTE. Our score has the potential to identify patients at increased risk for GI bleeding, but needs to be externally validated.

Authors contributions;

JC, LB, FM and MM conceived and designed the analysis and wrote the paper All the authors collected the data, revised and approved the final version.

Conflict of Interest

The present manuscript was supported by Sanofi, Leo Pharma, Rovi and the Catholic University of Murcia (Spain) sponsoring the RIETE registry with unrestricted educational grants. Payments were made to the FUENTE Fundation JC declared honoraria from Sanofi and support for attending meetings by MSD, Pfizer, BMS and Aspen. LB declared honoraria from Aspen, Bayer, BMS, Pfizer and Leo-Pharma and support for attending meetings by BMS, Pfizer, Leo-Pharma. FM, JAN, RV, JMP, AV,IQ, GSB and MM declared honoraria from Sanofi and support for attending meetings by Sanofi and Pfizer.

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Table I. Baseline characteristics of 87,431 patients with VTE, according to the existence of bleeding complications.

	Major GI bleeding	Non-major GI bleeding	Non-GI major bleeding	No bleeding
Patients, N	***778***	***815***	***1,462***	***84,376***
Clinical characteristics,				
Mean age (years±SD)	73±14‡	73±13‡	72±15‡	65±18
Male gender	393 (51%)	413 (51%)	604 (41%)‡	41,662 (49%)
Body weight (mean kg±SD)	71±15‡	75±15†	73±15‡	76±16
Initial VTE presentation,				
Symptomatic PE (vs. isolated DVT)	446 (57%)*	503 (62%)‡	967 (66%)‡	44,475 (53%)
Risk factors for VTE,				
Immobility ≥4 days	256 (33%)‡	214 (26%)†	431 (29%)‡	18,342 (22%)
Recent surgery	65 (8.4%)*	86 (11%)	211 (14%)‡	9,231 (11%)
Hormonal therapy or pregnancy	14 (1.8%)‡	21 (2.6%)‡	60 (4.1%)‡	5,679 (6.7%)
Active cancer	314 (40%)‡	203 (25%)‡	375 (26%)‡	14,573 (17%)
Metastatic cancer	214 (28%)‡	108 (13%)‡	217 (15%)‡	7,709 (9.1%)
Active cancer in the GI tract	130 (17%)‡	82 (10%)‡	43 (2.9%)	2,711 (3.2%)
None of the above (unprovoked)	250 (32%)‡	372 (46%)†	579 (40%)‡	42,913 (51%)
Prior VTE	122 (16%)	134 (16%)	192 (13%)	12,597 (15%)
Risk factors for bleeding,				
Recent bleeding outside the GI tract	9 (1.2%)	7 (0.9%)	70 (4.8%)‡	1,175 (1.4%)
Anemia	495 (64%)‡	383 (47%)‡	717 (49%)‡	27,893 (33%)
Platelet count <100,000/μL	36 (4.6%)‡	23 (2.8%)	68 (4.7%)‡	1,985 (2.4%)
Abnormal prothrombin time	115 (15%)‡	73 (9.0%)*	174 (12%)‡	5,955 (7.1%)
CrCl levels <60 mL/min	450 (58%)‡	406 (50%)‡	760 (52%)‡	27,936 (33%)
Non-cancer GI lesions,				
Recent major bleeding in the GI tract	60 (7.7%)‡	39 (4.8%)‡	9 (0.6%)	553 (0.7%)
Hiatal hernia	32 (4.1%)‡	22 (2.7%)	50 (3.4%)‡	1,758 (2.1%)
Gastroduodenal ulcer	22 (2.8%)‡	14 (1.7%)*	14 (1.0%)	711 (0.8%)
Liver cirrhosis	12 (1.5%)‡	3 (0.4%)	16 (1.1%)‡	264 (0.3%)
Esophagitis	10 (1.3%)†	3 (0.4%)	8 (0.6%)	440 (0.5%)
Esophageal varicosities	10 (1.3%)‡	1 (0.1%)	4 (0.3%)*	76 (0.1%)
Gastric erosions	9 (1.2%)†	7 (0.9%)	8 (0.6%)	347 (0.4%)
Angiodysplasia	3 (0.4%)*	4 (0.5%)†	2 (0.1%)	50 (0.1%)
Crohn's disease	3 (0.4%)	12 (1.5%)‡	4 (0.3%)	265 (0.3%)
Ulcerative colitis	2 (0.3%)	20 (2.5%)‡	3 (0.2%)	293 (0.3%)
Any of the above	127 (16%)‡	113 (14%)‡	105 (7.2%)‡	4,179 (5.0%)
Initial therapy,				
LMWH (o biosimilars)	682 (88%)	713 (87%)	1,251 (86%)	73,585 (87%)
Unfractionated heparin	65 (8.4%)‡	61 (7.5%)*	106 (7.3%)†	4,627 (5.5%)
Direct oral anticoagulants	6 (0.8%)‡	14 (1.7%)*	6 (0.4%)‡	2,620 (3.1%)
Fondaparinux	6 (0.8%)*	8 (1.0%)	20 (1.4%)	1,642 (1.9%)
Thrombolytic drugs	15 (1.9%)	14 (1.7%)	67 (4.6%)‡	1,099 (1.3%)
Inferior vena cava filter	120 (15%)‡	52 (6.4%)‡	270 (18%)‡	1,727 (2.0%)
Long-term therapy,				
Vitamin K antagonists	317 (41%)‡	430 (53%)†	635 (43%)‡	49,196 (58%)
LMWH (o biosimilars)	292 (38%)‡	277 (34%)‡	548 (37%)‡	23,442 (28%)

Direct oral anticoagulants	26 (3.3%)‡	66 (8.1%)	35 (2.4%)‡	8,560 (10%)
Concomitant therapies,				
Antiplatelets	145 (19%)†	167 (20%)‡	308 (21%)‡	12,125 (14%)
Corticosteroids	111 (14%)‡	95 (12%)‡	206 (14%)‡	6,720 (8.0%)
NSAIDs	114 (15%)	139 (17%)	285 (19%)‡	12,727 (15%)

Comparisons between patients with bleeding events vs. those that did not bleed: *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$

Abbreviations: GI, gastrointestinal; SD, standard deviation; VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; CrCl, creatinine clearance; LMWH, low-molecular-weight heparin; NSAIDs, non-steroidal antiinflammatory drugs.

Table II. Time elapsed since VTE diagnosis, therapies at bleeding and 30-day outcomes.

	Major GI bleeding	Non-major GI bleeding	Non-GI major bleeding
Patients, N	***778***	***815***	***1,462***
Time elapsed from VTE to bleeding,			
Median days (IQR)	35 (8-131)	67 (15-174)	23 (7-118)
From Day 0 to Day 10	237 (30%)	159 (20%)‡	493 (34%)
From Day 11 to Day 90	286 (37%)	321 (39%)	541 (37%)
Beyond Day 90	255 (33%)	335 (41%)‡	428 (29%)
Current therapy at bleeding,			
Thrombolytics	5 (0.6%)	1 (0.1%)	29 (2.0%)*
Low-molecular-weight heparin	400 (51%)	293 (36%)‡	697 (48%)
Unfractionated heparin	36 (4.6%)	27 (3.3%)	84 (5.7%)
Vitamin K antangonists	288 (37%)	408 (50%)‡	590 (40%)
Direct oral anticoagulants	37 (4.8%)	77 (9.4%)‡	38 (2.6%)†
Other	12 (1.5%)	9 (1.1%)	24 (1.6%)
For those on VKAs: INR at bleeding,			
INR <2.0	66 (26%)	87 (27%)	125 (25%)
INR 2.0-3.0	77 (30%)	135 (42%)†	181 (36%)
INR >3.0	114 (44%)	97 (30%)‡	202 (40%)
30-day outcomes,			
Major re-bleeding	59 (7.6%)	6 (0.7%)‡	54 (3.7%)‡
Non-major re-bleeding	13 (1.7%)	30 (3.7%)*	20 (1.4%)
Recurrent VTE	30 (3.9%)	14 (1.7%)*	56 (3.8%)
Overall death	253 (33%)	91 (11%)‡	435 (30%)
Fatal bleeding	145 (19%)	2 (0.3%)‡	288 (20%)
Fatal PE	7 (0.9%)	2 (0.3%)	18 (1.2%)

Comparisons between patients with major GI bleeding vs. the rest of subgroups: *p <0.05; †p <0.01; ‡p <0.001

Abbreviations: GI, gastrointestinal; VTE, venous thromboembolism; SD, standard deviation; IQR, inter-quartile range; VKAs, vitamin K antagonists; INR, International normalized range; PE, pulmonary embolism.

Table III. Time-course of major GI bleeding, anatomic lesions, treatment at bleeding and after bleeding, and 30-day outcomes.

	N	Major re-bleeding	Fatal GI bleeding	Recurrent VTE	Fatal PE	All-cause death
Patients, N	***778***	***59 (7.6%)***	***145 (19%)***	***30 (3.8%)***	***7 (0.9%)***	***253 (32%)***
Time elapsed from baseline,						
<7 days	168	22 (13%)	37 (22%)	10 (6.0%)	4 (2.4%)	73 (43%)
7-30 days	199	19 (9.5%)	46 (23%)	6 (3.0%)	2 (1.0%)	78 (39%)
31-90 days	156	11 (7.1%)	26 (17%)	8 (5.1%)	1 (0.64%)	52 (33%)
>90 days	255	7 (2.7%)‡	36 (14%)*	6 (2.4%)	0	50 (20%)‡
Anatomic lesions,						
Active cancer in the GI tract	130	12 (9.2%)	32 (25%)	7 (5.4%)	0	59 (45%)
Active cancer in other sites	184	20 (11%)	49 (27%)	11 (6.0%)	2 (1.1%)	85 (46%)
Non-cancer GI disorders	127	14 (11%)	23 (18%)	8 (6.3%)	1 (0.8%)	38 (30%)
Therapy at bleeding,						
Low-molecular-weight heparin	400	37 (9.3%)	102 (26%)	20 (5.0%)	5 (1.3%)	183 (46%)
Vitamin K antangonists	288	12 (4.2%)*	31 (11%)‡	7 (2.4%)	1 (0.35%)	45 (16%)‡
Direct oral anticoagulants	37	2 (5.4%)	3 (8.1%)*	0	0	7 (19%)†
Unfractionated heparin	36	8 (22%)*	7 (19%)	3 (8.3%)	1 (2.8%)	13 (36%)
Thrombolytics	5	0	2 (40%)	0	0	2 (40%)
Other	12	0	0	0	0	3 (25%)
Therapeutic decisions,¥						
Permanent discontinuation	242	21 (8.7%)	52 (21%)	5 (2.1%)	2 (0.83%)	103 (43%)
Discontinuation ≥5 days	146	8 (5.5%)	0	9 (6.2%)*	0	7 (4.8%)‡
Discontinuation <5 days	26	3 (12%)	2 (7.7%)	1 (3.8%)	0	3 (12%)†
Switch to another therapy	242	20 (8.3%)	13 (5.4%)‡	11 (4.5%)	2 (0.83%)	45 (19%)‡
Same therapy	31	4 (13%)	3 (9.7%)	3 (9.7%)	0	4 (13%)†

*p <0.05; †p <0.01; ‡p <0.001

¥ 91 patients dying within the first 24 hours were not included.

Abbreviations: GI, gastrointestinal; VTE, venous thromboembolism; PE, pulmonary embolism.

Table IV. Univariable and multivariable analysis for major GI bleeding.

	Univariable OR (95%CI)	Multivariable OR (95%CI)	Beta Coefficient	Assigned Points
Patients, N				
Clinical characteristics,				
Male gender	1.05 (0.91-1.21)	1.25 (1.07-1.45)†	0.220	0.2
Age ≥70 years	2.17 (1.87-2.52)†	1.41 (1.18-1.68)‡	0.341	0.3
Body weight ≥75 kg	0.59 (0.51-0.68)†	0.91 (0.78-1.07)	-	-
Initial VTE presentation,				
Symptomatic PE	1.19 (1.03-1.37)*	1.19 (1.03-1.38)*	0.177	0.2
Risk factors for VTE,				
Unprovoked	Ref.	Ref.	-	-
Active cancer in the GI tract	8.04 (6.48-9.97)‡	5.00 (3.96-6.31)‡	1.609	1.6
Active cancer in other sites	2.62 (2.16-3.17)‡	1.90 (1.55-2.33)‡	0.643	0.7
Transient risk factors	1.36 (1.13-1.63)†	1.16 (0.96-1.40)	-	-
Prior VTE	1.06 (0.87-1.29)	1.22 (1.00-1.49)*	0.200	0.2
Non-cancer GI lesions,				
Recent major bleeding in the GI tract	12.0 (9.09-15.8)†	3.53 (2.13-5.83)‡	1.260	1.3
Hiatal hernia	1.99 (1.39-2.84)†	1.21 (0.70-2.09)	-	-
Gastroduodenal ulcer	3.38 (2.20-5.20)†	1.44 (0.84-2.45)	-	-
Liver cirrhosis	4.78 (2.67-8.56)†	1.36 (0.61-3.01)	-	-
Esophagitis	2.49 (1.32-4.68)†	1.19 (0.59-2.38)	-	-
Esophageal varicosities	13.9 (7.19-26.9)†	3.98 (1.70-9.34)†	1.381	1.4
Gastric erosions	2.79 (1.43-5.43)†	1.38 (0.67-2.88)	-	-
Angiodysplasia	5.99 (1.87-19.2)*	2.08 (0.62-7.05)	-	-
Crohn's disease	1.19 (0.38-3.72)	1.01 (0.30-3.43)	-	-
Ulcerative colitis	0.70 (0.18-2.83)	0.47 (0.11-2.00)	-	-
Risk factors for bleeding,				
Recent bleeding outside the GI tract	0.80 (0.41-1.54)	0.67 (0.35-1.31)	-	-
Anemia	3.48 (3.00-4.03)†	2.14 (1.82-2.51)‡	0.759	0.8
Platelet count <100,000/μL	1.97 (1.41-2.77)†	1.11 (0.78-1.58)	-	-
Abnormal prothrombin time	2.25 (1.84-2.75)†	1.54 (1.25-1.90)‡	0.433	0.4
CrCl levels <60 mL/min	2.71 (2.35-3.13)†	2.01 (1.69-2.41)‡	0.700	0.7
Concomitant drugs,				
Antiplatelets	1.35 (1.12-1.61)†	1.16 (0.87-1.56)	-	-
Corticosteroids	1.89 (1.54-2.31)†	1.59 (1.15-2.19)†	0.462	0.4
NSAIDs	0.96 (0.79-1.17)	0.85 (0.64-1.12)	-	-

*p <0.05; †p <0.01; ‡p <0.001

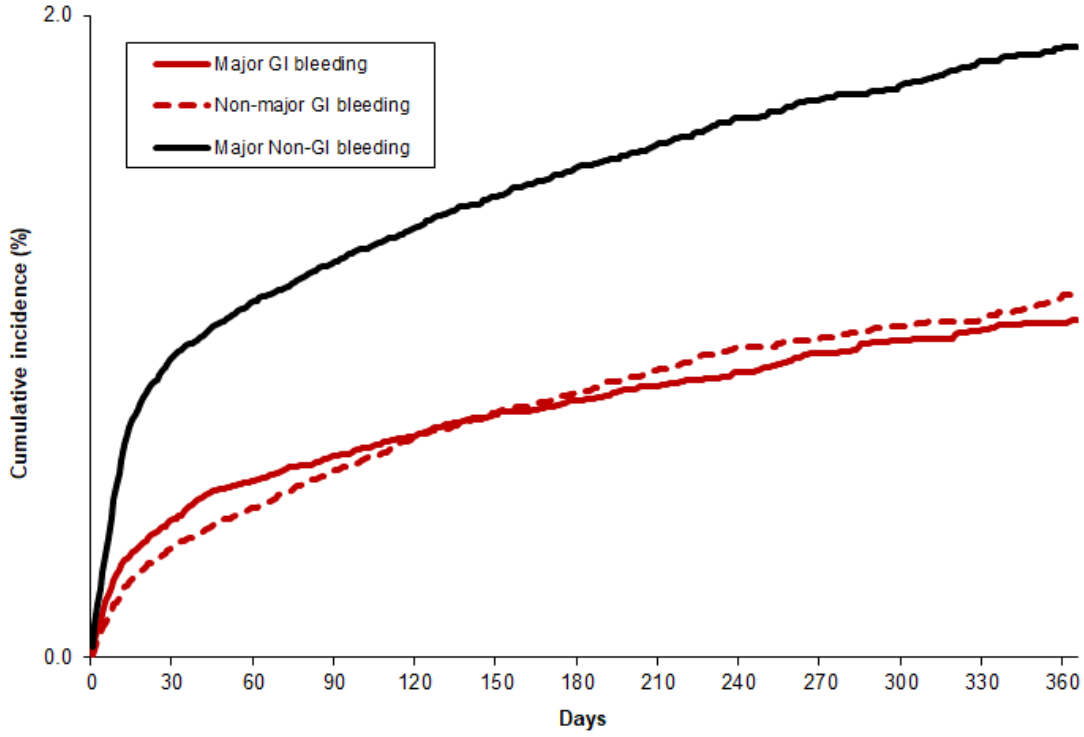
Abbreviations: GI, gastrointestinal; OR, odds ratio; CI, confidence intervals; PE, pulmonary embolism; VTE, venous thromboembolism; CrCl, creatinine clearance; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table V. Application of the prognostic score in the whole cohort, and also in patients receiving DOACs.

	N	Major GI bleeding	Fatal GI bleeding	Non-major GI bleeding	Major non-GI bleeding
All patients, N	***87,431***	***778 (0.89%)***	***145 (0.17%)***	***815 (0.93%)***	***1,462 (1.67%)***
Low risk	39,591	85 (0.21%)	1 (0.002%)	208 (0.52%)	312 (0.79%)
Intermediate risk	36,602	352 (0.96%)	53 (0.15%)	387 (1.06%)	816 (2.23%)
High risk	9,315	224 (2.41%)	59 (0.63%)	166 (1.78%)	294 (3.16%)
Very high risk	1,923	117 (6.08%)	32 (1.66%)	54 (2.81%)	40 (2.08%)
c-statistics	-	0.771	0.864	0.656	0.657
95% confidence intervals	-	0.755-0.786	0.841-0.886	0.637-0.674	0.645-0.669
Only patients on DOACs,	***8,791***	***28 (0.32%)***	***3 (0.03%)***	***68 (0.77%)***	***38 (0.43%)***
Low risk	5,519	6 (0.11%)	0	30 (0.54%)	18 (0.32%)
Intermediate risk	2,838	11 (0.39%)	0	26 (0.92%)	17 (0.59%)
High risk	373	9 (2.41%)	2 (0.53%)	10 (2.68%)	3 (0.80%)
Very high risk	61	2 (3.27%)	1 (1.64%)	2 (3.27%)	0
c-statistics	-	0.809	0.976	0.652	0.647
95% confidence intervals	-	(0.737-0.882)	(0.954-0.998)	(0.583-0.721)	(0.568-0.726)

Abbreviations: GI, gastrointestinal; DOACs, Direct Oral Anticoagulants

Figure 1. Cumulative incidence of bleeding complications during the course of anticoagulant therapy (first 365 days).



Days	10	30	90	180	270	360
At-risk patients	***86,351***	***83,314***	***78,438***	***59,546***	***34,558***	***21,802***
Major GI bleeding	237 (0.28%)	367 (0.43%)	523 (0.63%)	620 (0.80%)	666 (0.95%)	687 (1.04%)
Non-major GI bleeding	159 (0.19%)	294 (0.35%)	480 (0.58%)	616 (0.82%)	673 (1.00%)	701 (1.13%)
Major non-GI bleeding	493 (0.57%)	800 (0.94%)	1,034 (1.23%)	1,199 (1.53%)	1,267 (1.74%)	1,302 (1.90%)

Comparisons between major GI bleeding and other bleeds: *p <0.05; †p <0.01; ‡p <0.001

Figure 2. Cumulative incidence of major GI bleeding during the first 365 days of anticoagulation, according to the prognostic score.

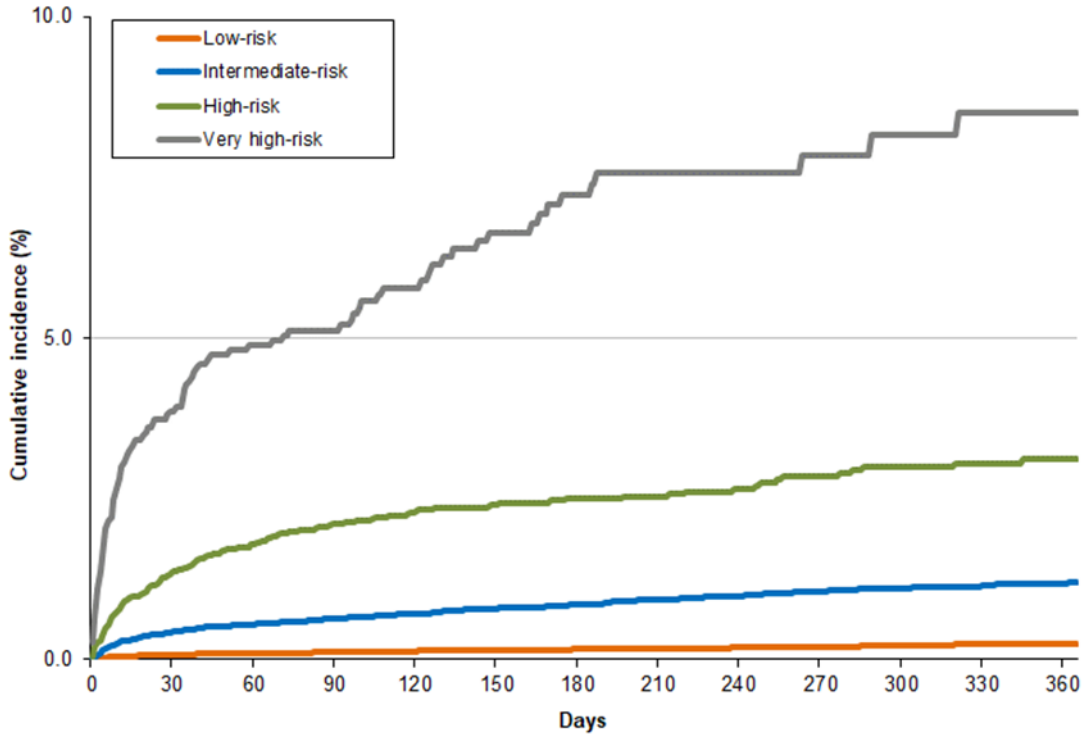


Figure 3. Cumulative incidence of fatal GI bleeding during the first 365 days of anticoagulation, according to the prognostic score.