Received: 27 April 2021 | Accepted: 23 July 2021

DOI: 10.1111/jth.15476

ORIGINAL ARTICLE

Recurrent bleeding and thrombotic events after resumption of oral anticoagulants following gastrointestinal bleeding: Communication from the ISTH SSC Subcommittee on Control of Anticoagulation

Matteo Candeloro[1] | Nick van Es[2] | Nathan Cantor[3] | Sam Schulman[4,5] | Marc Carrier[3] | Walter Ageno[6] | Jesus Aibar[4,7] | Marco Paolo Donadini[6] | Roisin Bavalia[2] | Marie-Pier Arsenault[4,8] | Michiel Coppens[2] | Noemi Ferrante[1] | Andrea D'Addezio[1] | Stefano Sormani[6] | Ettore Porreca[1] | Marcello Di Nisio[2,9]

[1]Department of Innovative Technologies in Medicine and Dentistry, G. D'Annunzio" University, Chieti, Italy

[2]Department of Vascular Medicine, Amsterdam Cardiovascular Sciences, Amsterdam University Medical Center, Amsterdam, the Netherlands

[3]Department of Medicine, Ottawa Hospital Research Institute at the University of Ottawa, Ottawa, Ontario, Canada

[4]Department of Medicine, Thrombosis and Atherosclerosis Research Institute, McMaster University, Hamilton, Ontario, Canada

[5]Department of Obstetrics and Gynecology, I.M. Sechenov First Moscow State Medical University, Moscow, Russia

[6]Department of Medicine and Surgery, University of Insubria, Varese, Italy

[7]Internal Medicine Department, Hospital Clínic, IDIBAPS – University of Barcelona, Barcelona, Spain

[8]Department of Internal Medicine, Hôpital Maisonneuve-Rosemont CIUSSS de l'Est-de-l'Île-de-Montréal, Montreal, Quebec, Canada

[9]Department of Medicine and Ageing Sciences, "G D'Annunzio" University,, Chieti-Pescara, Italy

Correspondence
Matteo Candeloro, G. D'Annunzio University, Via Dei Vestini 100, Chieti, Italy.
Email: matteo.candeloro@unich.it

Funding information
This project was supported by a grant from the International Society on Thrombosis and Haemostasis.

Abstract

Background: Gastrointestinal bleeding frequently complicates anticoagulant therapy causing treatment discontinuation. Data to guide the decision regarding whether and when to resume anticoagulation based on the risks of thromboembolism and recurrent bleeding are scarce.

Objectives: We aimed to retrospectively evaluate the incidence of these events after anticoagulant-related gastrointestinal bleeding and assess their relationship with timing of anticoagulation resumption.

Methods: Patients hospitalized because of gastrointestinal bleeding during oral anticoagulation for any indication were eligible. All patients were followed up to 2 years after the index bleeding for recurrent major or clinically relevant non-major bleeding, venous or arterial thromboembolism, and mortality.

Manuscript Handled by: Joost Meijers

Final decision: Joost Meijers, 23 July 2021

Results: We included 948 patients hospitalized for gastrointestinal bleeding occurring during treatment with vitamin K antagonists (n = 531) or direct oral anticoagulants (n = 417). In time-dependent analysis, anticoagulant treatment was associated with a higher risk of recurrent clinically relevant bleeding (hazard ratio [HR] 1.55; 95% confidence interval [CI] 1.08–2.22), but lower risk of thromboembolism (HR 0.34; 95% CI 0.21–0.55), and death (HR 0.50; 95% CI 0.36–0.68). Previous bleeding, index major bleeding, and lower glomerular filtration rate were associated with a higher risk of recurrent bleeding. The incidence of recurrent bleeding increased after anticoagulation restart independently of timing of resumption.

Conclusions: Anticoagulant treatment after gastrointestinal bleeding is associated with a lower risk of thromboembolism and death, but higher risk of recurrent bleeding. The latter seemed to be influenced by patient characteristics and less impacted by time of anticoagulation resumption.

KEYWORDS
anticoagulants, gastrointestinal bleeding, hemorrhage, mortality, thromboembolism

1 | BACKGROUND

Millions of patients worldwide receive long-term oral anticoagulant treatment for atrial fibrillation, prosthetic heart valve, or venous thromboembolism (VTE) to reduce the risk of ischemic and thrombotic events.[1–3] The use of oral anticoagulants can be complicated by the occurrence of major bleeding, with rates of about 2.1 per 100 patient-years in patients with atrial fibrillation receiving vitamin K antagonists (VKAs), and with approximately 30% lower risk in those treated with direct oral anticoagulants (DOACs).[4–7] Gastrointestinal bleeding accounts for approximately 30% to 40% of all anticoagulant-related major bleedings, causing permanent discontinuation of oral anticoagulation in up to 50% of patients.[4,7–9]

The decision regarding whether and when to resume anticoagulant therapy after gastrointestinal bleeding remains challenging and must balance the competing risks of thromboembolic events and recurrent bleeding. Several factors may influence the physician's decision on anticoagulation resumption and include, among others, patient characteristics, indication for oral anticoagulation, bleeding severity, risk factors for bleeding and thromboembolism, and the possibility to provide effective endoscopy and supportive treatment.[10] In addition, the clinical impact of thromboembolic events and recurrent bleeding in terms of case-fatality rate and effects on patient quality of life need to be carefully considered.[11] Two recent meta-analyses showed that resumption of anticoagulation after gastrointestinal bleeding was associated with a lower risk of thromboembolism and death, but increased risk of recurrent bleeding compared to permanent discontinuation of treatment.[12,13] These conclusions were based on a small number of heterogeneous, retrospective cohort studies of patients mostly treated with VKAs, with limited information on DOACs.

Current clinical practice guidelines and expert opinion suggest reintroducing oral anticoagulation in high-risk patients as soon as possible once hemostasis has been achieved.[1,7,14] However, uncertainty remains on the optimal timing of anticoagulant treatment resumption and relative importance of risk factors for bleeding and thromboembolism in the context of restarting anticoagulation after gastrointestinal bleeding.

The aims of this study were to evaluate the risk of recurrent bleeding, thromboembolic events, and mortality in patients with gastrointestinal bleeding during oral anticoagulation, and to assess the relationship of these outcomes according to the timing of anticoagulation resumption.

Essentials

- Whether and when to resume anticoagulation after gastrointestinal bleeding is unclear.
- Nine hundred forty-eight patients with gastrointestinal bleeding during anticoagulation were followed up for 2 years.
- Anticoagulant therapy was associated with lower thromboembolism and higher recurrent bleeding.
- Risk of recurrent bleeding seemed not influenced by time of anticoagulation resumption.

2 | METHODS

We conducted a multicenter, retrospective cohort study of patients 18 years or older who were hospitalized because of major or clinically relevant non-major gastrointestinal bleeding (index event) while using oral anticoagulation for atrial fibrillation, VTE, or prosthetic heart valves. The study was an official project of the Scientific

Subcommittee (SSC) Control of Anticoagulation of the International Society on Thrombosis and Haemostasis (ISTH). The study was conducted in three European (Chieti, Varese, and Amsterdam) and two Canadian (Hamilton and Ottawa) centers. Local investigators examined the medical records of all patients hospitalized because of gastrointestinal bleeding between January 2013 and December 2018. This time period allowed for inclusion of patients receiving DOAC treatment and a follow-up duration of up to 2 years after the index gastrointestinal bleeding. Patients were excluded if information on anticoagulant therapy was missing. The current report adheres to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidance for reporting of cohort studies.[15] The study was approved by local institutional review boards and ethics committees.

The following information was extracted from medical records: patient characteristics, concomitant medications of interest (e.g., aspirin and non-steroidal anti-inflammatory drugs), bleeding characteristics (site, severity, and source), bleeding management (e.g., endoscopy, supportive treatment with plasma, prothrombin complex concentrates, red cell and platelet blood transfusion, or administration of antidotes), duration of anticoagulant therapy discontinuation, use of therapeutic or prophylactic anticoagulation with low molecular weight heparin (LMWH) after the index gastrointestinal bleeding, clinical outcomes occurring during follow-up (thromboembolic events, recurrent bleeding, and death).

The index gastrointestinal bleeding was defined as upper gastrointestinal bleeding if endoscopy found a source of bleeding that involved the esophagus, stomach, or duodenum and/or the patient presented with melena or hematemesis. The index gastrointestinal bleeding was defined as lower gastrointestinal bleeding if the endoscopy detected a source of bleeding that was located in the colon or rectum and/or the patient presented with hematochezia or red blood in the stool.[16,17] The bleeding site was classified as unknown if the source of bleeding was not identified by the endoscopic evaluation, endoscopy was not performed, or the clinical presentation was not unequivocal.

All index gastrointestinal bleeding events were centrally adjudicated by three authors and classified as major or clinically relevant non-major according to the criteria of the ISTH.[18,19] Major gastrointestinal bleeding was defined as fatal bleeding (bleeding that directly caused or contributed to death) or bleeding causing a fall in hemoglobin level of 20 g L (1.24 mmol L) or more, or leading to transfusion of two or more units of whole blood or red cells. Clinically relevant non-major bleeding was defined as bleeding that did not meet the ISTH criteria for major bleeding but included at least one of the following: bleeding requiring medical intervention by a health-care professional, leading to hospitalization or increased level of care, or prompting a face to face (i.e., not just a telephone or electronic communication) evaluation.

2.1 | Outcomes

The primary safety outcome of the current analysis was clinically relevant recurrent bleeding, which was the composite of major bleeding and clinically relevant non-major bleeding defined according to ISTH criteria.[18,19] Secondary safety outcomes included major bleeding, clinically relevant non-major bleeding, and all-cause mortality.

The primary efficacy outcome was a composite of ischemic stroke, systemic embolism, acute myocardial infarction, and VTE. Definitions of primary efficacy outcomes are provided in Table S1 in supporting information. Secondary efficacy outcomes included the individual components of the primary efficacy outcome.

All thrombotic and bleeding events that occurred up to 2 years or the longest follow-up available were centrally adjudicated by three authors with any disagreement resolved through consensus. When needed, centers were asked to provide clarifications and additional details for all the outcomes of interest.

2.2 | Statistical analysis

Standard descriptive statistics were used to summarize baseline data. Cumulative incidences of study outcomes in the overall cohort were calculated at day 30, day 90, day 180, and 1 and 2 years after the index gastrointestinal bleeding using a competing risk approach that considered death not related to the outcome of interest as a competing risk event. Patients were censored at the time of death, at occurrence of one of the outcomes of interest, time of last clinical contact, or end of the 2-year follow-up, whichever came first.[20–22]

Cox regression analysis was performed considering anticoagulant treatment as a time-varying variable. We assessed for each time interval after the index gastrointestinal bleeding whether the patient was on anticoagulant treatment with oral anticoagulants or therapeutic dose LMWH.[20] Patients were considered off anticoagulant treatment if they received prophylactic or intermediate doses of LMWH. Univariable Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the associations between study outcomes and the following risk factors chosen based on previous studies: anticoagulant treatment status (on-treatment vs. off-treatment), age, sex, previous bleeding, cancer disease (active cancer and history of cancer, with the latter defined as solid or hematological cancer within the previous 5 years and not receiving active therapy), type of index gastrointestinal bleeding (major vs. clinically relevant non-major bleeding), endoscopy (upper endoscopy, colonoscopy, or both), supportive treatment (including one or more of the following: red cell or platelet blood transfusion, fresh frozen plasma, vitamin K, prothrombin complex concentrate, or a DOAC antidote), indication for anticoagulation (atrial fibrillation, prosthetic heart valves, VTE), and glomerular filtration rate (GFR, calculated with the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula assuming that all patients were non-Black) at admission.[20–22] All these variables were subsequently included in multivariable Cox proportional hazards models.[20–22] Proportional hazards assumptions were checked evaluating Schoenfeld residuals.

To explore the association between time-to-resumption of anticoagulant therapy and the primary outcomes, we excluded patients who had never interrupted anticoagulation within 90 days since the index gastrointestinal bleeding. We performed a landmark analysis with landmarks points at day 7, day 14, and day 21, chosen a priori based on previous studies[21–23] At each landmark point, patients were divided in two groups, on-treatment group and off-treatment group, based on whether they were on anticoagulants or off anticoagulants at the landmark. All patients who had experienced an outcome of interest or in whom follow-up was terminated before the landmark were excluded from the analysis at that landmark. Patients were censored at the time of death, last clinical contact, occurrence of the outcome, or at day 90, whichever came first. Univariate Cox proportional hazard models were used to estimate unadjusted HRs and 95% CIs. A sensitivity landmark analysis was performed for clinically relevant bleeding and thromboembolism censoring patients in the "off treatment" group at the time of anticoagulation resumption, and those in the "on treatment" group at the time of anticoagulant treatment interruption.

A two-sided *P*-value <.05 was considered to indicate statistical significance. All analyses were performed using R software, version 4.0.4 and RStudio version 1.1.423 – © 2009–2018 RStudio, Inc.

3 | RESULTS

Of 990 eligible patients, 42 were excluded due to lack of data about anticoagulant therapy management (i.e., exact dates of anticoagulation interruption or resumption). The main characteristics of the remaining 948 patients are summarized in Table 1. The mean age was 79 (±11) years and 504 (53.3%) were males. The most common comorbidities included arterial hypertension (73.1%), diabetes (27.3%), and chronic heart failure (44.8%).

The index gastrointestinal bleeding was classified as major bleeding in 710 patients (74.9%) and clinically relevant non-major bleeding in 238 (25.1%). The index bleeding event was classified as upper gastrointestinal bleeding in 482 patients (50.8%), lower gastrointestinal bleeding in 441 (46.6%), and unknown site gastrointestinal bleeding in 25 (2.6%).

3.1 | Anticoagulant treatment prior to and after index gastrointestinal bleeding

Oral anticoagulant treatment prior to the index gastrointestinal bleeding consisted of VKAs in 530 (55.9%) patients, rivaroxaban in 179 (18.9%), apixaban in 152 (16.0%), dabigatran in 83 (8.8%), and edoxaban in 4 (0.4%). Indications for anticoagulation included atrial fibrillation in 774 (81.6%), prosthetic heart valves in 117 (12.3%) of which 110 (11.6%) were mechanical valves and 7 (0.7%) biological valves, and VTE in 151 (15.9%). About a quarter of patients were receiving antiplatelet therapy upon admission ($n = 230$; 24.3%), which included aspirin (19%), clopidogrel (3.1%), ticagrelor (0.1%), or dual antiplatelet therapy (2.4%).

At hospital discharge, 81 (8.5%) patients discontinued antiplatelet drugs while 64 (6.8%) patients newly started antiplatelet treatment.

Bridging therapy with LMWH was started in 268 (28.3%) patients of whom 195 (20.6%) received prophylactic-dose LMWH and 73 (7.7%) therapeutic-dose LMWH. The proportion of patients receiving bridging therapy with LMWH was 35.2% in those who were treated with VKAs and 20.9% in patients on DOACs.

Overall, 244 (25.7%) patients permanently discontinued anticoagulant treatment after the index bleeding event, with proportions varying from 22.0% in patients who were receiving VKAs before admission to 36.0% in patients who were on apixaban (Figure S1 in supporting information).

Anticoagulant treatment was resumed in 629 (66.4%) patients, of whom 9 (1.4%) were discharged on LMWH, 363 (57.7%) on VKAs, and 257 (40.9%) on a DOAC. The median time elapsed between index bleeding and treatment resumption was 6 days (range 1–447). Among these patients, 531 (84.4%) resumed the same anticoagulant agent they were receiving prior to the index gastrointestinal bleeding, 19 (3.0%) patients receiving DOAC prior to the index bleeding were switched to VKAs, 24 (3.4%) patients on VKAs were switched to a DOAC, and 46 (7.3%) were switched from one DOAC to another. The type of anticoagulant treatment resumed according to indication for oral anticoagulation is shown in Figure S2 in supporting information. The proportion of patients who resumed or never interrupted anticoagulant treatment was 74.8% in those with atrial fibrillation, 68.2% in those with VTE, and 89.7% in patients with prosthetic heart valve. In exploratory analysis, type of index bleeding (major vs. clinically relevant non-major bleeding), site of bleeding, or main indication for anticoagulation were not associated with uninterrupted treatment (data not shown).

3.2 | Management of the index gastrointestinal bleeding

Endoscopy was performed in 784 (82.7%) patients with an attempt to treat the bleeding lesion in 272 (28.7%). In 679 (86.6%) patients, the endoscopic examination identified the main lesion responsible for the index gastrointestinal bleeding, which was a gastroduodenal ulcer in 24.6%, gastric or colon polyps in 14.9%, angiodysplasia in 9.1%, and gastrointestinal cancer in 7.1%.

Overall, 572 (60.3%) patients required at least one red blood cell transfusion and 285 (30.1%), 35 (3.7%), and 100 (10.5%) patients received vitamin K, fresh frozen plasma, or prothrombin complex concentrate, respectively. Four patients (0.4%) received DOAC antidote, of which three received idarucizumab and one andexanet. The proportion of cases managed with supportive therapy or proton pump inhibitors differed between patients with index upper, lower, or unknown site gastrointestinal bleeding (Table 2).

TABLE 1 Main patient characteristics on admission

	Overall *N* = 948	Upper gastrointestinal bleeding *N* = 482	Lower gastrointestinal bleeding *N* = 441	Unknown gastrointestinal bleeding site *N* = 25
Age, years, mean (SD)	78.89 (10.83)	78.61 (10.91)	79.26 (10.35)	77.88 (16.50)
Sex, male, *n* (%)	504 (53.2)	258 (53.5)	236 (53.5)	10 (40.0)
Index major bleeding, *n* (%)	710 (74.9)	397 (82.4)	290 (65.8)	23 (92.0)
Primary indication for anticoagulant treatment				
Atrial fibrillation	774 (81.6)	386 (80.1)	370 (83.9)	18 (72.0)
Prosthetic heart valves	117 (12.3)	59 (12.2)	54 (12.2)	4 (16.0)
Venous thromboembolism	151 (15.9)	77 (16.0)	69 (15.6)	5 (20.0)
Oral anticoagulant prior to index bleeding, *n* (%)				
Apixaban	152 (16.0)	75 (15.6)	73 (16.6)	4 (16.0)
Dabigatran	83 (8.8)	35 (7.3)	47 (10.7)	1 (4.0)
Edoxaban	4 (0.4)	1 (0.2)	3 (0.7)	—
Rivaroxaban	179 (18.9)	92 (19.1)	79 (17.9)	8 (32.0)
VKA	530 (55.9)	279 (57.9)	239 (54.2)	12 (48.0)
Antiplatelet therapy, *n* (%)				
Aspirin	177 (18.7)	95 (19.7)	74 (16.8)	8 (32.0)
Dual antiplatelet therapy	23 (2.4)	9 (1.9)	12 (2.7)	2 (8.0)
Clopidogrel	29 (3.1)	17 (3.5)	12 (2.7)	—
Ticagrelor	1 (0.1)	—	1 (0.2)	—
NSAID, *n* (%)	183 (19.3)	118 (24.5)	56 (12.7)	9 (36.0)
Comorbidities				
Hypertension, *n* (%)	693 (73.1)	352 (73.0)	325 (73.7)	16 (64.0)
Diabetes, *n* (%)	259 (27.3)	134 (27.8)	118 (26.8)	7 (28.0)
Chronic heart failure, *n* (%)	425 (44.8)	220 (45.6)	194 (44.0)	11 (44.0)
Chronic kidney disease, *n* (%)	764 (80.6)	394 (81.7)	352 (79.8)	18 (72.0)
Liver cirrhosis, *n* (%)	40 (4.2)	28 (5.8)	12 (2.7)	—
Previous stroke, *n* (%)	124 (13.1)	61 (12.7)	58 (13.2)	5 (20.0)
Previous TIA, *n* (%)	87 (9.2)	40 (8.3)	42 (9.5)	5 (20.0)
Previous AMI, *n* (%)	223 (23.5)	98 (20.3)	123 (27.9)	2 (8.0)
Previous VTE, *n* (%)	126 (13.3)	63 (13.1)	60 (13.6)	3 (12.0)
Previous bleeding, *n* (%)	223 (23.5)	100 (20.7)	120 (27.2)	3 (12.0)
Cancer disease, *n* (%)	253 (26.7)	121 (25.1)	126 (28.6)	6 (24.0)
CHA_2DS_2VASc, mean (SD)[a]	4.54 (1.68)	4.54 (1.64)	4.51 (1.71)	5.15 (1.98)
HASBLED, mean (SD)[b]	2.38 (1.15)	2.49 (1.18)	2.30 (1.12)	1.86 (0.85)

Abbreviations: AMI, acute myocardial infarction; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; TIA, transient ischemic attack; VKA, vitamin K antagonist; VTE, venous thromboembolism.

[a]Available in 859 patients only.

[b]Available in 870 patients only.

3.3 | Recurrent bleeding

During a median follow-up of 207 days (range 3–718 days), 210 (22.2%) patients experienced at least one recurrent clinically relevant bleeding, including 145 (15.3%) major bleeding and 65 (6.9%) clinically relevant non-major bleeding (Table 3). In total, there were 14 (9.7%) fatal bleeding events. The most frequent site of recurrent clinically relevant bleeding was the upper gastrointestinal

TABLE 2 Management of index gastrointestinal bleeding

	Overall *N* = 948	Upper gastrointestinal bleeding *N* = 482	Lower gastrointestinal bleeding *N* = 441	Unknown gastrointestinal bleeding site *N* = 25
Endoscopy, *n* (%)	784 (82.7)	435 (90.2)	332 (75.3)	17 (68.0)
Lesion treatment, *n* (%)	272 (28.7)	155 (32.2)	117 (26.5)	–
Supportive treatment, *n* (%)	726 (76.6)	405 (84.0)	301 (68.3)	20 (80.0)
Blood transfusion	572 (60.3)	331 (68.7)	222 (50.3)	19 (76.0)
Vitamin K	285 (30.1)	159 (33.0)	119 (27.0)	7 (28.0)
Fresh frozen plasma	35 (3.7)	22 (4.6)	13 (2.9)	–
Prothrombin complex concentrate	100 (10.5)	61 (12.7)	37 (8.4)	2 (8.0)
DOAC antidote	4 (0.4)	2 (0.4)	2 (0.5)	–
Proton pump inhibitor, *n* (%)	710 (74.9)	458 (95.0)	236 (53.5)	16 (64.0)
Anticoagulation interruption, *n* (%)	873 (92.1)	454 (94.2)	397 (90.0)	22 (88.0)
Bridge therapy with LMWH (%)				
Prophylactic dose	195 (20.6)	99 (20.5)	95 (21.5)	1 (4.0)
Therapeutic dose	73 (7.7)	39 (8.1)	34 (7.7)	–
Oral anticoagulant at discharge, *n* (%)				
Apixaban	150 (15.8)	67 (13.9)	79 (17.9)	4 (16.0)
Dabigatran	32 (3.4)	12 (2.5)	20 (4.5)	–
Edoxaban	2 (0.2)	–	2 (0.5)	–
Rivaroxaban	103 (10.9)	58 (12.0)	41 (9.3)	4 (16.0)
VKA	405 (42.7)	200 (41.5)	195 (44.2)	10 (40.0)
LMWH	12 (1.3)	8 (1.7)	4 (0.9)	–
None	244 (25.7)	137 (28.4)	100 (22.7)	7 (28.0)
Antiplatelet therapy at discharge, *n* (%)				
Aspirin	168 (17.7)	86 (17.8)	76 (17.2)	6 (24.0)
Dual antiplatelet therapy	14 (1.5)	2 (0.4)	12 (2.7)	–
Clopidogrel	30 (3.2)	14 (2.9)	15 (3.4)	1 (4.0)
Ticlopidine	1 (0.1)	1 (0.2)	–	–

Abbreviations: DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; VKA, vitamin K antagonist.

tract (*n* = 89; 42.4%), followed by the lower gastrointestinal tract (*n* = 77; 36.7%). In 58.1% of cases recurrent bleeding occurred in the same site of the index bleeding. Nine (4.3%) patients experienced an intracranial bleeding. The cumulative incidence of clinically relevant bleeding increased from 5.27% (95% CI 3.96–6.84) in the first 30 days to 25.26% (95% CI 22.31–28.32) after 2 years (Table 4). The incidence of recurrent bleeding, thromboembolism, and death according to the use of VKAs or DOACs at discharge are shown in Table S3 in supporting information.

In univariable analysis, anticoagulant treatment was not associated with recurrent clinically relevant bleeding (crude HR 1.38; 95% CI 0.97–1.95), major bleeding (crude HR 1.34; 95% CI 0.88–2.03), or clinically relevant non-major bleeding (crude HR 1.38; 95% CI 0.73–2.62). Significant predictors of recurrent clinically relevant bleeding were previous bleeding, index major bleeding, supportive treatment, and GFR (Table S2 in supporting information).

In multivariable analysis, the risk of recurrent clinically relevant bleeding was higher in patients on anticoagulant treatment (adjusted HR 1.55; 95% CI 1.08–2.22), patients with previous bleeding (HR 1.57; 95% CI 1.17–2.09), and in those who had an index major bleeding event (adjusted HR 1.91; 95% CI 1.21–3.01). The risk of recurrent major bleeding was lower in patients who underwent endoscopy and in those with higher GFR, whereas it was higher in patients with previous bleeding, cancer disease, index major bleeding, and prosthetic heart valve as indication for anticoagulation (Table 5).

TABLE 3 Outcomes according to index gastrointestinal bleeding site

	Overall N = 948	Upper gastrointestinal bleeding N = 482	Lower gastrointestinal bleeding N = 441	Unknown gastrointestinal bleeding site N = 25
Recurrent bleeding	210 (22.2)	104 (21.6)	101 (22.9)	5 (20.0)
Major bleeding	145 (15.3)	79 (16.4)	63 (14.3)	3 (12.0)
Major GI bleeding	106 (11.2)	56 (11.6)	50 (11.3)	–
CRNMB	65 (6.9)	25 (5.2)	38 (8.6)	2 (8.0)
Fatal bleeding	14 (1.5)	11 (2.3)	3 (0.7)	–
Fatal GI bleeding	8 (0.8)	7 (1.5)	1 (0.2)	–
Thromboembolism	77 (8.1)	42 (8.7)	35 (7.9)	–
AMI	3 (0.3)	1 (0.2)	2 (0.5)	–
Stroke	39 (4.1)	22 (4.6)	17 (3.9)	–
VTE	34 (3.6)	17 (3.5)	17 (3.9)	–
Systemic embolism	6 (0.6)	5 (1.0)	1 (0.2)	–
Death	185 (19.5)	102 (21.2)	81 (18.4)	2 (8.0)

Note: All results are presented as numbers and percentages.

Abbreviations: AMI, acute myocardial infarction; CRNMB, clinically relevant non-major bleeding; GI, gastrointestinal; VTE, venous thromboembolism.

TABLE 4 Cumulative incidence of recurrent bleeding, thromboembolism, and death since index gastrointestinal bleeding

Overall population (n = 948)	30 days	90 days	180 days	365 days	730 days
Clinically relevant bleeding	5.27 (3.96–6.84)	10.48 (8.6–12.57)	13.59 (11.45–15.92)	18.84 (16.32–21.5)	25.26 (22.31–28.32)
Major bleeding	3.87 (2.76–5.25)	7.76 (6.15–9.62)	9.95 (8.11–12.01)	13.16 (11.02–15.49)	17.5 (14.96–20.22)
CRNMB	1.4 (0.79–2.33)	2.73 (1.82–3.95)	3.67 (2.58–5.04)	5.77 (4.35–7.47)	7.98 (6.23–10.00)
Thromboembolism	2.36 (1.52–3.49)	3.58 (2.52–4.93)	4.62 (3.39–6.13)	5.86 (4.44–7.55)	7.42 (5.75–9.36)
Death	5.27 (3.96–6.84)	8.74 (7.02–10.68)	11.99 (9.97–14.21)	16.02 (13.67–18.55)	22.96 (20.05–26.00)

Note: Data are provided as numbers and percentages. Thromboembolism includes acute myocardial infarction, stroke, venous thromboembolism, and systemic embolism.

Values in brackets represent 95% confidence intervals.

Abbreviations: CRNMB, clinically relevant non-major bleeding.

3.4 | Thromboembolism

A total of 77 (8.1%) patients developed one or more thrombotic events during an average period of 175 days (range 3–718 days). Thrombotic events included acute myocardial infarction in 3 (3.9%) patients, ischemic stroke in 39 (50.1%), systemic embolism in 6 (7.8%), and VTE in 34 (44.2%). The cumulative incidence of thromboembolic events was 2.36% (95% CI 1.52–3.49) in the first 30 days and 7.42% (95% CI 5.75–9.36) at the end of the study period (Table 4).

In multivariable analysis, anticoagulant treatment was associated with a significantly lower risk of thromboembolism (adjusted HR 0.34; 95% CI 0.21–0.55; Table 5).

3.5 | Death

During the study period, 185 (19.5%) patients died after a median of 118 days (range 1–718). The cause of death was bleeding in 14 patients (7.6%), stroke in 19 (10.3%), respiratory failure in 20 (10.8%), acute myocardial infarction in 2 (1.1%), cancer progression in 10 (5.4%), other in 61 (33%), and unknown in 59 (31.9%) patients. The cumulative incidence of death increased from 5.27% (95% CI 3.96–6.84) in the first 30 days to 22.96% (95% CI 20.05–26.00) at the end of the study (Table 4).

In multivariable analysis, anticoagulant treatment (adjusted HR 0.50; 95% CI 0.36–0.68), GFR (adjusted HR 0.98 per 1 ml/min/1.73 m² increase; 95% CI 0.97–0.99), and previous bleeding (adjusted HR 0.63; 95% CI 0.43–0.91) were associated with a lower risk of death, whereas age (adjusted HR 1.03 per 1 year increase; 95% CI 1.02–1.05) and supportive treatment (adjusted HR 1.66; 95% CI 1.01–2.72) were associated with a higher risk (Table 5).

3.6 | Time to anticoagulation resumption

A total of 848 (89.5%) patients were included in the landmark analysis. During the first 90 days after the gastrointestinal index bleeding,

TABLE 5 Multivariable cox models

	Clinically relevant bleeding	Major bleeding	CRNMB	Thromboembolism	Death
	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)
Treatment, on-treatment	1.55 (1.08–2.22)	1.47 (0.96–2.26)	1.63 (0.85–3.15)	0.34 (0.21–0.55)	0.50 (0.36–0.68)
Age	1.01 (0.99–1.02)	1.00 (0.98–1.02)	1.02 (0.99–1.05)	1.00 (0.98–1.02)	1.03 (1.02–1.05)
Sex, male sex	1.05 (0.79–1.39)	1.04 (0.74–1.46)	1.05 (0.63–1.73)	0.87 (0.54–1.38)	1.11 (0.82–1.49)
Previous bleeding	1.57 (1.17–2.09)	1.52 (1.07–2.15)	1.56 (0.92–2.64)	0.56 (0.30–1.04)	0.63 (0.43–0.91)
Cancer disease	1.32 (0.97–1.78)	1.53 (1.07–2.18)	0.84 (0.47–1.51)	1.12 (0.68–1.85)	1.25 (0.91–1.71)
Index major bleeding	1.91 (1.21–3.01)	2.21 (1.23–3.97)	1.37 (0.66–2.85)	0.75 (0.39–1.46)	1.00 (0.64–1.57)
Endoscopy	0.69 (0.48–1.00)	0.61 (0.39–0.94)	0.99 (0.50–1.96)	1.83 (0.82–4.08)	0.76 (0.52–1.11)
Supportive treatment	0.96 (0.62–1.49)	1.14 (0.65–2.02)	0.72 (0.36–1.47)	2.19 (0.99–4.85)	1.66 (1.01–2.72)
Prosthetic valve	1.24 (0.80–1.90)	1.80 (1.13–2.85)	0.29 (0.09–1.01)	0.85 (0.35–2.06)	1.19 (0.72–1.96)
Atrial fibrillation	1.00 (0.58–1.72)	1.35 (0.71–2.56)	0.37 (0.12–1.18)	1.27 (0.48–3.32)	1.06 (0.54–2.06)
VTE	1.03 (0.58–1.82)	1.15 (0.58–2.28)	0.57 (0.18–1.85)	1.26 (0.50–3.20)	0.67 (0.34–1.33)
GFR, ml/min/1.73 m^2	0.98 (0.97–0.99)	0.98 (0.96–0.99)	1.00 (0.98–1.02)	1.00 (0.99–1.02)	0.98 (0.97–0.99)

Note: Supportive treatment includes one or more of the following: red blood cell transfusion, vitamin K, fresh frozen plasma, prothrombin complex concentrates or DOAC antidote.

Hazard Ratios for GFR and age refer to single unit increase.

Abbreviations: 95% CI, 95% confidence interval; CRNMB, clinically relevant non-major bleeding; GFR, glomerular filtration rate; HR, hazard ratio; VTE, venous thromboembolism.

TABLE 6 Landmark analysis

	On treatment	Off treatment	Crude hazard ratio (95% confidence intervals)
Landmark 7 days			
Clinically relevant bleeding	42/384	30/443	1.52 (0.95–2.43)
Thromboembolism	4/387	27/445	0.16 (0.05–0.45)
Death	15/389	52/446	0.30 (0.17–0.54)
Landmark 14 days			
Clinically relevant bleeding	45/490	16/298	1.63 (0.92–2.88)
Thromboembolism	5/493	17/298	0.16 (0.06–0.45)
Death	20/499	32/302	0.35 (0.20–0.62)
Landmark 21 days			
Clinically relevant bleeding	43/518	10/248	1.99 (1.00–3.96)
Thromboembolism	4/524	12/246	0.15 (0.05–0.45)
Death	19/531	24/253	0.35 (0.19–0.65)

there were 82 (9.7%) clinically relevant bleeding events, 36 (4.2%) thromboembolic events, and 76 (9.0%) patients died.

At all landmark points, patients on anticoagulant treatment had a significantly lower risk of thromboembolic events and mortality. The risk of bleeding increased after anticoagulation resumption independently of whether restart occurred during the first week or later time points (Table 6). In the sensitivity analysis, in which patients in the off-treatment group were censored at the time of anticoagulation resumption and patients in the on-treatment group were censored at the time of the anticoagulation interruption, results were materially unchanged (Table S4 in supporting information).

4 | DISCUSSION

The results of the current study show a substantial risk of recurrent clinically relevant bleeding in patients who experience gastrointestinal bleeding during anticoagulant treatment with DOACs or VKAs. Anticoagulant therapy after the index bleeding event is associated with lower risk of thromboembolism and death, but a higher risk of recurrent bleeding. The latter seemed to be influenced by specific patient characteristics and treatment of the index bleeding and less impacted by the time of resumption.

Several retrospective cohort studies consistently reported a lower risk of thromboembolism and death in patients restarting

VKAs or DOACs after a major gastrointestinal bleeding.[12,13,21,22,24,25] While the effects of anticoagulation resumption on recurrent bleeding have been conflicting, two recent meta-analyses concluded that restarting anticoagulation may increase this risk.[12,13] It is important to note that most of these earlier studies included patients treated with VKAs with few to no patients on DOACs. In a recent large retrospective cohort of patients with gastrointestinal bleeding during treatment with DOACs, resuming DOACs was not associated with thromboembolism or recurrent bleeding.[26] The apparent discrepancy of these data with previous and current findings may be related to differences in study populations, assumptions made to evaluate DOAC exposure, and assessment of clinical outcomes. Our results extend those from studies focusing on VKAs to patients treated with DOACs suggesting a favorable net clinical benefit for anticoagulation resumption. In the current study, anticoagulant treatment was considered as a time-varying variable, which allowed us to estimate more precisely the incidence of events during periods of effective exposure. In addition, the association between anticoagulant use and events was corrected for potential confounders, which included relevant patient characteristics as well as endoscopic treatment provided for the index bleeding event.[11]

Previous bleeding (prior to the index event) was associated with higher risk of recurrent bleeding independently of anticoagulation resumption, consistent with the results of a recent study of patients with atrial fibrillation treated with DOACs or VKAs.[27] The risk of recurrent bleeding was higher in patients with index major bleeding and lower in those who underwent endoscopy. Supportive treatment with either red blood cell transfusion, vitamin K, fresh frozen plasma, prothrombin complex concentrates, or DOAC antidote appeared to increase the risk of death. The latter association should be interpreted cautiously as it may be potentially confounded by the worse prognosis of patients receiving supportive treatment.[28] According to a recent survey, the most important factor influencing provider decision making regarding resumption of oral anticoagulants was the risk of recurrent bleeding followed by thrombosis risk.[10] Thus, if confirmed in future studies, our findings may help physicians identify patient subgroups with heightened risk of recurrent bleeding, who could benefit from closer clinical monitoring.

The optimal timing of anticoagulant treatment resumption is unclear. In a recent retrospective cohort, Majeed and colleagues found that restarting anticoagulation between 3 and 6 weeks was associated with the lowest risk of a composite outcome of recurrent bleeding and thromboembolism.[21] Qureshi and colleagues suggested that resumption of anticoagulation after the first week reduced thromboembolism without increasing recurrent bleeding.[22] In our study the risk of recurrent bleeding was particularly high in patients resuming anticoagulant treatment during the first week (11%) and tended to decrease only slightly in those restarting after the second or third week (8–9%). In agreement with previous observations, thrombosis rates were similar regardless of the duration of anticoagulant therapy interruption.[24] Taken together, these findings suggest that patient-related factors like previous bleeding and the management of index bleeding may be more relevant to guide decisions about anticoagulation resumption than timing since index event. Future prospective studies are warranted to evaluate the safety and efficacy of restarting anticoagulation at lower intensity or later time points in patients with bleeding risk factors in whom the risk of recurrent bleeding may outweigh the risk of thromboembolism.[29]

The strengths of the current study are the large size, long-term follow-up, and the central adjudication of all thrombotic and bleeding events. The study was performed at five large tertiary care medical centers in three countries, which may increase the generalizability of the findings.

There are some limitations that need to be discussed. The decision to discontinue, restart, and timing of resumption of anticoagulant treatment was not dictated by the study and was made by the physicians directly responsible for patient care. Several factors might have influenced this decision, potentially affecting the association between anticoagulation resumption and clinical events. For example, patients perceived at high risk for further bleeding probably were less likely to resume therapy, which may have underestimated the association between recurrent bleeding and anticoagulation restart. Similarly, patients in whom anticoagulation was discontinued may have been sicker and at higher risk for adverse events, which could confound the association between anticoagulation resumption and lower mortality. The risk of immortal bias was partly mitigated by the use of time-dependent analysis.

In exploratory univariable analysis there was no association between the use of antiplatelet agents at admission and at discharge with the outcomes (data not shown). We were unable to accurately track antiplatelet use, adherence, and persistence to anticoagulant treatment after the index gastrointestinal bleeding, which may have potentially affected the strength of the associations. Although the current study includes one of the largest cohorts of patients with gastrointestinal bleeding during anticoagulant treatment, the number of patients and outcomes was still relatively low to perform explorative analysis on relevant subgroups of patients like those receiving different DOACs or patients with prosthetic heart valves. Finally, due to the retrospective design, we were not able to collect information on all potentially relevant bleeding and thrombotic risk factors, and residual confounding cannot be excluded.

In summary, patients with gastrointestinal bleeding during anticoagulant treatment have a substantial risk of recurrent bleeding. The risk is particularly high in patients with previous bleeding, lower GFR, and in those with index major bleeding. The resumption of anticoagulant therapy is associated with lower risk of thromboembolism but higher risk of bleeding regardless of resumption time.

CONFLICTS OF INTEREST

Marc Carrier has received research funding from BMS, Pfizer, and Leo Pharma. He has also received honoraria from Bayer, Pfizer, BMS, Servier, and Leo Pharma. Sam Schulman has received research funding from Boehringer Ingelheim and Octapharma and honoraria from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Pfizer, and Sanofi. Walter Ageno has received research funding from Bayer and BMS-Pfizer and honoraria from Aspen, Bayer,

BMS-Pfizer, Daiichi Sankyo, Sanofi, Janssen, Portola, and Werfen. Marcello Di Nisio has received honoraria from Bayer, BMS-Pfizer, Daiichi Sankyo, Sanofi, and Leo Pharma. All other authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Study conception and design: Marcello Di Nisio, Matteo Candeloro; data acquisition: Nathan Cantor, Jesus Aibar, Marco Paolo Donadini, Roisin Bavalia, Marie-Pier Arsenault, Noemi Ferrante, Andrea D'Addezio, Stefano Sormani; statistical analysis: Matteo Candeloro, Nick van Es; interpretation of the data: Matteo Candeloro, Marcello Di Nisio, Nick van Es; drafting of the manuscript: Matteo Candeloro, Marcello Di Nisio; critical revision of the manuscript for important intellectual content: Sam Schulman, Marc Carrier, Walter Ageno, Michiel Coppens, Ettore Porreca; final approval of the manuscript: all authors.

ORCID

Matteo Candeloro https://orcid.org/0000-0001-9673-4073
Roisin Bavalia https://orcid.org/0000-0002-1806-1050
Marcello Di Nisio https://orcid.org/0000-0001-5930-7304

TWITTER

Matteo Candeloro @Matteocandeloro

REFERENCES

1. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2021;42(5):373-498. https://academic.oup.com/eurheartj/article/42/5/373/5899003.
2. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38(36):2739-2791. https://academic.oup.com/eurheartj/article/38/36/2739/4095039.
3. Heit JA. Epidemiology of venous thromboembolism. *Nat Rev Cardiol*. 2015;12(8):464-474. http://www.nature.com/articles/nrcardio.2015.83.
4. Piran S, Schulman S. Treatment of bleeding complications in patients on anticoagulant therapy. *Blood*. 2019;133(5):425-435. https://ashpublications.org/blood/article/133/5/425/272782/Treatment-of-bleeding-complications-in-patients-on.
5. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383(9921):955-962. https://linkinghub.elsevier.com/retrieve/pii/S0140673613623430.
6. van Es N, Coppens M, Schulman S, Middeldorp S, Büller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. *Blood*. 2014;124(12):1968-1975. https://ashpublications.org/blood/article/124/12/1968/33035/Direct-oral-anticoagulants-compared-with-vitamin-K.
7. Weitz JI, Pollack CV. Practical management of bleeding in patients receiving non-vitamin K antagonist oral anticoagulants. *Thromb Haemostas*. 2015;114(12):1113-1126.
8. Miller CS, Dorreen A, Martel M, Huynh T, Barkun AN. Risk of gastrointestinal bleeding in patients taking non-vitamin K antagonist oral anticoagulants: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2017;15(11):1674-1683.e3. https://linkinghub.elsevier.com/retrieve/pii/S1542356517305232.
9. Bassand J-P, Virdone S, Badoz M, et al. Bleeding and related mortality with NOACs and VKAs in newly diagnosed atrial fibrillation: results from the GARFIELD-AF registry. *Blood Adv*. 2021;5(4):1081-1091. https://ashpublications.org/bloodadvances/article/5/4/1081/475241/Bleeding-and-related-mortality-with-NOACs-and-VKAs.
10. Little DHW, Robertson T, Douketis J, et al. Management of antithrombotic therapy after gastrointestinal bleeding: a mixed methods study of health-care providers. *J Thromb Haemost*. 2021;19(1):153-160. https://onlinelibrary.wiley.com/doi/ https://doi.org/10.1111/jth.15111.
11. Carrier M. Systematic review: case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism. *Ann Int Med*. 2010;152(9):578. http://annals.org/article.aspx?doi= https://doi.org/10.7326/0003-4819-152-9-201005040-00008.
12. Little D, Chai-Adisaksopha C, Hillis C, et al. Resumption of anticoagulant therapy after anticoagulant-related gastrointestinal bleeding: a systematic review and meta-analysis [Internet]. *Thromb Res*. 2019;175:102-109.
13. Tapaskar N, Pang A, Werner DA, Sengupta N. Resuming anticoagulation following hospitalization for gastrointestinal bleeding is associated with reduced thromboembolic events and improved mortality: results from a systematic review and meta-analysis. *Dig Dis Sci*. 2021;66(2):554-566. http://link.springer.com/ https://doi.org/10.1007/s10620-020-06248-9.
14. Tomaselli GF, Mahaffey KW, Cuker A, et al. 2020 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants. *J Am Coll Cardiol*. 2020;76(5):594-622. https://linkinghub.elsevier.com/retrieve/pii/S0735109720351548.
15. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61(4):344-349. https://linkinghub.elsevier.com/retrieve/pii/S0895435607004362.
16. Bounds BC, Kelsey PB. Lower gastrointestinal bleeding. *Gastrointest Endosc Clin N Am*. 2007;17(2):273-288. https://linkinghub.elsevier.com/retrieve/pii/S1052515707000281.
17. Kamboj AK, Hoversten P, Leggett CL. Upper gastrointestinal bleeding: etiologies and management. *Mayo Clin Proc*. 2019;94(4):697-703. https://linkinghub.elsevier.com/retrieve/pii/S0025619619300916.
18. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. *J Thromb Haemost*. 2015;13(11):2119-2126. http://doi.wiley.com/https://doi.org/10.1111/jth.13140
19. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3(4):692-694. http://doi.wiley.com/ https://doi.org/10.1111/j.1538-7836.2005.01204.x.
20. Therneau T, Cynthia Crowson EA. Using time dependent covariates and time dependent coefficients in the cox model. 2020.
21. Majeed A, Wallvik N, Eriksson J, et al. Optimal timing of vitamin k antagonist resumption after upper gastrointestinal bleeding a risk modelling analysis. *Thromb Haemost*. 2017;117(3):491-499.
22. Qureshi W, Mittal C, Patsias I, et al. Restarting anticoagulation and outcomes after major gastrointestinal bleeding in atrial fibrillation. *Am J Cardiol*. 2014;113(4):662-668. https://linkinghub.elsevier.com/retrieve/pii/S0002914913022571.

23. Milling TJ, King B, Yue P, et al. Restart of anticoagulant therapy and risk of thrombosis, rebleeding and death after factor Xa inhibitor reversal in major bleeding patients. *Thrombo Haemost*. 2021;121(8):1097-1106.
24. Witt DM, Delate T, Garcia DA, et al. Risk of thromboembolism, recurrent hemorrhage, and death after warfarin therapy interruption for gastrointestinal tract bleeding. *Arch Intern Med*. 2012;172(19):1484. http://archinte.jamanetwork.com/article.aspx?doi= https://doi.org/10.1001/archinternmed.2012.4261.
25. Little DHW, Sutradhar R, Cerasuolo JO, et al. Rates of rebleeding, thrombosis and mortality associated with resumption of anticoagulant therapy after anticoagulant-related bleeding. *Can Med Assoc J*. 2021;193(9):E304-E309. http://www.cmaj.ca/lookup/doi/ https://doi.org/10.1503/cmaj.201433.
26. Sengupta N, Marshall AL, Jones BA, Ham S, Tapper EB. Rebleeding vs thromboembolism after hospitalization for gastrointestinal bleeding in patients on direct oral anticoagulants. *Clin Gastroenterol Hepatol*. 2018;16(12):1893-1900.e2.
27. Adam L, Feller M, Syrogiannouli L, et al. Novel bleeding risk score for patients with atrial fibrillation on oral anticoagulants, including direct oral anticoagulants. *J Thromb Haemost*. 2021;19:931-940. https://doi.org/10.1111/jth.15251.
28. García-Iglesias P, Villoria A, Suarez D, et al. Meta-analysis: predictors of rebleeding after endoscopic treatment for bleeding peptic ulcer. *Aliment Pharmacol Ther*. 2011;34(8):888-900. http://doi.wiley.com/ https://doi.org/10.1111/j.1365-2036.2011.04830.x.
29. Radaelli F, Dentali F, Repici A, et al. Management of anticoagulation in patients with acute gastrointestinal bleeding. *Dig Liver Dis*. 2015;47(8):621-627. Available from https://linkinghub.elsevier.com/retrieve/pii/S159086581500273X.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Candeloro M, van Es N, Cantor N, et al. Recurrent bleeding and thrombotic events after resumption of oral anticoagulants following gastrointestinal bleeding: Communication from the ISTH SSC Subcommittee on Control of Anticoagulation. *J Thromb Haemost*. 2021;19:2618–2628. https://doi.org/10.1111/jth.15476