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THERAPY IN PRACTICE

Management of Gastrointestinal Bleeding and Resumption of Oral Anticoagulant Therapy in Patients with Atrial Fibrillation: A Multidisciplinary Discussion

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Abstract

Direct oral anticoagulants (DOACs) are recommended for the prevention of thromboembolism in patients with atrial fibrillation (AF), and are now preferred over vitamin K antagonists due to their beneficial efficacy and safety profile. However, all oral anticoagulants carry a risk of gastrointestinal (GI) bleeding. Although the risk is well documented and acute bleeding well codified, there is limited high-quality evidence and no guidelines to guide physicians on the optimal management of anticoagulation after a GI bleeding event. The aim of this review is to provide a multidisciplinary critical discussion of the optimal management of GI bleeding in patients with AF receiving oral anticoagulants to help physicians provide individualized treatment for each patient and optimize outcomes. It is important to perform endoscopy when a patient presents with bleeding manifestations or hemodynamic instability to determine the bleed location and severity of bleeding and then perform initial resuscitation. Administration of all anticoagulants and antiplatelets should be stopped and bleeding allowed to resolve with time; however, anticoagulant reversal should be considered for patients who have life-threatening bleeding or when the bleeding is not controlled by the initial resuscitation. Anticoagulation needs to be timely resumed considering that bleeding risk outweighs thrombotic risk when anticoagulation is resumed early after the bleeding event. To prevent further bleeding, physicians should prescribe anticoagulant therapy with the lowest risk of GI bleeding, avoid medications with GI toxicity, and consider the effect of concomitant medications on potentiating the bleeding risk.

Key Points

While oral anticoagulants are recommended for the prevention of thromboembolism in patients with atrial fibrillation (AF), a major complication of their use is an increased risk of bleeding, including gastrointestinal (GI) bleeding.

Severe GI bleeding is associated with poor prognosis; however, reintroduction of oral anticoagulants after GI bleeding management is associated with increased survival rates.

The optimal management of GI bleeding in patients receiving anticoagulants relies on multidisciplinary care, including gastroenterologists and cardiologists, as well as intensivists and hemostasis specialists in particular cases, to provide an individualized optimal balance of benefit and risk.

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1 Introduction

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia that increases the risk of cardiovascular events such as stroke, systemic embolism, and heart failure and promotes the worsening of cardiac and noncardiac conditions [1, 2]. According to the Global Burden of Disease Study, there were 37.57 million [95% uncertainty interval (UI) 32.55–42.59] prevalent cases of AF and 3.05 million (95% UI 2.61–3.51) incident cases of AF worldwide in 2017 [2]. The prevalence of AF has nearly doubled between 1990 and 2017, and rates are expected to keep increasing due to the aging population [2].

European guidelines recommend the use of direct oral anticoagulants (DOACs) such as dabigatran, rivaroxaban, apixaban, or edoxaban for the prevention of stroke and systemic embolism in AF [3, 4]. Their mechanism of action is based on the direct inhibition of activated coagulation factors; dabigatran inhibits thrombin (factor IIa), while rivaroxaban, apixaban, and edoxaban inhibit factor Xa [5–10]. Overall, DOACs are preferred over vitamin K antagonists (VKA) such as warfarin in adult patients, except in the context of pregnancy and in patients with mechanical valve prosthesis, triple-positive antiphospholipid syndrome, or end-stage kidney disease [3, 11]. DOACs are being increasingly used due to their improved efficacy/safety ratio, predictable anticoagulant effect without need for routine coagulation monitoring, fixed dose regimens, and fewer food and drug interactions compared with VKAs [12]. However, gastrointestinal (GI) bleeding remains a serious and challenging complication of any anticoagulant medication [13]. The management of acute major bleeding in patients treated with anticoagulants is well codified [14], but there is a lack of standardized protocols as to how and when to resume anticoagulant therapy after GI bleeding. As such, international guidelines recommend the development of a hospital-based multidisciplinary approach including cardiologists, gastroenterologists, emergency physicians/intensive care specialists, hemostasis experts, and others to optimally treat patients with GI bleeding [3].

This article aims to critically discuss the optimal approach to the multidisciplinary management of GI bleeding in patients with AF receiving anticoagulants.

2 Risk of GI Bleeding Depending on the Type of Oral Anticoagulant

All anticoagulants may promote or potentiate bleeding from a preexisting GI lesion. Although the pathophysiology remains unclear [15], several mechanisms by which anticoagulant agents may contribute to GI bleeding have been suggested [16]. For example, warfarin has been associated with GI bleeding via a systemic decrease in vitamin-K-dependent clotting factors; because warfarin is not directly active, 95% of a dose is absorbed in the GI tract and the unabsorbed 5% does not have anticoagulant activity [13, 17, 18]. In contrast, factor Xa inhibitors are directly active and are not completely absorbed, so the unabsorbed drug may have a direct topical effect on GI tissues, potentially increasing the risk of bleeding [17]. The dabigatran prodrug has only 6% oral bioavailability, and the unabsorbed prodrug could be activated intraluminally during transit through the GI tract. Factor Xa inhibitors have higher (50–80%) oral bioavailability than dabigatran [19] and are reported to have different GI bleeding safety profiles. It is also possible that anticoagulants induce bleeding by compromising GI mucosal integrity and/or inhibiting its healing [17, 20].

The comparative bleeding risk of VKAs (warfarin) and DOACs in patients with AF has been evaluated in several clinical trials. In the RE-LY trial, the risk of major GI bleeding with dabigatran was dose dependent, and only higher doses of dabigatran [150 mg twice daily (BID) but not 110 mg BID] increased bleeding risk compared with warfarin [1.51% versus 1.02% per year, respectively; relative risk (RR) 1.50; 95% confidence interval (CI) 1.19–1.89; $p < 0.001$] [21]. Similarly, in the ENGAGE AF-TIMI 48 trial, edoxaban doses of 60 mg once daily (QD) but not 30 mg QD significantly increased GI major bleeding risk in patients versus warfarin [60 mg QD of edoxaban, 1.51% versus warfarin, 1.23% per year; hazard ratio (HR) 1.23; 95% CI 1.02–1.50 per year; $p = 0.03$; and 30 mg QD of edoxaban, 0.82% versus warfarin, 1.23%; HR 0.67; 95% CI 0.53–0.83; $p < 0.001$] [22]. The ROCKET AF trial showed that major GI bleeding was significantly higher in patients treated with 20 mg rivaroxaban QD compared with warfarin (2.00% versus 1.24% per year, respectively; HR 1.66; 95% CI 1.34–2.05; $p < 0.0001$) [23]. Similar rates of major GI bleeding were found in the ARISTOTLE trial between 5 mg apixaban BID and warfarin (0.76% versus 0.86% per year, respectively; HR 0.89; 95% CI 0.70–1.15; $p = 0.37$) [24]. In the absence of direct head-to-head comparisons between DOACs, no conclusions can be drawn regarding which drug has the lowest GI bleeding risk [25]. Differences between DOACs could be due to differences in dosage, reporting of GI bleeding, or the study population (e.g., compared with the RE-LY and ARISTOTLE trial populations, the ROCKET-AF trial population was older and had more comorbidities at baseline) [21, 23, 24]. Whether the different chemical structures and differences in the pharmacodynamic and pharmacokinetic characteristics have an impact on the GI bleeding risk between DOACs is still unknown [16, 26].

3 Clinical Factors that Predict Bleeding and Poor Prognosis in Anticoagulant-Treated Patients

Advanced age, intestinal ischemia, multiple comorbidities, blood cell transfusion, and in-hospital bleeding in the lower GI tract have been reported as risk factors for in-hospital mortality, post-discharge mortality, and 30-day hospital readmissions [27]. Hypertension [systolic blood pressure (SBP) > 160 mmHg], stroke, low hemoglobin (< 13 g/dL in men and < 12 g/dL in women), coexisting hepatic or renal diseases, and concomitant use of medications that affect hemostasis (e.g., antiplatelet therapy) increase morbidity and worsen outcomes in patients treated with anticoagulants [28].

The GI bleeding risk with DOACs depends on the dosage and type of DOAC used, on patient characteristics [ethnicity, older age (> 75 years), and comorbidities such as chronic kidney disease (CKD) and cirrhosis], and on concomitant use of other medications such as proton pump inhibitors (PPIs) or histamine H_2-receptor antagonists [13, 29, 30]. Acute coronary syndrome has also been related to an increased risk of GI bleeding [odds ratio (OR) 5.21] in patients treated with DOACs, especially those who are co-prescribed antiplatelet agents [13]. Another risk factor for DOAC-related GI bleeding is renal impairment. AF affects about 18% of patients with CKD and > 25% of patients with CKD older than 70 years [31]; compared with the general population, patients with CKD receiving DOACs have an increased risk of thromboembolism and bleeding due to altered pharmacokinetics, decreased clearance, and altered volume of distribution because of reduced kidney function and limited protein binding [32]. However, the benefit–risk profile of DOACs has been reported to be superior to that of VKAs in the early stages of CKD [32, 33]. Patients with cirrhosis are also at an increased risk of bleeding compared with the general population. No DOACs are recommended in Child–Pugh score C. In Child–Pugh score B, rivaroxaban is not recommended, while dabigatran, apixaban, and edoxaban should be used with caution [3]; however, more data are needed to evaluate how cirrhosis increases the bleeding risk in patients treated with DOACs [34].

Elderly patients present a particular challenge because of coexisting comorbidities, frailty, and concomitant medications increasing the risk of drug interactions [35]. A study comparing the risk of GI bleeding with dabigatran, rivaroxaban, or apixaban in patients with AF showed that rates of events for all DOACs increased among patients 75 years or older. However, apixaban had a lower risk of association with GI bleeding in the very elderly than dabigatran or rivaroxaban [36].

Several scores have been described to assess bleeding risk, especially in patients with AF exposed to long-term anticoagulation therapy. The HAS-BLED scale identifies patients at higher risk of bleeding by assessing the following risk factors: hypertension (SBP > 160 mmHg), abnormal renal and/or liver function, history of stroke or thromboembolism, history of bleeding or bleeding diathesis (severe anemia), age > 65 years, use of aspirin or nonsteroidal antiinflammatory drugs, and alcohol abuse [37]. The use of this tool may help to design individualized anticoagulant therapy on the basis of patient characteristics, especially in patients with an elevated bleeding risk [28]. In a systematic review commissioned by the PCORI including 38 studies on bleeding risk prediction, the HAS-BLED score had the best evidence for predicting bleeding risk [38]. However, this score and other bleeding scores (i.e., ATRIA) yielded only moderate discrimination ($c = 0.60$, 95% CI 0.59–0.62 for the HAS-BLED score and $c = 0.63$, 95% CI 0.61–0.65 for the ATRIA bleeding risk score in the ORBIT-AR Registry) and should be critically used [39].

4 Key Steps to Triage Patients on Active Anticoagulant Treatment and GI Bleeding in the Emergency Department

When a patient enters the emergency department with a suspected clinically relevant GI bleed, it is important to evaluate the patient's medical history, dosage, and timing of last DOAC intake [13], concomitant medications, and presenting/underlying conditions along with severity, location, and potential source of the bleeding [40] (Table 1, Fig. 1). Additionally, vital signs such as blood pressure, temperature, and cardiac and respiratory frequency as well as the status of hemorrhagic shock should be assessed [41, 42], and history of prior digestive system bleeding episodes should be investigated [42]. Possible bleeding locations other than the GI tract should be excluded [43]. Simultaneously, hemodynamic and cardiorespiratory stabilization must be performed. Resuscitation measures must be applied according to the Airway, Breathing, Circulation, Disability, Exposure (ABCDE) approach. Additionally, consider oxygen supplementation and orotracheal intubation to protect the patient's airway in case of persistent hematemesis or change in consciousness level [42, 44]. Oxygen supplementation should be administered with caution due to the potential release of free oxygen radicals that may negatively impact myocardium and cardiac function [45]. One of the immediate priorities in a patient with GI bleeding is to establish intravenous (IV) access in order to provide volume resuscitation. The European Society of Gastrointestinal Endoscopy recommends a restrictive red blood cell (RBC) transfusion with a target hemoglobin level between 7 and 9 g/dL; a higher target

Table 1. Multidisciplinary guidelines for resuming DOACs in a patient with upper gastrointestinal bleeding, considering endoscopic parameters and thromboembolic risk

	Low risk of thrombosis CHA_2DS_2-VASc score 0–1	High risk of thrombosis CHA_2DS_2-VASc score ≥ 2 or >3
Low risk of bleeding **Forrest ulcer > 2, OV with no red sign** Endoscopic procedure with low risk of bleeding	Rethink the need for DOACs?	Stop DOACs for 1–3 days and restart once stabilized
High risk of bleeding **Forrest 1 or 2 ulcer, OV with red sign** Endoscopic procedure with high risk of bleeding	Rethink the need for DOACs and, if necessary, restart after a 3-day break	Stop DOACs for 3 days and restart once stabilized with endoscopic control If possible, delay the endoscopic procedure

CHA_2DS_2-VASc congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease, age 65–74 years, sex category, *DOAC* direct oral anticoagulants, *OV* esophageal varices.

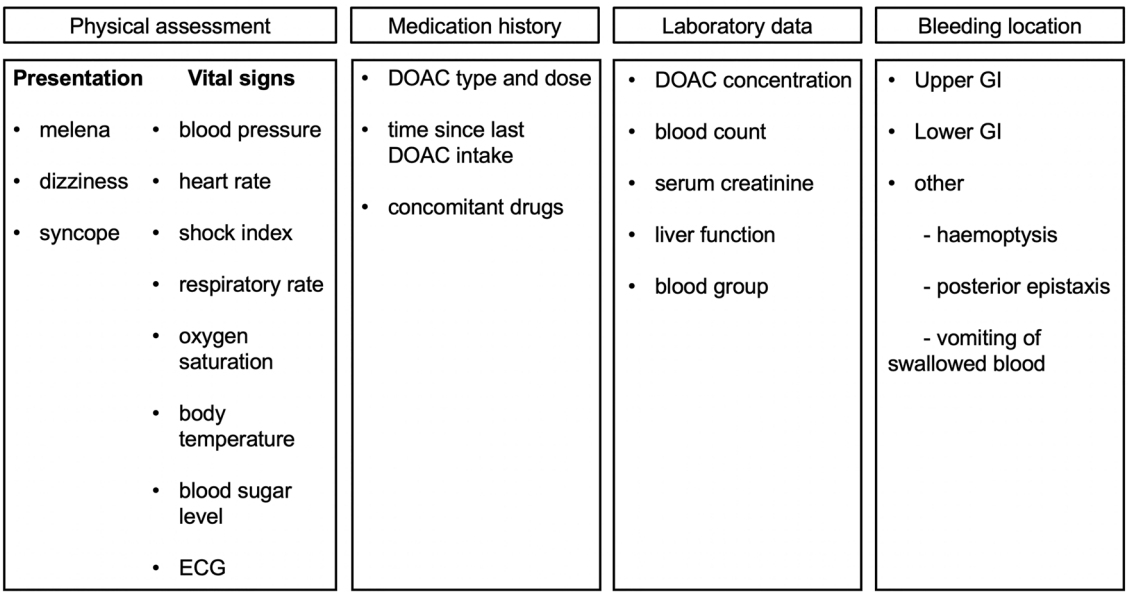

Fig. 1 Parameters to consider in the management of a patient at the emergency department with suspected clinically relevant GI bleeding. *DOAC* direct oral anticoagulant, *ECG* electrocardiogram, *GI* gastrointestinal, *INR* international normalized ratio

hemoglobin should be considered in patients with significant comorbidity, such as a history of myocardial infarction [42]. Several scales have been developed to define bleeding severity, including the Thrombolysis in Myocardial Infarction (TIMI), Global Usage of Strategies to Open Occluded Arteries (GUSTO), and Bleeding Academic Research Consortium (BARC) scales, and these are widely used in clinical trials.

The International Society on Thrombosis and Hemostasis (ISTH) defines major bleeding as symptomatic bleeding in a critical organ or area, and/or causing a ≥ 20 g/L fall in hemoglobin or requiring a transfusion of ≥ 2 units of whole blood or red cells [46, 47]. In addition to these parameters, the American College of Cardiology includes hemodynamic instability [increased heart rate, SBP < 90 mmHg, decrease in SBP > 40 mmHg, or orthostatic blood pressure changes, SBP drop of ≥ 20 mmHg or diastolic blood pressure (DBP) drop of ≥ 10 mmHg upon standing] [14]. The Haute Autorité de Santé (HAS) defines severe bleeding as bleeding that requires urgent and specific management; any other bleeding situation is classified as nonsevere. Severe bleeding events are those that are accompanied by one or more of the following criteria: externalized bleeding that cannot be stopped by application of conventional methods,

hemodynamic instability (SBP < 90 mmHg or ≥ 40 mmHg lower than usual, or mean arterial pressure < 65 mmHg, or signs of shock), need for an emergency procedure to stop the bleeding (e.g., endoscopy, interventional radiology, or surgery), need for packed RBC transfusion, and bleeding that is life-threatening or compromises function (including acute GI bleeding) [48, 49].

In patients with upper GI hemorrhage, the Glasgow-Blatchford score (GBS) has been useful for stratifying the risk of needing treatment to manage bleeding in patients treated with anticoagulants and includes the following parameters: hemoglobin and blood urea nitrogen levels, initial SBP, heart rate, presence of melena or syncope, and presence of heart failure or hepatic disease [50]. If a peptic ulcer is the likely cause of upper GI bleeding, IV PPIs (e.g., omeprazole bolus of 80 mg then 8 mg/h infusion) may be administered for 72 h, followed by early transition to oral PPI therapy. The platelet plug is best stabilized if the gastric pH is greater than 5.4, that can be achieved with various PPIs infusion regimen or an oral route when possible. In patients with cirrhosis, esophageal varices are the likely source of bleeding, and these patients should receive somatostatin analogs (e.g., octreotide) and antibiotics (e.g., ceftriaxone or fluoroquinolones) [51]. Somatostatin infusion decreases arterial blood flow to the stomach and duodenum and portal blood flow. Prophylactic antibiotherapy decreases infection, infection mortality rate and all-cause mortality in cirrhotic patients with gastrointestinal bleeding.

An upper endoscopy should be performed if a patient presents with melena, hematemesis, or hematochezia or hemodynamic instability (signs of hypovolemia and iron-deficiency anemia) to allow for the determination of bleeding cause and location [41, 52].

5 Role of Endoscopy in the Assessment and Management of Patients with GI Bleeding

It is often challenging to distinguish between upper and lower GI bleeding on the basis of initial symptoms. Endoscopies aid in determining the location and cause of bleeding to optimize patient management, stop bleeding, and prevent recurrence [53]. Physicians may consider administration of IV erythromycin before endoscopy, with ECG assessment of the QT interval and careful monitoring of potential arrhythmia in patients with cardiovascular disease or taking antiarrhythmic drugs. No alternative drug with such a prokinetic effect is currently available. Glycoprotein (P-gp) and CYP3A4/5 inhibitors such as erythromycin interact with DOACs [53–56], resulting in an increase in DOAC plasma concentration, which can potentially worsen or prolong bleeding events [57].

In emergency situations, the recommended timing of the endoscopy varies depending on whether the patient is suspected of having an upper or lower GI bleeding event, and it also differs between guidelines [52]. Different scores can be used in this scenario; the GBS is often used to determine the need for endoscopic treatment and transfusion, and to predict re-bleeding rate and prognosis [50]. This score has been validated as a predictive tool of in-hospital mortality and therapeutic endoscopic need, even prior to the identification of the bleeding source [58]. Patients with a GBS of 0 are considered to be at low risk and can be managed conservatively without the need for endoscopic investigation. The Forrest classification is used to categorize endoscopy findings such as active bleeding (Forrest Ia), high-risk lesion (Forrest Ib–IIc), and low-risk lesions without signs of active bleeding or recent hemorrhage (Forrest III) [59].

The Forrest classification can also be helpful for assessing the probability of bleeding recurrence, and can be used with other risk scores to weigh the benefit/risk of resuming anticoagulation [60]. The Rockall score system predicts the likelihood of death within 30 days by using patient age; accompanying shock; comorbidities such as heart, liver, and kidney disease; causative diseases of bleeding; and endoscopic bleeding stigmata [61]. It has been validated and is recommended by international guidelines [62].

Patients with suspected lower GI bleeding may require a colonoscopy to locate the bleeding site [51], for which bowel preparation is recommended [52]. Colonoscopies can detect diverticular bleeding or angiodysplastic bleeding [63]. Endoscopic methods of hemostasis for acute upper or lower GI bleeding include injection (usually diluted epinephrine or a special sclerosing agent), contact and non-contact thermal devices (unipolar or bipolar electrocoagulation, heater probes, and argon plasma coagulation), and mechanical devices (endoscopic clips and band ligation) [64, 65]. Patients who have had these procedures may undergo a repeat endoscopy 24 h later.

6 Use of Reversal Agents in Patients with GI Bleeding

Anticoagulants and antiplatelets should be stopped on admission in patients with GI bleeding. The pharmacokinetic profile (half-life) of DOACs makes time the best antidote for bleeding in most situations. However, physicians should consider anticoagulant reversal in patients who have life-threatening bleeding or when the bleeding is not controlled by the initial resuscitation methods described above [66]. For VKA antagonization, prothrombin complex concentrate (PCC) 25 IU/kg is recommended. DOAC reversal is indicated for a concentration over 50 ng/mL. Below this

threshold, bleeding is not considered to be related to DOACs [67].

The US Food and Drug Administration and the European Medicines Agency approved idarucizumab as a specific reversal agent for dabigatran in 2015. Idarucizumab is a humanized monoclonal antibody fragment that can be used for the emergency reversal of dabigatran's anticoagulant effect [68–71]. However, prohemostatic agents, namely PCC or activated PCC (aPCC) 30–50 U/kg IV, can be administered if a specific antidote is not available. Few data support the use of oral activated charcoal within 6 h of drug intake, especially in the context of overdose [66]. Regarding factor Xa inhibitors, the US Food and Drug Administration approved andexanet alfa for the reversal of apixaban and rivaroxaban in life-threatening or uncontrolled bleeding under its accelerated approval program in 2018 [72]. The approval was conditional on performance of an ongoing randomized clinical trial (ANNEXA-I NCT03661528). The European Medicines Agency also gave conditional approval in April 2019, and full marketing approval was granted in Japan in March 2022, including for the reversal of edoxaban in patients with life-threatening or uncontrolled bleeding. Andexanet alfa is a recombinant inactive form of factor Xa that binds to the factor Xa inhibitors. Andexanet alfa is administered as a bolus followed by a continuous infusion, with the dosage dependent on the DOAC dose and the time of last drug intake [72]. PCC 50 IU/kg or aPCC 30–50 IU/kg are recommended if a specific antidote is not available. A recent observational study suggested that aPCC (25 IU/kg or 50 IU/kg for intracerebral hemorrhage or 30 IU/kg for GI bleeding) could be an option in patients with life-threatening bleeding associated with apixaban or rivaroxaban. Indeed, a clinical hemostasis was achieved in 24/35 patients, including 10/10 patients with GI bleeding after aPCC administration [73].

However, given the methodological limitations of open-label single-cohort and observational studies, the contribution of idarucizumab, andexanet alfa, PCC, or aPCC to promoting and maintaining hemostasis in case of life-threatening bleeding remains uncertain. In the absence of a control group, it is unclear whether DOAC reversion leads to improved clinical outcomes and whether use of specific antidotes provides more efficacy and safety than prohemostatic agents; all the more so as most GI bleeding can be managed through drug clearance (i.e., short half-life) and maximum supportive measures (e.g., transfusion, procedural/surgical intervention).

7 Timing for Resuming Anticoagulant Therapy after GI Bleeding

The decision to resume anticoagulant therapy after a bleeding event is critically important and should balance the risk of re-bleeding in the case of resumption, and the risk of thromboembolism if anticoagulation is not resumed. This decision needs to be made on a case-by-case basis after thorough assessment of the risks and benefits [74] by a multidisciplinary team including a gastroenterologist, a cardiologist, and others if needed [3].

Because of the overlap in risk factors for bleeding and thrombotic events, patients who are suffering from anticoagulation-induced bleeding are also at higher risk of thrombotic events. Discontinuation of anticoagulation, a prothrombotic inflammatory response to bleeding, and RBC transfusions may lead to increased rates of thrombotic events. Clearly, balancing the risks of further bleeding versus potentially fatal thrombotic events is critical for decisions about if and when to resume antithrombotic therapy after bleeding.

Resuming treatment was associated with an overall positive effect on the clinical course of patients with AF after the occurrence of a major bleeding event compared with not resuming oral anticoagulants [75]. A systematic review and meta-analysis on the risk of resuming oral anticoagulants after an episode of GI bleeding concluded that resuming treatment seemed to be associated with a reduced risk of thromboembolism (70%) and mortality 235 (49%) despite an increased risk of recurrent GI bleeding (91%) [76]. Another systematic review and meta-analysis using data from > 5000 patients showed similar recurrent GI bleeding risk, and significantly reduced risks of any thromboembolic event in patients resuming oral anticoagulant therapy compared with those who did not. The mortality rate in patients who resumed anticoagulation (21.3%) was lower compared with patients who discontinued anticoagulation (31%), with a significantly lower risk of all-cause mortality (OR 0.499; 95% CI 0.419–0.595; $p < 0.0001$) associated with the resumption of anticoagulation [77]. However, several biases and confounding hinder the interpretation of these two meta-analyses. All the studies included were observational rather than randomized control trials, there was a substantial amount of heterogeneity among them, the timing of anticoagulant resumption varied widely, and outcomes were not reported on the basis of when anticoagulant was resumed. Kido and colleagues have shown a decreased risk of mortality and thromboembolic events without an increased risk of a recurrent GI bleeding event when resuming warfarin within 7–15 days of a GI bleed [78]. A prospective cohort study by Sengupta and colleagues and two review articles by Witt and Radaelly and colleagues, respectively, on the benefit/risk associated with resuming anticoagulation after a GI bleed recommended resuming anticoagulation therapy after no more than 2 weeks to reduce the risk of bleeding, thromboembolism, and mortality [75, 79, 80].

Currently, there are no tools designed to specifically assess the risk of bleeding recurrence at anticoagulation

resumption and to assess whether the risk of re-bleeding is higher than the risk of thrombosis.

Anticoagulation needs to be resumed in a timely manner, bearing in mind that bleeding risk outweighs thrombotic risk when anticoagulation is resumed early after the bleeding event [3]. This is well illustrated in the perioperative setting, where resuming anticoagulation early postoperatively increases the risk of bleeding since it compromises hemostasis [81].

However, the specific time when to resume anticoagulation is not well defined. Majeed et al. demonstrated that bleeding risk decreases over time after a GI bleeding event, especially after 21 days, whereas the risk of thromboembolism is stable over time and is often lower than the bleeding risk [82]. Data suggest that there is a threefold increase in the risk of bleeding if anticoagulation is resumed within 7 days of a hemorrhage compared with after 7 days, but there is no difference in the risk of bleeding if anticoagulants are resumed within 21 days versus after 21 days [82–84]. In the ARISTOTLE trial, resumption occurred at a median time of 15 days [85]. Similarly, in the REVERSE trial, 66% of the patients who had experienced a bleed resumed anticoagulation within 16 days [86].

The former version of the European Heart Rhythm Association (EHRA) guidelines on anticoagulants in patients with AF based the decision-making process on the assessment of factors that favor withholding anticoagulation (such as an unidentifiable site of bleeding, multiple angiodysplasia in the GI tract, no identifiable treatable cause, and older age) and those that favor resuming anticoagulation. The recommendation was to resume DOACs within 4–7 days following a major GI bleed but only if clinical benefits outweighed the risk of developing recurrent GI bleeding [87].

In the latest version of their guidelines, the EHRA changed their point of view, with the decision-making process suggesting a net assessment in favor of resuming anticoagulation and a recommendation to resume DOACs as early as clinically feasible (Fig. 2) [3].

The American College of Cardiology guidelines recommend determining the optimal timing for oral anticoagulant resumption on the basis of whether there is a greater risk of thromboembolism or bleeding. In conditions with high thrombotic risk, the recommendation is for early resumption of anticoagulation once hemostasis is achieved and the patient is clinically stable; for patients with moderate or high re-bleeding risk, individualized strategies are more appropriate [14].

Further studies and randomized controlled trials are urgently needed to establish optimal timing of DOAC resumption in patients after a GI hemorrhage according to baseline patient characteristics (age, comorbidities, indication for anticoagulants, source and severity of bleeding, risk of re-bleeding or thrombosis).

8 Minimizing the Risk of Recurrences in Patients Resuming Anticoagulants after GI Bleeding

As previously described, resuming anticoagulant treatment after a GI bleeding event generally provides clinical benefit. To prevent recurrent bleeding after a GI bleeding episode,

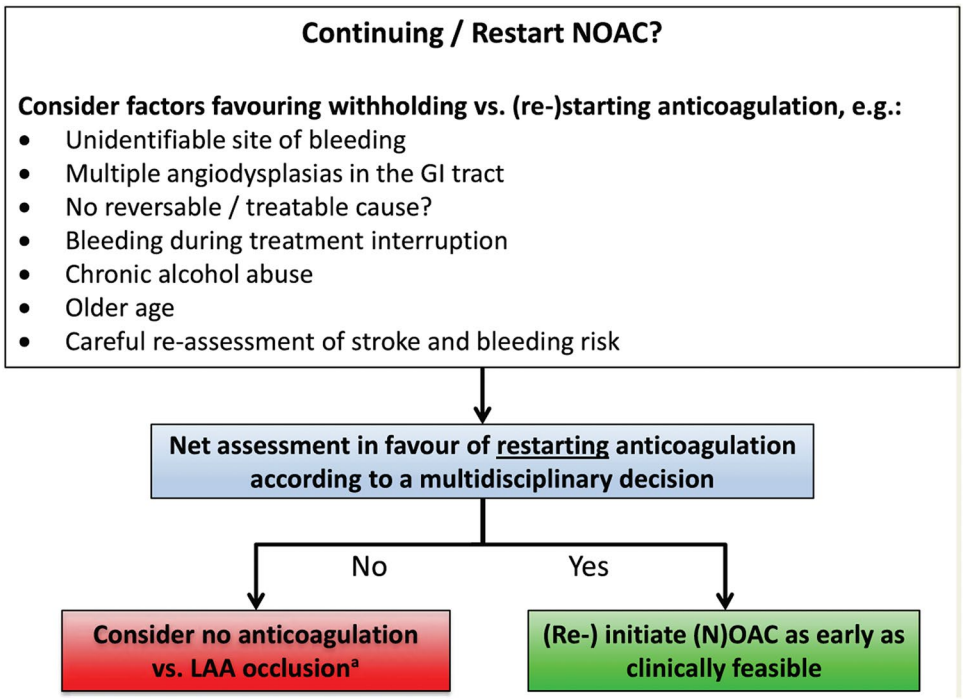

Fig. 2 Algorithm for the resumption of direct oral anticoagulants after a gastrointestinal hemorrhage according to the European Heart Rhythm Association guidelines [3]. *GI* gastrointestinal, *LAA* left atrial appendage, *NOAC* novel oral anticoagulants. Reproduced from Steffel et al. [3] by permission of Oxford University Press

it is important to evaluate the main risk factors favoring the occurrence of GI bleeding [88], such as the presence of a digestive luminal disease, older age, renal or liver dysfunction, hypertension, anemia, history of hemorrhage or stroke, genetic factors, malignancy, and concomitant treatments and diseases [11, 28, 30, 74]. Overall, despite a potential 23% increase in GI bleeding, DOACs have a 14% trend toward a relative risk reduction in major bleeding relative to warfarin [89]. Since the risk of bleeding appears to be higher with VKAs than with DOACs, it may be advisable to resume with a DOAC after a significant GI bleed.

However, several retrospective cohort studies of real-world patients starting DOAC therapy for AF have shown that, after adjustment for potential confounders, apixaban was associated with a significantly lower risk of major bleeding and GI bleeding compared with rivaroxaban or dabigatran [90–92].

Guidelines stress the need to minimize bleeding risk for all patients on oral anticoagulants by addressing modifiable risk factors such as concomitant use of aspirin, which increases the hazard for major bleeding events by at least 50% [12].

In summary, to prevent further bleeding, physicians should ensure the following steps are taken in a patient resuming anticoagulant therapy:

- Preferentially prescribe DOACs with the lowest risk of GI bleeding rather than VKAs. The choice of DOAC cannot be determined by evidence-based medicine but should be determined by the risk of GI bleeding.
- Comply with all guidelines and prescribing information, especially avoiding DOAC accumulation related to kidney disease.
- Consider the effect of concomitant medications on potentiating the bleeding risk (e.g., CYP3A4 or P-gp inhibitors, antiplatelet agents) [93].
- Avoid medications with GI toxicity (nonsteroidal antiinflammatory drugs).
- Initiate treatment with PPIs to reduce the risk of bleeding (although be cognizant of a possible interaction between PPIs and dabigatran).
- Test patients with peptic ulcers for *Helicobacter pylori* and initiate eradication therapy as needed.

9 Conclusions

Guidelines now recommend DOACs over VKAs for the prevention of thromboembolism in patients with AF due to their safety and efficacy profiles. However, the major complication with DOAC treatment is the increased risk of bleeding, particularly GI bleeding. Management of GI bleeding and resumption of oral anticoagulants in patients with AF are associated with increased survival rates. The optimal approach for patients with GI bleeding who are taking anticoagulants involves multidisciplinary care to provide an individualized optimal balance of benefit and risk for each patient.

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Declarations

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