

Review Article

Gastrointestinal Bleeding in Patients Receiving Antiplatelet and Anticoagulant Therapy: Practical Guidance for Restarting Therapy and Avoiding Recurrences

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Nowadays, many patients receive chronic antithrombotic therapy for various cardiac diseases. Antiplatelet drugs are widely used in patients with coronary artery disease. Dual antiplatelet therapy, with a combination of aspirin plus a P2Y₁₂ receptor inhibitor (such as clopidogrel, prasugrel or ticagrelor), is often necessary for a period of 12 months after an acute coronary event or after the implantation of a coronary stent.¹ Vitamin-K antagonists (VKA) are indicated in patients with atrial fibrillation, thromboembolic venous disease or a mechanical heart valve, while recently the novel oral anticoagulants (NOAC), such as dabigatran, rivaroxaban and apixaban, have been used increasingly in non-valvular atrial fibrillation and venous thromboembolism.²⁻⁴ Unfortunately, the main side effect of all antithrombotic drugs is bleeding. The gastrointestinal tract figures as one of the most common sites of a bleeding complication. When the indications are followed cautiously, the risk of bleeding is smaller than the risk of thrombosis and the prescription of antiplatelet or anticoagulant therapy is considered safe and necessary. However, the risk of a bleeding episode from the

gastrointestinal system is not negligible and if this complication occurs, the treating physician has to decide if, when, and how the patient should be restarted on antithrombotic therapy: discontinuation or delayed re-initiation of antithrombotic treatment may lead to thrombosis, while too early re-initiation may lead to recurrent haemorrhage.

For these practical issues there are, unfortunately, no randomised clinical trials to guide clinical practice. Any decision has to be based upon limited data from clinical series, epidemiology, and careful individual assessment of all relevant parameters. The aim of this review is to provide useful data that will help the clinician to choose the antithrombotic strategy with the smallest bleeding risk and to provide practical recommendations for the re-initiation of antithrombotic therapy after a gastrointestinal (non-variceal) haemorrhage.

Incidence of gastrointestinal haemorrhage

Gastrointestinal bleeding represents a serious medical condition, with mortality reaching 10%, and one that contributes to increased health costs worldwide. The

incidence of gastrointestinal bleeding is estimated at 100-200 cases per 100,000 general population per year, resulting in 300,000 hospitalisations annually.^{5,6} The ratio of upper to lower gastrointestinal bleeding is approximately 4-5 to 1, but in the elderly the ratio becomes smaller as diseases of the colon (diverticulosis, angiodysplasia, neoplasms) become more frequent.⁷

Over the last decades, successful therapies for eradication of *Helicobacter pylori*, the wider use of proton pump inhibitors (PPI) and the more careful prescription of non-steroidal anti-inflammatory drugs (NSAID) have led to a decreased incidence of (especially upper) gastrointestinal bleeding. Mortality remains around 10% for upper gastrointestinal and around 2-4% for lower gastrointestinal bleeding, despite the advances in endoscopic haemostatic interventions, as mortality is often related to the severity of the underlying concomitant disease rather to bleeding *per se*.

Any treatment with classical or novel antithrombotic drugs is expected to increase the risk of gastrointestinal bleeding.

A) Antiplatelets

Single administration of aspirin is the standard antiplatelet therapy in cardiovascular prevention. In primary prevention, however, the use of aspirin remains controversial and is probably not indicated (unless there is a very high cardiovascular risk) because of the possibility of gastric haemorrhage. In the collaborative meta-analysis of the antiplatelet therapy trialists, with data from 660,000 patient-years of follow up, the use of aspirin prevents, in absolute numbers, for every 10,000 individuals treated for one year, 5 new myocardial infarctions and one vascular death, at a cost of 3 major bleeding episodes (most of which are from the gastrointestinal tract).⁸ There is undoubtedly an unfavourable benefit-to-risk ratio. In contrast, in the CURE trial, involving patients with an acute coronary event, the administration of dual antiplatelet therapy with aspirin plus clopidogrel for a period of 9-12 months prevented (for every 1000 treated patients) 23 new cardiovascular events at a cost of 10 additional major bleeding episodes (1/3 of which were from the gastrointestinal tract).⁹ Here, the benefit-to-risk ratio is considered acceptable; thus, dual antiplatelet therapy is the established antithrombotic regime following an acute coronary syndrome or the implantation of an intracoronary stent.

The two newer antiplatelet agents that try to

replace the well studied clopidogrel are prasugrel and ticagrelor, both already in everyday clinical use. Both are stronger antiplatelet agents and are therefore related to more haemorrhages from the gastrointestinal system when compared with clopidogrel.¹⁰⁻¹² In fact, the existing guidelines for the management of patients with acute coronary syndromes caution against the use of prasugrel in patients at high bleeding risk, but still consider both newer drugs as having favourable benefit-to-risk ratios.¹ For every 1000 patients treated with prasugrel rather than clopidogrel, 19 fewer events are expected at the cost of 7 additional major bleeding episodes, while for ticagrelor versus clopidogrel the respective numbers are 22 and 6.

B) Anticoagulants (VKAs and NOACs)

For the main indications of anticoagulant therapy, such as atrial fibrillation and a mechanical heart valve, the benefit of reducing thromboembolic complications exceeds the risk of bleeding. Even among very elderly patients above 85 years old with atrial fibrillation, VKA therapy in comparison with aspirin not only reduces the odds for ischaemic stroke but is also safer as regards major bleeding complications.¹³ In general, the annual risk of major bleeding with warfarin is estimated at 2-3% and depends on the presence of several risk factors (as will be discussed later). Almost 45% of major bleeding episodes in patients with atrial fibrillation are from the gastrointestinal system.¹⁴ The NOACs already in use with an indication for non-valvular atrial fibrillation are dabigatran (direct thrombin inhibitor), rivaroxaban, apixaban and edoxaban (inhibitors of factor Xa).¹⁵ In comparison with warfarin, rivaroxaban at a dose of 20 mg once daily and dabigatran at a dose of 150 mg twice daily increase gastrointestinal bleeding in general, while dabigatran at a dose of 110 mg twice daily increases gastrointestinal bleeding in patients older than 75.^{14,16-18} Moreover, in the RE-LY trial, dabigatran was associated with an increase in lower gastrointestinal bleeding. Apixaban probably does not increase gastrointestinal bleeding when compared with warfarin.¹⁹ Edoxaban at a dose of 60 mg daily resulted in more gastrointestinal bleeds in comparison with warfarin, while the smaller dose of 30 mg was safer in terms of bleeding but less effective in preventing ischaemic strokes.²⁰

Table 1 summarises the data from the main studies of antithrombotic regimens regarding gastrointes-

tinal bleeding.^{8-11,14,16,17,19-24} In studies of dual antiplatelet therapy in acute coronary syndromes (such as CURE, PLATO, TRITON) the annual rate of gastrointestinal bleeding varied roughly from 1% to 2.5%. In studies of oral anticoagulants in atrial fibrillation (such as RE-LY, ROCKET-AF, ARISTOTLE) the annual rate varied from 1% to 3%. It should be noted that different antithrombotic strategies were compared and each study had a different population of patients with different baseline characteristics (for example, the patients in the studies of atrial fibrillation were 8-10 years older than those in the studies of coronary artery disease). As stated earlier, the newer, more potent antiplatelet drugs (prasugrel and ticagrelor) increase bleeding when compared with clopidogrel. Dabigatran, rivaroxaban and edoxaban, although safer than warfarin regarding intracranial haemorrhage, are not safer regarding gastrointestinal

bleeding.²⁵ It should also be noted that many of the studies in Table 1 excluded patients who were considered to be at high bleeding risk. Therefore, most probably, the risk of gastric haemorrhage was underestimated.²⁶

Risk factors for bleeding from antiplatelets and anticoagulants

The main risk factors favouring the occurrence of gastrointestinal bleeding are the presence of an underlying pathology, older age, renal dysfunction, a history of haemorrhage, and the prescription of antithrombotic therapy. Peptic ulcer is the most common cause of upper gastrointestinal bleeding (50% in older series, but around 33% in more recent ones). Oesophagitis, erosive gastritis and duodenitis follow in frequency, while rarer causes include Mallo-

Table 1. Major gastrointestinal haemorrhages in trials of different antithrombotic therapies.

Study	Indication	Duration	Antithrombotic therapies	Incidence of gastrointestinal bleeding among the compared groups
ATC ⁸	Myocardial infarction	2 years	Usual vs. antiplatelet	0.25% vs. 0.31%*
ATC ⁸	Stroke	2 years	Usual vs. antiplatelet	0.47% vs. 0.97%*
ATC ⁸	High risk	2 years	Usual vs. antiplatelet	1.71% vs. 2.58%*
CURE ⁹	ACS	12 months	ASA vs. ASA+clopidogrel	0.7% vs. 1.3%
TRITON ¹⁰	ACS	15 months	ASA+clopidogrel vs. ASA+prasugrel	1.22% vs. 1.61%
PLATO ¹¹	ACS	12 months	ASA+clopidogrel vs. ASA+ticagrelor	1.94% vs. 2.26%
ACTIVE-A ²¹	AF	3.6 years	ASA vs. ASA+clopidogrel	0.5% vs. 1.1% (per year)
Meta-analysis of AF trials ²²	AF	2-4 years	Usual vs. VKA	0.3% less (per year)*
ACTIVE-W ²³	AF	1.5 years	ASA+clopidogrel vs. VKA	2.42% vs. 2.21%* (per year)
RE-LY ^{16,17}	AF	2 years	A) Dabigatran 110/150 mg vs. Warfarin (<75 years old) B) Dabigatran 110/150 mg vs. Warfarin (>75 years old)	0.84%/1.22% vs. 1.03% (per year) 2.19%/2.80% vs. 1.59% (per year)
ROCKET-AF ¹⁴	AF	2 years	Rivaroxaban vs. Warfarin	3.15% vs. 2.16% (per year)
ARISTOTLE ¹⁹	AF	1.8 years	Apixaban vs. Warfarin	0.76% vs. 0.86% (per year)
ENGAGE-AF ²⁰	AF	2.8 years	Edoxaban 60/30 mg vs. Warfarin	1.51%/0.82% vs. 1.23% (per year)
Meschengieser ²⁴	Mechanical valves	2 years	Low intensity VKA+ASA vs. High intensity VKA	0.76% vs. 2.12% (per year)

*Major bleeding without specification of site (it is estimated that 30-45% of these are from the gastrointestinal system).

ACS – acute coronary syndrome; AF – atrial fibrillation; ASA – aspirin; VKA – vitamin-K antagonists.

ry-Weiss syndrome, angiodysplasia, neoplasms and Dieulafoy's lesion.²⁷⁻²⁹

Lower gastrointestinal bleeding (data from various series of patients) is due to diverticulosis (30-40%), haemorrhoids (5-14%), angiodysplasia or ischaemic vascular disease (10-37%), inflammatory disease (9-18%), cancer/polyp (10-14%), or other rarer causes.^{30,31} The antiplatelet drugs create ulcers and erosions in the gastrointestinal tract, while the anticoagulants provoke bleeding from existing lesions.

The chance of haemorrhage with aspirin monotherapy depends on the dose. A daily dose of 300 mg doubles the risk in comparison with a dose of 100 mg.³² For this reason, the equally effective but much safer smaller dose is preferred. Enteric-coated aspirin seems to bear a smaller risk for blood loss when compared with plain aspirin, although this matter is controversial.^{33,34} Coadministration of a second antiplatelet agent with aspirin increases the risk significantly (as explained earlier). In a case-control study, with adjustment for multiple risk factors, it was found that the relative risk for upper gastrointestinal bleeding was 3.7 for low-dose aspirin, 2.8 for clopidogrel and 16.4 for the combination (aspirin plus clopidogrel).³² Moreover, in the CURE trial, major bleeding episodes with the combination of aspirin and clopidogrel (75 mg) differed significantly with the aspirin dose. The bleeding rates were 4.9%, 3.5% and 2.5% when the dose of aspirin was 300 mg, 100-300 mg and <100 mg, respectively.⁹ In the PLATO trial, the optimal benefit-to-risk ratio was noted for ticagrelor plus low-dose aspirin, while the worst was evident for ticagrelor plus high dose aspirin (>300 mg).¹¹ NSAIDs are the most commonly used additional drugs that increase gastrointestinal bleeding.

The haemorrhagic risk with VKAs is related to certain predisposing factors. In patients with atrial fibrillation, several scoring systems have been proposed to calculate bleeding risk. These scores address bleeding risk in general and are not specific for the gastrointestinal tract. Still, they are relevant because the majority of bleeding episodes are, indeed, localised in the alimentary tract. The most popular scoring systems for bleeding are the HAS-BLED and the ATRIA (Table 2).³⁵ High international normalised ratio (INR) values are related to the occurrence of haemorrhagic complications, but it must be emphasised that, very frequently, bleeding can occur with the INR within therapeutic range.^{36,37}

Parameters relevant to the re-initiation of antithrombotic therapy

The management of the bleeding episode is beyond the scope of this article. Of course, discontinuing the antithrombotic treatment is important but the reversal of the antithrombotic effect of any drug is problematic. The antiplatelet effect cannot be reversed and in cases of continuing haemorrhage platelet infusion may be required. In order to reverse the effects of VKAs, vitamin-K, fresh frozen plasma (FFP), prothrombin complex concentrates (PCC), and activated recombinant factor VII may be used.³⁸ However, reversal may be delayed, followed frequently by a prothrombotic situation, and carries a risk of adverse reactions. NOACs have no specific antidotes, but have a fast elimination (provided renal function is not impaired) and do not seem to have a serious disadvantage in comparison with warfarin. FFP is frequently used, but it can serve only as a volume expander rath-

Table 2. Scoring systems for estimation of bleeding risk from VKA (based on series of patients with atrial fibrillation)

HAS-BLED score		ATRIA score	
Parameter	Points	Parameter	Points
Hypertension	1	Anaemia	3
Abnormal renal or liver function	1 or 2	Severe renal disease	3
Stroke	1	Age >75 years	2
Bleeding	1	Prior bleeding	1
Labile INR	1	Hypertension	1
Elderly (>65 years)	1		
Drugs or alcohol	1 or 2		
OVERALL SCORE	0-9	OVERALL SCORE	0-10
0-2=low risk (<2.5%/year)		0-3=low risk (<1%/year)	
3-4=medium risk (2.5-5%/year)		4=medium risk (1-5%/year)	
5-9= high risk (5-20%/year)		5-10= high risk (5-17%/year)	

INR – international normalised ratio.

er than a reversal agent. PCC may reverse the anti-Xa effect of rivaroxaban, but data are limited to healthy volunteers rather than patients with active haemorrhage. Once haemostasis is secure, the clinical question for the treating physician is if, when, and how the antithrombotic therapy should be restarted. The main parameters to take into consideration are the risk of recurrent bleeding and the thromboembolic risk of the underlying disease for which antithrombotic drugs were prescribed before the bleeding event. In fact, the official instruction of the American Society for Gastrointestinal Endoscopy (ASGE) proposes the re-initiation of antithrombotic treatment when the thromboembolic risk exceeds the risk of recurrent bleeding. This means that every case should be individualised and a common decision should be reached by both the cardiologist and the gastroenterologist, based on the indications and the history of each particular patient.³⁹

A) Risk for recurrent bleeding

The probability of bleeding recurrence in patients receiving antithrombotic therapy cannot be predicted with accuracy. It depends on several factors, such as endoscopic findings, the patient's haemodynamic instability, and the presence of comorbidities. Regarding the endoscopic findings, in patients with peptic ulcers and a clean base the recurrence rate is barely 5%, while in those patients with recent haemorrhagic stigmata recurrence may be as high as 55%. A recent review suggests that active bleeding, large ulcer size (>1-2 cm), and location of the ulcer at the posterior duodenal wall or along the lesser gastric curvature are factors related to high re-bleeding rates.⁴⁰ Several scoring systems have been proposed to calculate the gastrointestinal re-bleeding risk (e.g. Blatch-

ford, Rockall, and Baylor College). The most widely used is the Rockall score, which combines clinical and laboratory findings. It predicts the risk of recurrent bleeding after haemostasis and mortality. Patients with a Rockall score <2 are considered at low risk for recurrence and patients with a score >8 have high mortality (Table 3).⁴¹

In a randomised study of patients with bleeding peptic ulcer, the recurrence rate within 30 days was 22.5% for the placebo group versus just 6.7% for the group receiving omeprazole. In both groups, the majority of the recurrences were recorded within the first 5 to 7 days. After day 7, the recurrences were rare.⁴² A collective analysis of 93 studies of patients with peptic ulcer reported a 14% rate of recurrent bleeding within the first week, with aspirin or NSAID use, presence of *H. pylori*, and large ulcer size identified as important risk factors.⁴³ In patients with obscure gastrointestinal bleeding who were investigated by capsule endoscopy, the recurrences were more frequent in patients with insignificant rather than significant (but treatable) findings (50% vs. 27%). In general, the recurrences were fewer when a therapeutic intervention was carried out. The underlying pathology with most recurrences was angiodysplasia and ulcers without intervention.⁴⁴ Many studies of lower gastrointestinal haemorrhage have tried to propose some clinical prognostic criteria to stratify patients into high or low risk groups for recurrences, but no valid prognostic model exists. Patients with lower gastrointestinal haemorrhage from diverticular disease, without radical surgical treatment, have a recurrence rate of 9% within one year and 25% within 4 years.³⁰ When the cause of bleeding is treated surgically, for example with resection of diverticulae or removal of a neoplasm, bleeding recurrences are very rare.⁴⁵

Table 3. Scoring system to estimate the risk of recurrent gastrointestinal bleeding (Rockall score).

Variable	SCORE			
	0	1	2	3
Age	<60	60-79	>80	
Haemodynamic instability	No	SBP >100 mmHg HR >100/min	SBP <100 mmHg	
Comorbidity	No		Cardiac failure, ischaemic heart disease	Renal failure, liver failure, metastatic cancer
Diagnosis	Mallory-Weiss	All other	Gastrointestinal malignancy	
Evidence of bleeding	No		Blood, adherent clot, spurting vessel	

Patients with a Rockall score <2 are considered to be at low risk for recurrent bleeding. Patients with a score >8 have high mortality.
SBP – systolic blood pressure; HR – heart rate.

B) Thrombosis risk as a result of antithrombotic therapy discontinuation

What matters most for the clinician is for how long can a patient stay off any antithrombotic treatment. The risk of arterial or venous thrombosis depends, of course, on the indication for which the antithrombotic therapy was prescribed before the bleeding event.

i) Antiplatelet therapy

Conditions with high arterial thrombotic risk, if antiplatelet therapy is discontinued, include a recent placement of an intracoronary stent (1 month for a bare-metal stent, 6-12 months for a drug-eluting stent) and a recent acute coronary or cerebrovascular event (3 months). Moderate risk exists, if therapy is discontinued, after any vascular event beyond the first 3 months or after aortocoronary bypass surgery, while the risk is small when the antiplatelet drugs were given just for primary prevention. The risk of thrombosis and of a subsequent acute vascular event after discontinuation of antiplatelet therapy has been studied in large series of patients with coronary artery disease, bypass surgery or coronary stenting. In general, it is estimated that this risk is 3-fold (relative risk 3.14) as compared with continuation of therapy. In particular, for patients with a recent coronary stent the risk is extremely high (relative risk 89.7).^{46,47} The median time from discontinuation of antiplatelet therapy to the clinical presentation of a thrombotic adverse event is 10 days. Indeed, in observational registries it has been noted that, in as many as 10% of all acute coronary syndromes, the patient had discontinued antiplatelet therapy for some reason. The mean time from discon-

tinuation to myocardial infarction is 8 days, to stroke 14 days, and to ischaemic peripheral complication 25 days.⁴⁸ It is logical to conclude that antiplatelet therapy should not be discontinued for more than 10 days in high-risk situations. In fact, taking into consideration the average lifespan of platelets that are permanently inhibited, it is expected that after 7-10 days of antiplatelet therapy discontinuation, >90% of platelets will be fully active again. In the case of ticagrelor, which binds reversibly to the P2Y₁₂ receptor, platelets may be fully active after shorter discontinuation periods (4-5 days).

ii) Anticoagulant therapy

The most usual indication for oral anticoagulation is atrial fibrillation or the presence of a mechanical prosthetic heart valve. Less usual indications are venous thrombosis and pulmonary embolism. In Table 4, different patients with atrial fibrillation or a mechanical valve are stratified into groups with high (>10% per year), moderate (4-10% per year) or low (<4% per year) risk for thrombosis, if left without anticoagulation. The highest risk exists for patients with atrial fibrillation and prior ischaemic stroke, and for patients with a prosthetic mitral valve. These patients should not remain off anticoagulant therapy for long.⁴⁹⁻⁵¹ Pulmonary embolism carries a recurrence risk of around 2-4% per year unless thrombophilia exists.⁵²

The theoretical danger of thrombosis, when anticoagulation is withdrawn, may not agree with data from observational series of patients. For example, in patients with mechanical valves who remained without anticoagulation for 7-14 days after an intracerebral haemorrhage, no thrombotic events were noted.⁵³

Table 4. Thrombotic risk without anticoagulation.

High (>10%/ year)	Moderate (4-10%/ year)	Low (<4%/ year)
Prosthetic heart valve:		
<ul style="list-style-type: none"> Any mitral valve type Older type aortic valve (caged ball, tilting disk) Recent stroke (<6 months) 	<ul style="list-style-type: none"> Bi-leaflet aortic valve and any of the following: atrial fibrillation, prior stroke, hypertension, diabetes, congestive heart failure, age >75 	<ul style="list-style-type: none"> Bi-leaflet aortic valve without atrial fibrillation or other risk factor for stroke
Atrial fibrillation:		
<ul style="list-style-type: none"> CHADS₂ score 5-6 Recent stroke (<3 months) Rheumatic valve disease 	<ul style="list-style-type: none"> CHADS₂ score 3-4 CHADS₂ score 2 with prior stroke 	<ul style="list-style-type: none"> CHADS₂ score 0-1 CHADS₂ score 2 (but without prior stroke)

CHADS₂ score: C= Congestive heart failure: 1 point, H= Hypertension: 1 point, A= Age >75: 1 point, D= Diabetes: 1 point, S= Stroke or transient ischaemic attack: 2 points.

C) Restarting antithrombotic treatment after gastrointestinal bleeding: data from studies

There are very few randomised clinical trials to guide clinical practice. On the other hand, the clinical non-randomised series may be potentially biased regarding the re-initiation of anticoagulation. The treating physician, often with subjective criteria, restarts therapy in those patients whom he considers to have a low risk for recurrent bleeding, and delays it in those whom he considers (perhaps wrongly) as high risk.

In one study, 150 patients on chronic aspirin therapy who suffered an upper gastrointestinal haemorrhage were randomised immediately after endoscopic haemostasis to receive either low-dose aspirin or placebo for 8 weeks. All patients received pantoprazole for 72 hours intravenously (8 mg/h) and then orally. The rate of recurrent bleeding was 10.3% versus 5.4% for the aspirin and the placebo groups, respectively. All-cause mortality (due to both thrombosis and haemorrhagic complications) was, however, significantly lower in the aspirin group (1.3% vs. 10%).⁵⁴ These data, although derived from a relatively small cohort, support the practice of immediate endoscopic haemostasis coupled with high dose PPI and early re-initiation of aspirin (within 5 days), despite the risk of a recurrent bleed. Of course, it is logical to restart aspirin later (or even consider stopping it permanently) in patients who received it for primary prevention.⁵⁵

One retrospective study included 1329 patients (mean age 76) on oral anticoagulation who developed gastrointestinal bleeding. In 653 patients VKA therapy was restarted. In one analysis, taking into account the time of re-initiating therapy, a lower incidence of deaths and thrombotic events was noted (without an increase in recurrent bleeds) when anticoagulants were started after 7 days in comparison with starting therapy after 30 days.⁵⁶ In a different analysis, obviously of the same series of patients, a comparison of relatively early (15-30 days) versus later (after 30 days) restart of anticoagulation was made according to calculated haemorrhagic and thrombotic risks (using HAS-BLED and CHADS₂ scores). The risk of stroke within 12 months was clearly smaller with earlier re-initiation of anticoagulation in all patients. Recurrent bleeding within 3 months was twice as high only in patients with a high HAS-BLED score, but not different in those with a low HAS-BLED score. Therefore, an objective eval-

uation of the bleeding risk may be clinically useful in order to make decisions.⁵⁷

In another study, 442 patients (with various indications for oral anticoagulation) had gastrointestinal bleeding. Of these patients, 260 restarted therapy at a median of 4 days, while 182 discontinued it. Early restart was associated with a 95% reduction of thrombotic complications during 90 days' follow up (0.4% vs. 5.5%) and a non-significant doubling of haemorrhagic recurrences (10% vs. 5.5%).⁵⁸ Most bleedings were recorded in patients who started VKAs from day 1 to day 7. Finally, a small series followed 58 patients, with valvular disease but without a prosthetic valve, who were receiving oral anticoagulation and suffered gastrointestinal bleeding. Six of the 36 patients who discontinued anticoagulation had thromboembolic events. These events occurred from day 21 and beyond.⁵⁹ The above mentioned data suggest that restarting therapy around day 7 seems safe, and that a delay beyond day 21 should better be avoided.

Balancing the risks

With all the data presented above, the clinician has to decide whether, when, and how the patient's antithrombotic therapy should be restarted. The psychological reaction is to stop the antithrombotic drug (or at least delay restarting it) since it is considered responsible for the gastrointestinal bleeding. After the haemorrhage, a new situation sets in and a detailed informed discussion with the patient and his relatives about the risks is necessary.

Table 5 summarises various clinical factors related to either the risk of recurrent bleeding or the risk of thrombosis. The combination of such factors tips the balance for or against the early restarting of antithrombotic therapy. The patient in whom an early restart poses minimal concern is someone with a low recurrence risk (e.g. bleeding from a preventable cause, or bleeding treated radically) and, at the same time, high thrombotic risk. In contrast, a patient with a high recurrence risk (e.g. bleeding from angiodysplasia of the small bowel, bleeding despite good anticoagulation control), and low thrombotic risk (e.g. atrial fibrillation without prior stroke) may delay restarting therapy. Unfortunately, the majority of patients do not fall within such distinct risk groups and the decision to restart therapy is difficult and should be individualised.

Table 5. Clinical and other factors for and against early re-initiation of antithrombotic therapy.

FOR	AGAINST
Radical treatment of bleeding	Unknown underlying pathology, or untreatable cause
Bleeding with high INR value	Bleeding despite good INR control
Upper gastrointestinal bleeding that occurred without prior PPI use	Upper gastrointestinal bleeding despite use of PPI
High thrombotic risk if antiplatelet therapy discontinuation is prolonged: <ul style="list-style-type: none"> - recent stent - recent stroke 	Relatively low thrombotic risk: <ul style="list-style-type: none"> - antiplatelet treatment for primary prevention - anticoagulant therapy in patients with modern bi-leaflet aortic mechanical valve - anticoagulant therapy in patients with AF and low CHADS₂ score
High thrombotic risk if anticoagulant therapy discontinuation is prolonged: <ul style="list-style-type: none"> - mechanical valve - AF with high CHADS₂ score (especially with prior stroke) 	

AF – atrial fibrillation; INR – international normalised ratio; PPI – proton pump inhibitor.

Practical instructions for restarting antithrombotic therapy

A) Antiplatelets

If the bleeding episode occurred under single antiplatelet therapy, reducing the dose, switching to another antiplatelet agent, and adding PPI are the common options. If the bleeding episode occurred under dual antiplatelet therapy, reconsidering its indication is mandatory. If, indeed, the indication for dual therapy with aspirin plus P2Y₁₂ inhibitor is compelling, the aspirin dose should be kept to the minimum (75 mg daily). It is safer to combine aspirin with clopidogrel rather than with the newer agents. Adding PPI is logical and recommended by the relevant European and American guidelines.^{1,60} Avoiding NSAIDs is obvious.

B) Anticoagulants

The preventive use of PPI is important, as is avoiding the concomitant administration of NSAID or aspirin. It should be remembered that, in patients with chronic stable coronary artery disease who receive VKA, the coadministration of aspirin is not necessary.

If the bleeding episode occurred while the patient was receiving VKA, the following options may be considered:

- Continue VKA (perhaps with a lower INR target of 2.0-2.5) with more frequent INR monitoring, especially in conditions known to be related to high INR values (diarrhoea, infection, antibiotic use, decompensation of heart failure).
- Switch to NOAC, especially if bleeding occurred as a result of difficulty in controlling INR. However, both rivaroxaban and dabigatran in general have a higher risk of gastrointestinal bleeding as compared with warfarin. It should be remembered

that NOACs are not indicated for rheumatic atrial fibrillation or for mechanical heart valves.⁶¹

If the bleeding episode occurred while the patient was receiving a NOAC, the following options may be considered:

- Continue with the same drug, check renal function and consider a smaller dose. If dabigatran was given at the high dose of 150 mg twice daily, then switching to 110 mg twice daily is reasonable. This dose has been tested and found non-inferior to warfarin. Dabigatran at a dose of 75 mg twice daily is only recommended by the American Heart Association for patients with very low creatinine clearance (15-30 mL/min) but there are no data to ensure that this dose is effective in ischaemic stroke prevention. The European Society of Cardiology does not recommend this dose. Rivaroxaban has been given at a dose of 15 mg daily and apixaban at a dose of 2.5 mg twice daily in patients with renal dysfunction, but again it is unclear whether these smaller doses are effective in stroke prevention when administered to patients with normal renal function who had bled with the standard dose.
- Switch to an alternative NOAC. Although direct comparisons are lacking, apixaban seems safer as far as the risk of gastrointestinal haemorrhage is concerned.
- Switch to VKA. In this case we accept a small increase in intracerebral haemorrhage risk, but this complication is, anyway, rarer than gastrointestinal bleeding.

Conclusions

After an episode of gastrointestinal haemorrhage, a thorough examination of the circumstances of bleeding is needed. It is necessary to re-evaluate the need

for continuing the previous antithrombotic regimen. Any clinical decision regarding the re-initiation of therapy must take into consideration the risk of thrombosis and the risk of recurrence. No guideline can substitute for sound clinical judgment.

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