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POSITION STATEMENT

Position statement from the Indian Society of Gastroenterology, Cardiological Society of India, Indian Academy of Neurology and Vascular Society of India on gastrointestinal bleeding and endoscopic procedures in patients on antiplatelet and/or anticoagulant therapy

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Abstract

Antiplatelet and/or anticoagulant agents (collectively known as antithrombotic agents) are used to reduce the risk of thromboembolic events in patients with conditions such as atrial fibrillation, acute coronary syndrome, recurrent stroke prevention, deep vein thrombosis, hypercoagulable states and endoprostheses. Antithrombotic-associated gastrointestinal (GI) bleeding is an increasing burden due to the growing population of advanced age with multiple comorbidities and the expanding indications for the use of antiplatelet agents and anticoagulants. GI bleeding in antithrombotic users is associated with an increase in short-term and long-term mortality. In addition, in recent decades, there has been an exponential increase in the use of diagnostic and therapeutic GI endoscopic procedures. Since endoscopic procedures hold an inherent risk of bleeding that depends on the type of endoscopy and patients' comorbidities, in patients already on antithrombotic therapies, the risk of procedure-related bleeding is further increased. Interrupting or modifying doses of these agents prior to any invasive procedures put these patients at increased risk of thromboembolic events. Although many international GI societies have published guidelines for the management of antithrombotic agents during an event of GI bleeding and during urgent and elective endoscopic procedures, no Indian guidelines exist that cater to Indian gastroenterologists and their patients. In this regard, the Indian Society of Gastroenterology (ISG), in association with the Cardiological Society of India (CSI), Indian Academy of Neurology (IAN) and Vascular Society of India (VSI), have developed a "Guidance Document" for the management of antithrombotic agents during an event of GI bleeding and during urgent and elective endoscopic procedures.

Keywords Acenocoumarol · Antithrombotic agents · Apixaban · Dabigatran · Direct-acting anticoagulants · Edoxaban · Endoscopy · Factor Xa inhibitors · Fondaparinux · Gastrointestinal hemorrhage · Heparin · Rivaroxaban · Thrombosis · Warfarin

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Introduction

The use of antiplatelet and/or anticoagulant agents has increased over the last few decades for expanding indications. Antiplatelet agents such as aspirin and the P2Y12 receptor inhibitors (clopidogrel, prasugrel and ticagrelor) decrease the platelet aggregation, thus preventing thrombus formation, while anticoagulants such as heparins (unfractionated heparin and low molecular weight heparin), coumarins and indandiones (warfarin and acenocoumarol), factor Xa inhibitors (rivaroxaban, apixaban, fondaparinux and edoxaban) and thrombin inhibitors (dabigatran), prevent the clotting of blood by interfering with the native clotting cascade. These antiplatelet and anticoagulant drugs are collectively known as antithrombotic agents. They are used to decrease the risk of thromboembolic events in patients with high-risk conditions such as atrial fibrillation (AF), acute coronary syndrome, recurrent stroke prevention, deep vein thrombosis, hypercoagulable states and endoprostheses.

Gastrointestinal (GI) bleeding associated with antithrombotic agents is an increasing burden due to the growing population with multiple medical comorbidities, increasing use of antiplatelet agents and anticoagulants and advanced age [1–6]. The GI bleeding in patients using antiplatelets and/or anticoagulants is associated with an increase in short-term and long-term mortality. This increased morbidity and mortality risk may be attributed to the severe GI bleeding itself or due to disruption of the antithrombotic effect of these drugs, for which they were given in the first insistence, or myocardial ischemia resulting from anemia or hemodynamic shock. Even if the stoppage of antithrombotic agents is undoubtfully effective in controlling GI bleeding, the thromboembolic risk that follows their temporary discontinuation might be high [7, 8].

Recently, more and more diagnostic and therapeutic GI endoscopic procedures are being performed in patients using antithrombotic agents. Since endoscopic procedures hold a baseline risk of bleeding that depends not only on the type of procedure but also on patients' comorbidities and their medications, in patients already on antithrombotic therapies, the risk of intraprocedural and delayed bleeding is further increased. Interrupting or modifying the dose of these agents prior to any invasive procedures puts these patients at increased risk of new thromboembolic events in immediate future [7, 8].

Thus, the management of patients on antithrombotic agents who present with either GI bleeding or who require emergency or elective GI endoscopic procedures for non-bleeding indications has become a common and important clinical challenge for gastroenterologists. Therefore, it is imperative for each gastroenterologist to be aware of the indications and GI bleeding risk of antithrombotic agents and how to manage these patients who present with GI bleeding. Similarly, every endoscopists must be aware of the inherent bleeding risk for every endoscopic procedure, to what extent the risk is enhanced in patients taking antithrombotic agents and how the antithrombotic therapy should be altered for patients needing endoscopic procedures to minimize bleeding without increasing the risk of thromboembolic events.

Although many international GI societies have published guidelines for the management of antithrombotic agents during an event of GI bleeding and during urgent and elective endoscopic procedures, no Indian guidelines exist that cater to specific issues pertaining to Indian gastroenterologists and their patients. In this regard, the Indian Society of Gastroenterology (ISG), in association with the Cardiological Society of India (CSI), Indian Academy of Neurology (IAN) and Vascular Society of India (VSI), endeavored to develop a "Position Statement" for the management of antithrombotic agents during an event of GI bleeding and during urgent and elective endoscopic procedures. This guidance document was aimed at analyzing current evidence from the literature on antithrombotic-associated GI bleeding and also on GI endoscopy procedure-related basal bleeding risk and the risk of bleeding during antiplatelet and/or anticoagulant therapy. The objective was to provide evidence-based recommendations for the management of such patients. The guidance document will be very useful in assisting clinicians in improving care for patients on antiplatelets and/or anticoagulants who present with GI bleeding or who require emergency or elective diagnostic and therapeutic GI endoscopy in India.

Methods

For generating this guidance document, a taskforce was constituted, which had members from all four societies. The office-bearers of the societies chose the taskforce members based on their scientific work and publications related to the topic in question. The taskforce first identified contentious issues on various management aspects of patients on antithrombotic therapy who present with GI bleeding or who require an endoscopic procedure. These issues were allotted to individual members of the taskforce, who reviewed them in detail. A detailed literature search was performed and relevant literature pertaining to the topics was shared with the taskforce using Google drive. A Zoom meeting of the Taskforce was held on November 13 and 14, 2021, to discuss, debate and finalize the consensus statements. A live discussion was used (instead of the Delphi method) for consensus generation,

as it produces a better consensus as ideas and perceptions are introduced, broken down and reassessed. The statements were finalized by live discussion and only those statements were kept, which were agreed upon by ≥ 80% of the members. Total 37 statements were presented initially and finally, 24 statements were agreed upon, while the remaining were discarded. The evidence and recommendations in these guidelines have been graded according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system [9, 10] with minor modifications (Table 1). The strength of recommendations (strong and weak) thus reflects the quality (grade) of underlying evidence (high, moderate, low).

Table 1 Level of evidence and grade of recommendations (adapted from Grading of Recommendations, Assessment, Development and Evaluations [GRADE] system [9, 10] with minor modifications)

Level of evidence*		Confidence in the evidence
High or I	Data derived from meta-analyses or systematic reviews or from multiple randomized trials with high quality	Further research is unlikely to change our confidence in the estimate of benefit and risk
Moderate or II	Data derived from a single randomized controlled trial (RCT) or multiple non-randomized studies	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate
Low or III	Small studies, retrospective observational studies, registries	Any estimate of effect is uncertain
Recommendations – GRADE**		Wording associated with the grade of recommendation
Strong	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes and cost	"must," "should," or "we recommend"
Weak	Variability in preferences and values or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption	"can," "may," or "we suggest"

To make the GRADE system more objective, the type of studies from which pieces evidences are derived have been mentioned in the Level of Evidence section

*Level was graded down if there was a poor quality, strong bias or inconsistence between studies; level was graded up if there was a large effect size

**Recommendations reached by consensus of the members and included the quality of evidence, presumed patient-important outcomes and costs

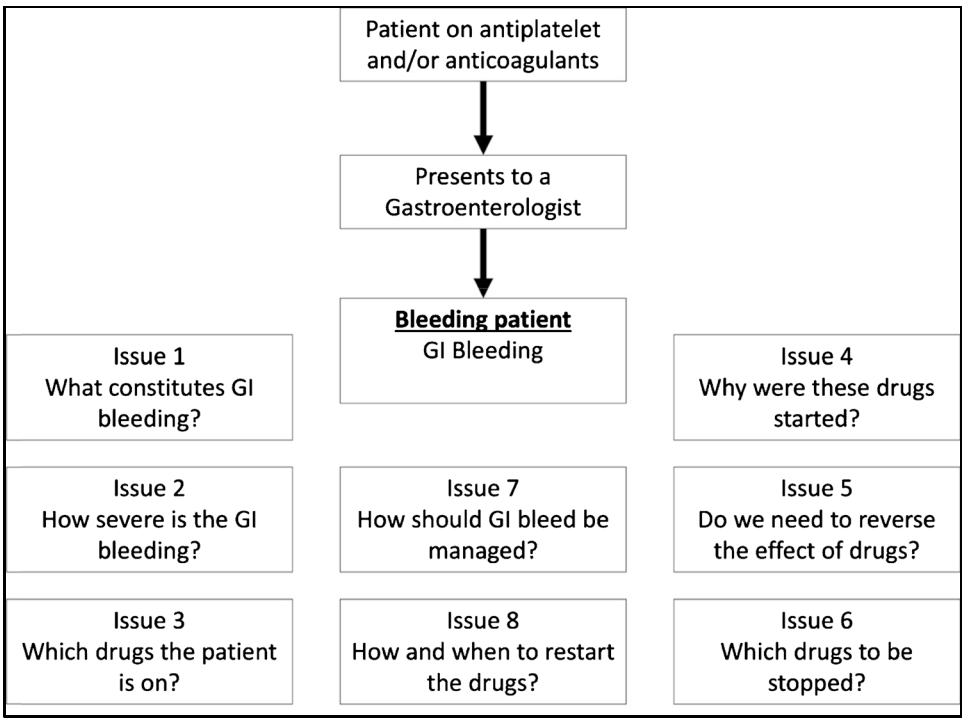


Fig. 1 Algorithm of issues that need to be addressed by the gastroenterologist when a patient on antiplatelet and/or anticoagulant presents with gastrointestinal bleeding. *GI* gastrointestinal

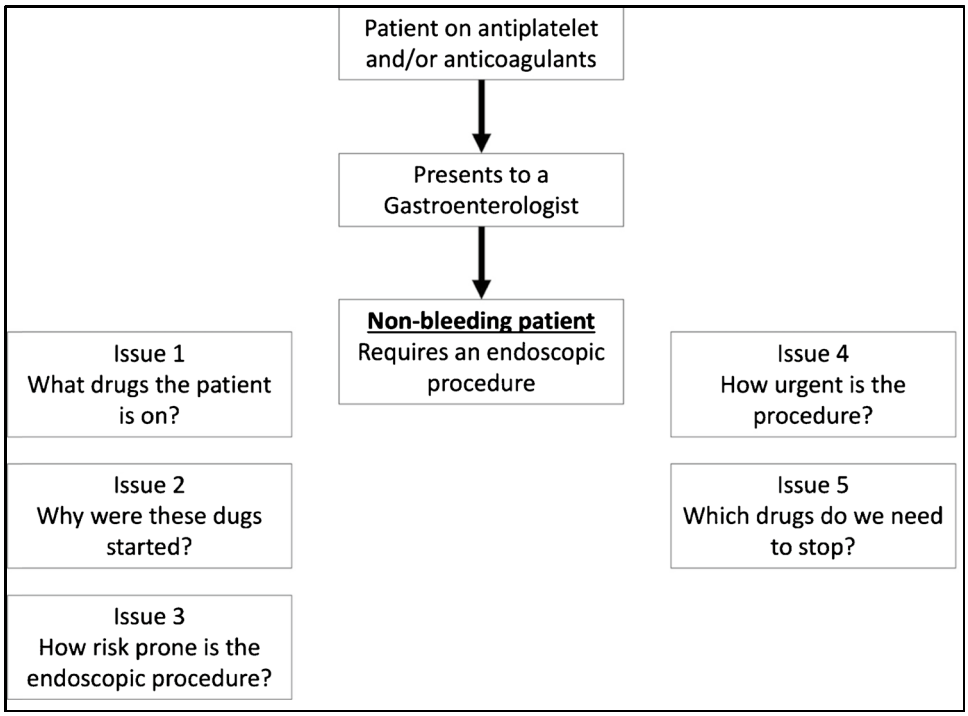
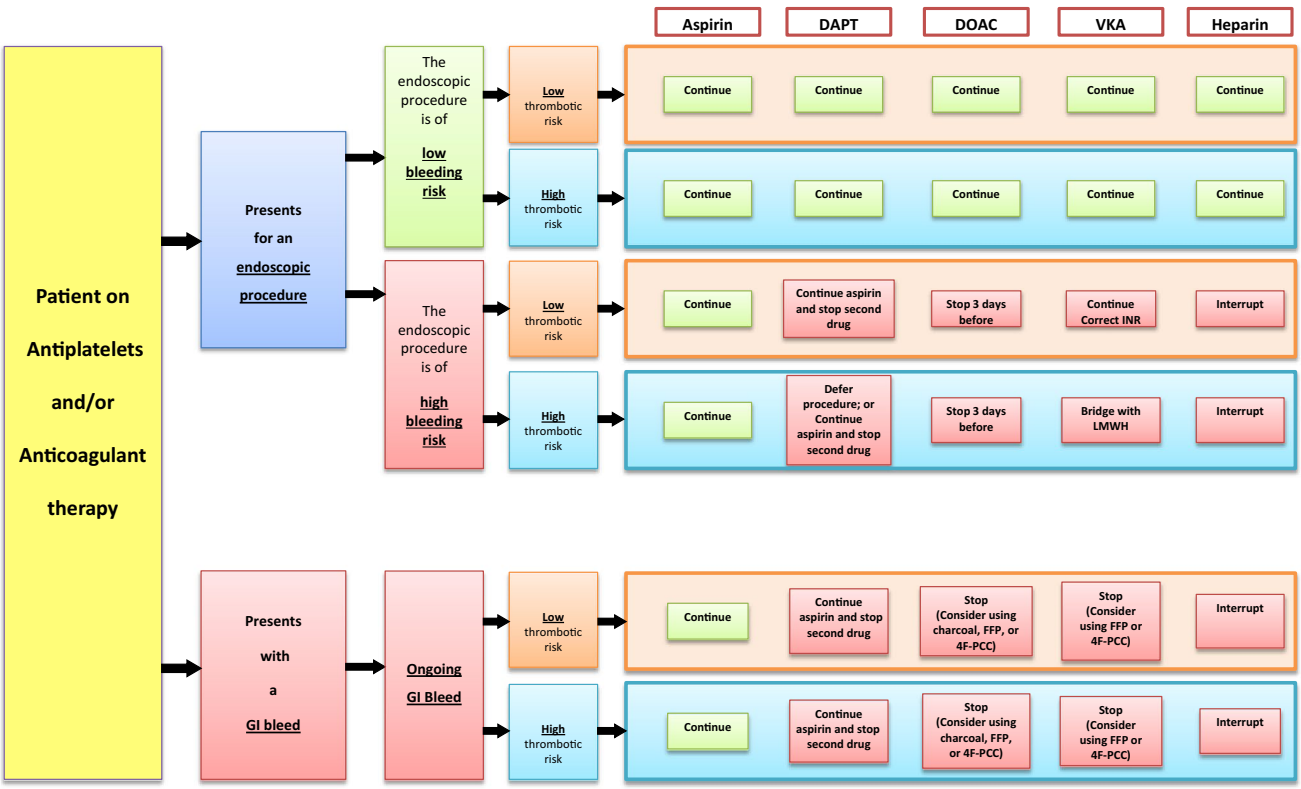


Fig. 2 Algorithm of issues that need to be addressed by the gastroenterologist when a patient on antiplatelet and/or anticoagulant presents for endoscopy for a non-bleeding indication



Algorithm 1 Summary of recommendations for antithrombotic therapy during endoscopy and gastrointestinal bleeding. *DAPT* dual antiplatelet therapy, *DOAC* direct-acting anticoagulant, *VKA* vitamin K antagonists, *INR* international normalized ratio, *LMWH* low molecular weight heparin, *FFP* fresh frozen plasma, *4F-PCC* four-factor prothrombin complex concentrate

Algorithms of issues

The taskforce developed two simple algorithms that list out all issues that need to be addressed by the gastroenterologists, when a patient on antiplatelet and/or anticoagulant therapy presents either with GI bleeding (Fig. 1) or who requires endoscopy procedure for the non-bleeding indication (Fig. 2). A summary of recommendations is given in Algorithm1.

What constitutes a GI bleed?

Consensus statements

#	Statement	Level of evidence	Strength of recommendation
1	Gastrointestinal (GI) bleeding is defined as bleeding into the GI tract characterized by hematemesis, melena, hematochezia or a positive nasogastric lavage	Moderate	Strong
2	GI bleeding is classified based on the site where the lesion is found as: • Upper GI bleeding (within the reach of upper GI endoscope) • Colonic bleeding (within the reach of a colonoscope) • Small bowel bleeding (lesion in small intestine)	Moderate	Weak

Gastrointestinal bleeding can fall into three broad categories: upper GI bleeding, colonic bleeding and small bowel bleeding. The anatomic landmark that separates upper and small bowel bleeding was considered the ligament of Treitz, also known as the suspensory ligament of the duodenum. This peritoneal structure suspends the duodenojejunal flexure from the retroperitoneum. However, a more practical way of categorising the source of bleeding depends on the reach of the endoscope. Upper GI bleeding can be defined as bleeding from a source within reach of the upper GI endoscope; colonic bleeding can be defined as bleeding from a source within reach of a colonoscope, while small bowel bleeding is the bleeding when the bleeding lesion is in the small intestine. Bleeding that originates from the upper GI source usually presents either as hematemesis or melena, whereas bleeding that originates from the small bowel or colon may present as melena or as hematochezia. Hematemesis is the regurgitation of blood or blood mixed with stomach contents. Melena is dark, black and tarry feces that typically have a strong characteristic odor caused by the digestive enzyme activity and intestinal bacteria on hemoglobin. Hematochezia is the passing of bright red blood via the rectum.

How do we grade the severity of GI bleeding?

Consensus statements

#	Statement	Level of evidence	Strength of recommendation
3	The GI bleeding severity is categorized as: • Severe GI bleeding: o Persistent bleeding within the first 24 h, or o Requirement for blood transfusion, or o > 20% decrease in hematocrit, or o Recurrent bleeding after 24 h of stability • Non-severe GI bleeding: any bleeding that does not fulfill any of criteria of severe GI bleeding, maybe considered as non-severe GI bleeding	Moderate	Strong
4	Severity of upper GI bleeding may also be assessed using the Blatchford score [11]	High	Strong

Resuscitation is the first and most important intervention when a patient suffering from GI bleeding arrives at the hospital. Airway protection is mandatory in patients with a decreased level of consciousness to prevent pulmonary aspiration, so tracheal intubation may be an option. Categorization of the severity of GI bleeding is of paramount importance for optimal management of the bleeding [12]. Severe GI bleeding may be defined as persistent bleeding within the first 24 hours, requirement for blood transfusion, or > 20% decrease in hematocrit, or recurrent bleeding after 24 hours of stability [13, 14]. Any bleeding that does not fulfill any of the criteria of severe GI bleeding may be considered non-severe GI bleeding. In addition, the severity of GI bleeding may also be classified based on various severity scores. The main scores for upper GI bleeding are Blatchford score [11], Albumin INR mental systolic blood pressure 65 (AIMS65) [15], Progetto Nazionale Emorragia Digestiva (PNED) [16] and admission and full Rockall [17]. Of these, the Blatchford score [11] is the most frequently used score.

Which antiplatelet and/or anticoagulant drugs is the patient on?

Consensus statements

#	Statement	Level of evidence	Strength of recommendation
5	Taking a detailed drug history and their indications is mandatory for any patient presenting with GI bleeding. The patient may be on following drugs: • Antiplatelet therapy o Single antiplatelet o Dual antiplatelets • Anticoagulants o Vitamin K antagonists o Heparin and its derivatives o DOACs • Combination therapy o Single antiplatelet + anticoagulant o Dual antiplatelets + anticoagulant	Moderate	Strong

A detailed history of antiplatelet, anticoagulant and non-steroidal anti-inflammatory medications and their indication is essential. The patient may be on single antiplatelets, dual antiplatelets, vitamin K antagonists, heparin and its derivatives, Direct-acting oral anticoagulants (DOACs) and combination therapy of antiplatelet and anticoagulants. The most commonly used anticoagulant remains warfarin. The two types of DOAC currently available are inhibitors of thrombin (dabigatran) and inhibitors of coagulation factor Xa (rivaroxaban, apixaban, edoxaban). They are indicated for patients with AF or venous thromboembolism (VTE), but not for patients with mechanical heart valves. There will be patients who had acute coronary syndrome with or without stenting and have AF, who will require DAPT for a period of one year and long-term warfarin. These patients are at considerable risk of GI bleeding and present a great challenge to clinicians. The crude incidence of major bleeding ranges from 3% to 16% in clinical studies [3, 4]. Compared to no antiplatelet therapy, the GI bleeding risk is increased by 1.8-fold during low-dose aspirin therapy and up to 7.4-fold with dual antiplatelet therapy [18]. Anticoagulant therapy is also associated with a higher risk of bleeding compared to antiplatelet agents [19]. Moreover, the combined intake of anticoagulants and antiplatelet agents raises the risk of upper GI bleeding by 60% and of lower GI bleeding by 30% [20].

What are the current indications for antiplatelet and/or anticoagulant drugs in the patient?

Consensus statements

#	Statement	Level of evidence	Strength of recommendation
6	All patients on antiplatelets and/or anticoagulants need to be categorized into those who have high thrombotic risk or low thrombotic risk	Low	Strong
7	Patients on antiplatelets with following indications have high thrombotic risk: • Acute coronary syndrome ≤ 6 months • Any type of cardiac stent ≤ 6 months • Stroke or transient ischemic attack (TIA) ≤ 6 months Patients on antiplatelets with all other indications have low thrombotic risk	High	Strong
8	Patients on anticoagulants with following indications have high thrombotic risk: • Non-valvular atrial fibrillation with a CHA2DS2-VASc score > 5 • Metallic mitral valve • Prosthetic valve with atrial fibrillation • < 3 months after VTE • Severe thrombophilia (protein C or protein S deficiency, antiphospholipid syndrome) Patients on anticoagulants with all other indications have low thrombotic risk	High	Strong

VTE venous thromboembolism

Antithrombotics are indicated for multiple indications and are prescribed by almost all medical specialties. They are intended to lower the risk of thrombosis, but generally at the cost of increasing the risk of bleeding. A substantial number of patients use two or more antithrombotics; however, combining two or three antithrombotics increases the bleeding risk twofold to fourfold compared with monotherapy [4, 21, 22].

The antithrombotic regimen should be tailored based on the patient's ischemic and bleeding risk profile. Depending on the indication, several tools were developed to assess the bleeding and ischemic risk. The Congestive heart failure, hypertension, age, diabetes mellitus, prior stroke or TIA or thromboembolism, vascular disease, age, sex category (CHA2DS2-VASc) score can be calculated to estimate the risk of stroke in patients with atrial fibrillation. Patients with a CHA2DS2-VASc score of 0 do not need anticoagulants, while patients with a CHA2DS2-VASc score of ≥ 1 for men and ≥ 2 for women are likely to benefit from anticoagulation [23].

Do we need to reverse the effect of antiplatelet/anticoagulant drugs who present with GI bleeding?

Consensus statements

#	Statement	Level of evidence	Strength of recommendation
9	For patients taking antiplatelet drugs, routine platelet transfusion has no benefit for patients with GI bleeding	Moderate	Strong
10	For patients taking anticoagulants and severe GI bleeding: • For any anticoagulant: use of FFP and four-factor prothrombin complex concentrate (4F-PCC) may be considered • If DOAC intake was within 2–4 h: charcoal could be considered • Specific agents (such as idarucizumab for dabigatran-induced anticoagulation and andexanet alfa for direct factor Xa inhibitors) can be used in selected patients to reverse anticoagulation in cases with life-threatening GI bleeding • For patients on vitamin K antagonists: reversal with IV vitamin K may be considered	Moderate	Strong

A retrospective study found that the use of platelet transfusions in patients with GI bleeding who are taking antiplatelet agents without thrombocytopenia ($< 100 \times 10^9$/L) did not reduce rebleeding but was associated with higher mortality [24].

There is biological plausibility of fresh frozen plasma (FFP) administration to reverse the effect of any anticoagulant in patients with GI bleeding; however, the evidence is not very strong. FFP should not be used routinely, but could be considered for patients with a life-threatening GI bleed or when INR exceeds the therapeutic range (> 3). 4-factor prothrombin complex concentrate (4F-PCC) is an effective alternative to FFP for urgent reversal of vitamin K antagonist therapy in major bleeding events, as demonstrated by clinical assessments of bleeding and laboratory measurements of INR and factor levels. In a phase, IIIb, multicenter, open-label, noninferiority trial, investigators compared nonactivated 4F-PCC with FFP for urgent vitamin K antagonist reversal in patients with GI bleeding. They found that effective hemostasis was achieved in 72.4% of patients receiving 4F-PCC vs. 65.4% receiving FFP, demonstrating a non-inferiority [25]. However, in another small cohort study of warfarin-treated patients requiring rapid reversal, it was found that in patients receiving FFP, INR did not normalize (range 1.6–3.8, mean 2.3), indicating an ongoing anticoagulated state in all patients [26]. In another case–control study of patients with GI bleeding prescribed vitamin K antagonist for venous thromboembolism, FFP use was associated with a higher risk of thrombotic events (OR: 4.22; 95% CI: 1.25–14.3) [27].

Activated charcoal single-dose administration in a dose of 50 g within six hours post-DOAC was shown to be beneficial in reversing the effect of DOAC [28, 29]; hence, it is recommended that if DOAC intake is within two to four hours, charcoal could be considered.

Idarucizumab, a monoclonal antibody fragment, binds dabigatran with an affinity that is 350 times as high as that observed with thrombin. In a study of patients with GI bleeding, idarucizumab showed a rapid and complete reversal of dabigatran activity in nearly all patients presenting with GI bleeding [30]. In 90 patients with GI bleeding associated with the use of a factor Xa inhibitor, treatment with andexanet markedly reduced anti-factor Xa activity and patients had good hemostatic efficacy maintained at 12 hours [31]. However, in view of the high cost and limited availability, these agents cannot be recommended routinely for all patients.

In the setting of clinically significant GI bleeding requiring therapeutic intervention, vitamin K 2–5 mg (oral or intravenous) reverses the anticoagulant effect (to INR ≤ 1.3) in 24–48 hours; hence, it may be considered. However, vitamin K use does not achieve rapid hemostasis in patients with acute bleeding [32].

Which antiplatelet/anticoagulant drugs need to be stopped in patients who present with GI bleeding?

Consensus statements

#	Statement	Level of evidence	Strength of recommendation
11	In patients with GI bleeding who are taking antiplatelet drugs: • If the patient is on aspirin monotherapy for primary prophylaxis of cardiovascular disease, it needs to be stopped • If the patient is on aspirin monotherapy for secondary prophylaxis of cardiovascular disease, aspirin need not be stopped during GI bleeding • If the patient is on clopidogrel monotherapy for secondary prophylaxis of cardiovascular disease, clopidogrel needs to be replaced by aspirin • If the patient is on dual antiplatelet therapy, aspirin need to be continued while the second antiplatelet drug need to be discontinued. The second antiplatelet need to be restarted within 5 days of control of GI bleeding	Moderate	Strong
12	In patients with GI bleeding who are taking anticoagulants, these drugs must be interrupted till bleeding is controlled	Moderate	Strong

Recent studies have found that the use of low-dose aspirin as a primary prophylaxis in adults resulted in a significantly higher risk of major bleeding and did not result in a significantly lower risk of cardiovascular disease [33–35]. Thus, it is recommended that if the patient is on aspirin monotherapy for primary prophylaxis of cardiovascular disease, it needs to be stopped when he presents with GI bleeding.

In patients taking aspirin for secondary prophylaxis, stopping aspirin in those presenting with GI bleeding will have minimal impact on the clinical course of GI bleeding because of the persistent antiplatelet effect of aspirin; hence, it need not be stopped [36, 37].

How should the GI bleed be controlled in patients taking antiplatelet/anticoagulants?

Consensus statements

#	Statement	Level of evidence	Strength of recommendation
13	Standard endoscopic techniques should be used for control of GI bleeding	High	Strong
14	However, bleeding should preferably be controlled using the mechanical methods and thermal methods need to be avoided	Moderate	Weak

In the case of GI bleeding, the Blatchford score or any other risk scoring system is used to predict outcomes. If a major bleed occurs, the priority is to restore hemodynamic stability, mainly by fluid resuscitation. A red blood cell transfusion should be considered when hemoglobin levels are below 7 or 9 g/dL for patients with severe comorbidities. Endoscopy should be performed within 24 hours after the bleeding has started [38]. Standard endoscopic techniques should be used for control of the GI bleeding [39–41]. Multiple modalities, both newer and conventional, are available and a combination of these techniques can be used to optimize endotherapy. The various modalities have their specific techniques, advantages and efficacy levels and are to be used in accordance with the availability of the technique, expertise and the patient and lesion-related factors to get the best outcome [40]. However, bleeding should preferably be controlled using mechanical methods (such as hemoclips) and thermal methods (such as bipolar probes) need to be avoided.

When and how to resume antiplatelet/anticoagulants once the bleeding is controlled?

Consensus statements

#	Statement	Level of evidence	Strength of recommendation
15	If the patient was on dual antiplatelet therapy: • Resume dual antiplatelet within 5 days of control of GI bleeding • It is preferable to use aspirin + clopidogrel • Shorten duration of DAPT to 6 months • Add a daily dose of PPI	High	Strong
16	If the patient was on aspirin monotherapy which was interrupted, it should be restarted as soon as possible and a PPI should be added	High	Strong
17	If the patient was on warfarin • Resume warfarin in 3–7 days (3 days for high thrombotic risk and 7 days for low thrombotic risk) • In high thrombotic risk conditions, consider overlapping LMWH with warfarin till therapeutic INR achieved • Ensure strict INR control	Moderate	Strong
18	If the patient was on DOAC • Resume DOAC 3 days after achieving hemostasis • Other options: o May consider switching to warfarin with strict INR control o Due to lower bleeding risk with apixaban, may consider switching to apixaban for cases on dabigatran or rivaroxaban	Moderate	Strong

Resuming antithrombotic therapy that might have contributed to GI bleeding seems risky and evokes high anxiety among physicians trying to decide whether resuming these drugs to prevent thromboembolic events or discontinuing antithrombotics in hopes of reducing the risk of recurrent bleeding is the best [42]. There are very few randomized clinical trials to guide clinical practice. A double-blind, placebo-controlled non-inferiority trial showed that after endoscopic hemostatic therapy, in patients who develop peptic ulcer bleeding while receiving low-dose aspirin, patients with early resumption of aspirin had lower all-cause mortality [43]. Thus, early resumption of aspirin therapy with proton-pump inhibitors in patients with GI bleeding and cardiovascular diseases is recommended.

Many observational studies [44–47] have assessed the outcomes associated with the resumption of anticoagulation after GI bleeding and the following important observations can be discerned from these studies: the risk of recurrent GI bleeding is not significantly increased in patients with the resumption of anticoagulants; resuming anticoagulation is associated with a significant reduction in the risk of thromboembolic events; and overall, mortality was significantly lower among patients resuming anticoagulation therapy. Thus, the available evidence favors the resumption of anticoagulation therapy as soon as possible [42]. Most guidelines recommend restarting anticoagulation as soon as possible after seven days of anticoagulant interruption in patients at low thrombotic risk and an earlier resumption of anticoagulation with heparin bridging, preferably within three days in patients at high thrombotic risk [48–50]. An analysis of 6264 patients with atrial fibrillation who were treated with either rivaroxaban or apixaban found rivaroxaban was associated with a higher risk of bleeding but similar risks of stroke/thromboembolism and mortality in comparison to apixaban [51]. In a large study of 381,054 patients, compared with dabigatran and rivaroxaban, apixaban was associated with a lower risk of GI bleeding (dabigatran: heart rate [HR], 0.64; 95% CI, 0.50–0.81; rivaroxaban: HR, 0.47; 95% CI, 0.43–0.51) [52].

What is the bleeding risk of an endoscopic procedure?

Consensus statements

#	Statement	Level of evidence	Strength of recommendation
19	The bleeding risk of any endoscopic procedure depends on whether the third layer of GI tract wall, the muscularis mucosae is breached or not	Low	Strong
20	All endoscopic procedures in which the muscularis mucosae is breached are considered high bleeding risk procedures. Conversely, all endoscopic procedures in which the muscularis mucosae is not breached are considered low bleeding risk procedures	Low	Strong

The planned endoscopic procedure type and its associated risk of postprocedural bleeding will influence the recommendation of discontinuation and reinitiation of antiplatelet and anticoagulant therapy. Generally, all endoscopic procedures in which the muscularis mucosae is breached are considered to be high bleeding-risk procedures, while those procedures in which the muscularis mucosae is not breached are considered to be low bleeding-risk procedures. Table 2 gives the list of endoscopic procedures according to their bleeding risk.

Table 2 List of endoscopic procedures according to their bleeding risk

Low bleeding risk procedures	High bleeding risk procedures
UGI endoscopy ± biopsy	Polypectomy
Colonoscopy ± biopsy	ERCP with sphincterotomy
Enteroscopy ± biopsy	EMR
ERCP without sphincterotomy	ESD
Biliary stenting	POEM
Pancreatic stenting	Stricture dilatation
Esophageal, enteral, colonic stenting	PEG
Diagnostic EUS	EUS-guided sampling
EST	EUS-guided biliary drainage
EVL	Cysto-gastrostomy/WON drainage
Gastric varices glue injection	Endoscopic necrosectomy
APC	Endoscopic procedures for GERD
Sharp/pointed foreign body removal	
Achalasia pneumatic balloon dilatation	
Spy glass cholangioscopy with laser lithotripsy	

UGI upper gastrointestinal, *ERCP* endoscopic retrograde cholangiopancreatography, *EUS* endoscopic ultrasound, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *POEM* peroral endoscopic myotomy, *PEG* percutaneous endoscopic gastrostomy, *EST* endoscopic sclerotherapy, *EVL* endoscopic variceal ligation, *APC* argon plasma coagulation, *WON* walled off necrosis, *GERD* gastro-esophageal reflux disease

How urgent is the endoscopic procedure (for non-GI bleed indications)?

Consensus statements

#	Statement	Level of evidence	Strength of recommendation
21	If patients who are on antiplatelet and / or anticoagulant therapy require an endoscopic therapy for non-bleeding indication, the urgency of procedure must be determined to plan the procedure	Low	Strong
22	Depending on urgency the procedures are categorized as follows: • Urgent: those procedures which are required to be carried out within 24 h (e.g. CBD stenting in patients with cholangitis) • Semi-urgent: those procedures which are required to be carried out between 2 and 7 days (e.g. CBD stone removal) • Elective: those procedures which can be deferred for weeks to months (e.g. POEM procedure for achalasia)	Low	Strong

CBD common bile duct

Whenever a patient who is on antiplatelet and/or anticoagulant therapy requires an endoscopic procedure for non-bleeding indication, the urgency of the procedure must be determined to plan the procedure. The endoscopic procedures can be categorized as urgent, that need to be carried out within 24 hours of presentation; semi-urgent, which need to be carried out between two and seven days of presentation; and elective procedures, which can be deferred by weeks to months. These cut-offs are arbitrary and there is very scarce scientific data to support the cut-off for each procedure. There is currently a lack of consensus among gastroenterologists in regard to the timing of semi-urgent or non-life-threatening procedures, according to a survey conducted during the coronavirus disease - 19 (COVID-19) pandemic [53]. There is a limited number of well-established evidence-based indications for emergency endoscopy; however, generally, there are two main established indications for emergency endoscopy: acute biliary pancreatitis and acute cholangitis. There is good evidence that emergency ERCP is helpful in patients with severe pancreatitis and stone impaction if performed within the first 24 hours after the onset of symptoms; however, emergency ERCP may not be beneficial for patients with mild pancreatitis if performed later than 72 hours (or 24 hours) after the onset of symptoms [54]. A recent systematic review and meta-analysis suggested that performing emergent ERCP within 48 hours in patients with acute cholangitis was associated with lower in-hospital mortality, 30-day mortality, organ failure and shorter length of stay [55].

Which antiplatelet/anticoagulant drugs need to be stopped in patients who require an endoscopic procedure?

Consensus statements

#	Statement	Level of evidence	Strength of recommendation
23	Urgent life-saving endoscopic procedures can be carried out regardless of antiplatelet/anticoagulant use, however, avoid cutting (such as sphincterotomy) if possible	High	Strong
24	For semi-urgent and elective endoscopic procedures, following protocol should be followed: • High bleeding risk procedures: o If the patient is on DAPT: ■ If possible, defer procedure till minimum DAPT period has passed ■ If can't defer, continue aspirin. Stop second drug 7 days before procedure. Restart 1–2 days after procedure o If the patient is on aspirin monotherapy ■ Continue aspirin o If the patient is on DOAC: ■ Stop DOAC 3 days before procedure. Restart 2–3 days after procedure o If the patient is on warfarin: ■ Stop warfarin 5 days before. Bring INR to < 1.5. Restart after the procedure ■ For high thrombotic risk conditions, switch over to LMWH 5 days before procedure, omit LMWH on the day of procedure. After the procedure overlap LMWH with warfarin till therapeutic INR achieved • Low bleeding risk procedures: o If the patient is on single or dual antiplatelet: ■ Continue all antiplatelet o If the patient is on DOAC: ■ Omit DOAC on the day of procedure o If the patient is on warfarin: ■ Ensure INR within therapeutic range	Moderate	Strong

DAPT dual antiplatelet therapy, *LMWH* low molecular weight heparin

It is recommended that urgent life-saving endoscopic procedures should be carried out regardless of antiplatelet/anticoagulant use. However, it is advisable to avoid cutting (such as sphincterotomy) if possible. If the bleeding occurs post-procedure, the same recommendations need to be followed as given above regarding GI bleeding in patients on antiplatelet/anticoagulant therapy.

For semi-urgent and elective endoscopic procedures, the timing of endoscopy can be planned in such a way that if any drug modification to antiplatelet/anticoagulant therapy is required, it can be done. For patients who are on DAPT and require endoscopic procedures which are of high bleeding risk, it is advisable to defer the procedure till the minimum DAPT period has passed. However, for semi-urgent procedures that cannot be deferred, a continuation of aspirin is advisable, while the second antiplatelet drug needs to be stopped seven days before the procedure and restarted one to two days after the procedure. A double-blind, randomized controlled trial showed that the continuation of clopidogrel did not significantly increase the risk of delayed post-polypectomy bleeding in patients who were on aspirin. Also, the cardio-thrombotic events were similar in both groups [56]. Similarly, another trial showed similar bleeding rates among patients randomized to continue DAPT vs. aspirin alone during cold snare polypectomy [57]. According to a systematic review published in 2009, if aspirin therapy is maintained, short-term discontinuation of a thienopyridine may be relatively safe in patients with drug-eluting stents [58]. If the patient is on aspirin monotherapy, it can be safely continued even during high-risk endoscopic procedures.

For patients who are on DOAC and require endoscopic procedures which are of high bleeding risk, it is advisable to stop DOAC three days before the procedure and restart two to three days after the procedure. In the Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) study, the incidence of 30-day thrombotic events and mortality was 0.7% and 0.5%, respectively, after DOAC temporary interruption [59]. While stopping and restarting DOAC is being considered, attention to creatinine clearance should also be made.

If the patient is on warfarin, it is advisable to stop warfarin five days before the procedure and check the INR. The INR needs to be brought to < 1.5 before the procedure. We restart warfarin after the procedure. For patients who have high thrombotic risk, it is advisable to switch over to LMWH five days before the procedure. The dose of LMWH needs to be omitted on the day of the procedure. After the procedure, overlap LMWH with warfarin till therapeutic INR is achieved.

For procedures that have low bleeding risk, if the patient is on single or dual antiplatelet, none of these needs to be stopped. If the patient is on DOAC, it needs to be skipped on the day of the procedure. If the patient is on warfarin, INR needs to be checked. If the INR is within the therapeutic range, the procedure can be carried out safely; however, if the INR is higher than the therapeutic range, it needs to be corrected to within the therapeutic range before the procedure.

Conclusion and future perspectives

Patients who are on chronic antiplatelet and/or anticoagulant agents for conditions such as coronary artery disease, atrial fibrillation, acute coronary syndrome, deep vein thrombosis, hypercoagulable states and endoprostheses represent a special population. Antithrombotic agent-associated GI bleeding is an increasing burden due to the growing population of advanced age, with multiple medical comorbidities and the use of combinations of antiplatelet agents and anticoagulants. In addition, diagnostic and therapeutic GI endoscopic procedures are being performed in these patients with increasing frequency. Management of patients on antithrombotic agents who present with either GI bleeding or who require emergency or elective GI endoscopic procedures for non-bleeding indications has become a common and important clinical challenge for gastroenterologists. In patients on antithrombotic agents, a multi-disciplinary team approach is indicated for decision-making regarding discontinuing these agents or using reversal agents to weigh the risks of ongoing hemorrhage or bleeding during endoscopy with the potential for thromboembolic events.

The present combined position statement from the ISG, CSI, NSI and VSI is the first such Indian guidance document for the management of these patients. We hope these consensus statements will help gastroenterologists, cardiologists, neurologists, vascular surgeons and general physicians in treatment and decision-making for these challenging patients. We also hope that with a uniform management protocol of these patients, we will be able to generate more data on the outcomes of these patients, which will further help in drafting further editions of these guidelines.

Declarations

Conflict of interest AC, AK, ACA, AK, AY, AB, ASM, AS, AnS, AM, DR, DNR, GM, JMKM, JR, JPSS, KP, MG, MP, MU, NS, PPM, PNS, PR, PK, PR, RK, RY, SN, SKS, SMH, SV, UCG, UM, VT, VD, VAS and ZN declare no competing interests.

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