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Review Article

Risk of Gastrointestinal Bleed and Endoscopic Procedures on Antiplatelet and Antithrombotic Agents

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Abstract

The use of antiplatelet and antithrombotic agents has increased hand in hand with the number and complexity of endoscopic procedures. Hence, the endoscopists are often faced with considering endoscopy in patients on these agents. In this setting, to make informed decision, four key aspects are need to be considered. The type of antithrombotic or antiplatelet agent used and its characteristics, risk of thromboembolic events (which can lead to ischemic stroke or acute coronary syndrome, both of which carry high morbidity) due to withholding the drug, risk of bleeding (increases with invasiveness of procedure), and timing of procedure (elective or urgent) are the key factors to consider. We aim to discuss the risk of gastrointestinal bleed and endoscopic procedures on antiplatelet and antithrombotic agents focusing on Indian context based on recent Asia-pacific guidelines along with other existing guidelines.

Keywords: *Antiplatelets, antithrombotic agents, endoscopy, gastrointestinal bleeding*

Introduction

Gastrointestinal (GI) bleed is one of the most common medical emergencies in day-to-day practice. With increase in age and comorbidities, the use of antithrombotic agents (antiplatelet and anticoagulant agents) is widely prevalent, and this has added an additional dimension in the management of patients with GI bleed or those requiring a therapeutic endoscopic procedure. A balance between the risk of procedural hemorrhage and the risk of thromboembolism on discontinuation of antithrombotic agents is essential. Knowledge of drug pharmacokinetics and urgency of the procedure are the other facts to consider [Table 1]. A close cooperation is essential between physician, cardiologist, and the endoscopist for the proper management of such patients who require GI endoscopy.

Types of Antiplatelet or Antithrombotic Drug

The endoscopist should inquire about the drugs (antiplatelet and antithrombotic agents) that the patient is taking. The knowledge of mechanism of action, onset and offset of action, pharmacokinetics, drug interactions, and risk of bleeding with each agent is essential for periendoscopic management of patients on antiplatelet or antithrombotic agents. The timing of discontinuation before endoscopy and resumption after endoscopic hemostasis is discussed in detail later in the manuscript. Summary of properties of oral antiplatelets and anticoagulant agents is given in Table 2.[1,2]

Host's Risk of Thrombosis

Risk of thrombosis on stopping antithrombotic agents depends on underlying cardiovascular/cerebrovascular/peripheral vascular status or presence of prothrombotic states. This determines the risk of thrombosis and timing of resumption of antiplatelets or antithrombotic agents.

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Table 1: Key factors to consider for periprocedural management of patients on antiplatelets and anticoagulants undergoing endoscopy

Drug factors	Host's risk of thrombosis	Host's risk of bleeding	Timing of procedure
Mechanism of action	Cardiovascular status (acute coronary syndrome or stable CAD)	Ultrahigh-risk procedure	Urgent
Dose and efficacy	Cerebrovascular status		
Duration of action	Peripheral vascular status	High-risk procedure	
Renal/hepatic clearance	Prothrombotic states		Elective
Drug interactions	Prosthetic valve		
Onset of action	Atrial fibrillation	Low-risk procedure	
Risk of bleeding	Structural cardiac valve disease		
	History of venous thumbs-embolism		

CAD=Coronary artery disease

Risk of thrombosis post coronary stent/coronary artery disease/cerebrovascular or peripheral arterial disease

The risk of stent thrombosis due to discontinuation of antithrombotic agents can be very high, high, and moderate/low based on timing of discontinuation after acute coronary syndrome/percutaneous coronary intervention (ACS/PCI): <6 weeks, 6 weeks–6 months, and >6 months, respectively, according to APAGE/APSDE guidelines.[3] Stable coronary artery disease, cerebrovascular disease, and peripheral arterial disease also fall under low-risk category. For very high-risk category, the procedure should be deferred, and for high-risk cases, defer procedure if possible to >6 months. For low-risk cases, the procedure should not be deferred. The difference between high and low risk is that for discontinuing antithrombotic agents, high-risk patients need heparin-bridging therapy. These have been detailed in Table 3.

This recommendation is based on a recent retrospective cohort study based on data of 42,000 patients undergoing surgery within 24 months of placement of coronary stent. The incidence of major adverse cardiac events (MACEs) after surgery within 6 weeks, 6 weeks to 6 months, 6–12 months, and >12–24 months was 11.6%, 6.4%, 4.2%, and 3.5%, respectively. MACE incidence was not different between drug-eluting stent (DES) and bare metal stent (BMS), and risk of MACEs was stable after 6 months in both DES and BMS.[4]

On the other hand, the British Society of Gastroenterology/European Society of GI Endoscopy (BSG-ESGE) and the American Society of Gastroenterology (ASGE) guidelines are based on the 2014 American College of Cardiology/American Heart Association guidelines that stated that the risk of noncardiac surgery is high in patients with BMS placed within 1 month or DES placed within 12 months.[5] The American College of Chest Physicians recommends delaying noncardiac surgery for 6 weeks for BMS and 6 months in case of DES.[6]

Risk of thrombosis in prothrombotic states

Different societies have stratified patients according to their risk of thromboembolism during discontinuation of warfarin. The criteria for bridging therapy differ in different guidelines. In ESGE guidelines, nonvalvular atrial fibrillation (AF) was considered low risk irrespective of their CHA2DS2VASc score (congestive heart failure – 1 point, hypertension – 1 point, age ≥75 years – 2 points, diabetes mellitus –1 point, stroke – 2 points, vascular disease – 1 point, age 65–74 years – 1 point, female sex – 1 point, and total points – 9) as there is a significantly higher risk of bleeding with bridging therapy compared to no bridging therapy in RE-LY trial.[7] However, the data could not be extrapolated to patients with mitral stenosis or CHA2DS2VASc score >5 due to small number of such patients. The role of bridge therapy in AF with mitral stenosis is also controversial, and the result of BRIDGE trial which showed foregoing bridging therapy is noninferior to periprocedural heparin bridging to prevent arterial thromboembolism with lower risk of bleeding.[8] In ESGE guidelines, AF with mitral stenosis is regarded as high risk of thromboembolism, but in APAGE/APSDE guidelines, it is regarded as low risk with no need for bridging therapy. As patients of nonvalvular AF with CHA2DS2VASc score >5 have a high risk of thromboembolism, bridging therapy has been recommended by APAGE/APSDE guidelines. In contrast, the cutoff of the same score is >2 in ASGE guidelines.[3,9,10]

Although there are differences in the various guidelines, the basic concept is either there is a high or low risk of thromboembolism in the absence of anticoagulant, and the high-risk patients need bridging therapy by unfractionated heparin (UFH) (ASGE and APAGE/APSDE) or low-molecular-weight heparin (LMWH) (BSG/ESGE). The most recent guidelines are by

Table 2: Summary of properties of commonly used oral antiplatelets and anticoagulant agents

	Mechanism of action	Dose	Efficacy	Onset of action	Duration of action	Renal/hepatic clearance	Drug interaction	Risk of bleeding
Aspirin	Irreversible inhibition of platelet cyclooxygenase (COX)-1	75-300 mg/day, 160 mg/day for complete inhibition of platelet COX-1	25% reduction in the risk of cardiovascular death, MI, or stroke	5-30 min	Antiplatelet effect persists for 7-10 days	Liver 90%, renal 10%	Acetazolamide and alcohol increases the toxic effects of salicylates	1%-3% per year
Clopidogrel and Prasugrel	Inhibit ADP- induced platelet aggregation by irreversibly blocking P2Y12	Clopidogrel-75 mg/day, loading dose - 300 mg; Prasugrel -10 mg/day, 5 mg/ day for <60 kg and age >75 kg	Compared with aspirin, clopidogrel reduces the risk of cardiovascular death, MI, and stroke by 8.7%, Prasugrel is ten times more potent than clopidogrel	Onset of action 4-6 h, prasugrel has more rapid onset of action	Antiplatelet effect persists up to 5-7 days	Renal and hepatic clearance 50% each	CYP2C19 inhibitor. Concomitant use of omeprazole can reduce antiplatelet effect	Combining clopidogrel with aspirin increases risk of major bleeding to about 2% per year
Warfarin	Vitamin K antagonist interferes synthesis of the Vitamin K-dependent clotting factors: II, VII, IX, and X	Starting dose is 5-10 mg, lower dose with CYP2C9 or VKORC1 polymorphisms	>60% reduction in thromboembolic events when maintained in therapeutic range	Delayed until 5 days as reduced levels of factor II and X are achieved by that time	Half-life 25-60 h, mean 40 h, duration of action 2-5 days	Metabolized by CYP2C9 (major) and CYP3A4 (minor) pathways. metabolites excreted in stool and urine	Amiodarone, azoles, clopidogrel, fluoxetine, isoniazid, metronidazole, furosemide, valproate can increase risk of bleeding with warfarin	Major bleeding risk is <5%/year if INR is 2-3, Risk of major bleeding increases with INR >4, especially in elderly
Dabigatran	Direct Thrombin inhibitor	150 mg twice daily, half dose in renal insufficiency	Noninferior to well-managed Vitamin K antagonist therapy for treatment of VTE: In pooled analysis of trials,	1-4 h	24 h, Half-life 11-17 h, Depends on CrCl	80% renal -dialyzable, Contraindicated in CrCl <30 ml/ min and CTP-C Cirrhosis	Interaction with drugs metabolized by P-glycoprotein (P-gp) pathways	39% reduction in the risk of major bleeding, a 63% reduction in intracranial bleeding
Apixaban	Factor Xa inhibitor	5 mg twice daily, half dose if age >80 years, Body weight <60 kg, Cr >1.5 g/dl	recurrent fatal and nonfatal VTE occurred in 2.0% of those given direct oral anticoagulants	1-4 h	24 h, Half-life 12 h	25% renal, not dialyzable, Contraindicated in CTP-C Cirrhosis, caution in CTP-A and B	Interaction with drugs metabolized by CYP3A4/ P-gp	and a 64% reduction in fatal bleeding compared to warfarin but higher
Rivaroxaban	Factor Xa inhibitor	20 mg once daily, 15 mg once daily with a creatinine clearance of 15-49 mL/min	compared with 2.2% of those given a Vitamin K antagonist Timing of discontinuation of DOACs before endoscopy: 2 days for all	1-4 h	24 h, Half-life 7-11 h	66% renal- not dialyzable, Contraindicated in CTP-B and C Cirrhosis	Interaction with drugs metabolized by CYP3A4/ P-gp	rate of GI bleeding as unabsorbed active drug in the gut exacerbates bleeding

Contd...

Table 2: Contd...

	Mechanism of action	Dose	Efficacy	Onset of action	Duration of action	Renal/hepatic clearance	Drug interaction	Risk of bleeding
Edoxaban	Factor Xa inhibitor	60 mg daily, 30 mg daily with CrCl of 15-50 mL/min, body weight <60 kg or receiving potent P-gp inhibitors such as dronedarone or verapamil	DOACs except dabigatran For dabigatran it depends on CrCl CrCl - 30-50:4d CrCl - 50-80:3d CrCl - > 80: 2d	1-4 h	24 h, Half-life 9-11 h	35% renal - not dialyzable, can be used with caution in CTP-C	Interaction with drugs metabolized by P-gp	Antidote Activated charcoal within 3 h Idaru -cizumab and dialysis for only dabigatran

COX=Cyclooxygenase, MI=Myocardial infarction, CYP=Cytochrome P 450, VKORC1=Vitamin K epoxide reductase complex, P-gp=P-glycoprotein, CrCl=Creatinine clearance, DOACs=Direct oral anticoagulants, VTE=Venous thromboembolism, CTP=Child- Turcott-Pugh

Table 3: Thrombotic risk category and antithrombotic therapy management in elective endoscopic procedures

TE risk	Low	High	Very high
	ACS/PCI >6 months stable CAD, cerebrovascular disease, peripheral vascular disease	ACS/PCI 6 weeks-6 months	ACS/PCI <6 weeks
Deferring procedure	Do not defer	Defer>6 months	Defer procedure
Aspirin	Continue aspirin	Continue aspirin	
P2Y12 stopping	Stop P2Y12 for 5 days	Stop P2Y12 for 5 days	
P2Y12 resumption	Resume P2Y12 after adequate hemostasis	Resume P2Y12 after adequate hemostasis	
Warfarin stopping	Stop warfarin 5 days before	Stop warfarin 5 days before	
Warfarin resumption	Resume warfarin after adequate hemostasis	Resume warfarin after adequate hemostasis	
Bridging therapy	No heparin bridging	Heparin bridging	
DOAC stopping	Stop DOAC 2 days before	Stop DOAC 2 days before	
DOAC resumption	Resume DOAC after adequate hemostasis	Resume DOAC after adequate hemostasis	
Bridging therapy	No heparin bridging	Heparin bridging	

ACS=Acute coronary syndrome, PCI=Percutaneous coronary intervention, DOAC=Direct-acting oral anticoagulant, CAD=Coronary artery disease

Table 4: Risk stratification for discontinuation of warfarin therapy with respect to the requirement of heparin bringing

High risk for TE (bridging therapy required)	Low risk for TE (bridging therapy not required)
VTE <3 months	VTE >3 months
Prosthetic valve with AF, nonvalvular AF with CHA2DS2-VASc >5	Nonvalvular AF with CHA2DS2-VASc ≤5, xenograft heart valve, AF with mitral stenosis
Metallic mitral valve	Metallic aortic valve
Severe thrombophilia (protein C, protein S and antithrombin III deficiency, antiphospholipid antibody, multiple abnormalities)	Nonsevere thrombophilia (heterozygous factor V deficiency or prothrombin gene mutation)

TE=Thromboembolism, VTE=Venous thromboembolism

APAGE/APSDE which has stratified patients according to the need for bridging therapy which is required obviously in high-risk patients [Table 4].[3,9,10]

Host's risk of bleeding

Incidence of gastrointestinal bleeding in the setting of acute coronary syndrome

Risk of bleeding from any site in the setting of ACS is between 3.2% and 9.1%, and majority of the life-threatening bleed are GI. Reported rates of GI bleeding in the setting of ACS are estimated to be 1%–3%, and those who develop GI bleed have a 4–7-fold increased risk of mortality.[11-15] Abbas *et al*. reported bleeding rate of 2.3% and mortality of 10%.[16] Increasing age, female sex, previous bleeding, and renal impairment are predictors of bleeding from any site after PCI according to GRACE study, whereas risk factors for GI bleed are age, prior history of ulcer, *Helicobacter pylori* infection, nonsteroidal anti-inflammatory drugs usage, sepsis, and mechanical ventilation.[11,14]

Among the antiplatelets, aspirin is ulcerogenic whereas clopidogrel is not. Hence, risk of GI bleeding with aspirin is more than clopidogrel alone, and similar

risk with dual antiplatelets is more than aspirin alone. Interestingly, statins which are almost always used in the setting of ACS, lower risk of GI bleed probably by increasing gastric mucosal prostaglandin production.[11,17]

Minor bleeding is not uncommon during endoscopic procedures, but bleeding is considered to be clinically significant if hemoglobin falls by >2 g/dl or there is a need for blood transfusion and hospitalization.[11] Bleeding can be immediate or delayed up to 2 weeks following the procedure. The odd's ratio of serious GI bleed with aspirin, clopidogrel, and dual antiplatelet therapy (DAPT) according to a population-based study is 1.9, 1.8, and 7.4, respectively.[18]

Risk stratification of elective endoscopic procedures

Based on complexity and nature of therapeutic intervention, endoscopic procedures can be high risk (>1% risk of bleeding) or low risk (<1% risk of bleeding). These have been listed in Table 5. Low-risk procedures do not warrant discontinuation of antithrombotics (irrespective of type of agent except for warfarin if INR is supratherapeutic, i.e., >3.5). For high-risk procedures, anticoagulants and P2Y12 antagonists should be discontinued, and aspirin can be continued. In high-risk procedures such as colonoscopic polypectomy and endoscopic sphincterotomy, aspirin has been found to be safe.[19-21] Few procedures have ultrahigh risk of bleeding such as endoscopic submucosal dissection (ESD) and endoscopic mucosal resection of large polyps (>2 cm) and aspirin should be stopped during these procedures as there is a high risk of hemorrhage with continued use of aspirin.[22-24] Current APAGE/APSDE guidelines have added an additional ultrahigh-risk group which was not included in earlier ASGE guidelines although BSG-ESGE guidelines have recognized this very high-risk group but did not stratify this group [Table 1].[3,9,10]

Timing of Procedure

Other than balancing risk of GI bleed/procedure and risk of thrombosis on discontinuation of antithrombotic agents, important factors to consider are the settings of endoscopy (elective or urgent). Yet another important fact to consider is timing of resumption of antithrombotic agents after endoscopic hemostasis. Various societies have developed different guidelines for the management of those patients. In this review, we shall stress on Asia-Pacific guidelines.[3]

Single antiplatelet agent

Urgent endoscopy

Aspirin primarily used for secondary prevention of cardiovascular diseases in Asia-Pacific region including India reduces vascular events and deaths by one-third and one-sixth, respectively.[9] Patients with ACS usually require DAPT as all intraplatelet pathways are not blocked by aspirin, a cyclooxygenase inhibitor. Other nonaspirin antiplatelets are used usually along with aspirin and are hence discussed in section of DAPT.

Stopping aspirin

Emergency endoscopy should not be delayed in aspirin users. If emergency endoscopy is not available, then aspirin can be withheld.[3] This is because the effect of aspirin usually lasts up to 7–9 days after cessation.[6]

Resumption of aspirin

Aspirin should be started promptly after endoscopic hemostasis. APAGE/APSDE recommends resumption of aspirin 3–5 days after hemostasis.[3] ESGE also recommends stopping aspirin for 3 days after treatment of high-risk stigmata during endoscopic hemostasis.[9] Available evidence resumption of aspirin after nonvariceal upper GI bleed comes from a double-blind placebo-controlled trial done in Hong Kong by Sung *et al*. One hundred and fifty-six aspirin

Table 5: Classification of elective endoscopic procedures according to risk of bleeding

Low-risk procedures (<1%)	High-risk procedures (>1%)	Ultrahigh-risk procedures
Diagnostic endoscopy with biopsy	Therapeutic endoscopy- dilatation of strictures, injection or banding of varices	ESD*
Therapeutic procedures like esophageal/colonic/enteral stenting (0.5%-1%) and APC	PEG/PEG-J* Ampullectomy	EMR* of large polyps (>2 cm)
	Polypectomy (0.3%-10%)	
EUS without FNA*	EUS + FNA*	
ERCP* with pancreatic or biliary stunting	ERCP* with sphincterotomy±balloon sphincteroplasty	
Diagnostic push or device-assisted enteroscopy (0.2%)	POEM*	
Video capsule endoscopy	Cystoenterostomy, *endoscopic therapy for Zenker's diverticulum	

*POEM=Peroral endoscopic myotomy, EUS=Endoscopic ultrasound, FNA=Fine needle aspiration, EMR=Endoscopic mucosal resection, ESD=Endoscopic submucosal dissection, ERCP=Endoscopic retrograde cholangiopancreatography, PEG/PEG-J=Percutaneous endoscopic gastrostomy/jejunostomy

users with cardiovascular disease with actively bleeding peptic ulcers were randomized to resume aspirin or placebo immediately after endoscopic hemostasis. At 8 weeks, ten times all-cause mortality was noted in nonaspirin users compared to aspirin users. A thirty-day rebleeding rate was two times higher in aspirin group.[3,25] Hence, resumption of aspirin after treatment of nonvariceal GI bleeding is critical as possibility of serious cardiovascular outcomes due to nonresumption of aspirin outweigh risk of rebleeding due to resumption of aspirin.

Role of platelet transfusion

ASGE guidelines recommend platelet transfusion for life-threatening GI bleed in patients on aspirin, but available evidence is on the contrary.[10] In a retrospective cohort study, rebreeding rate was similar after platelet transfusion but associated with high mortality.[26]

Elective endoscopy

For low- and high-risk procedure, aspirin can be continued, but it has to be stopped prior to ultrahigh-risk procedures [Table 5].

Dual antiplatelet therapy

Urgent endoscopy

Stopping clopidogrel

Given the high risk of stent thrombosis in initial 6 months after coronary stent placement, the APAGE/APSDE guidelines recommend discussion with cardiologist before stopping antiplatelet therapy.[3,27] If both antiplatelets are stopped, the median time to stent thrombosis is as short as 7 days, whereas it is 122 days if only clopidogrel is stopped.[28] This is the rationale of stopping clopidogrel alone. With higher prevalence (25%) of slow metabolizers of CYP2C19 in Asian population compared to Western population (5%), drug interaction of clopidogrel with high-dose proton-pump inhibitor cannot be ruled out.[3,29] Although not validated, this represents another cause for stopping clopidogrel rather than aspirin in these settings.

Resuming clopidogrel and other P2Y12 inhibitors

Other P2Y12 inhibitors such as prasugrel (irreversible) and ticagrelor (reversible) are more potent and associated with higher bleeding complications. There is no head-to-head comparison of bleeding risk between prasugrel and ticagrelor. Among DAPTs, the comparative bleeding risk is as follows: prasugrel + aspirin > ticagrelor+ aspirin > clopidogrel + aspirin.[30-32] The days by which platelet function returns to normal in prasugrel, clopidogrel, and ticagrelor are 7 days, 5 days, and 3–5 days. Hence, reinitiation of prasugrel and clopidogrel (both irreversible inhibitor) should be done after 5 days, whereas ticagrelor (reversible inhibitor) can be resumed after 2–3 days. There are no data on GI procedure risk with new antiplatelet agent vorapaxar, a protease-activated receptor 1 antagonist, which is not yet available in India.[3]

Elective endoscopy on dual antiplatelet therapy

For low-risk procedures, stopping DAPT therapy is not recommended. For high-risk procedures stop P2Y12 inhibitors 5 days before endoscopy and continue aspirin and resume DAPT after adequate hemostasis. For ultrahigh-risk procedures, both antiplatelets should be stopped. For high-risk procedures, the management of antithrombotic therapy varies according to thrombotic risk category: very high, high, and moderate to low [Table 3].[3] As short period of triple antithrombotic therapy (DAPT plus anticoagulant) followed by 1 year of double therapy (DAPT or single antiplatelet and oral anticoagulant) is often used in patients with ACS/PCI and nonvalvular AF, the management of anticoagulants (warfarin and direct-acting oral anticoagulants (DOACs) is mentioned in Table 3. The status of anticoagulants and endoscopy procedures will be discussed later.

Warfarin

Emergency endoscopy

Stopping warfarin and reversal of anticoagulation

All the guidelines recommend stopping warfarin in case of serious life-threatening bleeding.[3,9,10] Reversal of anticoagulation is recommended in all patients on warfarin according to irrespective of INR level according to ASGE guidelines, but APAGE/APSDE recommends reversal only if INR >2.5. The basis of this recommendation is a very high success rate of endoscopic hemostasis (>95%) if INR is between 1.5 and 2.5.[33,34]

Reversal agents

The options of reversal are four-factor prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP). The advantages of the former are faster onset of action, less fluid overload, lower infection risk, and no need for ABO mismatching. Four-factor PCC has to be combined with Vitamin K to replenish factor VII as it has a very short half-life (4 h). The optimal dose of Vitamin K for reversal is also an area of debate.[35] ASGE recommends 5–10 mg of Vitamin K whereas APAGE/APSDE recommends low-dose Vitamin K (1–2.5 mg) based on finding of RCTs which shows that the optimal dose for reversal is 1–2.5 mg.[36,37] Low dose is also recommended based on the fact that early initiation of warfarin therapy may be required in patients with high thromboembolic risk. In patients with high thromboembolic risk, heparin-bridging therapy should be started given the slow onset of action of warfarin after reinitiation. ESGE recommends LMWH for bridging therapy, whereas ASGE and APAGE/APSDE recommend UFH due to its

shorter half-life (1–2 h compared to 4–5 h for LMWH) which allows rapid reversal in the event of rebleeding.[38]

Resumption of warfarin

The thrombotic risk of individual patient dictates the optimal time of resumption of warfarin. Resuming warfarin at 7–30 days reduces thromboembolism risk significantly without increasing bleeding risk but resuming <7 days increases rebleeding risk by 2-fold.[39] Hence, ESGE guidelines recommend to restart warfarin at 7–15 days following bleeding event.[9] Whereas APAGE/APSDE guidelines recognize that early rebleeding risk significantly decreases after day 3, so early resumption of warfarin is recommended at day 3 in patients with high thromboembolic risk as time to re-anticoagulation may be prolonged.[3]

Bridging therapy based on risk of thromboembolism

Already been discussed earlier in section of risk of thrombosis in prothrombotic states.

Direct-acting oral anticoagulants

Urgent endoscopy

Stopping direct-acting oral anticoagulants

The management of acute bleeding in patients on DOACs is covered in details in APAGE/APSDE guidelines, whereas specific recommendations are not provided by ASGE or ESGE guidelines.[3,9,10]

For management in such situations, the following are to be considered.

Severity of bleeding: if bleeding is not life-threatening, then temporary discontinuation of DOACs will be sufficient with hemodynamic support. For life-threatening bleed, antidotes such as activated charcoal, monoclonal antibody against dabigatran (idarucizumab 5 gm), or dialysis in case of dabigatran (rest are nondialyzable) can be used.[40-42]

1. Timing of last DOAC intake: Activated charcoal is effective as antidote if given within the first 3 h as most DOACs have peak action at 3 h[40]
2. Creatinine clearance: All the DOACs are contraindicated for creatinine clearance below 15 ml/min. Dabigatran is contraindicated for creatinine clearance below 30 ml/min
3. Pharmacokinetic properties of individual DOACs: DOACs have fast onset of action (1–4 h), with a half-life of 12 h. Eighty percent of dabigatran is eliminated by renal route, and hence, it is dialyzable whereas other DOACs are not. Most of the DOACs should be discontinued 2 days before high-risk endoscopic procedure, except for dabigatran for which time of discontinuation varies according to creatinine clearance [Table 2].

The role of FFP or four factor PCC in severe bleeding with DOACs is doubtful in view of the scarcity of clinical data.[5,43]

Measurement of anticoagulant activity of DOACs can be done by specific factor assays as recommended in ESGE

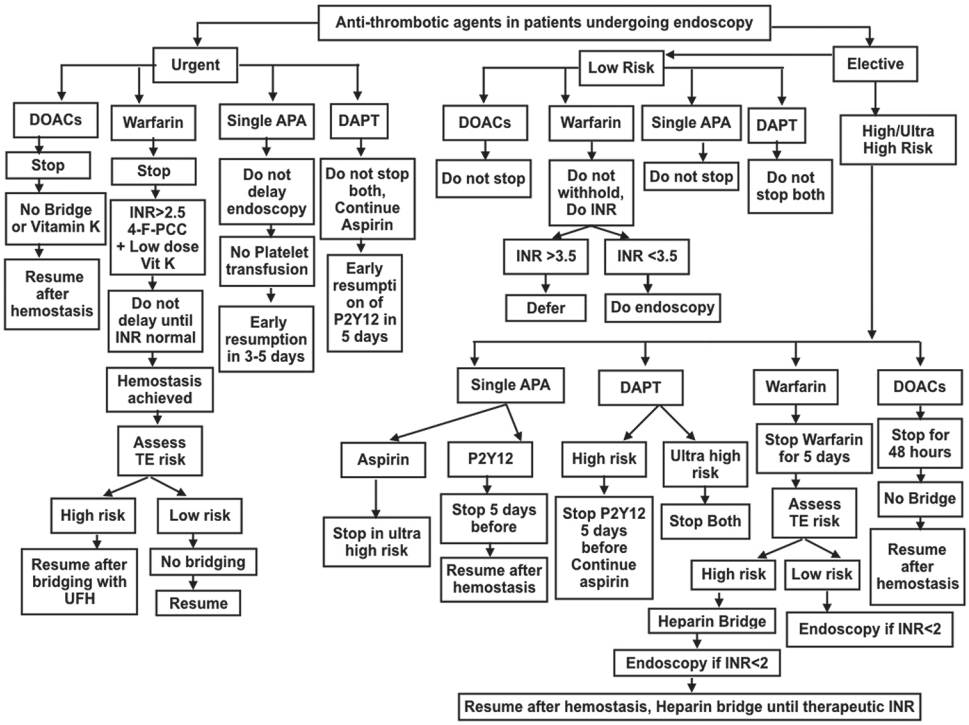

Figure 1: Concise algorithmic management outline of patients on antiplatelet or antithrombotic therapy requiring urgent or elective endoscopy

Table 6: Comparison and major differences between the existing guidelines

	APAGE-APSDE	ASGE	ESGE
		Nonvariceal upper GI bleeding	
Platelet transfusion for life-threatening bleeding	Not recommended	Considered as an option for patients on antiplatelets	An option for patients on DOACs
Patient on DAPT	Continue Aspirin, after endoscopic hemostasis, withhold 2nd agent for 5 days	Liaison with cardiologist	Continue aspirin, consult cardiologist for resuming second antiplatelet agent
Patient on warfarin Role of Vitamin K for reversal	Low-dose Vitamin K 1-2.5 mg	ACCP - 5-10 mg Vitamin K	5-10 mg
Resumption of warfarin	By day 3 after hemostasis, high TE risk - UFH bridging		By 7-15 days following bleed, no mention about bridging
Resumption of DOACs	By day 3, no need for bridging	Not mentioned	Not mentioned
		Elective endoscopic procedures	
High bleeding risk	Ultrahigh-risk factors introduced	Did not cover ultrahigh-risk procedures	Recognizes ultrahigh-risk procedures
Timing of elective endoscopy in ACS/ coronary stents	<6 weeks - defer 6 weeks-6 months - high risk, risk independent of type of stent	DES with DAPT - Defer up to 12 months	DES: <12 months BMS: <1 month Risky to discontinue second antiplatelet agent
Bridge therapy	Nonvalvular AF with CHA2DS2-VASc>5	Nonvalvular AF with CHA2DS2-VASc >2	Not indicated in nonvalvular AF irrespective of CHA2DS2 VASc score
DOACs	Low risk - do not omit High risk - resume after hemostasis - no heparin bridging	Same as APAGE-APSDE, except heparin bridging if resumption not possible within 12-24 h	Low risk - omit morning dose of DOACs on the day High Risk - delay resumption of DOACs for 24-48 h, no heparin bridging

APAGE=Asian pacific association of gastroenterology, APSDE=Asian Pacific Society for Digestive Endoscopy, ESGE=European Society of Gastrointestinal Endoscopy, ASGE=American Society of Gastroenterology, DOACs=Direct oral anticoagulants, ACS=Acute coronary syndrome

guidelines but is not recommended by APAGE/APSDE due to nonavailability issues.[3,9]

Resumption of direct-acting oral anticoagulants after hemostasis

Early resumption without heparin bridging is recommended as these agents have short half-life (12 h) and fast onset of action (1–4 h). Concerns about early rebleeding should not defer the resumption of DOACs as most of the times rebleed can be controlled in a predictable way.[3]

Elective endoscopy

DOACs should be stopped only before high or ultrahigh-risk procedures at least 48 h before endoscopy (timing may vary according to creatinine clearance: CrCl) [Table 2]. Bridging anticoagulation is not warranted neither before nor after endoscopic hemostasis with resumption of DOACs after adequate hemostasis without undue delay.

For low-risk procedures, although ESGE guidelines recommend stopping morning dose of DOACs, APAGE/APSDE guidelines do not recommend stopping DOAC even on the day of procedure given very low risk of such procedures.[3,9]

Triple and double antithrombotic therapies

As discussed in section of DAPT, in patients with nonvalvular AF and ACS/PCI, a short period of triple antithrombotic (DAPT + 1 oral anticoagulant) followed by dual therapy (single antiplatelet + 1 oral anticoagulant) for up to 1 year is recommended. The European Society of Cardiology recommends to stop one of the antiplatelets during bleed with triple therapy and discontinuation of antiplatelet for bleed during dual therapy. In patients with nonvalvular AF and ACS/PCI and low risk of stroke, they recommend DAPT alone for 1 year without anticoagulant.[44] The APAGE/APSDE guidelines recommend discussion with a cardiologist in this complex situation.[3]

Conclusion

The literature of endoscopy in patients with antithrombotic is still evolving, and many of the recommendations by various societies are based on indirect evidence. The most recent APAGE/

APSDE guidelines published in 2018 are developed specifically to meet the needs of Asia-Pacific region to manage patients on antithrombotic who need elective or emergency endoscopy given the higher incidence of nonvariceal upper GI bleed and more common performance of invasive endoscopic procedures such as ESD in this region. The comparison with other guidelines has been highlighted in Table 6. The main aim of this review was to simplify this complex subject of managing patients on antithrombotics requiring endoscopy which has been summarized in Figure 1.

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Conflicts of interest

There are no conflicts of interest.

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