Current Guidelines on Antithrombotic Management in Patients Undergoing Gastrointestinal Endoscopy

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ABSTRAK

Prosedur endoskopi seringkali digunakan untuk mendiagnosis ataupun terapi. Endoskopi memiliki risiko baik saat prosedur maupun setelah prosedur. Pasien dengan terapi antitrombotik, baik antiplatelet dan/atau antikoagulan, sebagai terapi penyakit yang mendasari memiliki risiko tinggi untuk perdarahan dan tromboemboli pada prosedur ini. Dokter perlu mempertimbangkan risiko dan keuntungan untuk melakukan penyesuaian pada terapi antitrombotik, dengan tujuan untuk menurunkan risiko perdarahan dan tromboemboli. Untuk prosedur risiko rendah, pada umumnya tidak memerlukan penyesuaian terapi. Untuk prosedur risiko tinggi, ada beberapa penyesuaian berdasarkan tipe medikasi dan kondisi pasien secara spesifik. European Society of Gastrointestinal Guidelines Endoscopy (ESGE) dan British Society of Gastrointestinal (BSG); American Society of Gastrointestinal Endoscopy (ASGE); dan terakhir Asian Pacific Association of Gastroenterology (APAGE) dan Asian Pacific Society for Digestive Endoscopy (APSDE) telah mengeluarkan panduan untuk membantu dokter dalam mengambil keputusan pada kasus pasien endoskopi dengan terapi antitrombotik. Artikel ini bertujuan untuk membandingkan setiap pedoman untuk memudahkan proses pengambilan keputusan. Walapun demikian, kondisi pasien dapat berbeda satu sama lain, sehingga pengambilan keputusan akhir perlu dipertimbangkan secara cermat pada setiap kondisi pasien.

Kata kunci: *Antitrombotik, Antikoagulan, Antiplatelet, Gastrointestinal endoskopi*

ABSTRACT

Endoscopic procedure is commonly used to make diagnosis or therapy. Endoscopy has risk on the procedure or after the procedure. Patient with antithrombotic therapy, both antiplatelet and/or anticoagulant, for underlying diseases has higher risk for bleeding and thromboembolic events in this procedure. The physician should consider risk and benefit for adjusting the antithrombotic therapy, in addition to minimize bleeding and thromboembolic events. For low risk procedure, adjustments in antithrombotic therapy usually not necessarily needed. For high risk procedure, there are several adjustments based on the type of medication and patient's condition in specific. European Society of Gastrointestinal Guidelines Endoscopy (ESGE) and British Society of Gastrointestinal (BSG); American Society of Gastrointestinal Endoscopy (ASGE); and lastly Asian Pacific Association of Gastroenterology (APAGE) and Asian Pacific Society for Digestive Endoscopy (APSDE) have published guidelines to help physician to make decisions regarding antithrombotic therapy management during endoscopy. This article compares and contrasts the approach of each guideline, in design to help the decision-making process. However, each patient's clinical condition may differ from one to another and should be considered carefully in making a final decision.

Keywords: *Anticoagulant, Antiplatelet, Antithrombotic, Gastrointestinal endoscopy.*

INTRODUCTION

Endoscopic procedure is commonly used by physicians to establish diagnosis or direct therapy for gastrointestinal problems. This procedure can be classified as low risk and high risk procedure based on bleeding risk. Low risk procedures include diagnostic and biopsy, pancreas stenting, endoscopic ultrasound (EUS), and enteroscopy without polypectomy. High risk procedures include polypectomy, Endoscopic Retrograde Cholangio-pancreatography (ERCP) with sphincterotomy, dilatation of stricture, endoscopic submucosal dissection (ESD), and endoscopic mucosal resection (EMR).[1–3]

There are several preparations before endoscopic procedure can be performed, one of the preparation is adjustment therapy for patients with antiplatelet and/or anticoagulant therapy. Physician should consider the bleeding risk associated with endoscopic procedures and the potential thromboembolic risks of stopping antithrombotic therapy. Patients with these medications have higher thrombotic and bleeding risk. The provider should consider several factors for patients taking these medications who require endoscopy such as the urgency of the procedure, the bleeding risk both from endoscopic procedure and antithrombotic drugs, and the risk of thromboembolic event.[2]

European Society of Gastrointestinal Guidelines Endoscopy (ESGE), British Society of Gastrointestinal (BSG), American Society of Gastrointestinal Endoscopy (ASGE), Asian Pacific Association of Gastroenterology (APAGE), and Asian Pacific Society for Digestive Endoscopy (APSDE) have published guidelines to help physician make decisions regarding antithrombotic therapy management during endoscopy. The published guidelines are: (1) Guidelines in patients on antiplatelet or anticoagulant therapy, including direct oral anticoagulants: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines, (2) The management of antithrombotic agents for patients undergoing GI endoscopy from ASGE, and (3) Management of patients on antithrombotic agents undergoing emergency and elective endoscopy: joint Asian Pacific Association of Gastroenterology (APAGE) and Asian Pacific Society for Digestive Endoscopy (APSDE) practice guidelines. This paper will review the comparison between BSG-ESGE, ASGE, and APAGE-APSDE guidelines.

LOW RISK ENDOSCOPY

All guidelines explain the use of antithrombotic therapy, antiplatelet agents and anticoagulants during peri-endoscopic period, while there are several different approaches in evaluation for patients with these medications who require endoscopy. BSG-ESGE and APAGE-APSDE classify procedure based on low

Table 1. Low risk procedure based on BSG-ESGE, ASGE and APAGE-APSDE

	BSG-ESGE	ASGE	APAGE-APSDE
Low Risk Procedure	- Diagnostic and biopsy procedure - Biliary or pancreatic stenting - Diagnostic EUS - Device-assisted enteroscopy without polypectomy	- Diagnostic and biopsy procedure - ERCP with stent, without sphincterotomy - Enteroscopy - Capsule endoscopy - Enteral Stent - EUS without fine needle aspiration (FNA) - Argon Plasma Coagulation - Barrett's ablation	- Diagnostic endoscopy with biopsy - ERCP with stenting - EUS without FNA - Diagnostic push or device assisted enteroscopy - Capsule endoscopy - Esophageal, enteral, and colonic stenting - Argon plasma coagulation
Therapy	- P2Y12 receptor antagonist: continue therapy - Warfarin: continue therapy with monitoring of INR level - DOAC: reduce one dose in the morning of the procedure	- Continue thienopyridines - Continue warfarin and NOAC - Continue ASA/NSAID	- Continue antiplatelet agents and/or anticoagulants

risk or high risk of bleeding and ASGE classify based on urgency of the procedure to make decision on peri-endoscopic therapy.

Table 1 shows ASGE and APAGE-APSDE include more specific procedures compares to BSG-ESGE. The BSG-ESGE guidelines are more detailed in the adjustment therapy of P2Y12 receptor antagonist, warfarin, and Direct Oral Anti-Coagulant (DOAC), while ASGE and APAGE-APSDE do not mention changing therapy in low risk procedure. All guidelines recommend continuing warfarin, BSE-ESGE suggests to monitor the level of INR before the procedure, if INR within therapeutic range, continue daily dose of warfarin, if INR above therapeutic range but lower than 5, reduce daily dose until INR returns to therapeutic range. All guidelines also recommend to continue DOAC/NOAC, while BSE-ESGE specifically suggests reducing one dose in the morning of the procedure. Aspirin suggested to be continued since there is no evidence that aspirin or NSAIDs can increase the risk of bleeding after diagnostic, mucosal biopsy or polypectomy, but BSG-ESGE and APAGE-APSDE specifically mention there is an exception for endoscopic submucosal dissection (ESD), large colonic endoscopic mucosal resection (EMR) (>2 cm), upper gastrointestinal EMR, and ampullectomy, all antithrombotic agent should be stopped.[1,3] Several studies show minimal risk of bleeding and no severe bleeding event occurs, both in diagnostic and mucosal biopsy endoscopy, even among patients taking antithrombotic agent.[4–9] These results are in line with the guidelines recommendation.

HIGH RISK ENDOSCOPY

For high risk endoscopy, APAGE-APSDE has similar classification with BSG-ESGE and ASGE, but BSG-ESGE includes esophageal,

Table 2. High risk procedure based on BSG-ESGE, ASGE, and APAGE-APSDE

	BSG-ESGE	ASGE	APAGE-APSDE
High Risk Procedure	- Polypectomy - ERCP with sphincterotomy - Ampullectomy - EMR/ESD - Therapy of varices - PEG - EUS with FNA - Dilatation of strictures - Esophageal, enteral, or colonic stenting	- Polypectomy - ERCP with sphincterotomy - Ampullectomy - EMR/ESD - Therapy of varices - PEG/PEJ - EUS with FNA - Balloon enteroscopy - Endoscopic hemostasis - Tumor ablation - Cyst gastrostomy - Pneumatic/Bougie dilation	- Polypectomy - ERCP with sphincterotomy - Ampullectomy - Therapy of varices - PEG/PEJ - EUS with FNA - Dilatation of strictures
Ultra High Risk Procedure	-	-	- ESD - EMR (> 2 cm)
Therapy	- P2Y12 receptor antagonist: 1. Low risk condition*: stop 5 days before endoscopy. 2. High risk condition*: stop 5 days before endoscopy. - Warfarin: 1. Low risk condition**: stop 5 days before endoscopy. 2. High risk condition**: stop 5 days before endoscopy; heparin bridging - DOAC: 1. Take last dose of drug ≥48 hours before procedure	- Stop P2Y12 receptor antagonist 5-7 days before endoscopy - Discontinue anticoagulant, restart warfarin on the same day (on low risk condition**) or bridging therapy (on high risk condition**) - Continue ASA/NSAID	- Stop P2Y12 receptor antagonist 5 days before. - Warfarin: 1. Low to moderate risk**: stop 5 days before endoscopy. No heparin bridging 2. High risk condition**: stop 5 days before endoscopy. Heparin bridging - Withhold DOACs 2 days beforehand - If the patient has cardiac events (ACS or PCI) <6 weeks, cancel the procedure - For ultra-high-risk procedure, patient should stop all antithrombotic agents.

*) Risk stratification based on thrombotic risk, Low Risk Condition: Ischemic Heart Disease without coronary stent, Cerebrovascular Disease, Peripheral Vascular Disease; High Risk Condition: Coronary Artery Stents (>12 months after inserting drug-eluting stent, >1 month after inserting metal coronary stent)

enteral, or colonic stenting and ASGE include balloon enteroscopy, endoscopic hemostasis, tumor ablation, cyst gastrostomy, and pneumatic/ bougie dilation into high risk procedure as shown in **Table 2**. APAGE-APSDE specifically mention ESD and EMR more than 2 cm classified into ultra-high-risk procedure. For ultra-high-risk procedure, they recommend to stop all antithrombotic agent due to high risk of imbalance hemostasis. In general, all of guidelines recommend stopping P2Y12 receptor antagonist 5 days before the procedure. BSG-ESGE detail more specific information for patient with "low risk" and "high risk" condition based on underlying cardiovascular disease. All guidelines suggest stopping warfarin 5 days before the procedure and adjustment therapy applied based on low or high risk patient's condition. Heparin bridging therapy is recommended for patient with high risk of thromboembolic events who undergo high risk procedure. BSG-ESGE explain the bridging therapy can be started by substitution therapy with low molecular weight heparin (LMWH) 2 days after stopping warfarin, while APAGE-APSDE recommends using unfractionated heparin since it has shorter half-life. However, physician should be aware of the potential risk of bleeding since study shows bridge anticoagulation therapy is associated with high incidence of bleeding after polypectomy.[10,11]

BSG-ESGE proposes to take last dose of DOAC at least 48 hours before the procedure in normal kidney function and for patients taking Dagibratan with CrCl 30-50 mL/min, it should be stopped at least 72 hours before the procedure or liaise with hematologist if patient with severely impaired renal function. **Table 3** describes the adjustment of the time of stopping DOAC based on creatinine clearance levels and type of drugs by ASGE. APAGE-APSDE specifically recommend not to take Dabigratan at all, if CrCl below 30 mL/min.

Endoscopic polypectomy relatively has lower risk of bleeding and perforation compare to other high risk procedure.[12] Intraprocedural bleeding of patients undergoing polypectomy only occurs in 0.5-2.2% of patients, the risk is getting higher along with the size of the polyp and this type of bleeding can be controlled immediately on procedure. Risk of postprocedural bleeding even rarer (0.3-0.6%) and more associated in patients with risk factor such as size, morphology, location of the polyp, and other comorbidities (age, hypertension, renal disease, use of anticoagulant).[13,14] Another studies indicated an increased risk of bleeding and thrombotic event on patient with anticoagulant and antiplatelet therapy who underwent polypectomy endoscopy.[11,15–17]

Table 3. DOAC interruption on patient with impaired kidney function

Type of Drugs	Creatinine Clearance (mL/min)	Timing of Discontinuation before procedure (day)
Dagibratan	>80	2-3
	50-80	2-3
	30-49	3-4
	<29	4-6
Apixaban	>60	1 or 2
	30-59	3
	15-29	4
Rivaroxaban	>90	>1
	60-90	2
	30-59	3
	15-29	4

Postprocedural bleeding occurs in 5-7% patients who underwent EMR and generally identified within first 48 hours after the procedure.[18–20] A study showed from 2715 patient who underwent therapeutic ERCP, 122 (4.5%) patients had bleeding complication and 69.7% of them occurs intraprocedural.[21] Bleeding after EUS-FNA was found in 2.4% of cases on patients with antithrombotic therapy.[22] The incidence of hemorrhagic events after gastric ESD ranges from 3% to 15.6%.[23–35]

RISK FOR THROMBOEMBOLIC EVENT IN PATIENTS WITH MECHANICAL HEART VALVE(S) OR VTE ON COAGULATION THERAPY

There are some differences in stratifying risk of thromboembolic event on patient on coagulation therapy. **Table 4** shows comparison between BSG-ESGE, ASGE, and APAGE-APSDE classification. In general, patients with severe underlying disease with other

Table 4. Risk for thromboembolism of patient on coagulation therapy

	BSG-ESGE	ASGE	APAGE-APSDE
VTE	Low Risk - Atrial fibrillation without valvular disease - >3 months after venous thromboembolism - Thrombophilia syndromes High Risk - Atrial fibrillation and mitral stenosis - <3 months after Venous Thromboembolism (VTE)	Low Risk - >12 months previous and no other risk factor Medium Risk - VTE within the past 3-12 months - Non-severe thrombophilia - Recurrent VTE - Active cancer High Risk - <3 months from previous VTE - Severe thrombophilia	Moderate to Low Risk - ACS or PCI >6 months ago - Stable coronary arterial disease High Risk - ACS or PCI 6 weeks-6 months ago - Non-valvular atrial fibrillation - <3 months after VTE - Severe thrombophilia Very High Risk - ACS or PCI <6 weeks
Mechanical Heart Valve(s)	Risk - Prosthetic metal heart valve in aortic position - Xenograft heart valve High Risk - Prosthetic metal heart valve in mitral position - Prosthetic metal heart valve and AF.	Low Risk - Bileaflet aortic valve prosthesis without AF Medium Risk - Bileaflet aortic valve prosthesis with risk factor (AF, CVA or TIA, hypertension, diabetes, CHF, Age >75 years) High Risk - Mitral valve prosthesis - Caged ball or tilting disc aortic valve prosthesis - Recent CVA or TIA (within 6 months)	High Risk - Prosthetic valve with atrial fibrillation - Metallic mitral valve.

comorbidities and recent cardiac events have higher risk for thromboembolism.

Previous studies have shown an increased occurrence for developing thromboembolic events after endoscopic procedure (OR: 3.58) for patients relative to controls.[36] Other factors such as rebleeding and anticoagulant management factors (e.g. INR correction, reversal agent use, and drug interruption) were associated with thromboembolic events.[37] All guidelines recommend restarting the warfarin after the procedure since studies show there is an association between the resumption of warfarin and reduction of thromboembolic events.[38] However, there is no exact time to restart the warfarin therapy. BSG-ESGE recommends restarting daily dose warfarin on the evening after the procedure, while APAGE-APSDE recommends restarting the warfarin therapy after 3 days.

CONCLUSION

All guidelines classify patients based on thromboembolic risk and classified procedure based on bleeding risk. They also described whether antithrombotic therapy needs to be stopped or not, but differ in the detail. For all procedure, Aspirin should be continued with some exception, where special consideration should be applied in patients requiring ESD, large colonic EMR (>2cm), upper gastrointestinal EMR, and ampullectomy. For low risk procedure, all antithrombotic therapy can be continued, whereas BSG-ESGE recommends monitoring INR levels carefully. For high risk procedure, all guidelines stratify patients based on the risk of thromboembolic events, but in different approaches, on the other hand, the adjustment therapy is quite similar. P2Y12 receptor inhibitor should be stopped at least 5 days before the procedure, BSG-ESGE has more consideration

for patient with history of having drug eluting stent or metal stent. All guidelines recommend warfarin should be stopped at least 5 days before the procedure and should be restarted after the procedure to minimize thromboembolic events. Patients with high risk thromboembolic events are recommended to have bridging therapy, but we should be aware of potential risk of delayed bleeding after the procedure. DOAC should be stopped in patients with high risk procedure at least 48 hours or maybe more in patients with impaired renal function. In the end, the decision to adjust antithrombotic therapy has to be individualized in consideration of patient's condition and risk of the procedure.

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