International Journal of Medical and Health Research
www.medicalsciencejournal.com
ISSN: 2454-9142
Received: 02-08-2023, Accepted: 17-08-2023, Published: 04-09-2023
Volume 9, Issue 5, 2023, Page No. 21-27

Strategy for managing antithrombotic therapy in periprocedural period in gastrointestinal endoscopy

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Abstract
The main function of antithrombotic therapy is to reduce the risk of thromboembolic episodes in patients with high risk. Although their important role in cardiovascular prevention, these agents are the most often reason for bleeding when undertaking endoscopic procedures. On the other, hand there is also a risk of thromboembolic sequelae if they are withheld. The bleeding risk depends on the type of endoscopic procedure, define as low or high-risk ones. The recommendation in high-risk endoscopic procedures is to stop the antithrombotic agents and to initiate therapy with LWMH for patients on vitamin K antagonist known as "bridging". There is no need antithrombotic therapy in endoscopic procedures with lower bleeding risk to be withheld. The strategy for managing this therapy when these patients need gastrointestinal (GI) endoscopic procedures should be based on balancing the bleeding risk against the thromboembolic risk in collaboration with cardiologist.

Keywords: Anticoagulants, antiplatelet agents, gastrointestinal bleeding, management, endoscopic procedures

Introduction

Anticoagulants and antiplatelets are widely used drugs for a number of cardiovascular and thrombotic conditions. These drugs increase the risk of bleeding during endoscopic procedures and on the other hand, discontinuation of their administration carries a risk for thromboembolic events. The assessment of the use of antithrombotic drugs in the periprocedural period in gastrointestinal endoscopy creates difficulties, as the thrombotic risk and the risk of bleeding are different for each patient [50].

Anticoagulants in endoscopic procedures

Anticoagulant intake is increasing worldwide, mainly due to the increasing incidence of patients with atrial fibrillation [7]. Indications for their use are also mechanical heart valves, deep venous thrombosis, hypercoagulable conditions [22]. About 2% of the population in developed countries take anticagulants, with the incidence of adult patients reaching 8-10% [7]. Annually, about 10% of patients taking anticoagulants require temporary discontinuation of therapy due to surgical or other invasive selective procedures, such as gastrointestinal endoscopy [10]. A serious complication of anticoagulant therapy is severe GIT bleeding, with an incidence of approximately 1-4% per year and a fatal incidence of up to 10% [19, 2]. About 15% of patients with acute upper GIT bleeding and up to 32% of patients with lower GIT bleeding take anticoagulants [33, 44].

The recommendations of the British Gastroenterology Association (BSG) and the European Gastrointestinal Endoscopy Association (ESGE) for anticoagulant therapy in patients undergoing routine endoscopy are based on stratification of patients at risk categories according to the risk of bleeding in the endoscopic procedure and thromboembolic risk (tabl. 1 and tabl. 2) [47, 48, 50].

Table 1: Endoscopic procedures with high and low risk of bleeding

High risk endoscopic procedures	Low risk endoscopic procedures
• polypectomy	• diagnostic procedure +/- biopsy
• ERCP with sphincterotomy	• placement of biliary or pancreatic stent
• ampullectomy	• enteroscopy without polypectomia
• varices therapy	* ERCP without sphincterotomy APC/ablation of barett's esophagus
• dilatation of strictures	
• PEG / PEJ *	
• EUS with TAB	
• EMR / ESD	
• stent placement on the esophagus, small intestine, colon	
* - endoscopic hemostasis	
- tumor ablation	
- biliary / pancreatic sphincterotomy	
- therapeutic balloon-assisted enteroscopy	
- cystogastrostomy	

ERCP - endoscopic retrograde cholangiopancreatography; PEG - percutaneous endoscopic gastrostomy; PEJ- percutaneous endoscopic jejunostomy; EUS – endoscopic ultrasound; TAB - fine-needle aspiration biopsy; EMR - endoscopic mucosal resection; ESD - endoscopic submucosal dissection; APC - argon plasma coagulation
* Endoscopic procedures included in the guideline of the American Society of Gastrointestinal Endoscopy

Table 2: Conditions with high and low thromboembolic risk

Condition with high thromboembolic risk	Condition with low thromboembolic risk
Mechanical mitral valve	Mechanic aortic valve
Mechanical mitral valve and AF	Biological valve
AF and mitral stenosis	AF without valve pathology
< 3 months after venous thrombembolism	> 3 m after venous thromboembolism Thrombophilia

AF – atrial fibrillation

Vitamin K antagonists

Studies have found that gastrointestinal bleeding is a typical complication of vitamin K use antagonists as a difference in risk between vitamin K antagonists (VKA) and direct-acting oral anticoagulants (DOAC) were not observed [19, 22]. A meta-analysis involving 23 prospective studies, comparing the use of DOAC (apixaban, dabigatran, doxaban and rivaroxaban) and vit K antagonists on the risk of massive gastrointestinal bleeding, did not show any difference (RR 1.08) [5]. On the other hand, a meta-analysis of 43 prospective randomized trials reported a slightly increased risk of gastrointestinal bleeding with DOAC compared to vit. K antagonists (OR 1.45) [23]. A Finnish study in 100,000 patients reported a risk of 2.3% per year for hospitalized ones for gastrointestinal bleeding at the start of therapy and 0.9% during long-term treatment. The risk was the highest in the first 30 days of initiating anticoagulant therapy [40]. The risk of severe bleeding also depended on comorbidity, concomitant therapy, duration of anticoagulant therapy and indications for anticoagulation (the incidence is 2.5% in patients with atrial fibrillation and 0.5% in patients with pulmonary embolism) [5].

The risk of bleeding increases when using an anticoagulant with an antiplatelet agent and especially with two antiplatelet agents. The "Stent Anticoagulation Restenosis Study" reported a higher number of bleeding events with an anticoagulant and Aspirin compared to the Aspirin-only group - 6.2% to 1.8% [31], as bleeding events from the GIT were not reported. In a retrospective analysis of 666 patients on triple therapy with aspirin, clopidogrel and enoxaparin, with short-term use in patients with acute coronary heart disease, gastrointestinal bleeding was observed in 2.7% of the patients on day 30 [37]. In a Danish retrospective study of 118,606 patients, bleeding cases were reported with triple therapy with aspirin, clopidogrel and vit. K antagonist - 15.7% per year, and in double therapy group with vitamin K antagonist and clopidogrel - 13.9% per year [20]. Comparing monotherapy with vitamin K antagonist with dual therapy with clopidogrel a 3.1-fold increase in risk and respectively 3.7-fold increase with triple therapy was reported. The gastrointestinal bleeding was 5.1% per year, a 5.38 times increase compared to oral anticoagulant monotherapy. The risk of bleeding after myocardial infarction with triple therapy was 1.4 times higher than with vitamin K antagonist therapy and antiplatelet agent. The proportion of patients with fatal GIT bleeding compared with non-fatal cases was 45.3% to 33.8% [30]. In a prospective study where bleeding was targeted, a significantly higher frequency was reported. Episodes of bleeding were reported annually in 19.4% of patients on dual therapy and in 44.4% of patients on triple therapy, with 2% to 8.8% of patients experiencing GIT bleeding [17].

In the study by Sorensen *et al*. the risk of hospitalization due to hemorrhage associated with various antithrombotic regimens was investigated. It covered 40,812 patients over the age of 30 who were admitted to a hospital with a myocardial infarction for the first time. They were divided into the following groups: monotherapy with aspirin, clopidogrel or vitamin K antagonist; double therapy with aspirin plus clopidogrel, aspirin plus vitamin K antagonist, or clopidogrel plus vitamin K antagonist or triple therapy involving all three drugs. The risk of bleeding, recurrent myocardial infarction and death has been assessed. During the mean follow-up of 476.5 days (SD ± 142.0), 1891 (4.6%) patients were admitted to hospital with bleeding. The annual bleeding rate was 2.6% for the aspirin group, 4.6% for clopidogrel, 4.3% for the vitamin K antagonist, 3.7% for the aspirin plus clopidogrel, 5.1% for the aspirin plus vitamin antagonist. K, 12.3% for clopidogrel plus vitamin K antagonist and 12.0% for triple therapy. With aspirin as the reference drug, the corrected risk factor for bleeding was 1.33 (95% CI 1.11-1.59) for clopidogrel, 1.23 (0.94-1.61) for vitamin K antagonist, 1.47 (1.28-1.69) for aspirin plus clopidogrel, 1.84 (1.51-2.23) for aspirin plus vitamin K antagonist, 3.52 (2.42-5.11) for clopidogrel plus vitamin K antagonist, and 4.05 (3.08-5.33) for triple therapy. 702 (37.9%) of 1852 patients with non-fatal bleeding had a recurrent myocardial infarction or died during the study period compared with 7178 (18.4%) of 38 960 patients without non-fatal bleeding (HR 3.00, 95% CI 2.75-3.27, p <0.0001). In patients with myocardial infarction, the risk of bleeding increases with the number of antithrombotic drugs used [43].

According to the recommendations of BSG and ESGE, anticoagulants could be continued in low-risk endoscopic procedures, but should be discontinued in all high-risk procedures. In procedures with a low risk of bleeding, the INR values should be checked one week before the procedure and should be at therapeutical limits. For INR values above therapeutical limits but below 5, it is recommended to reduce the daily dose until therapeutic levels are reached. Discontinuation of VKA may also be considered in diagnostic procedures that are likely to become high-risk, such as colonoscopy polypectomy [47, 48, 50]. In this regard, studies have shown that it is safe to perform a polypectomy of a colon polyp below 10 mm without interrupting the VKA, provided that endoscopic clips are prophylactically inserted [13] or that an endoloop polypectomy technique is used to reduce the risk of late bleeding [25].

In patients on vitamin K antagonist therapy who is undergoing an endoscopic procedure with a high risk of bleeding but a low thrombotic risk is recommended to discontinue vitamin K antagonist intake 5 days before the procedure for Warfarin, 3 days for acenocoumarol /Fig.1/. For this period, the INR values reach ≤ 1.5 in 93% of patients. After the endoscopic procedure, the intake of vitamin K antagonist can be restored on the same day at the usual daily dose [47, 48].

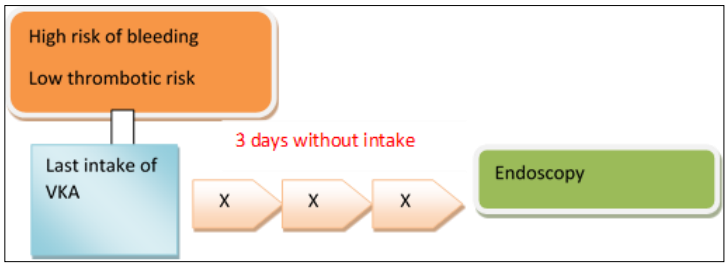

Fig 1: Intake of VKA (Acenocoumarol) in endoscopic procedures with high bleeding risk for conditions with low thrombotic risk.

In endoscopic procedures with a high risk of bleeding and conditions with a high thrombotic risk, it is recommended to discontinue the oral anticoagulant and switch to bridging therapy with a direct-acting parenteral anticoagulant, usually low molecular weight heparin (LMWH) /100 UI / kg 2x / in order to reduce the periprocedural risk of thromboembolism / Fig. 2 /.

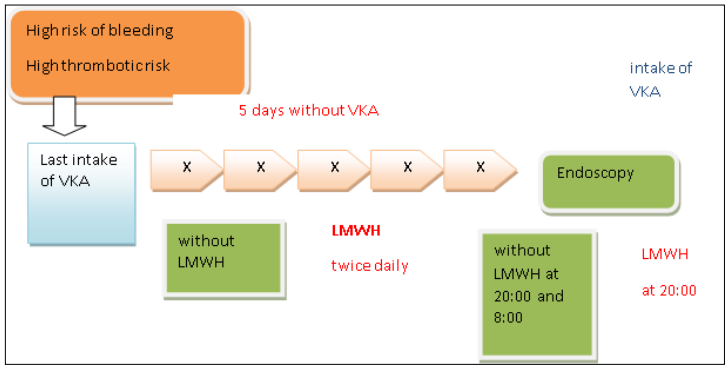

Fig 2: Intake of VKA in endoscopic procedures with high bleeding risk and conditions with high thrombotic risk

LMWH should be discontinued 24 hours before the procedure and resumed the next day in a low risk post-procedural bleeding or after 48 hours in a high risk post-procedural bleeding (according to the 2012 ACCP guideline) [11]. On the other hand, ESGE's recommendations for bridging heparin therapy do not include patients who are traditionally considered to be at high risk for thromboembolic events, such as those with non-valvular atrial fibrillation and previous thromboembolic events and / or CHADS2 score 5 or 6, and those with recent (up to 3 months) venous thromboembolism [10].

DOAC

After decades in which vit. K antagonists were the only oral anticoagulants, the spectrum of these drugs was expanded to include a new class of drugs, such as direct oral anticoagulants - directly inhibiting thrombin / dabigatran - Pradaxa / or activated factor Xa (Rivaroxaban – Xarelto; Apixaban- Eliquis). DOAC have a number of advantages over vit. K antagonists - due to more predictable pharmacokinetics, are prescribed in a fixed dose, no routine monitoring of coagulation status is required. The rapid onset of action / 1-4 hours / and short half-life / 9-17 hours / makes the initiation and interruption of therapy relatively easier and safer than vitamin K antagonists [50].

There is also a risk of bleeding when taking DOAC. In a retrospective study in patients stratified into three age groups with non-valvular atrial fibrillation and dabigatran, rivaroxaban or apixaban, Mayo researchers evaluated the incidence of total GIT bleeding and compared rivaroxaban with dabigatran in 31,574 patients, apixaban with dabigatran in 13,084 patients and for apixaban with rivaroxaban in 13,130 patients. Apixaban was found to have the most favorable safety profile for GIT compared to dabigatran and rivaroxaban in the three age groups. Rivaroxaban has the most unfavorable safety profile for the GIT. Patients using apixaban were with 61% less likely to experience GIT bleeding than those on dabigatran (HR 0.39; 95% CI, 0.27-0.58). Dabigatran patients were with 20% less likely to bleed than rivaroxaban (HR, 1.20; 95% CI, 1.00-1.45). It is observed that the cases of bleeding from the GIT in patients taking DOAC increase with age, with the greatest risk observed in persons aged 75 years and older. The researchers concluded that Apixaban had the safest profile of the three drugs studied in this age group [1].

Due to the short half-life of DOAC, they can be discontinued hours before the endoscopic procedure, and due to the rapid onset of action, anticoagulation is achieved within a few hours after inclusion [50]. These pharmacokinetic properties of DOAC eliminate the need for bridging heparin therapy. On the other hand, this class of drugs is not indicated for use in patients at high thrombotic risk [47, 48]. On table 3 are presented some anticoagulants and the interval without intake before the endoscopic intervention.

Table 3: Anticoagulants and interval without intake before the endoscopic procedure.

Drug	Mechanism of action	Pause before endoscopy
Coumarins	Vit K antagonist	3-5 d
Rivaroxaban (Xarelto®)	direct Xa-inhibitor	GFR > 90 1d
		GFR 60-90 2d
		GFR 30-59 3d
		GFR 15-29 4d
Apixaban (Eliquis®)	direct Xa-inhibitor	GFR > 60 1-2d
		GFR 30-59 3d
		GFR 15-39 4d
Dabigatran (Pradaxa®)	direct thrombin-inhibitor	GFR >50 2-3d
		GFR 30-49 3-4d
		GFR<30 4-6d
LMWH	antithrombin-activator	24 h

*GFR – glomelural filtration rate

For endoscopic procedures with a low risk of bleeding, ESGE recommends skipping the morning dose of DOAC. The optimal window for the endoscopic procedure is considered to be when the anticoagulant effect is relatively low - about 10 hours after the last dose for drugs taken twice daily and about 20 hours - for once-daily medication (Rivaroxaban). In high-risk procedures - the last dose is recommended to be taken 48 hours before the endoscopic procedure, for Dabigatran (with CrCl - 30-50 ml / min) - 72 hours before the manipulation /Fig.3/ [47, 48].

Dabigatran

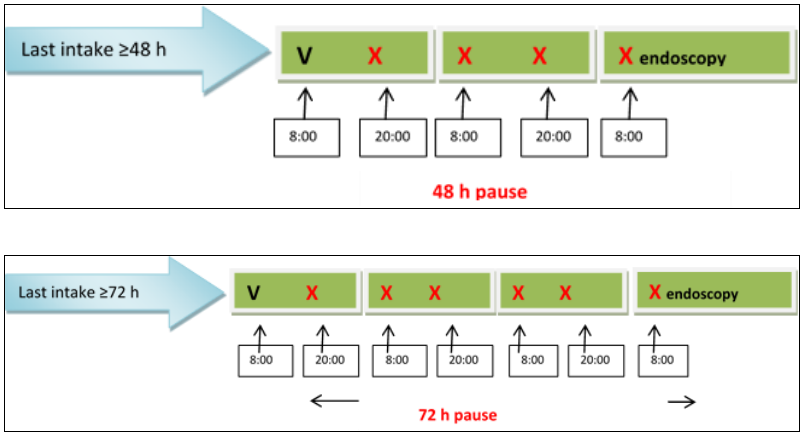

Fig 3: Intake of DOAC in endoscopic procedures with high bleeding risk and conditions with low thrombotic risk.

Antiplatelet agents

Antiplatelet agents are widely used drugs in clinical practice, mainly for primary and secondary prevention of cardio vascular diseases [46]. The use of antiplatelet agents has been associated with outweighing clinical benefits [50], but may nevertheless cause upper and lower GIT bleeding [29, 12, 50]. Antiplatelet agents lead to the formation of erosions and ulcers in the duodenum and stomach, and can provoke bleeding from existing ones [29]. The role of antiplatelet agents for bleeding from the large intestine, mainly from diverticula [50], as well as for bleeding from the small intestine, mainly in erosive enteropathy, is also discussed [12]. Antiplatelet agents also increase the risk of bleeding on endoscopy. A retrospective study suggests that the risk of bleeding in mucosal biopsy varies between 0.02% -0.1%, increasing in those patients taking antiplatelet agents as well as with the number of biopsies [11]. In a prospective study, a bleeding episode requiring endoscopic haemostasis was observed in 2.2% of 1015 patients who underwent polypectomy of colonic polyps less than 10 mm with endolup technique [42]. In this study, antiplatelet monotherapy (aspirin or ticlopidine) was associated with a 4-fold increase in the risk of bleeding (95% CI 1.5-10.6) [39-50]. A study by Lanas and Gargallo found that the risk of severe upper GIT bleeding was high when two antiplatelet agents were included in the therapy and was increasing 1.8-fold with low-dose aspirin and 7.4-fold with aspirin and clopidogrel [28].

A meta-analysis of prospective studies involving more than 100,000 patients found that the risk of total bleeding (OR 1.70) as well as of severe or significant bleeding (OR 1.31) was increased with medications [41]. Another meta-analysis showed an increase in the risk of bleeding annually by 0.13% for severe bleeding and by 0.12% for light bleeding with prolonged use of aspirin. The relative risk remains 2.22 for severe gastrointestinal bleeding and 1.23 for fatal bleeding [34]. The CAPRIE STUDY showed a lower risk of gastrointestinal bleeding with Clopidogrel compared to Aspirin (RR 1.45) [8]. The use of an antibody against GP2II3a in patients with myocardial infarction increases the risk of bleeding [27]. The risk of bleeding from GIT with double antiplatelet therapy was found to be higher than with monotherapy and reaches HR 2.7 [9]. In triple antiplatelet therapy, when cilostazol was added to aspirin and clopidogrel, the same risk of bleeding was observed compared to dual antiplatelet therapy - 2.39% vs. 2.04%, but the risk of gastrointestinal bleeding was significantly higher with triple antiaggregation (OR 2.46) [6]. In the study of Luis *et al*. the risk of upper gastrointestinal bleeding associated with the use of low doses of acetylsalicylic acid (75 to 300 mg / d) alone and in combination with other gastrotoxic drugs was assessed in 2049 patients. Researchers found that the risk of upper GIT bleeding was increased in low-dose aspirin (RR, 1.80; 95% CI, 1.59 to 2.03) or clopidogrel users (RR, 1.67; 95% CI, 1.24 to 2.24) compared with non-users. The risk of upper GIT bleeding was significantly increased when aspirin is used in combination with clopidogrel (RR 2.08; 95% CI, 1.34 to 3.21), with oral anticoagulants (RR 2.00; 95% CI, 1.15 to 3.45), low / medium dose nonsteroidal anti-inflammatory drugs (RR 2.63; 95% CI, 1.93 to 3.60), high dose nonsteroidal anti-inflammatory drugs (RR, 2.66; 95% CI, 1.88 to 3.76) or with high-dose oral corticosteroids (RR, 4.43; 95% CI, 2.10 to 9.34) compared to low-dose aspirin monotherapy. The risk was not significantly increased when co-administered with statins (RR, 0.99; 95% CI, 0.81 to 1.21) or low-dose oral corticosteroids (RR, 1.01; 95% CI, 0.58 to 1.77) [15].

In the study of Weil *et al*. the risks of hospitalization due to peptic ulcer bleeding (gastric or duodenal) were determined against the background of prophylactic regimens with aspirin of 300 mg daily or less in 1121 patients. In 144 (12.8%) cases, regular use of aspirin (at least five days a week in the previous month) was found compared to 101 (9.0%) patients in the control hospitalized group and to 77 (7.8 %) community controls. The odds ratio was increased for all doses of aspirin taken, whether compared to hospital or municipal controls (compared to combined controls: 75 mg, 2.3 (95% CI 1.2 to 4.4), 150 mg, 3.2 (1.7 to 6.5), 300 mg 3.9 (2.5 to 6.3) Results are not affected by obscuring factors such as age, gender, previous ulcerative disease or dyspepsia or concomitant use of non-aspirin NSAIDs Researchers have not established a conventional prophylactic regimen of aspirin which is without risk of complications of peptic ulcer [49, 50].

On the other hand, the potential cardiovascular risk associated with discontinuation of antiplatelet agents is ignored [21]. If the patient is on long-term antiplatelet therapy for primary or secondary cardiovascular prevention, a cardiovascular event may occur when antiplatelet agents are discontinued for several days. Most (60-70%) of serious cardiovascular events occur within 10 days of antiplatelet discontinuation [4, 45].

The use of antiplatelet agents in routine endoscopic procedures is based on an assessment of the risk of bleeding during endoscopy and the patient's thrombotic risk [4]. BSG and ESGE recommend that antiplatelet agents are continued in patients undergoing endoscopic procedures with a low risk of bleeding [47, 48]. Aspirin can be continued with all endoscopic procedures, except for ESD, colon EMR over 2 cm, upper EMR and ampullectomy. The risk of thrombosis versus the risk of bleeding should be assessed in these procedures for each patient [47]. In patients receiving dual antiplatelet therapy, only clopidogrel should be discontinued 5 days before high-risk endoscopic procedures when the risk of thrombosis is low. In case of high thrombotic risk, a consultation with a cardiologist is required [47, 3]. When the thrombotic risk of stopping clopidogrel is high (30 days after coronary stent placement), the endoscopic procedure should be postponed. Clopidogrel can be resumed after the procedure when endoscopic haemostasis has been achieved [3]. On the table. 4 is shown the interval without administration of major drugs from the group of antiplatelet agents before endoscopic intervention.

Table 4: Antiplatelet agents and interval without intake before the endoscopic procedure.

Drug	Mechanism of action	Pause before endoscopy
Aminosalicylic acid	irreversible COX-inhibitor	7-9 d
Clopidogrel (Plavix®)	ADP-receptor antagonist	5-7 d
Prasugrel (Effient®)	ADP- receptor antagonist	5-7 d
Ticagrelol (Brilique®)	ADP- receptor antagonist	3-5 d

The use of antithrombotic drugs is associated with an increased risk of bleeding from the GIT. In endoscopic interventions, it is necessary to balance the risk of bleeding and the thromboembolic risk in each individual patient. In addition to assessing the risk of bleeding, the endoscopist must be familiar with the criteria for assessing cardiovascular risk. In this area collaboration with a cardiologist is essential, especially in the manipulation of certain patients.

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