SAS Journal of Medicine
Abbreviated Key Title: SAS J Med
ISSN 2454-5112
Journal homepage: https://saspublishers.com

OPEN ACCESS

Hepato-Gastroenterology

Management of Antithrombotic Drugs in Digestive Endoscopy

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DOI: 10.36347/sasjm.2023.v09i05.020 | **Received:** 08.04.2023 | **Accepted:** 13.05.2023 | **Published:** 18.05.2023

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Abstract **Review Article**

Summary: The endoscopic management of patients under antithrombotic treatment implies several factors related to the patient and the endoscopic procedure, an assessment of the bleeding and thrombotic risk is primordial in the admission, the day of the endoscopy an adjustment of the procedure equipment may be proposed according to the estimated bleeding risk, the post endoscopic management consist of discussing the resumption of treatment according to the bleeding and thrombosis risk without forgetting to educate the patient about the risk of bleeding, which may be delayed after the endoscopy, sometimes requiring reassessment in consultation or even hospitalization to monitor the progress.

Keywords: antithrombotic treatment, endoscopic management, thrombosis risk, patient.

INTRODUCTION

The number and complexity of procedures performed by gastroenterologists is continually advancing. In addition, the number and complexity of antithrombotic agents is increasing in the context of a more elderly population and the increased incidence of prothrombotic diseases

During an endoscopic procedure, the trained clinician must balance the thrombotic risk associated with the pre-existing medical condition for which the antithrombotic therapy is used with the potentially life-threatening bleeding risk associated with the procedure.

In order to decide whether to continue or stop using an antithrombotic before an endoscopic procedure, it is necessary to understand its mechanism of action and its target on the elements involved in hemostasis.

Physiology:

The haemostasis system takes place in three stages: primary haemostasis, coagulation and fibrinolysis. Thus, the therapeutic targets of antithrombotic agents are:

Platelet Antiaggregant: Platelet aggregation
Anticoagulants: Formation of thrombin
Fibrinolytics: Fibrin degradation
Primary hemostasis: platelet aggregation

The platelet nail, or white thrombus, is the final product of primary hemostasis, which is secondarily consolidated by the activation of coagulation processes [1, 2].

Coagulation:

The coagulation cascade has a common pathway that links the intrinsic and extrinsic pathways. Activated factor X with its cofactor (factor V), in conjunction with calcium, tissue and platelet phospholipids, converts prothrombin to thrombin.

Fibrinolysis:

Thrombin converts circulating fibrinogen to fibrin and activates factor XIII, which cross-links fibrin, leading to stable coagulation [3].

Management of antithrombotic drugs in digestive endoscopy:

To successfully balance the bleeding and thrombotic risk, the endoscopist, being first and foremost a clinician, must take into consideration several factors ranging from the justification of the indication for the endoscopic procedure and its degree of urgency, the evaluation of the patient's terrain as a candidate for endoscopy as well as the indication for antithrombotic treatment and the control of the endoscopic procedure and its various risks; this can be summarized in 3 important steps: pre-endoscopic management, per-endoscopic management and post-endoscopic management.

1. Pre-endoscopic management:

Communication with the patient is crucial before the endoscopic procedure, a good interrogation including the age and history of the patient and all the details about the medication intake, coordination with the prescribing physician of the antithrombotic medication is sometimes necessary to ensure the right indication. The patient must be implicated in the discussion and informed of the risks involved in the endoscopic procedure.

a. Assessment of thrombotic risk:

The endoscopist must distinguish vascular diseases with a high thrombotic risk in order to participate in the discussion with the referring physician.

The CHADS2 score is a tool developed in 2001 to assess the risk of developing ischemic stroke in people with atrial fibrillation (AF) without associated valvular pathology, i.e. to assess the appropriateness of anticoagulant treatment.

The CHA2DS2-VASc score [4], developed in 2010, is derived from the CHADS2 score. It includes additional items and different ratings.

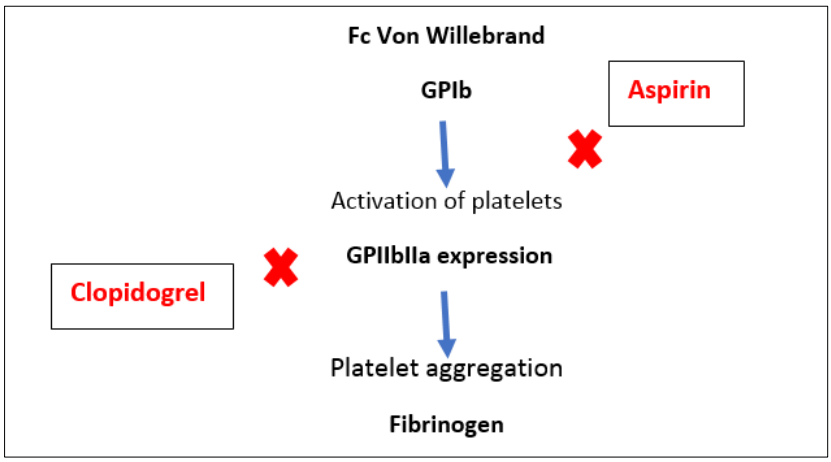

Figure 1: Mechanism of action of Platelet antiaggregant

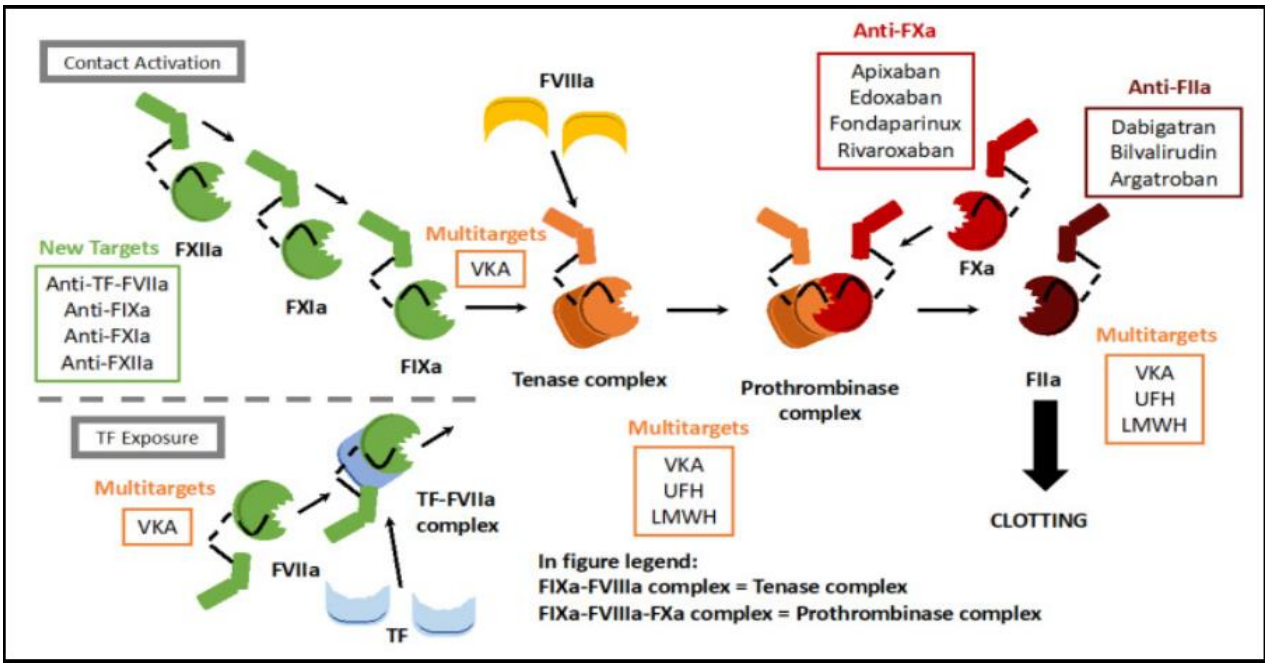

Figure 2: Mechanism of action of anticoagulant drugs [17]

Table 1: Suggested Risk Stratification for Perioperative Thromboembolism [5]

Risk category	Mechanical heart valve	Atrial fibrillation	Venous thromboembolism
High	Mitral valve prosthesis; caged-ball or tilting disc aortic prosthesis; stroke or TIA within 6 mo	CHA_2DS_2-VASc score $\geq$ 6; stroke or TIA within previous 3 mo; rheumatic valvular heart disease	VTE within 3 mo; severe thrombophilia*
Moderate	Bi-leaflet aortic valve prosthesis and at least one of the following risk factors: atrial fibrillation, previous stroke or TIA, hypertension, diabetes, congestive heart failure, age > 75 y	CHA_2DS_2-VASc score 4 to 5 or previous stroke or TIA more than 3 mo before	VTE within 3 to 12 mo; nonsevere thrombophilia†; recurrent VTE; active cancer
Low	Bi-leaflet aortic valve prosthesis and no other risk factors for stroke	CHA_2DS_2-VASc score 2-3 (assuming no previous stroke or TIA)	VTE > 12 mo previous and no other risk factor

(Modified from Douketis and colleagues[4] with permission from the American College of Chest Physicians 9th Edition Perioperative Antithrombotic Management Guidelines).
*Severe thrombophilia is defined as deficiency in protein C, protein S, or antithrombin; antiphospholipid antibodies; and those with multiple abnormalities.
†Nonsevere thrombophilia is defined as heterozygous factor V Leiden or prothrombin gene mutation.
TIA, transient ischemic attack; VTE, venous thromboembolism.

CHA2DS2-VASc Risk	Score
CHF or LVEF ≤ 40%	1
Hypertension	1
Age ≥75	2
Diabetes	1
Stroke/TIA/ Thromboembolism	2
Vascular Disease	1
Age 65 - 74	1
Female	1

Figure 3: CHA_2DS_2-VASc score

Bleeding risk assessment:
Patient-related factors:

HAS-BLED is a score developed in 2010 using data from 3978 patients to assess the 1-year bleeding risk in patients with atrial fibrillation on anticoagulant therapy [6].

But this score was validated just for antivitamin K (VKA) not for direct oral anticoagulants (DOA)

Major bleeding is defined as intracranial bleeding, hospitalization, decrease in hemoglobin> 2 g/dL and/or transfusion.

HAS-BLED Criteria	Score
Hypertension	1
Abnormal renal or liver function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (> 65 years)	1
Drugs or alcohol (1 point each)	1 or 2

Total Score	Bleeds per 100 patient years
0	1.13
1	1.02
2	1.88
3	3.74
4	8.7
5	12.5

Figure 4: HAS-BLED score for bleeding risk

Endoscopic procedure factors:

The European Society for Gastrointestinal Endoscopy (ESGE) published in 2016, its recommendations in association with British Society of Gastroenterology (BSG) for endoscopy in patients on antiplatelet or anticoagulant therapy, including direct oral anticoagulants. On the other hand, the American Society for Gastrointestinal Endoscopy (ASGE) and the Asian Pacific Society for Digestive Endoscopy (APSDE) have published guidelines for the management of antithrombotic drugs in digestive endoscopy [7-9].

Table 2: Bleeding risk of endoscopic procedures according to digestive endoscopy societies

	ESGE-BSG	ASGE	APSDE
Low bleeding risk	-Digestive endoscopy with or without biopsy -Biliopancreatic stenting -Enteroscopy without polypectomy -Diagnostic echo-endoscopy	-Digestive endoscopy with or without biopsy -ERCP with stent without sphincterotomy - Intestinal stent placement -Videocapsule -Enteroscopy -Argan plasma coagulation -Barett's resection -Diagnostic EUS	-Digestive endoscopy with or without biopsy -ERCP with stent placement - Esophageal or intestinal or colonic stenting -Videocapsule -Enteroscopy -APC
High bleeding risk	-Polypectomy -Sphincterotomy -Ampullectomy Mucosectomy, sub-mucosal dissection -Stricture dilatation, POEM, percutaneous endoscopic gastrostomy (PEG) -Treatment of varices -EUS+FNA -Esophageal, intestinal or colonic stenting	-Polypectomy -Sphincterotomy -Ampullectomy Mucosectomy, sub-mucosal dissection -Pneumatic dilatation/candle -PEG - Treatment of varices -EUS+FNA -Balloon enteroscopy -Endoscopic hemostasis -Tumor ablation	-Polypectomy -Sphincterotomy -Ampullectomy - Dilation of stenosis - Percutaneous endoscopic gastrostomy -Treatment of varices -EUS+FNA

Whether stenting is high or low risk is controversial, given the paucity of studies in this area. A retrospective review of 85 patients with esophageal stenting described a risk of bleeding of up to 5.3% [10].

A US national survey of esophageal SEMS insertion reported a bleeding complication rate of 0.5% [11].

Depending on the bleeding risk associated with the procedure recommendations have been developed for whether to discontinue antithrombotic therapy.

Table 3: Antithrombotic bleeding risk management according to digestive endoscopy societies

Antithrombotic treatment	Affiliated Societies	Low bleeding risk	High bleeding risk
Aspirin	EGSE	**Continue except:** colonic mucosectomies > 2cm, DSM, upper GI mucosectomies (whatever their size) and ampullectomy	
	ASGE	For all endoscopies, ASGE recommends continuing aspirin	
Clopidogrel	ESGE	Continue as a single or dual antiaggregant	Low thrombotic risk **Stop 5 days** before endoscopy and continue aspirin For patients on High thrombotic risk Continue aspirin and discuss with the cardiologist the risk/benefit balance of stopping clopidogrel
	ASGE	**Continue**	**Stop** 5 to 7 days before the endoscopy
Antivitamin K	ESGE	Continue if INR is within therapeutic range.	Low thrombotic risk **Stop 5 days** before and check before endoscopy that the INR is below 1.5 High thrombotic risk Temporary stop of and relay with low molecular weight heparin
	ASGE	**Continue**	**Stop 5 days** before and relay with heparin in case of high thrombotic risk
Direct oral anticoagulants	ESGE	Omit taking direct oral anticoagulants on the day of the procedure	**Stop 2 days** patients under Dabigatran with creatinine clearance between 30 and 50ml/min, the last dose should be taken 3 days before the endoscopy
	ASGE	**Continue**	Stop for 1 to 6 days depending on the type of AOD and renal clearance

2. Per-endoscopic management:

Antithrombotic management continues at the time of endoscopy; the endoscopist should master the bleeding risk associated with each procedure, and the interventional maneuvers to reduce this risk.

It is sometimes suggested to use a hemostatic clip after polypectomy in patients who require re-introduction of antithrombotic medications within 24 hours. Prophylactic clip may be favorable if the post-polypectomy bleeding rate is ≥3.4% (anticoagulant bleeding risk) or ≥ 2.5% (antiplatelet bleeding risk) [13, 14].

Cold snare polypectomy is preferred for removal of small colorectal polyps in anticoagulated patients [18, 20], and can be proposed for <1 cm lesions in patients on antithrombotic therapy [15, 19].

3. Post-endoscopy management:

Management of the bleeding risk associated with antithrombotic medication does not stop on the day of the procedure, delayed bleeding has been described after certain endoscopic procedures; the patient must be informed of this risk and the necessity to consult early to act at the optimal moment, the restarting of antithrombotic medication is also discussed according to the thrombotic and bleeding risk.

In a meta-analysis of 12 articles including 14,313 patients, to study the risk of post-polypectomy bleeding, the rate of delayed post-polypectomy bleeding was 1.5%. Cardiovascular disease, hypertension, polyp size>10 mm, and right colon polyps were identified as important risk factors [12].

From the available studies, for patients on VKAs with high thromboembolic risk, it is recommended to start unfractionated heparin (UFH) or low molecular weight heparin (LMWH) as early as possible when there is no risk of major bleeding and continued until INR reaches a therapeutic range with warfarin. In patients with a lower thromboembolic risk, warfarin should be restarted within 24 hours of the procedure.

Due to the shorter duration of direct oral anticoagulants, if treatment cannot be restarted within 24 hours of a high-risk procedure, bridging therapy with UFH or LMWH should be considered for patients at high risk of thrombosis.

All antiplatelet agents should be restarted shortly after hemostasis [16].

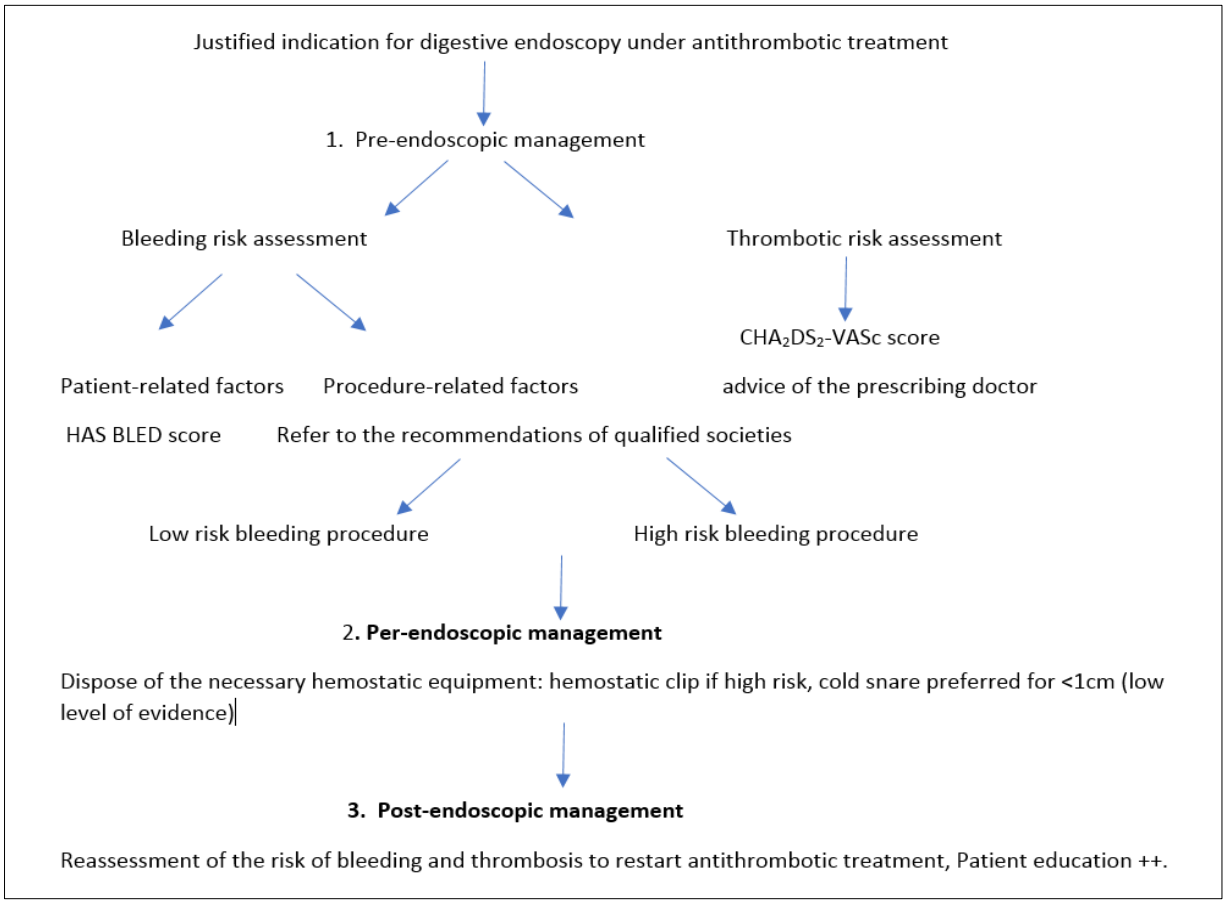

Figure 5: Summary of steps in the management of antithrombotic drugs in digestive endoscopy

CONCLUSION

A patient receiving antithrombotic medication requires management on 3 levels: before admission to endoscopy, on the day of the endoscopy and after the endoscopy for a greater balance between the bleeding and thrombosis risk.

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