Anticoagulation Management Around Endoscopy: GI Perspective

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EDUCATIONAL OBJECTIVES

- Understand risks of holding anticoagulation before and after GI endoscopy
- Understand safety of maintaining anticoagulation during GI endoscopy
- Understand variable risks of GI procedures as they relate to anticoagulation decision-making

FACULTY Q&A

- Anticoagulation for GI endoscopy should be held whenever possible to minimize bleeding risk -- True or False?

- Internists and Gastroenterologists need to have a thorough knowledge of anticoagulation options, mechanisms of action, and duration of action -- True or False?

- Anticoagulation after GI endoscopy should resume as soon as possible to avoid cardiovascular and/or thromboembolic sequelae -- True or False?

Anticoagulation Management for Endoscopy

- Decisions depend on the maintenance drug regimen, procedure risk, and cardiovascular risk factors
  - Drugs
    - Antiplatelet agents (APA)
    - Anticoagulants
  - Procedure risk
    - Low bleeding risk
    - High bleeding risk
  - Cardiovascular risk factors
    - Atrial fibrillation
    - Coronary artery disease (CAD)
    - History of venous thromboembolism (VTE) and/or valve replacement

Anticoagulation Management for Endoscopy

- Additional consideration is made for elective versus emergent endoscopy indications

Anticoagulation Management for Endoscopy

- Antiplatelet agents (APA)
  - Aspirin
  - NSAIDs
  - Dipyridamole (Persantine)
  - Cilostazol (Pletal)
  - Thienopyridines
    - Clopidogrel (Plavix)
    - Prasugrel (Effient)
    - Ticlodipine (Ticlid)
    - Ticagrelor (Brilinta)

Anticoagulation Management for Endoscopy

- Antiplatelet agents (APA) – cont'd
  - GPIIb/IIIa Inhibitors
    - Tirofiban (Aggrastat)
    - Abciximab (ReoPro)
    - Eptifibatide (Integrilin)
  - PAR-1 Inhibitor
    - Vorapaxar (Zontivity)

Antiplatelet Agents (APA)

TABLE 2. Antithrombotic drugs: duration of action and approach to reversal when indicated

Drug class	Specific agent(s)	Duration of action	Approach to reversal based on procedural urgency	
			Elective	Urgent
APAs	Aspirin	7-10 days	NA	Hold, can give platelets
	NSAIDs	Varies	NA	Hold
	Dipyridamole (Persantine)	2-3 days	Hold	Hold
	Cilostazol (Pletal, Otsuka Pharmaceutical Co., Ltd., Tokushima, Japan)	2 days	Hold	Hold
	Thienopyridines: clopidrogrel (Plavix) prasugrel (Effient) ticlodipine (Ticlid) ticagrelor (Brilinta)	5-7 days: clopidogrel, 3-5 days: ticagrelor 5-7 days: prasugrel 10-14 days[98]: ticlopidine	Hold	Hold
	GPIIb/IIIa inhibitors: tirofiban (Aggrastat) abciximab (ReoPro) eptifibatide (Integrilin)	tirofiban: 1-2 seconds abciximab: 24 hours eptifibitide: 4 hours	NA	Hold HD: tirofiban
	PAR-1 inhibitor: vorapaxar (Zontivity)	5-13 days	Hold	Hold

Anticoagulation Management for Endoscopy

- Anticoagulants
  - Warfarin (Coumadin)
  - Unfractionated Heparin (UFH)
  - Low Molecular Weight Heparin (LMWH)
    - Enoxaparin (Lovenox)
    - Dalteparin (Fragmin)
  - Fondaparinux (Arixtra)
  - Direct Factor Xa Inhibitor (NOACs)
    - Rivaroxaban (Xarelto)
    - Apixaban (Eliquis)
    - Edoxaban (Savaysa)

Anticoagulation Management for Endoscopy

- Anticoagulants – cont’d
  - Direct Thrombin Inhibitors (NOACs)
    - Dabigatran (Pradaxa)
    - Desirudin (Iprivask)

Anticoagulants

Anticoagulants	Warfarin (Coumadin)	5 days	Hold	Vitamin K, PCC
	UFH	IV 2-6 hours SQ 12-24 hours	Hold	Protamine sulfate* (partial)
	LMWH: enoxaparin (Lovenox) dalteparin (Fragmin, Pfizer Inc, New York, NY, USA)	24 hours	Hold	Protamine sulfate, consider rVIIa
	Fondaparinux (Arixtra)	36-48 hours		Protamine sulfate, consider rVIIa
	Direct factor Xa Inhibitor: rivaroxaban (Xarelto) apixaban (Eliquis) edoxaban (Savaysa)	See Tables 7 and 8	Hold	Charcoal (if last intake within 2-3 hours); nonactivated PCC or activated PCC
	Direct thrombin inhibitor, oral: dabigatran (Pradaxa) IV: Desirudin (Iprivask, Aventis Pharmaceuticals Inc., Bridgewater, NJ, USA)	See Table 9	Hold	Charcoal (if last intake within 2-3 hours); nonactivated PCC or activated PCC; HD

NSAIDs, Nonsteroidal anti-inflammatory drugs; *NA*, not applicable; *HD*, hemodialysis; *PCC*, prothrombin complex concentrate; *rVIIa*, recombinant factor VIIa.
*Caution: Can cause severe hypotension and anaphylaxis.

Xarelto Considerations

TABLE 8. Periprocedural management of rivaroxaban (Xarelto)[54]

Creatinine clearance (mL/min)	Time to onset of action (h)	Timing of discontinuation before high-risk endoscopic procedure (day)
>90	2-4	≥1
60-90	2-4	2
30-59	2-4	3
15-29	2-4	4

Eliquis Considerations

TABLE 7. Periprocedural management of apixaban (Eliquis)[54]

Creatinine clearance (mL/min)	Time to onset of action (h)	Timing of discontinuation before high-risk endoscopic procedure (day)
>60	1-3	1 or 2
30-59	1-3	3
15-29	1-3	4

Savaysa Considerations

TABLE 9. Periprocedural management of edoxaban (Savaysa)[99]

Creatinine clearance (mL/min)	Time to onset of action (h)	Half-life (h)	Timing of discontinuation before high-risk procedure (h)
>60	1-2	8.6	At least 24
30-60	1-2	9.4	At least 24
15-30	1-2	16.9	At least 24
≤15	1-2	No data	No data

Pradaxa Considerations

TABLE 6. Periprocedural management of dabigatran (Pradaxa)[53]

Creatinine clearance (mL/min)	Time to onset of action (h)	Half-life (h)	Timing of discontinuation before procedure	
			Moderate procedural bleeding risk (2-3 half-lives)	High procedural bleeding risk (4-5 half-lives)
>80	1.25-3	13 (11-22)	1-1.5 days	2-3 days
50-80	1.25-3	15 (12-34)	1-2 days	2-3 days
30-49	1.25-3	18 (13-23)	1.5-2 days	3-4 days
≤29	1.25-3	27 (22-35)	2-3 days	4-6 days

Procedure Risk

Higher-risk procedures	Low-risk procedures
Polypectomy	Diagnostic (EGD, colonoscopy, flexible sigmoidoscopy) including mucosal biopsy
Biliary or pancreatic sphincterotomy	ERCP with stent (biliary or pancreatic) placement or papillary balloon dilation without sphincterotomy
Treatment of varices	
PEG placement*	Push enteroscopy and diagnostic balloon-assisted enteroscopy
Therapeutic balloon-assisted enteroscopy	Capsule endoscopy
EUS with FNA†	Enteral stent deployment (Controversial)
Endoscopic hemostasis	EUS without FNA
Tumor ablation	Argon plasma coagulation
Cystgastrostomy	Barrett's ablation
Ampullary resection	
EMR	
Endoscopic submucosal dissection	
Pneumatic or bougie dilation	
PEJ	

PEJ, Percutaneous endoscopic jejunostomy.
*PEG on aspirin or clopidogrel therapy is low risk. Does not apply to DAPT.
†EUS-FNA of solid masses on ASA/NSAIDs is low risk.

Procedure Risk

TABLE 10. Summary for available evidence for bleeding risk with common endoscopic procedures on antithrombotic agents

	Therapeutic warfarin/heparin	Thienopyridine	ASA/NSAID
Diagnostic EGD/colonoscopy +/- biopsy	Low risk[100]	Low[112]	Low[104]
Colonoscopic polypectomy	High risk[75,101-109]	High[113]	Low[75,98,115]
Sphincterotomy	High[110]	Unknown	Low[17]
EUS/FNA	High[111]	Unknown	Low[111]
PEG (does not apply to DAPT)	Unknown	Low for clopidogrel only[114]	Low[114]

ASA, acetylsalicylic acid, or aspirin; *NSAID*, nonsteroidal anti-inflammatory drug; *DAPT*, dual antiplatelet therapy.

Cardiovascular Risk Factors – Atrial Fibrillation

CHA_2DS_2-VASc score or assessment	Risk of stroke (CVA)	% Risk of annual CVA
0	Low	0
1	Moderate	1.3
2	High	2.2
3	High	3.2
4	High	4.0
5	High	6.7
6	High	9.8
7	High	9.6
8	High	6.7
9	High	15.2

CHA_2DS_2-VASc, 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], Sex category, ie, female sex [1 point].
CVA, cerebrovascular accident.

Cardiovascular Risk Factors – Atrial Fibrillation

TABLE 11. Approach to bridge therapy for warfarin (Coumadin)[69-70]

Condition	Associated diagnosis	Management
AF	None CHA_2DS_2-VASc score < 2	No bridge recommended
	Mechanical valves History of CVA CHA_2DS_2-VASc score ≥ 2	Bridge therapy recommended
Valvular heart disease	Bileaflet mechanical AVR	No bridge recommended
	Mechanical AVR and any thromboembolic risk factor Older-generation mechanical AVR Mechanical mitral valve replacement	Bridge therapy recommended

AF, atrial fibrillation; *CHA_2DS_2-VASc*, Congestive heart failure, Hypertension, Age $\geq$ 75 years [2 points], Diabetes Mellitus, Stroke [2 points], Vascular disease, Age 65-74 years, Sex category [ie, female sex]; *CVA*, cerebrovascular accident; *AVR*, aortic valve replacement.

Cardiovascular Risk Factors – CAD

- High Coronary Thrombosis Risk
  - Drug-eluting stent (DES) within last 12 months
  - Bare metal stent (BMS) within last 1 month
  - BMS within last year with acute coronary syndrome (ACS)

Cardiovascular Risk Factors – CAD

- Consider other clinical risk factors predisposing to higher rate of stent thrombosis and modify approach to APA therapy accordingly
  - 1/5 patients suffering 1st stent thrombosis will experience 2nd stent occlusion at a rate of 0.6% per year over the next 3 years with a cumulative risk of cardiac death of 27.9%
  - History of stent occlusion, ACS or ST elevation myocardial infarction, multi-vessel percutaneous coronary intervention, diabetes, renal failure, or diffuse CAD are at higher risk of stent occlusion or ACS with alteration of APA therapys

CAD with Dual Antiplatelet Therapy (DAPT)

TABLE 12. Best practice recommendations for the management of DAPT[36]

Avoid cessation of all antiplatelet therapies after PCI with stent placement.
Avoid cessation of clopidogrel (even when aspirin is continued) within the first 30 days after PCI and either DES or BMS placement when possible.
Defer elective endoscopic procedures, possibly up to 12 months, if clinically acceptable from the time of PCI to DES placement.
Perform endoscopic procedures, particularly those associated with bleeding risk, 5-7 days after thienopyridine drug cessation. ASA should be continued.
Resume thienopyridine and ASA drug therapy after the procedure once hemostasis is achieved. A loading dose of the former should be considered among patients at risk for thrombosis.
Continue platelet-directed therapy in patients undergoing elective endoscopy procedures associated with a low-risk for bleeding.

DAPT, dual antiplatelet therapy; *BMS*, Bare metal stent(s); *DES*, drug-eluting stent(s); *PCI*, percutaneous coronary intervention; *ASA*, acetylsalicylic acid, or aspirin.

History of venous thromboembolism (VTE) and/or valve replacement

TABLE 5. Risk for thromboembolic event in patients with mechanical heart valve(s) or VTE on anticoagulation[37]

Clinical indication for warfarin therapy		
Annual risk	**Mechanical heart valve**	**VTE**
High	• Any mitral valve prosthesis • Any caged-ball or tilting disc aortic valve prosthesis • Recent (within 6 months) CVA or TIA	• Recent (within 3 months) VTE • Severe thrombophilia (deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities)
Medium	• Bileaflet aortic valve prosthesis and one or more of the following risk factors: AF, prior CVA or TIA, hypertension, diabetes, congestive heart failure, age ≥ 75 years	• VTE within the past 3-12 months • Nonsevere thrombophilia (heterozygous factor V Leiden or prothrombin gene mutation) • Recurrent VTE • Active cancer (treated within 6 months or palliative)
Low	• Bileaflet aortic valve prosthesis without AF and no other risk factors for CVA	• VTE > 12 months previous and no other risk factors

VTE, venous thromboembolism; *CVA*, cerebrovascular accident; *TIA*, Transient ischemic attack; *AF*, atrial fibrillation.

History of venous thromboembolism (VTE) and/or valve replacement

- Bioprosthetic valves are considered low risk

Factoring In All Variables

TABLE 13. Management of antithrombotic agents in the elective endoscopic setting

CV risk			Endoscopy-induced bleeding risk: Low		Endoscopy-induced bleeding risk: High
	Low	AC	1. Continue warfarin and NOAC	AC	1. Discontinue AC 2. Restart warfarin on same day of procedure 3. Delay reinitiating NOACs until adequate hemostasis is achieved
		APA	1. Continue standard doses of ASA/NSAIDs 2. Continue thienopyridines	APA	1. Continue standard doses of ASA/NSAIDs* 2. Discontinue thienopyridines at least 5 days before switch to ASA† 3. Dual APA, hold thienopyridines for at least 5 days, continue ASA†
	High	AC	1. Continue warfarin and NOAC	AC	1. Discontinue AC 2. Bridge therapy‡ 3. Restart warfarin on same day of procedure 4. Delay reinitiating NOACs until adequate hemostasis is achieved
		APA	1. Continue standard doses of ASA/NSAIDs 2. Continue thienopyridines	APA	1. Continue standard doses of ASA/NSAIDs 2. Discontinue thienopyridines at least 5 days before endoscopy or switch to ASA† 3. Dual APA, hold thienopyridines for at least 5 days, continue ASA†

AC, Anticoagulants; *APA*, antiplatelet agent; *NOAC*, novel oral anticoagulant; *ASA*, acetylsalicylic acid, or aspirin; *NSAID*, nonsteroidal anti-inflammatory drug; *CV*, cardiovascular.

*There is evidence to hold APA in patients undergoing ESD and EMR who have a low risk for a thromboembolic event.[116]

†Ticagrelor should be held for 3-5 days, and all other thienopyridines should be held for 5-7 days.

‡In moderate-risk patients (from Table 5), the decision to use bridging therapy and the degree of intensity should be individualized and the patient's wishes considered.[40]

Factoring All Variables – Urgent/Emergent

- Patients on APA
  - We recommend consultation with prescribing specialist before stopping APA therapy in situations of significant GI bleeding in patients with recently placed DES (within 1 year) or BMS (within 30 days), or within 90 days of ACS. The risk of adverse cardiac events associated with cessation of APA therapy likely exceeds the benefit of decreasing post-endoscopic bleeding (moderate).
  - We recommend patients on APA therapy with life-threatening or serious GI bleeding should have these agents held after discussion with their cardiologist (moderate).

Factoring All Variables – Urgent/Emergent

- Patients on anticoagulant therapy
  - We recommend patients with acute GI bleeding on anticoagulation therapy have anticoagulant agents held to facilitate achievement of hemostasis (moderate).
  - We recommend either 4-factor PCC and vitamin K or fresh frozen plasma be given for life-threatening GI bleeding in patients on warfarin anticoagulant therapy (moderate)
  - We suggest endoscopic therapy not be delayed in patients with serious GI bleeding and an INR < 2.5 (low).
  - We suggest patients who require anticoagulation therapy receive UFH because of its relatively short half-life after successful endoscopic hemostasis for high-risk stigmata (low).

FACULTY Q&A

- Anticoagulation for GI endoscopy should be held whenever possible to minimize bleeding risk -- True or False?

- Internists and Gastroenterologists need to have a thorough knowledge of anticoagulation options, mechanisms of action, and duration of action -- True or False?

- Anticoagulation after GI endoscopy should resume as soon as possible to avoid cardiovascular and/or thromboembolic sequelae -- True or False?

FACULTY Q&A

- Anticoagulation for GI endoscopy should be held whenever possible to minimize bleeding risk -- False!

- Internists and Gastroenterologists need to have a thorough knowledge of anticoagulation options, mechanisms of action, and duration of action – True!

- Anticoagulation after GI endoscopy should resume as soon as possible to avoid cardiovascular and/or thromboembolic sequelae – True!