Management of antithrombotic agents before endoscopy

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Communication from the ASGE Standards of Practice Committee

GUIDELINE

The management of antithrombotic agents for patients undergoing GI endoscopy

Prepared by: ASGE STANDARDS OF PRACTICE COMMITTEE

Guideline

Endoscopy in patients on antiplatelet or anticoagulant therapy, including direct oral anticoagulants: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines

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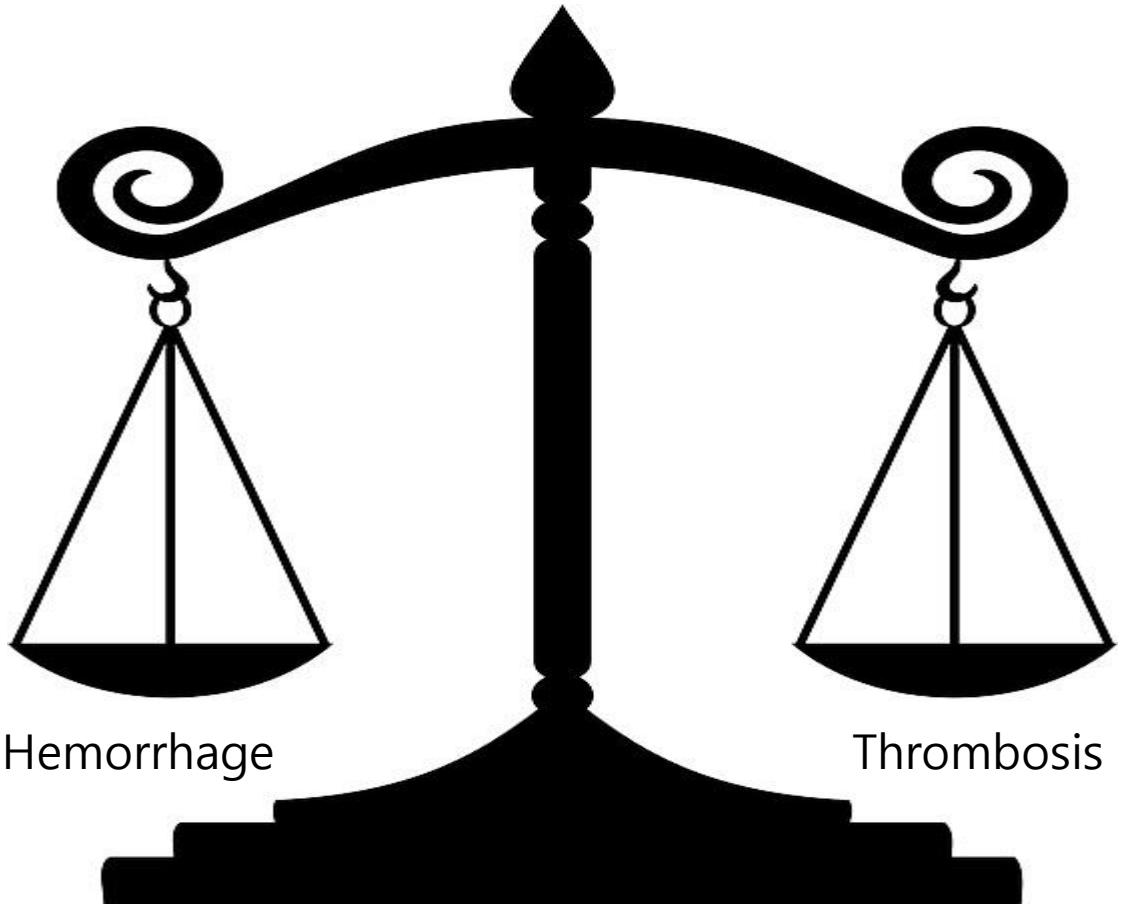
Risk vs Benefit



Hemorrhage – rarely fatal, controlled by endoscoic therapeutic measures, TAE, operation

Thrombotic event - lifelong disability, major cardiac event, death

Bleeding risk of the procedure

Anti-thrombotic agent

Risk of thromboembolic events

How to manage

Procedure risk for bleeding

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.

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	

Mucosal biopsy sampling performed as part of these procedures confers a low risk of GI bleeding.

Eso. Stent 5.3% vs 0.5~1%

* Higher-risk procedures with a potential for bleeding that requires an intervention, such as hospitalization, transfusion, endoscopic treatment, or surgery

Procedure risk for bleeding

Table 1 Risk stratification of endoscopic procedures based on the risk of haemorrhage.

High risk	Low risk
Endoscopic polypectomy	Diagnostic procedures ± biopsy
ERCP with sphincterotomy Sphincterotomy + large balloon papillary dilatation Ampullectomy	Biliary or pancreatic stenting Device-assisted enteroscopy without polypectomy
Endoscopic mucosal resection or endoscopic submucosal dissection	
Endoscopic dilatation of strictures in the upper or lower GI tract	
Endoscopic therapy of varices	
Percutaneous endoscopic gastrostomy	
Endoscopic ultrasound with fine needle aspiration	
Oesophageal, enteral or colonic stenting	

Marking (including clipping, electrocoagulation, tattooing)

JGES 2014

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, 102, 103, 104, 105, 106, 107, 108, 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]

Risk of Bleeding after Polypectomy

- **3% to 10%**
- depends on a number of factors, including the **polyp size**, **location, morphology** (nonpolypoid, sessile, pedunculated), **resection technique** (cold or hot forceps, cold snare, or snare cautery), and **type of cautery used**

Polypectomy and Warfarin

- In a randomised controlled trial (RCT)
- 159 polyps<1cm in 70 patients
- Hot vs **Cold snaring** of polyps in anticoagulated patients (**without discontinuation of warfarin)**
  - **Immediate haemorrhage**

    23.0% vs **5.7%** (P = .042)
  - **Delayed haemorrhage** (requiring intervention within 2 weeks after polypectomy)

    14% vs **0%** (*P* = .027)

Gastrointest Endosc. 2014; 79: 417–423

Polypectomy and Warfarin

- Colonoscopy는 Low-risk endoscopic procedure 이지만
  Colonoscopy에서 22.5-32.1%에서 polyp이 발견되고,
  Bowel cancer screening 시에는 42%에서 polyp이 발견되므로
  결국 Colonoscopy에서 routine하게 warfarin 중단을 고려해야할 수 있다.

- 일시적으로 Warfarin 중단했을 때에도 Post-polypectomy의 높은 risk에 관련이 있음을 환자에게 설명해두어야한다.

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Bleeding risk of the procedure

Anti-thrombotic agent

Risk of thromboembolic events

How to manage

Anti-thrombotics

- **Anti-platelet agents (APAs)**
  - Aspirin
  - Clopidogrel, prasugrel, ticlopidine, ticagrelor
- **Anti-coagulants (ACs)**
  - **Warfarin**
  - Heparin derivatives : unfractionated [UFH], low molecular weight [LMWH], fondaparinux
  - **NOAC** (New or Novel Oral Anti-Coagulants)
    (Non-vitamin K antagonist Oral Anti Coagulants)
    = **DOAC** (Direct Oral Anti-Coagulants)
    - Dabigatran : direct thrombin inhibitor
    - Ribaro**xa**ban : direct factor **Xa** inhibitor
    - Api**xa**ban : direct factor **Xa** inhibitor
    - Edo**xa**ban : direct factor **Xa** inhibitor

Blood Thinners

There are 2 types of blood thinners, anticoagulants and antiplatelet drugs.

Conditions That May Benefit From an Antiplatelet Drug

- Heart disease or prior heart attack
- Blood vessel disease
- Prior stroke or transient ischemic attacks
- Diabetes
- Being overweight or having metabolic syndrome
- Being a smoker
- Taking certain other medications
- Certain operations, such as angioplasty

Conditions That May Benefit From an Anticoagulant

- **Atrial fibrillation** (abnormal heart rhythm)
- Prior surgery on a heart valve
- **Congenital** (since birth) heart defect
- Deep vein thrombosis
- Pulmonary embolism
- Pulmonary hypertension

Anti-platelet agents (APAs)

- **Decrease platelet aggregation**

  → preventing thrombus formation.

  - aspirin (acetylsalicylic acid [ASA])
  - thienopyridines : P2Y12 receptor antagonists
    (eg, clopidogrel, prasugrel, ticlopidine, and ticagrelor)
  - the protease-activated receptor-1 (PAR-1) inhibitor vorapaxar
  - glycoprotein IIb/IIIa receptor inhibitors (GPIIb/IIIa inhibitors) (eg, abciximab, eptifibatide, and tirofiban)
  - nonsteroidal anti-inflammatory drugs

Aspirin

- **Irreversible inhibition** of the cyclooxygenase **1 and 2** enzyme systems.
- Alone or in combination with other APAs.
- Inhibit platelet aggregation
- **Prophylaxis of secondary** cardioembolic phenomena **after** occurrence of a **stroke or MI**
- In patients with a **>10% 10-year risk of heart attack or stroke**, **primary** cardioprophylaxis with low-dose ASA therapy is recommended.
- After cessation of ASA, **7 to 9** days are required to regain full platelet function

Ticlopidine (Ticlid)

- First widely available thienopyridine agent
- Hematologic side effects (such as neutropenia, thrombotic thrombocytopenia purpura, and hemolytic uremic syndrome)

Clopidogrel (Plavix)

- Inhibitor of adenosine diphosphate (ADP)-induced platelet aggregation
- **Clopidogrel plus aspirin** is more effective than aspirin alone at attenuating clinical events in acute, platelet-initiated, presentations.
- **Irreversible** and platelet function has been demonstrated to return to normal **5–7 days** after withdrawal of clopidogrel, based on the regenerative production of clopidogrel-naive platelets.

Clopidogrel (Plavix)

- Approved for **secondary** prevention of **MI or stroke and established peripheral vascular disease**
- **Efficacy can be limited**
  - **variations** of the **ABCB13435 TT and CYP2C19 genotypes of cytochrome P450 enzymes**

    → **alter hepatic metabolism** of the clopidogrel prodrug to its active thiol metabolite.

    → variable antiplatelet effects and **adverse cardiac events**,

    including **stent thrombosis** and **post–percutaneous coronary intervention ischemic events**.

Prasugrel (Effient)

- Third-generation thienopyridine agents
- **Prodrug** that requires conversion by **the cytochrome P450 hepatic enzymes**
  - the activation of prasugrel occurs **in a single hepatic step**
- **Unaffected** by variants of the CYP2C19 or ABCB1 genotypes.
- **Risk of increased bleeding**
  - **Should not be used in** patients with **active bleeding, a history of transient ischemic attack or CVA, or likely to undergo urgent coronary bypass graft surgery.**
- **Irreversible** inhibition of the P2Y12 receptor; thus, the minimum duration of discontinuation of prasugrel that allows for restoration of normal platelet aggregation is **5 to 7 days**.

Ticagrelor (Brilinta)

- Third-generation thienopyridine agents
- the first **reversible** oral P2Y12 antagonist and an alternative therapy for ACS.
- Quickly absorbed, does **not require metabolic activation**, and has a **rapid antiplatelet effect** that closely parallels drug-exposure levels
- **Reversible inhibition** of the P2Y12 receptor permits a shorter interval of discontinuation, **3 to 5 days**, to recover adequate platelet function.

Vorapaxar (Zontivity)

- Approved by the US FDA in 2014, and by the European Medicines Agency in 2015
- Competitive and selective inhibitor of **protease-activated receptor (PAR-1)**, the major **thrombin** receptor on human platelets.
- Preventing cardiovascular events in patients with a **history of MI** or **peripheral arterial disease**
- Administered in **addition to aspirin or DAPT**
- **Increased risk of moderate or severe bleeding**
  - in 4.2% versus 2.5% (placebo) and a 66% increased risk of bleeding overall.
- **Contraindicated** (d/t increased risk of intracranial haemorrhage)
  - Previous history of stroke
  - Transient ischaemic attack (TIA)
  - Intracranial haemorrhage
- Significant inhibition of platelet aggregation that remains up to **4 weeks** after discontinuation.
- The actual impact of this drug on the GI tract is relatively unknown

Drug class	Specific agent(s)	Duration of action	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

Ischemic heart disease

- **Antiplatelet therapy** >> anticoagulant therapy
- Revascularization therapy
  - coronary artery **surgery** → **aspirin alone**
  - **stents** → **aspirin and clopidogrel for 12 months**
    then aspirin indefinitely.
- **Unstable angina with a troponin release**

  → **prasugrel or ticagrelor**

  (more rapidly acting and more potent, newer, agents)

Ischemic heart disease and coronary artery stents

- **DAPT** (to prevent stent thrombosis)
  - **Drug-eluting stent (DES)** : **12 months**
  - **Bare metal stent (BMS)** (used in <10% of cases)
    : minimum **1 month**

→ **lifetime aspirin**

Dual anti-platelet therapy (DAPT)

- Aspirin plus either clopidogrel, prasugrel or ticagrelor
- **Increases the risk of bleeding (x3)**, either spontaneously or when a non-cardiac interventional procedure is required.
  - clopidogrel>aspirin alone,
  - ticagrelor plus aspirin>clopidogrel plus aspirin
  - **prasugrel plus aspirin**>any of the other combinations

Anticoagulants

- Prevent the clotting of blood by interfering with the native clotting cascade
- 4 drug classes
  - vitamin K antagonists (eg, warfarin),
  - heparin derivatives
    (eg, unfractionated [UFH], low molecular weight [LMWH], fondaparinux)
  - direct factor **Xa** inhibitors (eg, rivaro**xa**ban, api**xa**ban, edo**xa**ban)
  - direct thrombin inhibitors (eg, dabigatran, hirudins, argatraban).

NOAC
=DOAC

Warfarin (Coumadin)

- Oral anticoagulant
- Inhibits the vitamin K–dependent clotting factors II, VII, IX, X and proteins C and S.
- Its activity is measured via the International Normalized Ratio (INR).
- The INR decreases to **<=1.5** in approximately 93% of patients within **5 days** of discontinuing therapy

Parenteral & Subcutaneously administered anticoagulants

- **UFH - intravenously**
  - **half-life of 60 to 90 minutes**,
  - effects **dissipate 3 to 4 hours after discontinuation**.
- **LMWH (enoxaparin and dalteparin) - subcutaneously**
  - at therapeutic doses for bridging and for the treatment of VTE.
  - at reduced doses for the prevention of VTE in low-risk patients.
  - **The last dose** of these agents should be given **24 hours before** the anticipated procedure **at 50% of the total daily dose.**
- **Fondaparinux (Arixtra) - subcutaneously**
  - synthetic and specific inhibitor of factor **Xa**.
  - perioperative DVT prophylaxis , initial treatment of acute DVT/pulmonary embolism.
  - a high affinity for antithrombin III, which potentiates inhibition of factor Xa.
  - The minimum recommended time for discontinuation of this drug before a high-risk procedure is **36 hours**.
- **Desirudin (Iprivask) - subcutaneously**
  - Direct **thrombin** inhibitor approved for DVT prophylaxis after hip replacement
  - Recommendations are to discontinue this medication **10 hours before** a high-risk procedure

Drug class	Specific agent(s)	Duration of action	Approach to reversal based on procedural urgency	
			Elective	Urgent
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 Table 7, Table 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

NOAC (DOAC) - Indication

- **Dabigatran** is approved in the United States for prevention of CVA and systemic embolism in patients with **nonvalvular AF**.
- **Rivaroxaban (Xarelto)** is approved in the United States for prevention of VTE after orthopedic surgery, treatment of **VTE**, and prevention of CVA and systemic embolism in patients with **AF**
- **Apixaban (Eliquis)** is FDA approved for prevention of systemic embolism in **AF** patients, postorthopedic surgery prevention of **VTE**, and for treatment and reduction of recurrence of **VTE**.
- **Edoxaban (Savaysa)** is FDA approved for **AF and VTE** treatment indications.

NOAC (DOAC) - Indication

- Licensed for
  - prevention of stroke and systemic embolus in patients with non-rheumatic **AF**
  - prevention and treatment of **deep vein thrombosis and pulmonary embolus**
- **Should not be used** in patients with **metal heart valve prostheses**

NOAC (DOAC) – Advantage & Risk

- Advantages of DOACs are:
  - ▶ the absence of need for routine monitoring
  - ▶ a reduced need for dose adjustment
  - ▶ the absence of food interactions
  - ▶ limited drug interactions
  - → **Easier initiation and interruption than with warfarin**
- **Difficulty in monitoring by PT, aPTT**
  - Dabigatran - The Hemoclot® thrombin inhibitor assay
  - Anti-Xa anticoagulants - anti-Xa levels
- **Specific antidotes are not yet available for clinical use**
  - Dabigatran : **idarucizumab** (Praxbind) is approved for use in cases of life-threatening, uncontrolled bleeding or prior to emergency surgery

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NOAC (DOAC) – Advantage & Risk

- Compared with VKAs, DOACs are associated with a **lower** overall risk of **major haemorrhage** and particularly a significant **reduction** in the risk of **intracranial bleeding**
- The incidence of **gastrointestinal bleeding** was **increased** with **dabigatran and rivaroxaban** compared to **warfarin** in large RCTs, although this was confined to the elderly (>75 years old) in a real-world study
  - **Dabigatran (Pradaxa)**
    - Increase in the rate of lower GI bleeding in the higher dabigatran dose.
      - Low bioavailability (6.5%) → high concentration in the faeces
        → local anticoagulant effect at the bowel wall
    - NSAIDs should be avoided as their concomitant use was associated with an increased bleeding risk in the RE-LY study.

NOAC (DOAC) - Excretion

- All DOACs are **excreted** to some extent **by the kidneys**
- **Dabigatran** pharmacokinetics are most influenced by renal function. **(80% of excretion occurs via the kidneys)**
  - Creatinine clearance (CrCl)
    - **30–50mL/min** : stopped **at least 72 hours before** the procedure
    - **<30mL/min** : **Dabigatran therapy is contraindicated**

NOAC (DOAC) – Time for action

- **Therapeutic intensity** of anticoagulation is restored **within 3 hours** of taking a therapeutic dose of a DOAC.
- we suggest a **delay in reintroducing a DOAC after a high-risk procedure.**
  - usually be 24–48 hours
  - EMR or ESD : a longer period of discontinuation in a low thrombotic risk category.

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)	Timing of discontinuation before procedure: 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

*** idarucizumab** (Praxbind) is approved for use **in cases of life-threatening, uncontrolled bleeding or prior to emergency surgery**

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

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

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

Bridging therapy in **DOAC ?**

- **Fast on and off effects of DOACs**.
- In the Dresden DOAC registry **heparin bridging** for patients on **rivaroxaban** did **not reduce cardiovascular events** and led to a significantly **higher rate of major bleeding** compared to no bridging (2.7% vs 0.5%, P=0.01)

Eur Heart J 2014; 35: 1888–1896

- A sub-study of the RE-LY trial found that **bridging** of **dabigatran** **with LMWH** resulted in **higher rates of major bleeding** (6.5% vs 1.8%,P<0.001) with **no reduction in thromboembolism** compared to no bridging.

Thromb Haemost 2015; 113: 625–632

Bridging therapy in **DOAC ?**

- There are no data to inform optimal timing of resumption of NOACs after endoscopic procedures.
- **If a NOAC cannot be restarted within 24 hours after a high-risk procedure because of concern regarding the adequate hemostasis**, then **thromboprophylaxis (ie, UFH bridge) should be considered** for patients **at high risk for thromboembolism**.

Bleeding risk of the procedure

Anti-thrombotic agent

Risk of thromboembolic events

How to manage

Probability of thromboembolic events

- The probability of a thromboembolic event related to the temporary interruption of antithrombotic therapy for an endoscopic procedure depends on
  - **Indication for antithrombotic therapy**
  - Individual patient characteristics

Risk of stopping antithrombotic therapy before elective endoscopy

- When antithrombotic therapy is required
  - **for a short period of time** (ie, after VTE or bare metal stent insertion)
    : elective procedures **should be delayed** until such therapy is no longer indicated.
  - **for a longer period of time** (ie, after drug-eluting stent placement or post-ACS), **careful consideration of the cardioembolic risk must be made before** temporary drug cessation
- Decisions about discontinuing or temporary cessation of these agents **should be individualized and discussed**,
  - before the endoscopic procedure
  - **with the patient**
  - **the prescribing provider** (cardiologist, neurologist, hematologist, primary care physician)

Cessation of APA (DAPT)

- A systematic review of 161 reported cases of stent thrombosis in **Drug-eluting stent placement**
  - Patients who **discontinued both ASA and a thienopyridine**
    : median time to event of **7 days**.
  - In those who **discontinued thienopyridine but remained on ASA**
    : median time to an event was **122 days**.
    : a total of **6 cases (6%)** of stent thrombosis within **10 days** of thienopyridine cessation
- **If aspirin is maintainted, short-term discontinuation from drug-eluting coronary stent placement** might be relatively **safe but still carry some risk.**

Circulation. 2009; 119: 1634–1642

CV risk stratification for discontinuation

Discontinuation of antiplatelet

High risk	Low risk
Drug eluting coronary artery stents within 12 months of placement	Ischaemic heart disease without coronary stents
Bare metal coronary artery stents within 1 month of placement	Cerebrovascular disease
	Peripheral vascular disease

Discontinuation of warfarin

High risk	Low risk
Prosthetic metal heart valve in mitral position	Prosthetic metal heart valve in aortic position
Prosthetic heart valve and atrial fibrillation	Xenograft heart valve
Atrial fibrillation and mitral stenosis*	Atrial fibrillation without valvular disease
<3 months after venous thromboembolism	>3 months after venous thromboembolism Thrombophilia syndromes (discuss with haematologist)

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.

Cessation of anticoagulant

- **The absolute risk of an embolic event** in patients whose anticoagulation is **interrupted for 4 to 7 days** is approximately **1%**.
- After temporary discontinuation of **warfarin**, **reinitiation** of drug should occur **within 4 to 7 days of initial drug discontinuation to ensure no increased risk of thromboembolic event** and can occur **on the same day** in many patients

Atrial fibrillation

This score ranges from 0 to 9 and considers thromboembolic risk factors of
Congestive heart failure (1 point),
Hypertension (1 point),
Age ≥ 75 years (2 points),
Diabetes (1 point),
Stroke (2 points),
Vascular disease (prior myocardial infarction [MI], peripheral artery disease, or aortic plaque) (1 point),
Age 65 to 74 years (1 point),
Sex category (female) (1 point)

CHA_2DS_2-VASc scoring system

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

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

Role of bridge therapy in warfarin

- To reduce the risk of thromboembolic events, patients on warfarin may be switched to a shorter-acting anticoagulant in the peri-endoscopic period.
- Evidence for the use of UFH and LMWH (enoxaparin) as bridge therapies for endoscopic procedures in patients on warfarin is limited.
- A meta-analysis showed that **vitamin K antagonist–treated patients** receiving periprocedural bridging therapy with heparin appear to be at **increased risk** of both overall and major **bleeding** and at **similar risk of thromboembolic events** compared with non-bridged patients.

Circulation. 2012; 126: 1630–1639

Role of bridge therapy in warfarin

- A recently published randomized controlled trial
- Periprocedural heparin bridging in 1884 patients with **nonvalvular** AF undergoing an elective invasive procedure.
- Bridging versus no-bridging
- heparin-bridged group experienced
  - **more major bleeding** (3.2% vs 1.3%) than the non-bridged group,
  - with **no difference in arterial thromboembolism** (.3% vs .4%).

N Engl J Med. 2015; 373: 823–833

Approach to bridge therapy for warfarin (Coumadin)[69, 70]

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

Bleeding risk of the procedure

Anti-thrombotic agent

Risk of thromboembolic events

How to manage

			Endoscopy-induced bleeding risk: Low	Endoscopy-induced bleeding risk: High
CV risk	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††

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)	Timing of discontinuation before procedure: 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

*** idarucizumab** (Praxbind, Boehringer Ingelheim, Inc, Ridgefield, CT, USA) and is approved for use **in cases of life-threatening, uncontrolled bleeding or prior to emergency surgery**

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

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

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

BSG and ESEG guideline of Aspirin (2016)

- For **all endoscopic procedures** we recommend **continuing aspirin** (moderate evidence, strong recommendation), **with the exception** of

  ESD

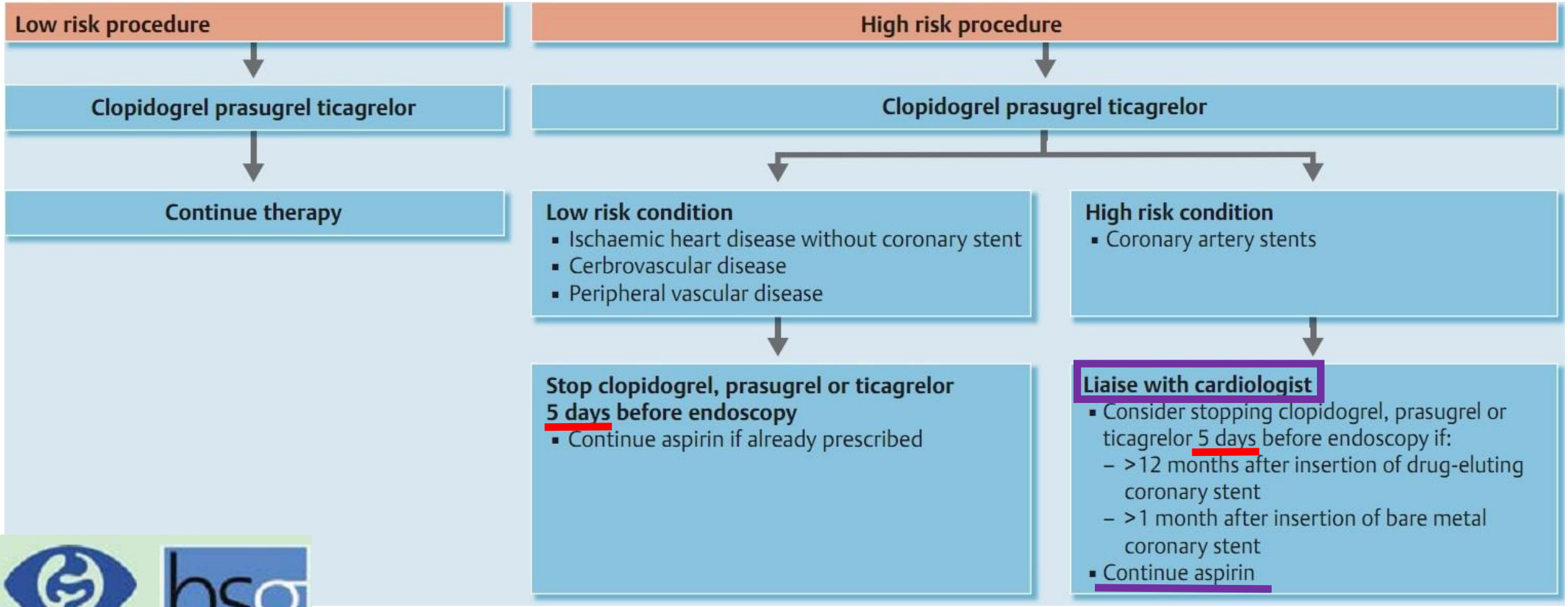
  large colonic EMR (>2cm)

  upper gastrointestinal EMR

  ampullectomy.

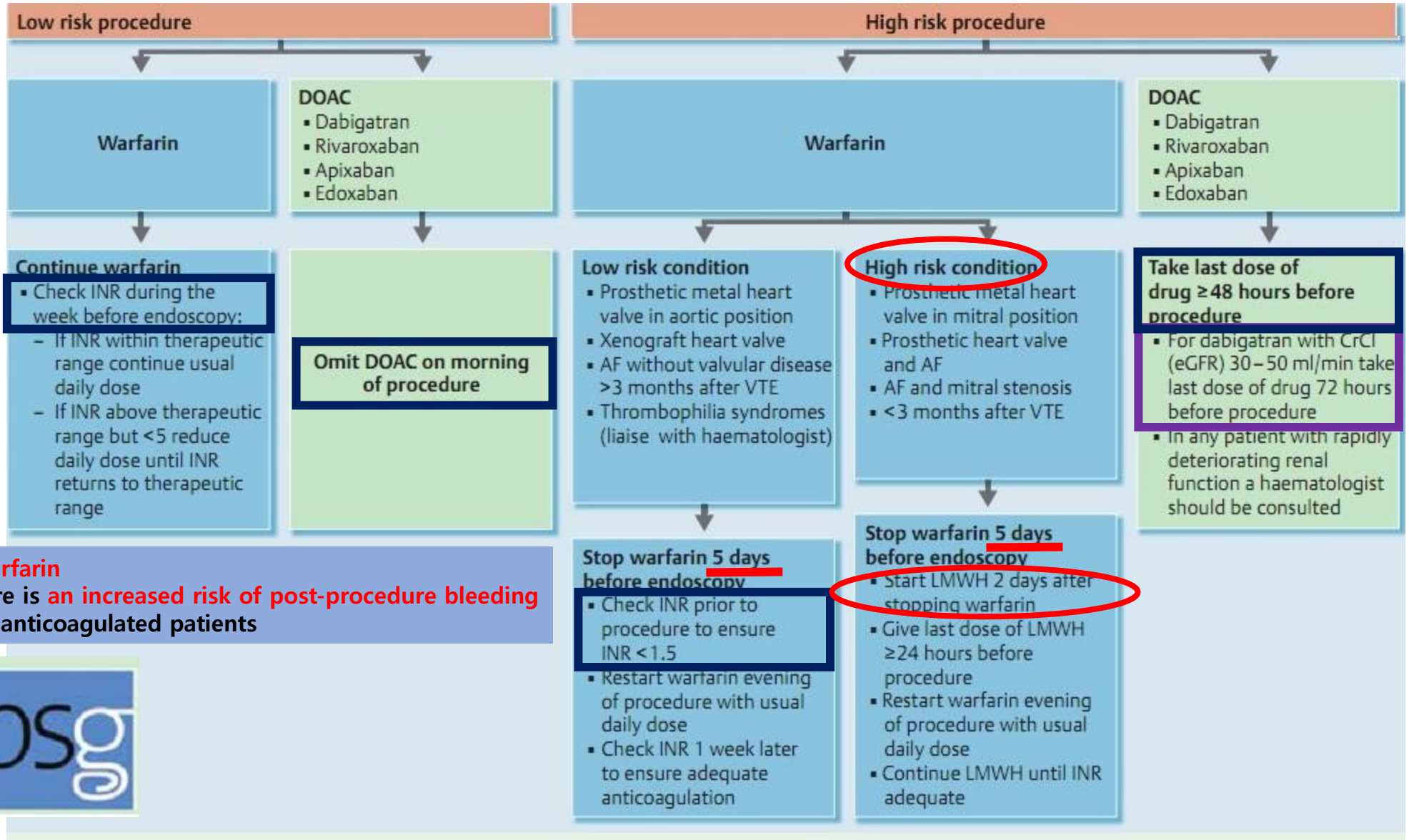
  → aspirin discontinuation **should be considered on an individual patient basis depending on the risks of thrombosis** vs haemorrhage (low quality evidence, weak recommendation).

BSG and ESEG guideline of antiplatelet (2016)



ESGE bsg

BSG and ESEG guideline of anticoagulants(2016)



All patitents on warfarin
: advising that there is an increased risk of post-procedure bleeding compared to non- anticoagulated patients

ESGE bsg

Japanese guideline (2014)

Endoscopy / Monotherapy	Standard endoscopy	Biopsy	Low risk of bleeding	High risk of bleeding
Aspirin	◎	○	○	○ or withdraw for 3–5 days
Thienopyridine	◎	○	○	ASA/CLZ replacement or withdraw for 5–7 days
Antiplatelet agent other than thienopyridine	◎	○	○	Withdraw for 1 day
Warfarin	◎	○ therapeutic range	○ therapeutic range	Heparin replacement
Dabigatran	◎	○	○	Heparin replacement

◎ = withdrawal is not required. ○ = withdrawal is required on a case by case basis.

Mucosal biopsy should **not** be carried out if the **PT-INR was ≥3.0** within the week before biopsy. (JGES 2014)

Summary of guidelines for high-risk bleeding

Recommended discontinuation (days)			
Low CV risk			
	ASGE	**ESEG**	**Japanese**
Aspirin	지속	지속	지속하거나 3-5일 중단
Clopidogrel	단독: 5일 중단, Dual APA: 5일 중단, ASA는 유지	5일 중단	ASA 으로 변경 또는 5-7일 중단
Warfarin	5일 중단, 시술일 저녁 재시작	5일 중단, 시술전 INR<1.5확인, 시술일 저녁 평소 용량으로 재시작	중단하고 heparin bridge
NOAC (DOAC)	GFR 에 따라 중단 적절한 지혈이 될 때까지 중단유지 하였다가 재시작	최소 48시간 중단 (정상 GFR), dabigatran은 (GFR 30-50ml/min)일 경우 72시간 중단	중단하고 heparin bridge
High CV risk			
	ASGE	**ESEG**	
Aspirin	지속	지속	
Clopidogrel	단독: ASA로 변경 Dual APA: 5일 중단, ASA는 유지	ASA 유지, 협진 (중단여부) DES 는 coronary stent 12개월 후, BMS 는 1개월 후에 가능	
Warfarin	5일 중단하고 bridge 시술일 저녁 재시작	5일 중단 후 2일 후부터 LMWH으로 bridge, 시술 전 24시간 전에 마지막 LMWH투여, 시술전 INR<1.5확인 시술 저녁 평소 용량으로 warfarin 재시작, target INR 도달할 때까지 LMWH 유지	
NOAC (DOAC)	중단하고 bridge, 적절한 지혈이 될 때까지 중단유지하였다가 재시작	최소 48시간 중단 (정상 GFR), dabigatran은 (GFR 30-50ml/min)일 경우 72시간 중단	