Management of patients with antiplatelet and anticoagulation before and after endoscopy

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Communication from the ASGE Standards of Practice Committee

GUIDELINE

The management of antithrombotic agents for patients undergoing GI endoscopy

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

Guidelines

- **Bleeding risk of the procedure**
  - 내시경 검사 또는 시술 종류에 따른 출혈 위험성
- **Anti-thrombotic agent**
  - 사용하고 있는 약제의 종류
- **Risk of thromboembolic event**
  - 환자의 기저질환에 따른 혈전 또는 색전의 위험성

Procedure risk for bleeding

Higher-risk procedures	Low-risk procedures
Polypectomy (bleeding: 3-10%)	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* Aspirin or clopidogrel: low risk	Push enteroscopy and diagnostic balloon-assisted enteroscopy
Therapeutic balloon-assisted enteroscopy	Capsule endoscopy
EUS with FNA† Solid masses on ASA/NSAIDs is low risk	Enteral stent deployment (Controversial) Eso.stent 5.3% vs 0.5~1%
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	

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	

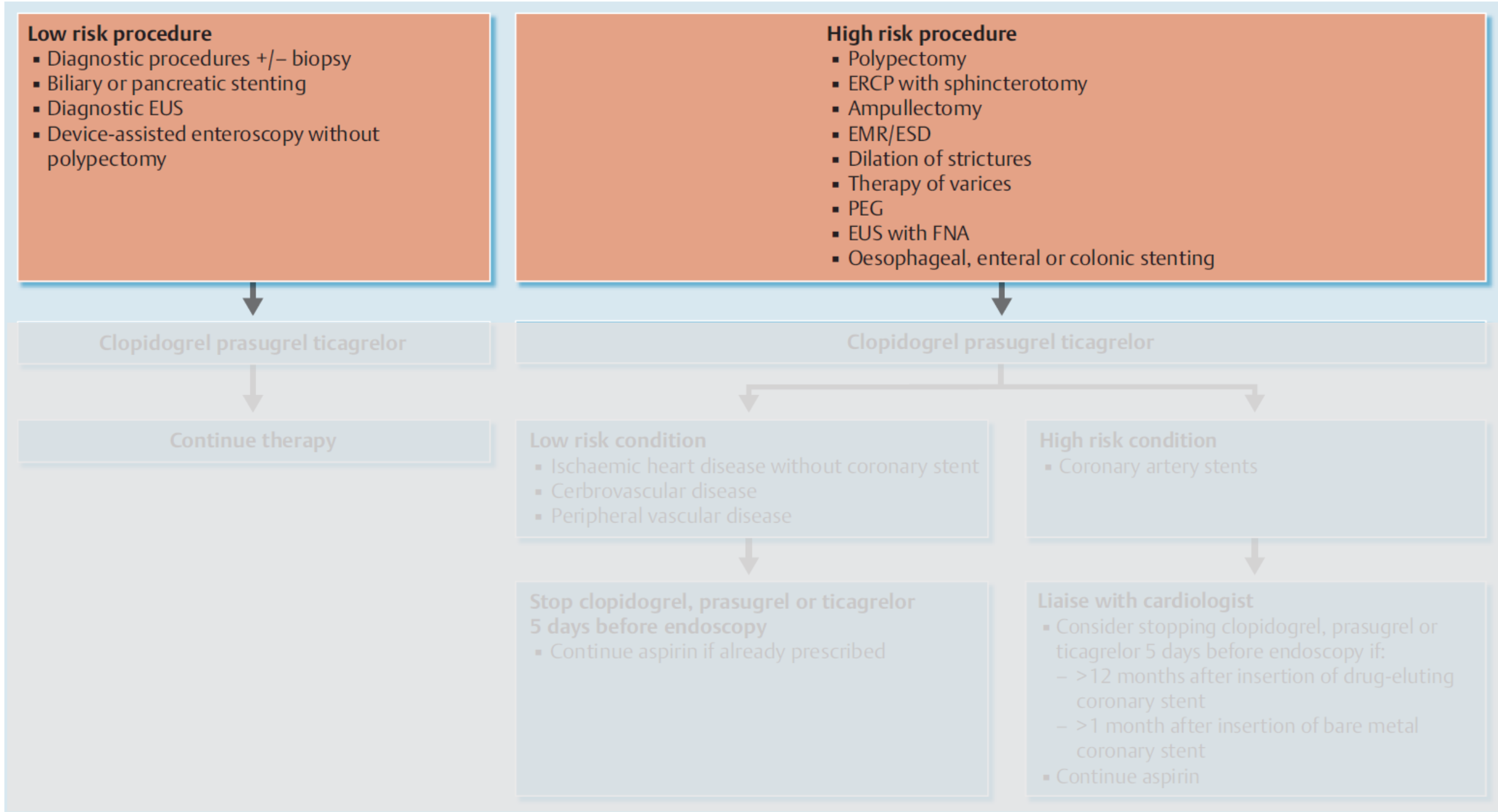


Fig. 1 Guidelines for the management of patients on P2Y12 receptor antagonist antiplatelet agents undergoing endoscopic procedures.

- Anti-thrombotic agent
- Risk of thromboembolic event

Anti-thrombotics

Anti-platelet agent (APAs)	Anti-coagulant (ACs)
Ischemic heart disease	Atrial fibrillation
Blood vessel disease	Prior surgery on a heart valve
Prior stroke or TIA	Congenital heart defect
Diabetes	DVT
Metabolic syndrome	Pulmonary embolism
Angioplasty	Pulmonary hypertension

Anti-platelet agent (APAs)

- Decreased platelet aggregation -> preventing thrombus formation

1. Aspirin (acetylsalicylic aicd)
2. Thiopyridines = P2Y12 receptor inhibitor
   (clopidogrel, prasugrel, ticagrelor, ticlopidine)
3. Protease-active receptor-1 (RAR-1) inhibitor: vorapaxar
4. Glycoprotein IIb/IIIa receptor inhibitor
   (abciximab, eptifibatide, tiofiban)
5. Nonsteroid anti-inflammatory drugs (NSAIDS)

Aspirin

- Irreversible inhibition of the cyclooxygenase 1 and 2 enzyme systems.
- Secondary Prophylaxis : Hx of stroke or MI
- Primary prophylaxis: >10% 10-year risk of heart attack or stroke
- Cessation of ASA, 7 to 9 days to regain full platelet function

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).

P2Y12 receptor inhibitor

- **Ticlopidine(Ticlid)**
  - Hematologic side effect (neutropenia, thrombotic thrombocytopenic purpura, HUS)
  - Irreversible, 5-7days
- **Clopidogrel (Plavix)**
  - Irreversible, 5-7days
- **Prasugrel (Effient)**
  - Prodrug (conversion by cytochrome p450)
  - Risk of increased bleeding -> Contraindication (Hx of CVA or TIA)
  - Irreversible, 5-7days
- **Ticagrelor (Brilinta)**
  - Rapid onset(not require metabolic activation)
  - Reversible inhibition, 3-5days

Ischemic heart disease

- **Antiplatelet therapy** >> anticoagulant therapy
  - Revascularization therapy
    - coronary artery surgery -> aspirin alone
    - stents -> aspirin and clopidogrel for 12 months

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

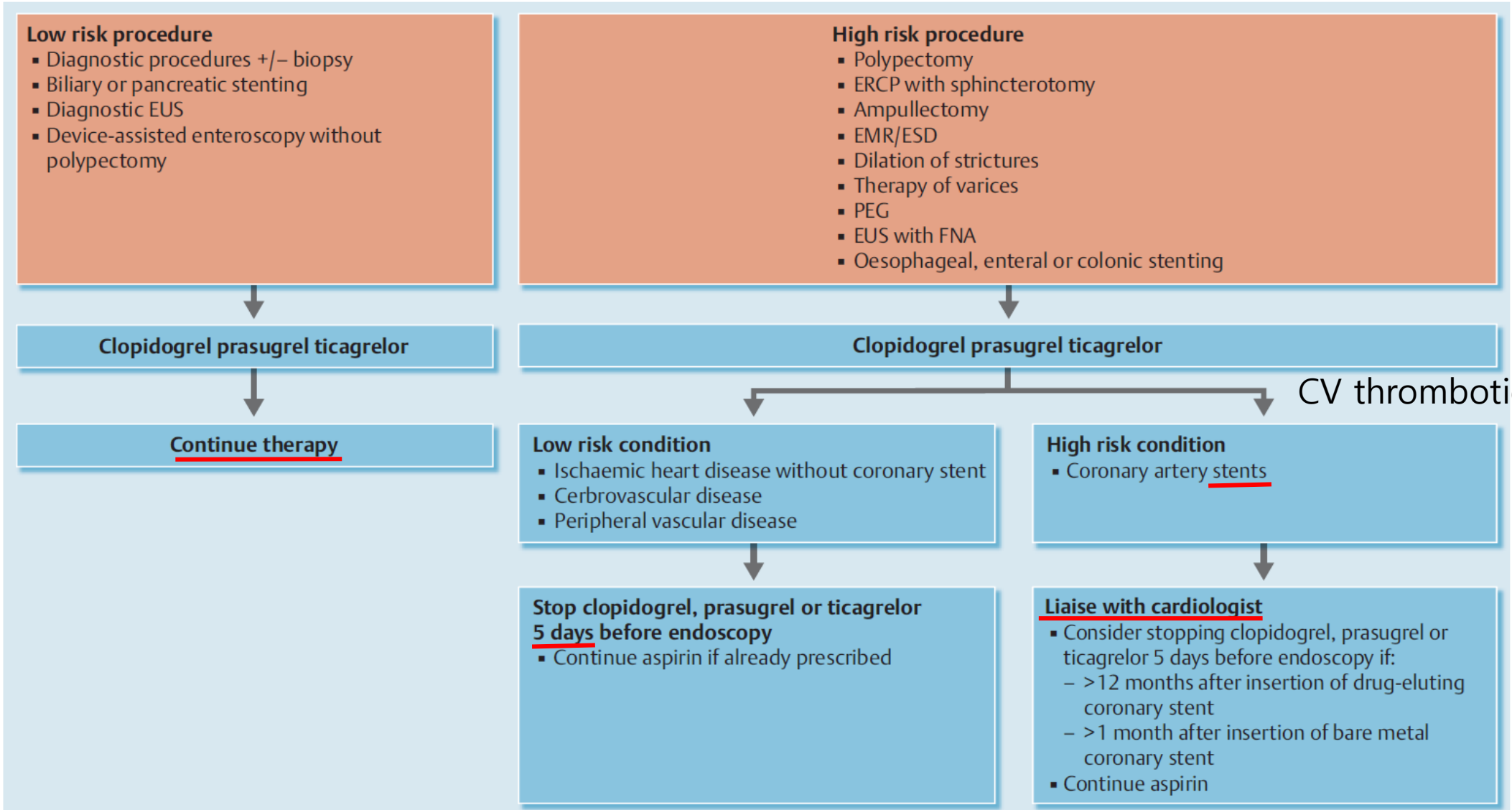
  => lifetime aspirin

BSG and ESEG guideline of 2YRA(2016)

Table 2 Risk stratification for discontinuation of clopidogrel, prasugrel or ticagrelor based on the risk of thrombosis.

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

BSG and ESEG guideline of 2YRA(2016)



DAPT of ASGE guideline (2016)

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.

Vorapaxar (Zontivity)

- Approved by the US FDA in 2014, and by the European Medicines Agency in 2015
- Inhibitor of **protease-activated receptor (PAR-1)**, the major **thrombin** receptor on platelets.
- Preventing cardiovascular events in patients with a **history of MI** or **peripheral arterial disease**
- Addition to aspirin or DAPT
- **Increased risk of moderate or severe bleeding**
  : 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

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

Anticoagulants

- Prevent the clotting of blood by interfering with the native clotting cascade

- 4 drug classes
  1. Vitamin K antagonists (eg, warfarin),
  2. Heparin derivatives (UFH, LMWH, fondaparinux)
  3. Direct factor Xa inhibitors
     (rivaroxaban, apixaban, edoxaban)
  4. Direct thrombin inhibitors
     (dabigatran, hirudins, argatraban).

Warfarin (Coumadin)

- Oral anticoagulant
- Inhibits the vitamin K–dependent clotting factors
  : II, VII, IX, X, 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 (IV)**
  - Half-life of 60 to 90 minutes,
  - Effects dissipate 3 to 4 hours after discontinuation.
- **LMWH (enoxaparin and dalteparin) –** SC
  - 24 hours before the anticipated procedure at 50% of the daily dose.
- **Fondaparinux (Arixtra) -** SC
  - Inhibitor of factor Xa.
  - Discontinuation of this drug before a high-risk procedure is 36 hours.
- **Desirudin (Iprivask) –** SC
  - Thrombin inhibitor
  - Discontinue this medication 10 hours before a high-risk

Bridging therapy

- **UFH IV**
  - 시술 3-4 시간 전 중단
  - 시술 2-6 시간 내 restart

- **LMWH(enoxaparin, dalteparin) SC**
  - 시술 24전 중단
  - 시술 48 시간 후 restart (2012 ACCP guidelines)

Bridging therapy indication

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 ≥ 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.

Bridging therapy indication

Table 3 Risk stratification for discontinuation of warfarin therapy with respect to the requirement for heparin bridging.

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)

* Uncertainty exists regarding the thrombotic risk of temporarily discontinuing warfarin in patients with atrial fibrillation and mitral stenosis following the BRIDGE trial [17], but there is insufficient evidence at present to alter the risk category.

ESGE bsg

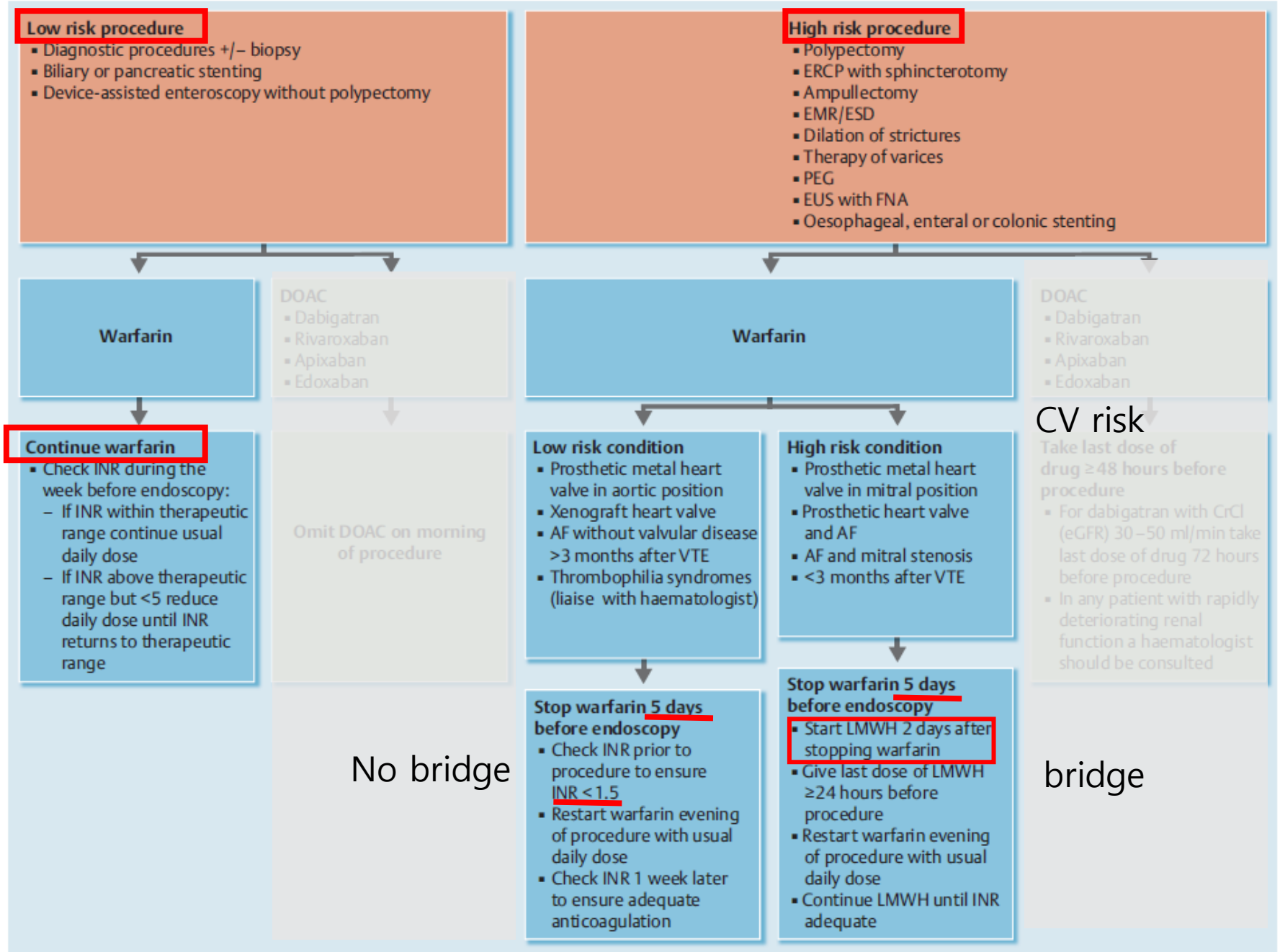
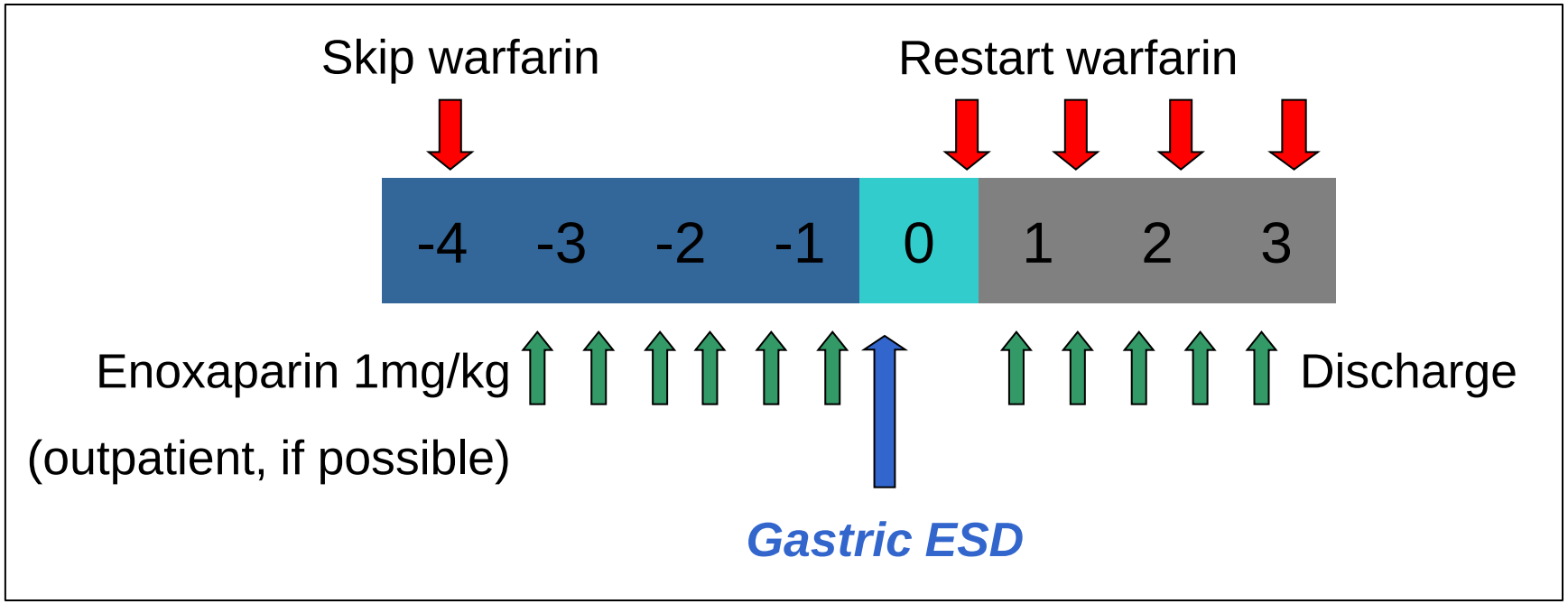
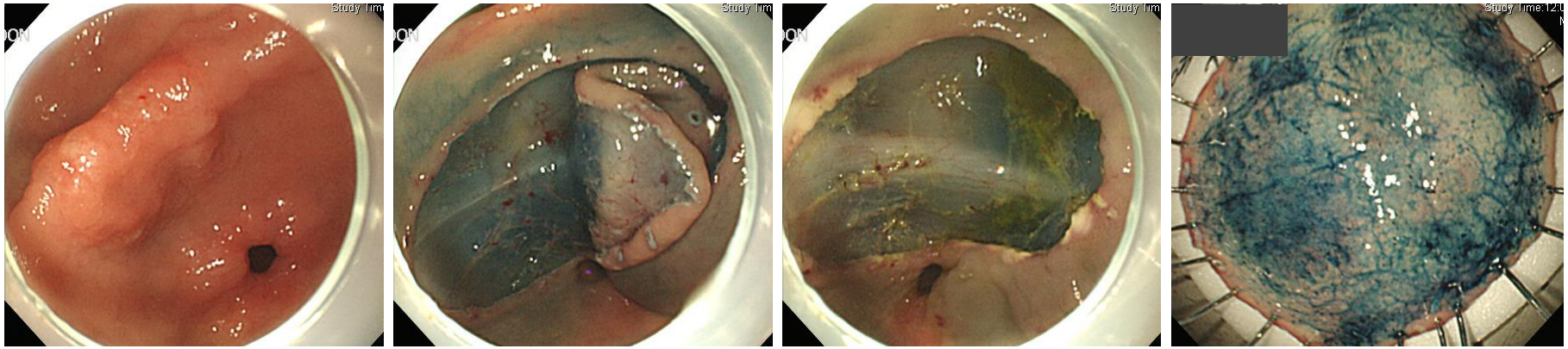


Fig. 2 Guidelines for the management of patients on warfarin or direct oral anticoagulants (DOAC) undergoing endoscopic procedures.

Discontinuing warfarin for gastric ESD





NOAC (DOAC)

- Direct thrombin inh. (Dabigatran) / Direct factor Xa inh. (Rivaroxaban, apixaban, edoxaban)

- Specific antidotes are not yet available for clinical use
  - Dabigatran : idarucizumab (Praxbind)

- **For low-risk endoscopic procedures** : 시술 당일 아침에만 중단
  - 개인차가 있으나 복용 후 2-6시간에 peak level을 갖기 때문에 아침에 skip 하면 trough level 에서 biopsy sample이 가능함

- **For high-risk endoscopic procedures**
  - 적어도 시술 48시간 전에 중단
  - Dabigatran : CCr 30-50mL/min 은 72시간 전에 중단
  - 복용 후 3시간 이내 therapeutic dose 에 도달하기 때문에 시술 24-48시간 후에 재복용 시작

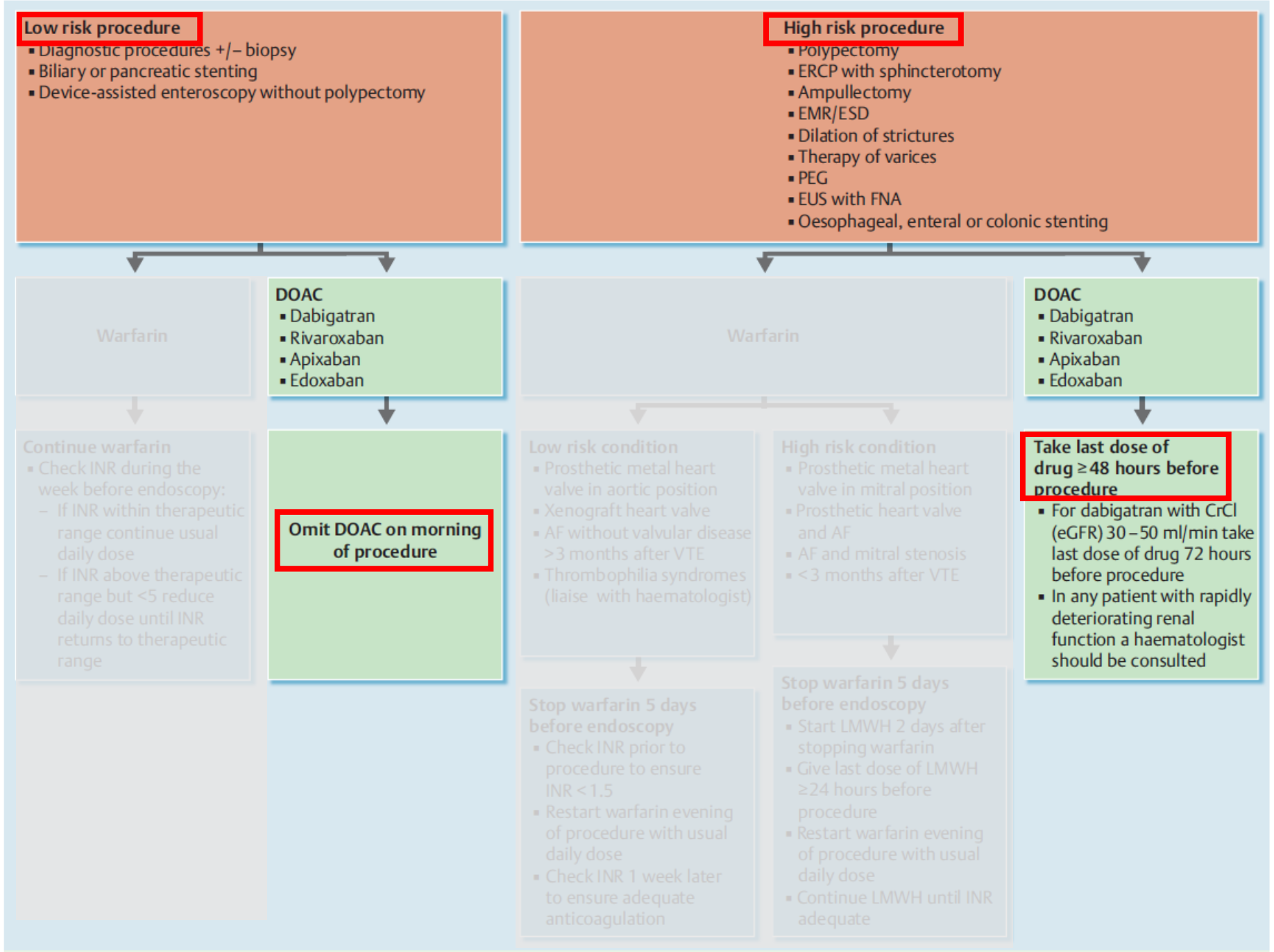


Fig. 2 Guidelines for the management of patients on warfarin or direct oral anticoagulants (DOAC) undergoing endoscopic procedures.

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

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

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

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

Bridging therapy in **DOAC ?**

- **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)

- **Sub-study of the RE-LY trial**

  : 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.

Thienopyrine계 복용시 가이드라인

출혈 저위험 시술

약물지속

출혈 고위험 시술

혈전 저위험군

시술 5일전 중단

아스피린 유지

시술 중 지혈 충분했다면
약물 재투여

혈전 고위험군

심장내과 전문의와 상의

시술후 loading dose 고려

Thienopyridine
Clopidogrel
Prasugrel
Ticagrelor

와파린 복용 가이드라인

출혈 저위험 시술

와파린 지속

INR 검사
(치료범위내로)

출혈 고위험 시술

혈전 저위험군

시술 5일전 와파린 중단

INR 검사 (시술전 1.5이내로)

시술 당일 저녁 와파린
평소용량 복용

시술 1주후 INR 재검사

혈전 고위험군

5일전 와파린 중단

와파린 중단 2일후 LMWH 시작

시술 24시간전 마지막 LMWH 주입

시술 당일 저녁 와파린 평소용량 시작

INR 치료범위 될때까지 LMWH 지속

NOAC 복용시 가이드라인

출혈 저위험 시술

↓

시술당일 아침만
NOAC 중단

출혈 고위험 시술

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혈전 저위험군

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시술 48시간전 마지막
NOAC 복용

시술 24시간 이후 NOAC
재시작 고려

↓

혈전 고위험군

↓

시술 48시간전 마지막
NOAC 복용

시술 24시간 이후 NOAC
재시작 고려

Conclusion

- **Bleeding risk of the procedure**
  - 내시경 검사 또는 시술 종류에 따른 출혈 위험성
- **Anti-thrombotic agent**
  - 사용하고 있는 약제의 종류
- **Risk of thromboembolic event**
  - 환자의 기저질환에 따른 혈전 또는 색전의 위험성

Thanks