



Anticoagulants/antiplatelets and therapeutic endoscopy

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Introduction

- ▶ Types APA-ACO
- ▶ Interaction PPI-APA?
- ▶ High and low Cardiovascular risk
- ▶ High risk endoscopic procedures
- ▶ Recommendations
 - ▶ ASGE
- ▶ Practical proposals



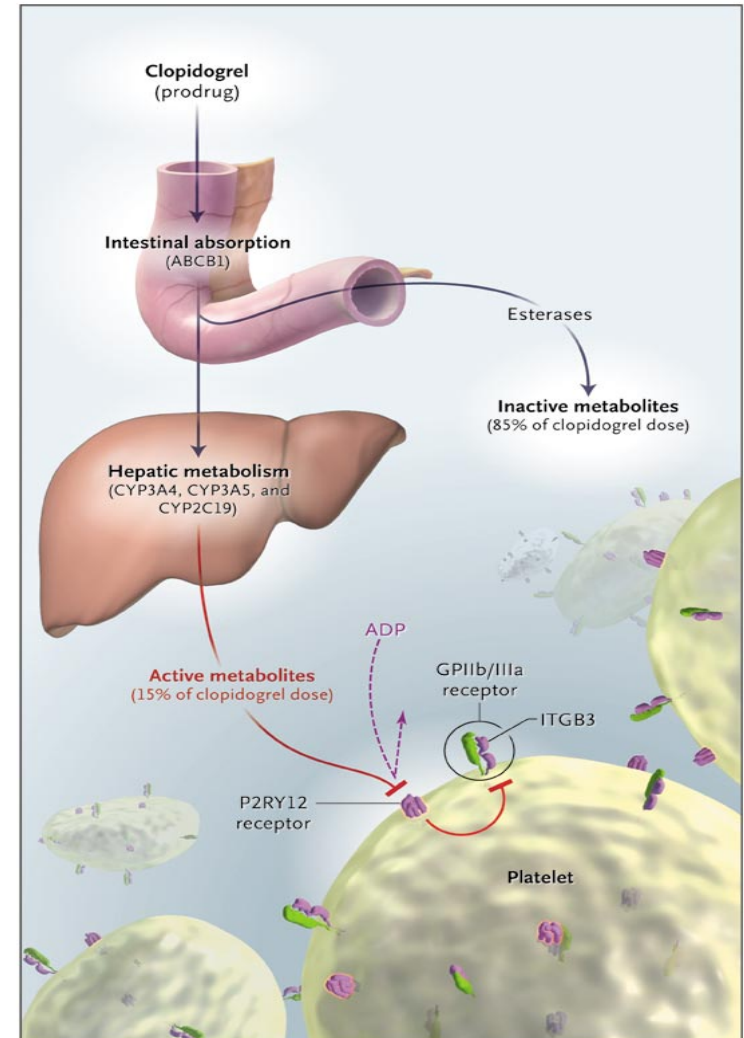
Types of anticoagulants and APA

- ▶ AAS
 - ▶ Irreversible inhibition of cyclo-oxygenase
- ▶ Thienopyridine (clopidogrel, prasugrel)
 - ▶ Inhibits platelet activation induced by adenosine diphosphate
 - ▶ PRODRUG requires biotransformation to an active metabolite by cytochrome P-450 (CYP) enzymes, including CYP2C19
- ▶ Vitamin K antagonists (VKA)
 - ▶ Warfarin, phenprocoumon, and acenocoumarol are orally active vitamin K antagonists (VKA) which decrease hepatic synthesis of a number of coagulation factors, including Factor X.
- ▶ Heparins
 - ▶ Unfractionated heparin (UFH), low molecular weight heparin (LMWH), inhibit the activity of Factor Xa indirectly by binding to circulating antithrombin (AT III)
- ▶ New drugs:
 - ▶ fondaparinux (Arixtra® GSK) // heparin as anti-thrombin but more selective for Factor Xa)
 - ▶ rivaroxaban (Xarelto® Bayer, direct anti-Xa, prothrombinase: acts by cleaving prothrombin which yields the active thrombin)
 - ▶ GP IIb/IIIa inhibitors
 - ▶ Eptifibatide (Integrilin) and tirofiban (Aggrastat) have a short duration (+- 4 hs of action, whereas abciximab (Reopro) may last up to 24 hours

Clopidogrel

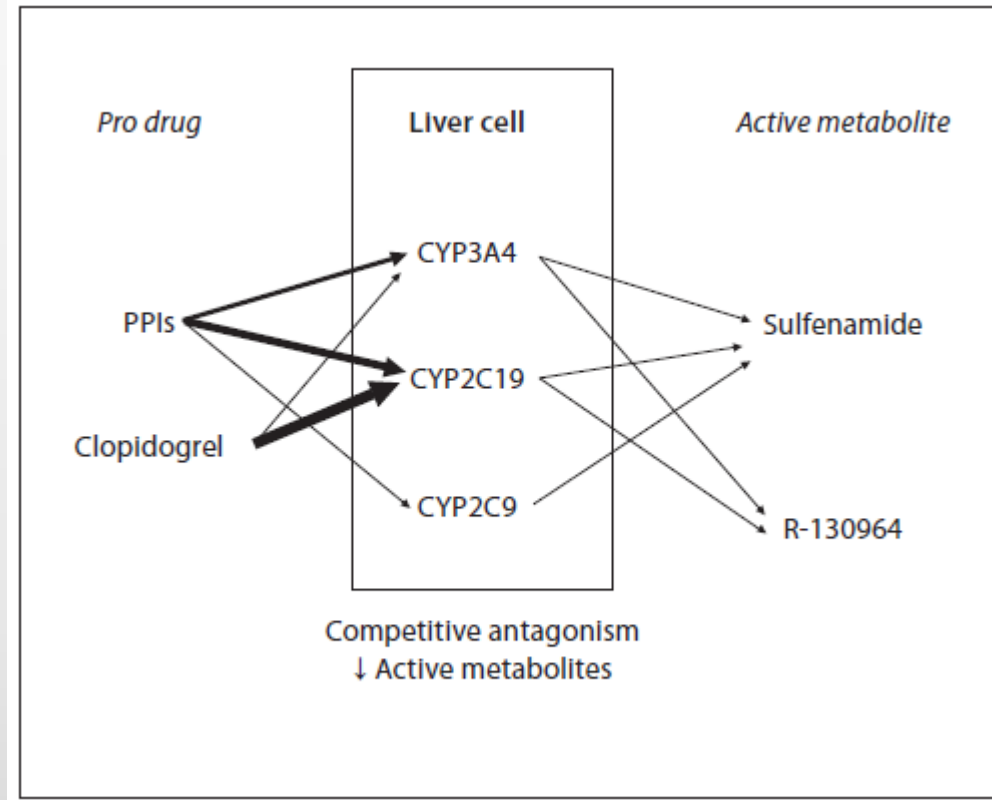
-Intestinal absorption of the prodrug clopidogrel is limited by an intestinal efflux pump P-glycoprotein coded by the ABCB1 gene.

-The minority is bioactivated by various cytochrome P450 (CYP) isoforms into active metabolites. - These metabolites irreversibly antagonize the adenosine diphosphate (ADP) receptor (coded by the P2RY12 gene), which in turn inactivates the fibrinogen receptor (the glycoprotein [GP] IIb/IIIa receptor coded by the ITGB3 gene) involved in platelet aggregation.



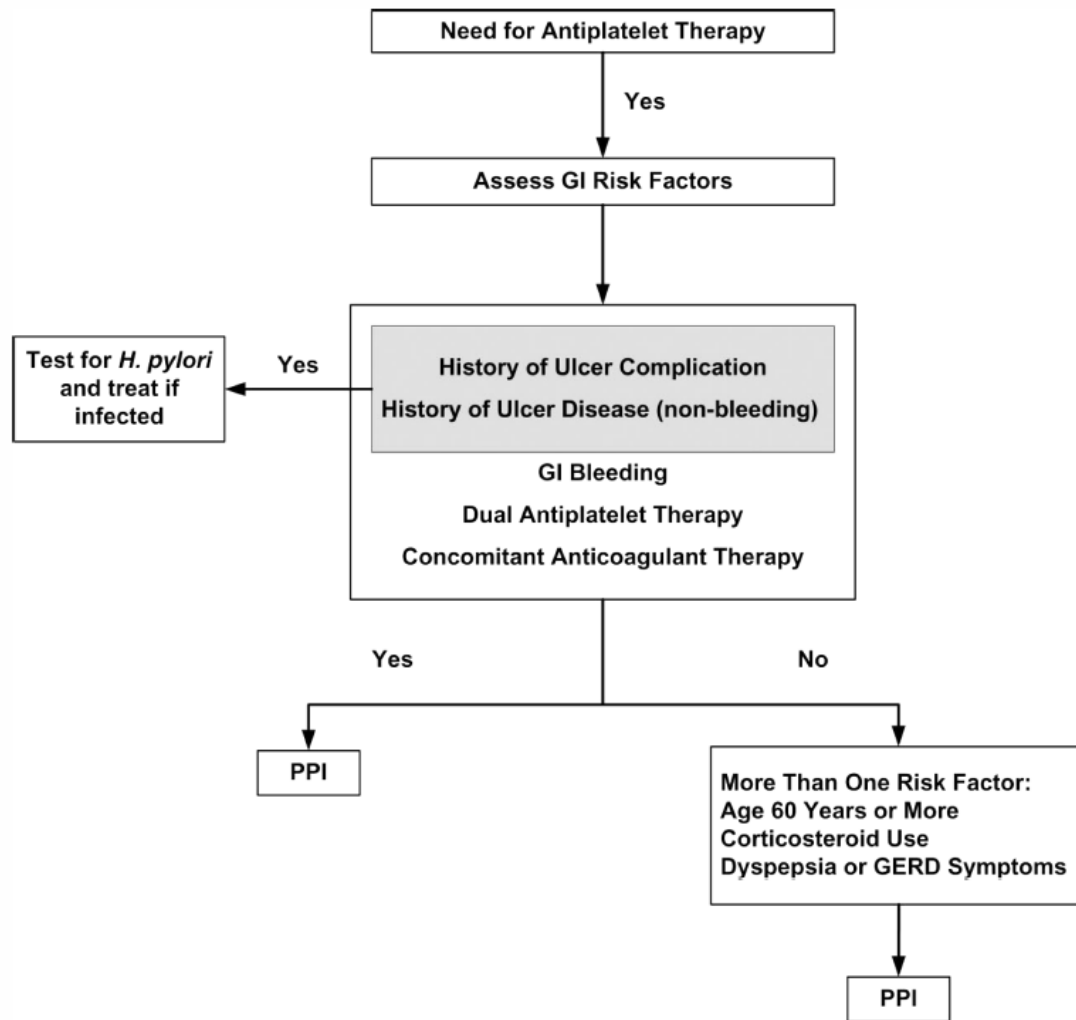
Clopidogrel et CYP 450

- ▶ Active metabolism of clopidogrel is mainly mediated by CYP2C19
- ▶ There are genetic differences in the activity of CYP2C19.
- ▶ Active metabolism of clopidogrel is affected by CYP2C19 genotypes.
- ▶ The main metabolizing enzyme of proton pump inhibitors (PPIs) is CYP2C19.
- ▶ Therefore, the anti-platelet function of clopidogrel is attenuated by concomitant use of PPIs.





ACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use





Inhibiteurs de la pompe à protons et statines : utilisation et prescription

2.1. **Prévention** des lésions gastro-duodénales chez un **patient à risque** qui prend un AINS.

Un patient à risque se trouve dans une des situations suivantes:

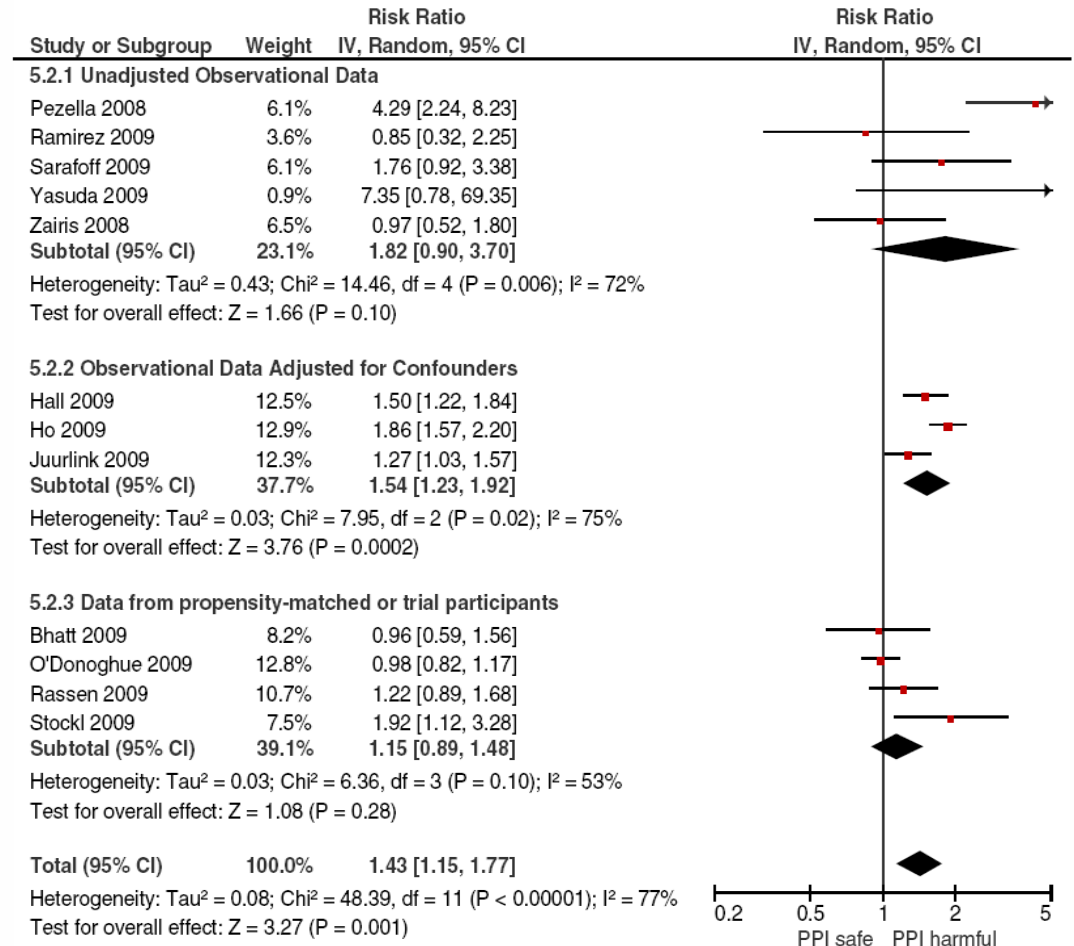
- > 65 ans
- co-morbidité importante
- antécédents d'ulcères peptiques
- antécédent d'un ulcère compliqué (saignement; perforation)
- AINS + corticoïdes
- AINS + acide salicylique
- AINS + autre médicament antiagrégant
- AINS + anticoagulant: coumarine ou autre.



Meta-analysis

Figure 2: Meta-analysis of myocardial infarction or acute coronary syndrome with clopidogrel and PPI use

- ▶ Review of 23 studies, of which the majority in abstract form
- ▶ Only the overall pooled data of observational studies suggests that concomitant clopidogrel and PPI use may be associated with adverse cardiovascular events.
- ▶ Analysis of propensity-matched or randomized trial participants showed no associated risk



Channeling Bias!

- ▶ 18139 new pts
- ▶ 32% PPI
 - ▶ Older, more comedication and comorbidity
 - ▶ If PPI
 - ▶ Risk x1.93 Acute coronary syndrome
 - ▶ 1.79 instable angor
 - ▶ 4.76 bleeding!!

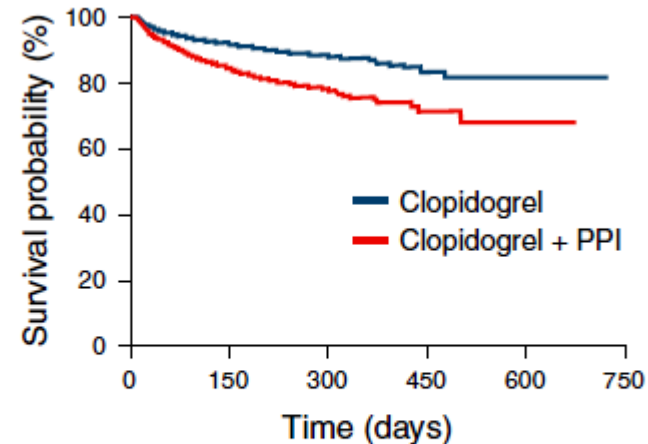


Figure 1. Kaplan–Meier plot of the event-free survival (+95% confidence interval). A statistically significant difference was found between both the groups ($P \leq 0.0001$, Log rank test). PPI, proton pump inhibitor.



Channeling bias

This is most likely attributable to channeling bias:

- ▶ patients using a PPI have increased baseline cardiovascular and GI risk profiles
- ▶ based on
- ▶ (i) patients' characteristics at the start of clopidogrel
- ▶ and (ii) increased hazard risk for GI complications while using a PPI.

Table 3. Multivariate analysis of the association between types of PPI used and the occurrence of adverse outcomes

	No. of patients	Hazard ratio	95% Confidence interval
Omeprazole	1,826	1.622	1.379–1.907
Pantoprazole	2,618	1.827	1.606–2.079
Esomeprazole	1,092	1.833	1.518–2.214
Rabeprazole	133	1.758	1.073–2.881

PPI, proton pump inhibitor.



Bleeding risk

Number of person years' treatment needed to produce one excess case of serious upper gastrointestinal bleeding. Estimates are based on data for people aged 50 or above

Exposure	Total drug exposure in background population (person years)	NNTB: person years ⁻¹ (95% CI)
Aspirin alone	40 599	1040 (725 to 1641)
Clopidogrel alone	2 391	8800 (NNTB 723 to ∞; NNTB 1832 to ∞)
VKA alone	13 205	985 (550 to 2372)
Dipyridamole alone	8 007	873 (445 to 2557)
Aspirin and clopidogrel	739	124 (54 to 312)
Aspirin and VKA	1 213	184 (93 to 407)
Dipyridamole and aspirin	7 713	595 (348 to 1201)

NNTB=number needed to treat for one patient to benefit; NNTB=number needed to treat for one patient to be harmed; VKA=vitamin K antagonist.

BMJ. 2006 October 7; 333(7571): 726.

doi: 10.1136/bmj.38947.697558.AE.



Hallas et al BMJ 2006



Cliniques
universitaires
Saint-Luc

Anticoagulants and APA

TABLE 2. Antithrombotic drugs: duration of action and routes for reversal

Drug class	Specific agent(s)	Duration of action	Routes for reversal	
			Elective	Urgent
Antiplatelet agents	Aspirin	10 days	NA	Transfuse platelets
	NSAIDs	Varies	NA	Transfuse platelets
	Dipyridamole	2-3 days	Hold	Transfuse platelets
	Thienopyridines (clopidogrel, ticlopidine)	3-7 days	Hold	Transfuse platelets ± desmopressin if overdose
	GP IIb/IIIa inhibitors (tirofiban, abciximab, eptifibatid)	Varies	NA	Transfuse platelets; in case of overdose, some agents can be removed with dialysis
Anticoagulants	Warfarin	3-5 days	Hold	FFP ± vitamin K, consider protamine sulfate*
	Acénocoumarol	2-3 days	Hold	FFP, vitamin K, consider protamine sulfate*
	Unfractionated heparin	4-6 h	Hold	Hold or consider protamine sulfate*
	LMWH	12-24 h	Hold	Hold or consider protamine sulfate*

NA, Not applicable; NSAID, nonsteroidal anti-inflammatory drug; GP, glycoprotein; FFP, fresh frozen plasma; LMWH, low molecular weight heparin.

*Caution: Can cause severe hypotension and anaphylaxis.

Risk for thromboembolic event

Higher-risk condition

Atrial fibrillation associated with valvular heart disease, prosthetic valves, active congestive heart failure, left ventricular ejection fraction <35%, a history of a thromboembolic event, hypertension, diabetes mellitus, or age >75 y

Mechanical valve in the mitral position

Mechanical valve in any position and previous thromboembolic event

Recently (<1 y) placed coronary stent

Acute coronary syndrome

Nonstented percutaneous coronary intervention after myocardial infarction

Low-risk condition

Uncomplicated or paroxysmal nonvalvular atrial fibrillation

Bioprosthetic valve

Mechanical valve in the aortic position

Deep vein thrombosis

Risk of embolism, stroke or peripheral ischemia in case of mechanical valve:

- no R → 4% / y
- antiplatelet agent → 2 % / y
- anticoagulant (warfarine) → 1% / y

ASGE Risk of bleeding

Higher-risk procedures

Polypectomy

Biliary or pancreatic
sphincterotomy

Pneumatic or
bougie dilation

PEG placement

Therapeutic
balloon-assisted
enteroscopy

EUS with FNA

Endoscopic hemostasis

Tumor ablation by any
technique

Cystogastrostomy

Treatment of varices

Low-risk procedures

Diagnostic (EGD, colonoscopy,
flexible sigmoidoscopy)
including biopsy

ERCP without sphincterotomy

EUS without FNA

Enteroscopy and diagnostic
balloon-assisted enteroscopy

Capsule endoscopy

Enteral stent deployment
(without dilation)





ESGE Risk of bleeding

Haemorrhagic risk	Endoscopic technique	% risk
Low (<0.1%) to Moderate (>0.1% and <1%)	Oesogastroduodenoscopy and Colonoscopy +/- biopsy	<0.01-%
	Enteroscopy +/- biopsy	0.2%
	EUS	<0.1%
	Dilation of benign or malignant digestive stricture	<1%
	EUS with FNA of a solid mass	0.21%-0.96%
	Digestive stent	0.5%
	(ERCP) without endoscopic sphincterotomy (ES)	0.26%
High risk (>1%)	Colonic polypectomy	1.6 - 3.3%
	Endoscopic Sphincterotomy	2-3%
	Sphincteroclasia	0%-16%
	EUS with FNA of cystic lesion	0-6%
	Gastrostomy	2.5%
	Oesophageal varices by ligation (OVL)	2-5%
	Submucosal dissection	1-22%
	Mucosectomy	4-14% [37]
	Ampullectomy	8% [95]





Practical proposals

- ▶ Endoscopic procedures for diagnostic purposes only rarely cause digestive bleeding (<0.1%)
 - ▶ treatment with APA may be continued without increasing the risk of bleeding.
- ▶ Certain endoscopic procedures infrequently cause bleeding (<1%), which is slight or easily controlled during the procedure,
 - ▶ They may be conducted in patients taking APA under certain conditions or treatment modifications.
- ▶ For procedures involving high haemorrhagic risk (>1%) or when control of induced bleeding is impossible
 - ▶ APA treatment should as a rule be discontinued if the thrombotic risk to the patient permits. If this is not the case, in patients defined as having a high risk of thrombosis, the endoscopic procedure should be postponed or replaced by a less invasive alternative when one exists.





Practical proposals

- ▶ When patients are under dual APA for high thrombotic risk, aspirin will in most of cases be continued to maintain a prevention during the cessation period of clopidogrel or prasugrel.
- ▶ For patients taking only clopidogrel, a switch with aspirin can be done for the time of the procedure if prevention can't be discontinued



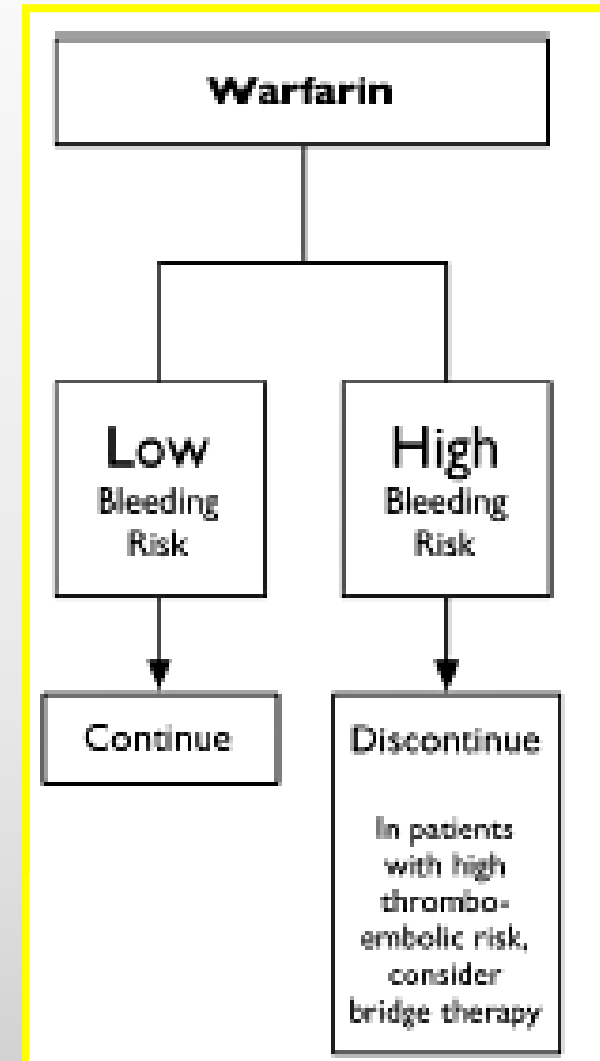
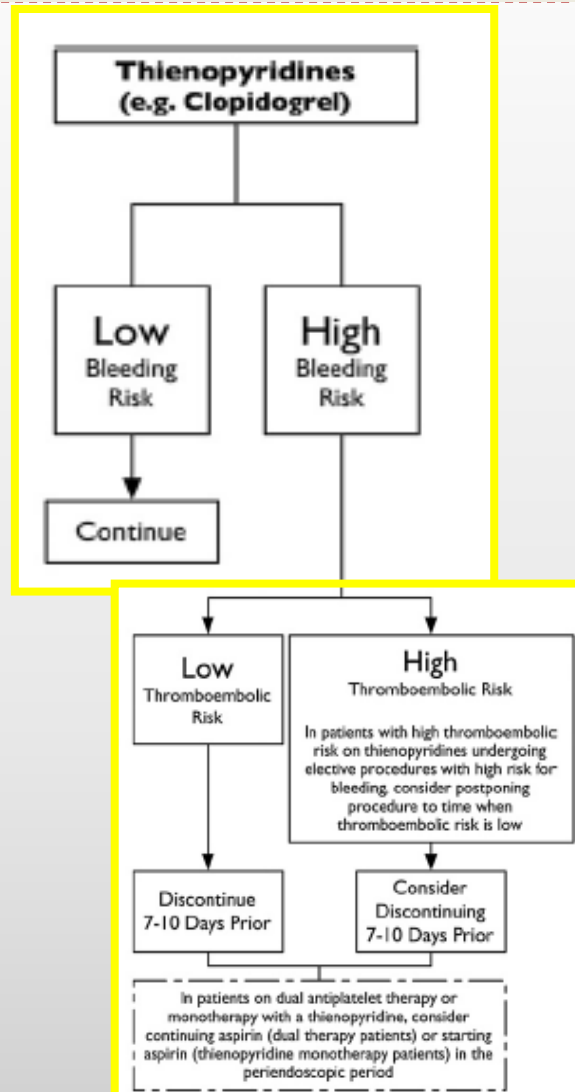
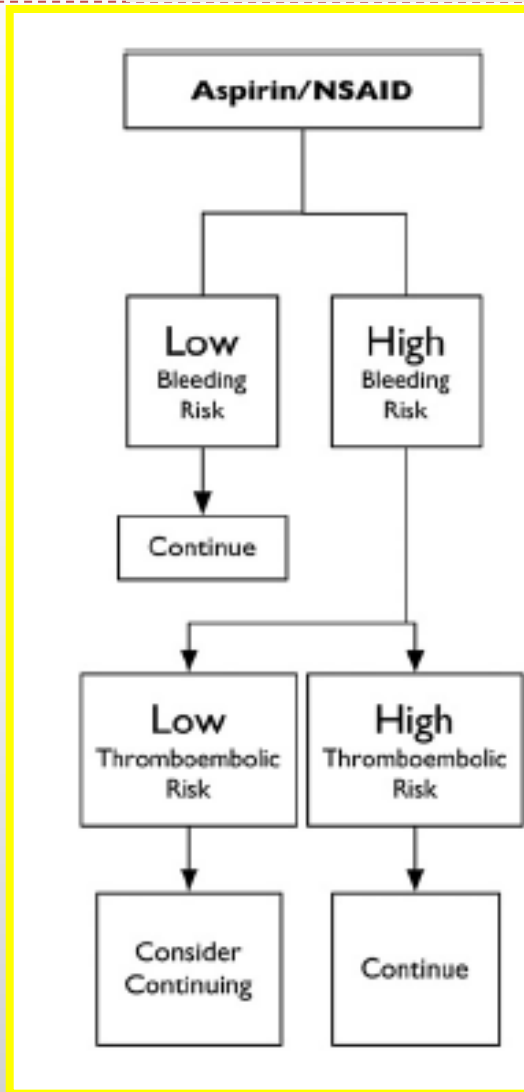


Practical proposals

- ▶ When stopping?
 - ▶ 3 days before for AAS
 - ▶ 5 days before for clopi (7 days for prasugrel)
 - ▶ 3 days before for anti-vit K
 - ▶ 12 h before for LMWH
- ▶ APA treatment should be resumed no later than 24 to 48 hours after the procedure but may be delayed on a case by case basis



ASGE proposed algorithms: elective endoscopy





Elective endoscopy: warfarin

- ▶ Temporary anticoagulant treatment (DVT, coronary stent, acute ischemia)
 - ▶ Postpone endoscopic procedures
- ▶ Procedure with a low thromboembolism risk
 - ▶ No alternative anticoagulation
- ▶ Procedure with high thromboembolism risk
 - ▶ Shift to LMWH or unfractionated heparin



Warfarin in low and high thromboembolism risk: Elective endoscopy

TABLE 5. Perioperative management of warfarin for patients with atrial fibrillation or valvular heart disease undergoing elective endoscopy

Condition	Associated diagnosis	Management
Atrial fibrillation	None	Hold warfarin 3-5 days before procedure. Restart warfarin within 24 h.*
	Mechanical valve(s) and/or history of cerebrovascular accident, transient ischemic attack, or systemic embolism	Hold warfarin and start UFH when INR ≤ 2.0 . Stop UFH 4-6 h before procedure and restart after procedure. Resume warfarin on the evening of the procedure and continue both agents until INR is therapeutic.* Therapeutic doses of SQ UFH or LMWH may be considered in lieu of IV UFH.
Valvular heart disease	Mechanical bileaflet, aortic valve	Hold warfarin 48-72 h before procedure for a target INR < 1.5 . Restart warfarin within 24 h.*
	Mechanical mitral valve or mechanical aortic valve plus any of the following: atrial fibrillation, previous thromboembolic event, left ventricular dysfunction, hypercoagulable condition, mechanical tricuspid valve or > 1 mechanical valve	Hold warfarin and start UFH when INR ≤ 2.0 . Stop UFH 4-6 h before procedure and restart after procedure. Resume warfarin on the evening of the procedure and continue both agents until INR is therapeutic.* Therapeutic doses of SQ UFH or LMWH may be considered in lieu of IV UFH.

High risk

Low risk

UFH, Unfractionated heparin; INR, international normalized ratio; SQ, subcutaneous; LMWH, low molecular weight heparin.

*Continuation or reinitiation of anticoagulation should be adjusted according to the stability of the patient and estimated risks surrounding the specific intervention/procedure performed. This table was adapted from the following guidelines: 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines³⁰ and American College of Cardiology/American Heart Association 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.³²

Mortality reported with LMWH use in cas of mechanical valves!



Polypectomy

- ▶ No increased risk with aspirin
- ▶ Higher risk
 - ▶ Anticoagulants
 - ▶ Sessile polyp and size of polyp > 1 cm
 - ▶ Cardiovascular disease, age > 65
 - ▶ Poor preparation
 - ▶ Concomitant use of AAS and clopidogrel OR 1.3

Polypectomy can be carried out under aspirin

Polypectomy can be carried out under clopidogrel if size < 1 cm?

Mucosectomy, ESD, ampullectomy: stop all APA

Reducing risk with clips? Endoloops? Blended current?





Sphincterotomy

- ▶ Aspirin does not increase the risk of bleeding
- ▶ Data are insufficient for clopidogrel
- ▶ Risk for bleeding:
 - ▶ Cholangitis
 - ▶ Coagulation disorders, Anticoagulation <3 days
 - ▶ Low case volume
 - ▶ Bleeding during procedure
 - ▶ Decreased risk with balloon dilation (<10mm)

Recommendations

- No aspirin discontinuation (for recognized indication, or need for urgent ES)
- Clopidogrel should be discontinued 5 days before ES or BD
- Large balloon dilatation should not be performed under APA or aspirin
- Biliary stenting without ES should be considered in patients taking APA



Dilatation

- ▶ ASGE recommend discontinuation of APA
- ▶ Esophageal
 - ▶ Large series (2750 dilatations): no bleeding
 - ▶ Achalasia: 1.6% risk
- ▶ Colon and bowel
 - ▶ Risk 0-7%
- ▶ Stents: no significant risk
- ▶ Summary:
 - ▶ Aspirin may be continued for any benign or malignant dilatation, or stenting
 - ▶ Clopidogrel should be discontinued (expert opinion)



Gastrostomy and varia

- ▶ The haemorrhagic risk of PEG in patients on APA is poorly evaluated but the procedure appears possible in patients on aspirin (higher but NS risk)
- ▶ The haemorrhagic risk of diagnostic enteroscopy in patients on APA is poorly evaluated and no data are available for the spiral over-tube method (Spirus)
- ▶ Esophageal varices ligations is always preferable to sclerotherapy due to the risk of delayed bleeding (5% vs. 4-25%). No data are available for patients on APA.
- ▶ APC can be performed under aspirin

Coronel MJ, et al. Does Aspirin Increase the Risk of Bleeding for Percutaneous Endoscopic Gastrostomy Procedure? *Gastrointestinal Endoscopy*. 2006; 63(5): AB113

Richter JA, et al Use of High-Dose Aspirin or Clopidogrel Before or After Percutaneous Endoscopic Gastrostomy Is Not Associated With Post-Procedural Bleeding *Gastrointestinal Endoscopy*. 2010; 71(5): AB114





Urgent endoscopy

- ▶ Warfarin
 - ▶ Vit K 1-2mg IV and FFP
 - ▶ PPSS or Factor VIIIa
 - ▶ Success of therapeutic endoscopy
 - ▶ 246 Patients (95 % with INR between 1.3 and 2.7)
 - ▶ 94.7 % (233/246).

- ▶ APA
 - ▶ Stop
 - ▶ Platelets IV

- ▶ Acute coronary syndrom (1-3 % bleeding risk)
 - ▶ → 4-7x risk of mortality when bleeding occurs
 - ▶ → 1-2% complications due to the endoscopic procedures

- ▶ No data on appropriate timing of resuming treatment
 - ▶ Consider control endoscopy?

CONCLUSIONS

- ▶ Use of PPI in patients at risk of bleeding
- ▶ Mortality associated with discontinuation of APA!!
- ▶ Low risk procedures should be done under APA
- ▶ High risk procedures:
 - ▶ Discontinuation should be discussed with cardiologist or referring physician, following algorithms and on a case by case basis
 - ▶ Especially in high bleeding risk and high thromboembolism risk...
😊

Stop only 3 days before for aspirin, anti-Vit K and 5 days before endoscopy for clopidogrel

APA treatment should be resumed no later than 24 to 48 hours after the procedure

No Data on newer drugs...