Colonoscopy and Management of patients under anti-thombotic therapy

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INTRODUCTION

- The use of antithrombotic agents (aspirin, thienopyridines, warfarin, etc.) to prevent thrombotic events has significantly increased with the expanding elderly population and use of coronary stents.
- For these patients, we have to deal with two risks : the thromboembolic risk if the antithrombotic drug is stopped, and the bleeding risk of the endoscopic procedure.
- Life-threatening events due to stents thrombosis are well documented after APA discontinuation.
- Many studies have demonstrated that aspirin alone would not increase the risk of complications after colonoscopy, including polypectomy

Guidelines : Anti-thrombotic agents and digestive endoscopy

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- 2006 : French guidelines (SFED) :
  - Endoscopy 2006 ;38:632-38
- 2007 : Japanese guidelines :
  - Digestive Endoscopy 2007;19:161-66
- 2008 : British guidelines
  - Gut 2008 ;57:1322-29
- 2009 : US guidelines (ASGE)
  - Gastrointest Endoscopy 2009 ;70 :1060-70
- 2011 : European guideline (ESGE)
  - Endoscopy 2011 ;43 : 445-58

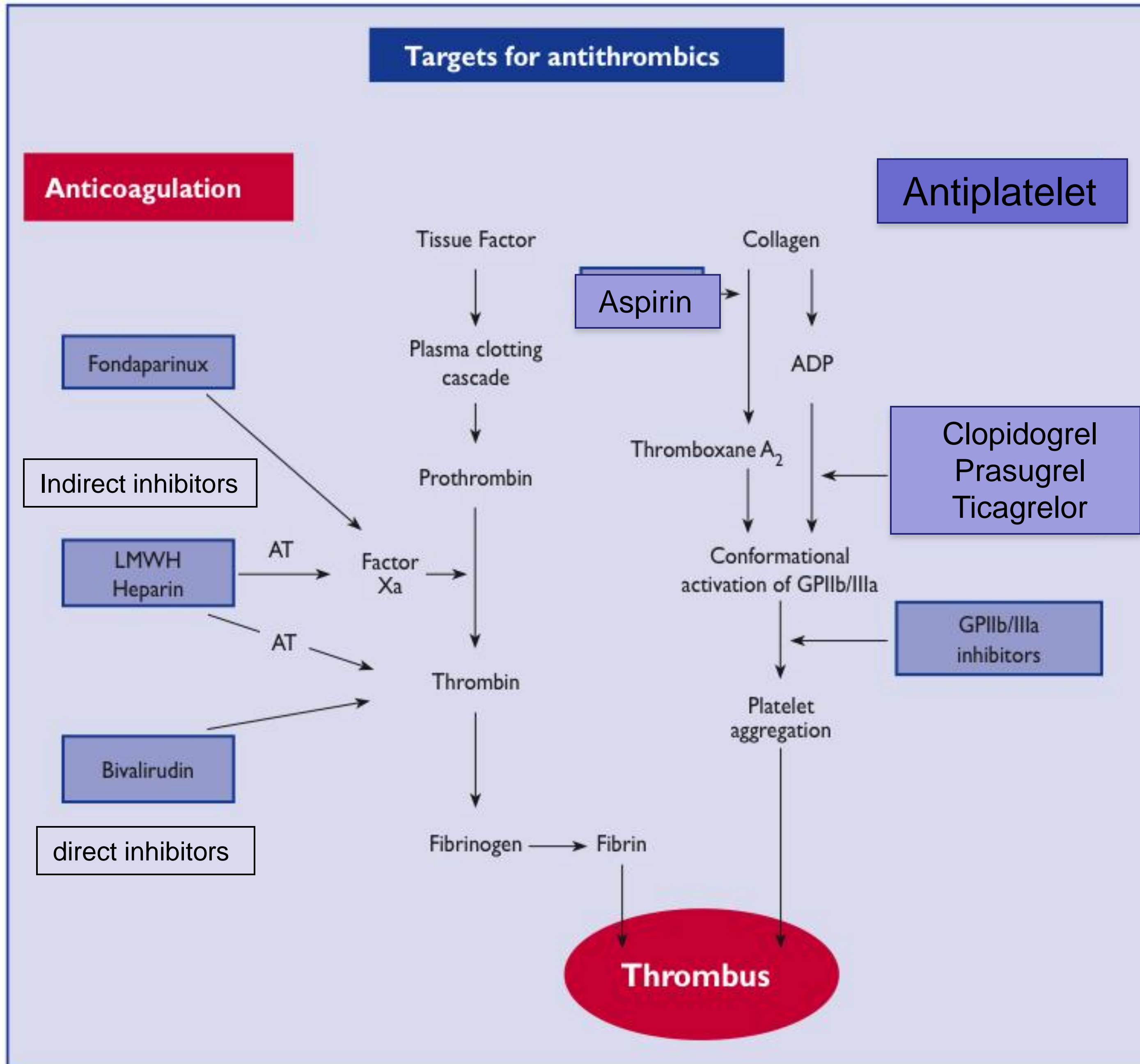
Anticoagulants and APA

« Not the same drugs, not the same risks »

- Heparine (UFH or LWMH), oral anticoagulants : warfarin or new anti-thrombin)
  - inhibit the clotting cascade through an antithrombin(direct or not) action.
  - Coagulation inhibition can be easily monitored by blood tests
  - Substitution of VKA by heparin allows a short discontinuation of anti-thrombotic action.
  - treatement must be stopped before all invasive procedures such as polypectomy and resumed only few hours after (6 – 12 h)
- Bleeding complications are more frequent with ACG and occur when the treatement is resumed.

APA : How do they inhibit platelet activation ?

- Aspirin :
  - targets the COX-1 with irreversible inhibition of thromboxane A2
- Clopidogrel – Prasugrel (Thienopyridines)
  - Prodrugs antagonist of the $P2Y_{12}$ receptor (ADP activator)
  - biotransformed into molecules that bind irreversibily this receptor,
- Ticagrelor (pyrimidines)
  - New class of antagonist of $P2Y_{12}$, without biotransformation, which bind *reversibily* the receptor.
  - It has a more rapid onset and a quicker offset than clopidogrel
- inhibitors of GP IIb/IIIa receptors :
  - Abciximab , Eptifibatide, Tirofiban (intra-venous drugs) inhibit the final common pathway of platelet activation



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The thrombotic risk of patients with coronary stenting

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- Patients presenting with High thrombotic risk
  - 4 to 6 weeks after stroke or stents implantation
  - 6 to 12 months for drug eluting stents
- Other patients with associated risk factors :
  - Age, diabete, kidney failure, inflammatory diseases
  - History of stent thrombosis or complex coronary stenosis
  - resistance to clopidogrel (mutation CyP2C19)

Indications of APA in patients with a high thrombotic risk

→ Dual APA is always required : aspirin + clopidogrel

→ Prasugrel is indicated in case of resistance to clopidogrel

→ The place of ticagrelor is not well precised and side effects are frequent (dyspnea)

→ short discontinuation of clopidogrel or prasugrel is possible after cardiologists advice

→ We should never stop aspirin

Is it possible to evaluate the coagulation in patients under APA ?

- No routine test is available to check platelets activity
- « Verify Now », « VASP » are used in cardiologic intensive care to adjust the loading dose of clopidogrel
- These tests are not reliable to assess the over-bleeding risk due to APA taking.
- genetic testing for the response to clopidogrel could be used in the next future*

** Roberts JD. Lancet March 2012*

APA : « Stop and Start » modalities

Drugs	Onset of effect	Duration of effect	Withdrawal before procedure
Aspirine	2- 4 h	5 days	**3 - 5 days**
Clopidogrel	2-4 h	3-10 days	**5 days**
Prasugrel	30 mn	5-10 days	**7 days**
Ticagrelor	30 mn	3-4 days	**5 days**

Resume the treatement as soon as possible and no later than 24 to 48 hours after the endoscopic procedure

Could we substitute APA ?

- No proven efficacious alternative therapy can be proposed as substitute
  - LMWH have been advocated without proof of efficacy
- Preventive platelets transfusions are not recommended

Colonoscopy in patients taking APA

- What’s the bleeding risk of colonoscopy and polypectomy
- Is the bleeding risk higher under APA ?
- What’s the endoscopic preventive measures ?

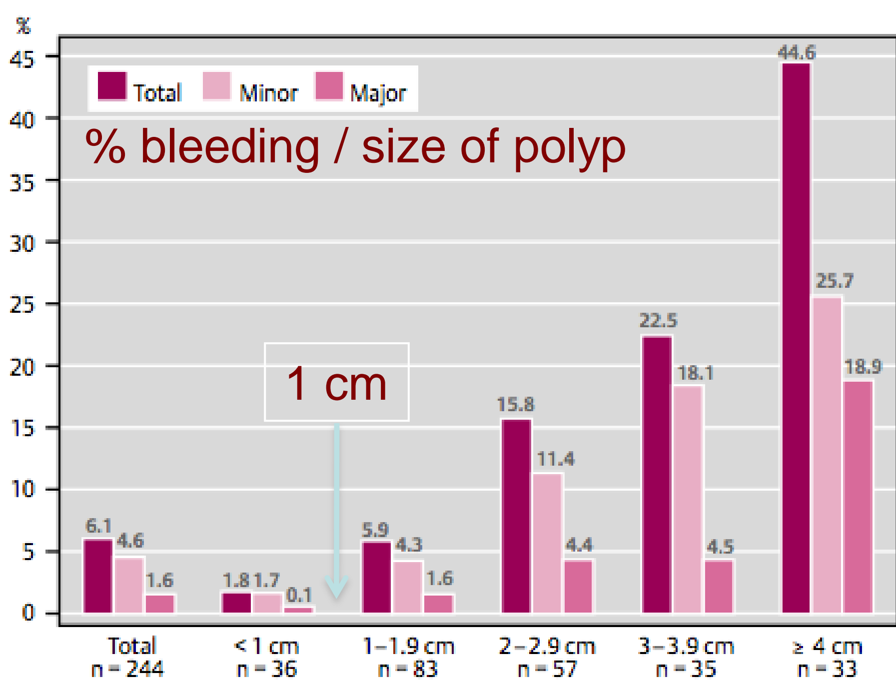
Bleeding risk of diagnostic colonoscopy with or without biopsies under APA

- Aspirin or clopidogrel are not considered as factors increasing the bleeding risk of standard forceps biopsies*
- We recommend to continue the treatement even in cases of dual APA therapy
- Expert opinion : reduce the number of biopsies if dual APA therapy or in case of low platelet count

* Yao M. (NIH survey) Gastrointest Endosc 2009;69:906-10.

Bleeding complications after colon polypectomy

– MUPS * : 4000 polypectomies
– Global bleeding rate : 8,6 % and severe bleeding in 1.6 %



Risk factors of bleeding :
→ Polyp size > 1 cm
+ right colon

** Munich Polypectomy Study , Heldwein. Endoscopy 2005; 37:1116-22*

Bleeding risk of Polypectomy recent studies at UEGW 2011

- 15 000 polyp resections :
- Bleeding rate : 0.74 % (117 cases) only 14 u/APA

- Polyp size is a predictive risk factor
- No relationships with site, shape or APA

- Bleeding occurs in the 72 hours after the procedure

** Kakimoto. Gut 2011;60 (suppl 3) UEGW A 197*

Bleeding risk of polypectomies under aspirin

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Studies	N patients	Bleeding %	aspirin	Definite Risk factors
Yousfi 2004	20636	0.5 %	No	Polyp size >1cm
Hui 2004	1657	2.2%	No	Anti-coagulant
Heldwein 2005	2257	1.6%	No	Polyp size > 1cm
Kim 2006	5152	Delayed = 0.4% immed = 2.8%	No	anticoagulant
Sorbi 2005	14575	0.5%	No	Size and anticoag
Sawhney 2008	5000	1%	No	Anticoagulant
Beppu 2011	2874	1.1%	No	Anticoagulant

Aspirin is never considered as a predictive bleeding risk factor

Results of the French endoscopic survey

3265 colonoscopies with 1012 polyp resections collected within 450 endoscopists during a week on november 2011

Predictive risk factors	**Comparative rates**	**P value**
Age > 50 years	0,7% vs 1,2% *	NS
Gender M/F	1,2% vs 0,9 %	NS
Left vs Right Colon	0,8 vs 1,5 %*	NS
Shape : Sess /Ped	0,8 vs 2,6 %*	NS
Size : < 1cm vs > 2cm	0,7% vs 8,2 %	P< 0,001
Aspirin : Yes / No	0,5% vs 0,2%	NS

The rate of complications is increasing with the size of the polyp.

* *Tendency for these factors*

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ESGE Recommendations polypectomy under aspirin

- **It is recommended that aspirin is not discontinued irrespective of polyp size (grade B)**

Bleeding risk of Polypectomy under Clopidogrel

	Group A (on clopidogrel) (n = 142)	Group B (not on clopidogrel) (n = 1243)
Overall PPB	8 (5.6%)*	38 (3.0%)*
Immediate PPB (intraprocedural)	3 (2.1%)	26 (2.1%)
Delayed PPB (postprocedural)	5 (3.5%)	12 (1%)
Significant PPB† (all delayed)	3 (2.1%)	5 (0.4%)

- Overall post-polypectomy bleeding (PPB) rate is not statisticaly different but delayed PPB is threefold higher.
- Risk factors includes the concomitant use of aspirin and clopidogrel
- In patients under one APA , clopidogrel could be replaced by aspirin for the time of polypectomy

  - *Singh GIE 2010;71:998-1005*

ESGE Recommendations polypectomy under clopidogrel

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- Clopidogrel must be withdrawn if polyp > 1 cm have to be resected (Grade C)
- When polyps must be resected in patients which cannot discontinue clopidogrel, preventive measures should be readily available.(grade B)
- For large polyps, biopsy sampling with deferral of polypectomy should be considered (Grade D)

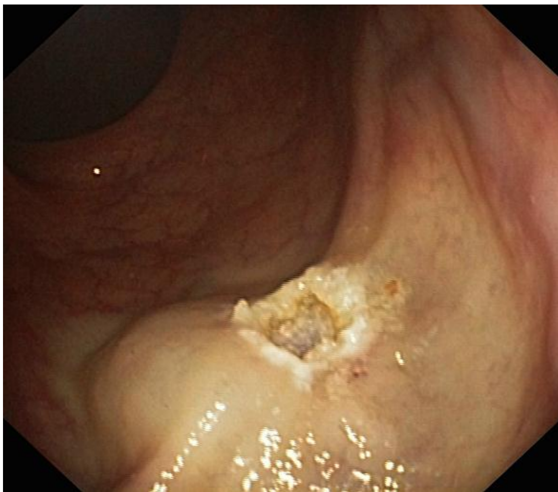
** We have no data for endoscopic procedures under new APA , prasugrel or ticagrelor, which are more potent than clopidogrel.*

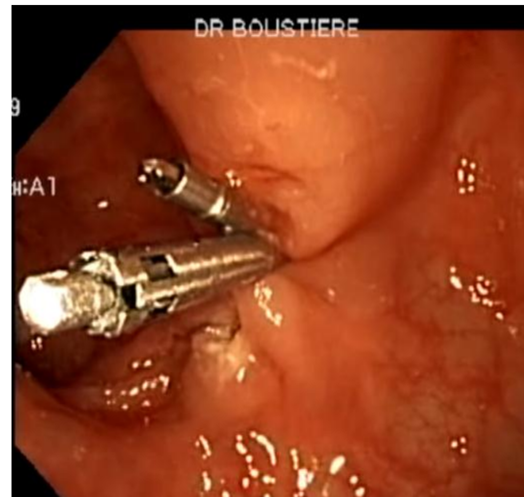
Efficacy of endoscopic measures to prevent post-polypectomy bleeding

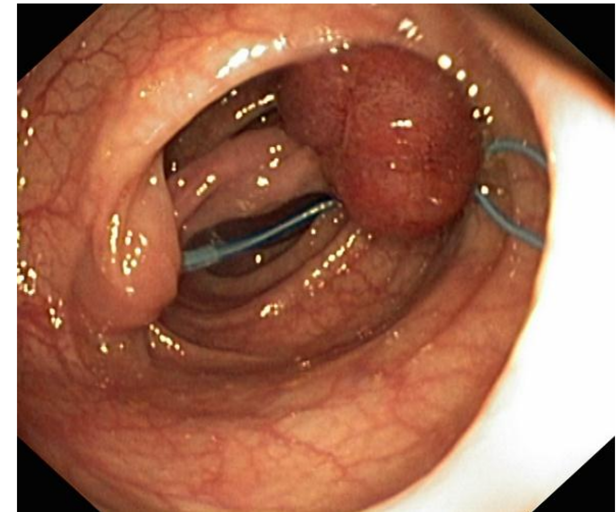
Randomized control trials of endoscopic interventions (polyp > 1cm)				
Studies	**N patients**	**Methods compared**	**Bleeding incidence**	P value
Dobrowolski 2004	69	Adrenaline vs no intervention	2% vs 16 %	<0.05
Kouklakis 2009	64	Detachable loop + clip vs adrenaline	3.1% vs12.5%	0.02
Paspatis 2006	159	Adrenaline + detachable loop vs adrenaline	2.3% vs 10.6%	0.02
Lee	475	Argon plasma coag vs no intervention	9.8% vs 9.5 %	ns

post-polypectomy bleeding under APA : preventive measures are usefull

✓ For polyps > 1cm,
- adrenaline injection is always better than nothing
- clips or detachable loop should be used according to the shape of polyps and the skill of endoscopic teams.







Take home messages

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- ✓ We need to assess the thrombotic risk of patients with cardiologist advice if APA must be discontinued
- ✓ We should always confirm the indication of a colonoscopy and give the patient a complete information
- ✓ Most of endoscopic procedures such as colonoscopy with polypectomy can be performed under aspirin without significantly increasing the rate of bleeding complications.
- ✓ We must use all disposable endoscopic procedures, adapted to the size and shape of polyps to prevent post-polypectomy bleeding.
- ✓ In risky situations, we have to anticipate complications and to be prepared to deal with them if they occur.