ANTITHROMBOTIC MANAGEMENT PRE AND POST ENDOSCOPY

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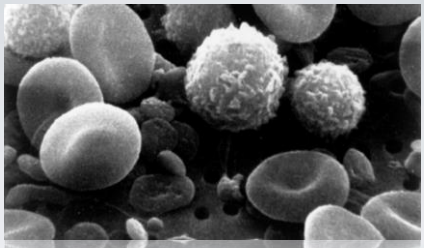
- None

Learning Objectives

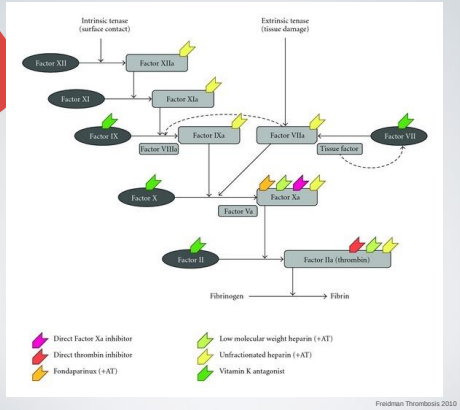
- Review anticoagulants and antiplatelets
- Review management of antithrombotics in the setting of elective endoscopy
  - When to stop?
  - When to restart?
- Management of GI bleeding in the presence of novel antithrombotic agents



ANTITHROMBOTIC REVIEW

Overview of Antithrombotics

- Anticoagulants
  - Warfarin (Coumadin)
  - Unfract. heparin
  - Low-molecular weight heparin
  - Fondaparinux
  - Dabigatran (Pradaxa)
  - Rivaroxaban (Xarelto)
  - Apixaban (Eliquis)
  - Edoxaban (Savaysa)
- Antiplatelets
  - ASA (Aspirin)
  - ASA and dypyridamole (Aggrenox)
  - Clopidogrel (Plavix)
  - Ticlopidine (Ticlid)
  - Prasugrel (Effient)
  - Ticagrelor (Brilinta)



Warfarin

- Advantages:
  - Wide range of approved indications: DVT/PE, AF, mechanical heart valves, Low EF
  - Reversible with Vit K, FFP, Prothrombin complex concentrates (PCC)
- Disadvantages:
  - Monitoring of PT required
  - Levels are affected by dietary factors and drugs as warfarin is metabolized by cypP450
  - Narrow therapeutic window
  - Slow onset and offset

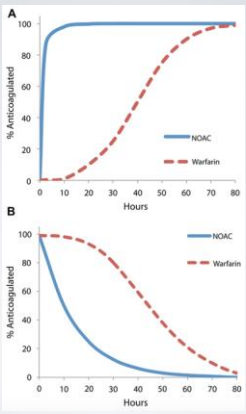
New Oral Anticoagulants

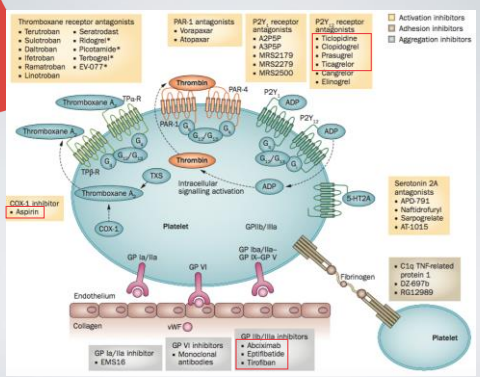
- Advantages:
  - Stable anticoagulation levels
  - Rapid onset, relatively rapid offset
- Disadvantages:
  - Reversal not uniformly possible
  - Anticoagulant effect cannot be quantified using routine coagulation tests
  - $t_{1/2}$ may be affected by renal function
- Agents:
  - Dabigatran (Pradaxa)
  - Rivaroxaban (Xarelto)
  - Apixaban (Eliquis)
  - Edoxaban (Savaysa)

Anticoagulant Pharmacokinetics

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Thrombin	Fxa	Fxa	Fxa
Half-life*	13 h +	5 h +	7 h +	9 h +
Dosing	110–150 mg BID	10-30 mg OD	2.5-5 mg BID	15-30 mg OD
Peak plasma conc.	0.5-2 h	2-4 h	3-4 h	1-3 h
Plasma protein binding**	34-35%	92-95%	87%	40-59%
Renal elimination	80%	33%	27%	35%
Liver metabolism	-	+	+	-

* Dependent on renal clearance
** High protein binding limits dialysability





Glycoprotein IIb/IIIa Inhibitors

- Aggregation inhibitors
- Advantages:
  - Very short therapeutic effect
- Disadvantages:
  - IV only
- Agents:
  - Abciximab (Reopro)
  - Eptifibatide (Integrilin)
  - Tirofiban (Aggrastat)

$P2Y_{12}$ Receptor antagonists

- Activation inhibitors
- Advantages:
  - Reversible platelet inhibition
- Disadvantage:
  - Long therapeutic effect
- Agents:
  - Clopidogrel (Plavix)
  - Ticlopidine (Ticlid)
  - Prasugrel (Effient)
  - Ticagrelor (Brilinta)

Antiplatelet Pharmacokinetics

Agent	Half-life	Reversibility	Time to maximal platelet inhibition
Aspirin	3 hrs	Irreversible	-
Aspirin/dypyridamole (Aggrenox)	13 hrs*	Irreversible	7 d
Clopidogrel (Plavix)	0.5 hrs	Irreversible	3-5 d
Prasugrel (Effient)	7 hrs	Irreversible	4 hr
Ticagrelor (Brilinta)	9 hrs	Reversible	4 hr

* High protein binding

Adapted from Baron T, NEJM 2013

PERI-ENDOSCOPY MANAGEMENT

Procedural Risk Assessment

Low Risk	High Risk
Diagnostic EGD, colonoscopy, flexible sigmoidoscopy (including biopsy)	Polypectomy
Diagnostic balloon-assisted enteroscopy	Therapeutic balloon-assisted enteroscopy
ERCP without sphincterotomy	Sphincterotomy
EUS without FNA	EUS with FNA
Enteral stent deployment (without dilation)	Pneumatic or bougie dilation
Capsule endoscopy	PEG placement
	Hemostasis
	Tumor ablation
	Variceal eradication (EBL, glue)

ASGE GIE 2009

Thrombosis Risk Assessment

Low Risk	Moderate Risk	High Risk
AF CHADS 0-2	AF CHADS 3-4	AF CHADS 5-6
Bioprosthetic valve with no RF for stroke	Bileaflet aortic valve with RF for stroke	Mechanic aortic valve or any mitral valve prosthesis
Previous VTE >12 m with no other risk factors	Previous VTE 3-12 m	Previous VTE <3 m; Cancer-associated VTE
	Non-severe thrombophilia*	Severe thrombophilia*
		CVA in prev 6 m
		Recent PCI**

* Non-severe = Heterozygous factor V Leiden or prothrombin gene mutation;
Severe = deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities
** 4–6 weeks for bare metal stents, 6–12 months for drug-eluting stents

Chest 2012
ASGE GIE 2009

Other Considerations

- What are the consequences of thrombosis?
  - E.g. stroke or in-stent thrombosis vs provoked upper extremity DVT
- Can the patient withstand a GI bleed?
  - Critically ill
  - Red cell alloimmunization; JW
- How difficult will it be to treat a GI bleed?
  - Novel anticoagulants
  - Therapeutic DBE/SBE
- Can the procedure be postponed?
  - Duration of anticoagulation

Other Considerations

- Is bridging effective?
  - Bruise Control trial, pacemaker and defibrillator surgery, patients at moderate or high thrombotic risk, randomly assigned to bridging with heparin compared with continuation of warfarin
    - Clinically significant device pocket hematoma in 54/338 (16%) of patients with bridging compared with 12/343 (3.5%) in patients who continued warfarin (p<0.001)
- Are there contraindications to LMWH?
  - Renal impairment

Birnie NEJM 2013

Antithrombotic Endoscopic Management Approach

		PROCEDURAL RISK	
		Low	High
THROMBOSIS RISK	Low	May continue	Stop
	High*	Continue	Stop, consider shorter interval, consider bridging

* Or individuals at moderate risk with multiple risk factors for thrombosis

Warfarin: High Risk[2]

Pre-operative management for patients at **high thrombotic risk**

Day -5	Day -4/-3	Day -2	Day -1	Surgery
Last dose of warfarin	Omit warfarin	Check INR: -If greater than 2 give 1 mg vit K orally and recheck day -1 - If 1.5 – 2.0 give1 mg oral vit K and recheck day -1. Start on dalteparin 100 U.kg^{-1} twice daily - If equal or less than 1.5 start on dalteparin 100 U.kg^{-1} twice daily	Recheck INR if greater than 1.5 on day -2 and give 1 mg vit K if greater than 1.5 Last dose of 100 U.kg^{-1} dalteparin in the morning (24 hours before surgery)	Check INR if greater than 1.5 on day -1

Postoperative warfarin management for patients at **high thrombotic risk**

Surgery	D +1	D+2	D+3	D+4	D+5	D + 6
Prophylactic dalteparin once a day by weight start 6 – 8 hrs post op	Warfarin at usual dose Continue prophylactic dalteparin		Warfarin at usual dose. Increase to twice daily prophylactic dalteparin		Warfarin at usual dose. Increase dalteparin to 100 U.kg^{-1} twice daily. Continue until INR is greater than 2.0	

Voen Anes 2015

Novel Anticoagulants: High Risk[2]

- No consensus
- Bridging associated with much higher risk of peri-procedural bleeding
- Half-life based approach:
  - Minor surgery — 2-3 $t_{1/2}$
  - Major surgery — 4-5 $t_{1/2}$
  - Use the upper limit of $t_{1/2}$ to calculate time off without bridging

Veen Anes 2015

Novel Anticoagulants: When to restart

- Depends on procedural risk of bleeding and risk of thrombosis
  - Low risk procedure — 24 hrs
  - High risk procedure — >48-72 hrs
  - Sphincterotomy — 3-5 d
  - Large sessile polypectomy — increased risk for up to 14 d

Novel Anticoagulants: Practical considerations

- Consider biliary stent without sphincterotomy for patient on a NOAC who require urgent ERCP (e.g. biliary sepsis)
- If high risk of delayed bleeding (sessile polypectomy), consider LMWH post-procedure rather than novel anticoagulant

Anticoagulant Endoscopic Management Summary

Drug	Half-Life	When to stop	When to resume
Dabigatran	CrCl >80: ~13 h CrCl 50-80: ~15 h CrCl 30-50: ~18 h CrCl <30: ~27 h	CrCl 30-50: Omit Day -3* CrCl >50: Omit Day -2*	Low risk: 24 hr High risk: 48-72 hr***
Riveroxaban	5–19 h**	CrCl 15-30: Omit Day -3 CrCl >30: Omit Day -2	
Apixaban	CrCl >50: ~7–15 h CrCl 30–50: ~17 h	CrCl 15-50: Omit Day -3 CrCl >50: Omit Day -2	

*Extends half-life (CrCl 30-50 ~27 h; CrCl <30 ~37 h final disease)
**Increased in older adults
*** Consider LMWH if procedure carries a high risk of delayed bleeding complications (e.g., variceal banding)

Adapted from Baron et al.NEJM 2013

Antiplatelet Agents: Practical considerations

- Continue ASA even in high risk procedures
- Consider aspirin bridge for Aggrenox given it's with long washout period and combination with ASA
- Exercise caution in discontinuing therapy in patients with PCI — risk of in-stent thrombosis within 1st year caries significant risk of mortality
- Agents that irreversibly inhibit platelet function wear off by a function of the drug half-life and replenishment with newly formed platelets, which occurs at a rate of 10–15% per day, thus full restoration of normal levels takes 7–10 days

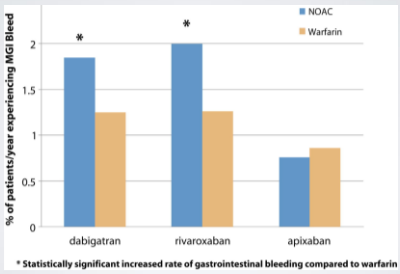
Antiplatelet Endoscopic Management Summary

Agent	When to stop	When to restart	Time to maximal platelet inhibition
Aspirin	Continue	-	-
Aspirin/dypyridamole (Aggrenox)	7-10 d ?start ASA	1 d	7 d
Clopidogrel (Plavix)	5 d	1 d	3-5 d
Prasugrel (Effient)	7 d	1-2 d	4 hr
Ticagrelor (Brilinta)	5 d	1-2 d	4 hr

Adapted from Baron T, NEJM 2013

NOVEL AGENTS AND GI BLEEDING

Novel Anticoagulants and GI Bleeding



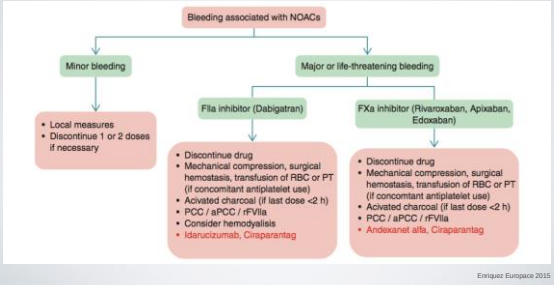
Desai GIE 2013

Anticoagulants: Acute GI Bleeding Management

Drug	PTT	TT	Initial management	Ongoing, life-threatening bleeding
Dabigatran	⇧	⇧	Consider activated charcoal if dose ingested in previous 2 hrs	Hemodialysis *
Riveroxaban	⇧	⇧		**
Apixaban	±	±		**

* Consider activated PCCs, FEIBA, rFVIIa only in extreme emergencies given risk of thrombosis. Unactivated PCC (Octaplex, Beriplex) do not work with Dabigatran
* Consider unactivated PCC (Octaplex, Beriplex). Factor Xa inhibitor reversal agents are undergoing clinical trials)

Anticoagulants: Acute GI Bleeding Algorithm



Acute GI Bleeding: Practical considerations

- Most important info:
  - When was the last dose? What is the PTT?
- Time is your friend (resuscitation will enhance renal drug excretion)
- The hematologist on call is also your friend
- Nevertheless, urgent endoscopy with endoscopic therapy should be performed in the unstable bleeding patient even if the patient is fully anti-coagulated

Antiplatelets: Acute GI Bleeding Management

Drug	Initial management	Ongoing, life-threatening bleeding*
ASA	Continue	Consider platelet transfusion
Plavix	Hold	
Clopidogrel (Plavix)		
Prasugrel (Effient)		
Ticagrelor (Brilinta)		

Further Reading

- Veen and Makris. Anesthesia 2015;Jan;70 Suppl 1:58-67, e21-3.
- Parekh et al. New Anticoagulants and Antiplatelet Agents: A Primer for the Clinical Gastroenterologist. Am J Gastroenterology 2014;109:9-19.
- Abraham and Castillo. Novel Anticoagulants: bleeding risk and management strategies. Current Opinion in Gastroenterology 2013;29:6.
- Baron et al. New Anticoagulant and Antiplatelet agents. CGH 2014;12:187-195.

Peri-Procedural Use of Anti-Thrombotic Agents

Anti-thrombotic agent	Recommended interval between last dose and procedure*	Recommended interval between therapeutic intervention and next dose*
Anticoagulant agent		
Warfarin (Coumadin)	5 d	<24 hr
Unfractionated heparin	4 hr	48 hr
Low-molecular weight heparin	24 hr	48 hr
Fondaparinux	48 hr	
Dabigatran (Pradaxa)	3-5 d GFR ≥50 ml/min, 7 d GFR <50	2-7 d
Rivaroxaban (Xarelto)	3 d GFR ≥50 ml/min, 5 d GFR 30-49 ml/min, 7 d GFR <30	2-7 d
Apixaban (Eliquis)	2 d GFR ≥50 ml/min, 3 d GFR 30-49 ml/min, 5 days GFR <30	2-7 d
Antiplatelet agent		
ASA (Aspirin)	Continue	N/A
ASA/dipyridamole (Aggrenox)	7-10 d - consider ASA bridge	1 d
Clopidogrel (Plavix)	5 d	1 d
Ticlopidine (Ticlid)	10-14 d	
Prasugrel (Effient)	7 d	1-2 d
Ticagrelor (Brilinta)	5 d	1-2 d

*GFR creatinine clearance in mL/min. Decision must be individualized, based on risks of thrombosis and bleeding and on discussion with prescribing physician of anti-thrombotic agent.

Questions