Anticoagulants: Newer Drugs, Mechanisms, and Perioperative Updates

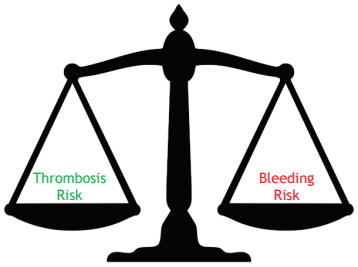
Megan Albertz, MD
Pediatric Cardiac Anesthesiologist, Children's Hospital Colorado
Assistant Professor, University of Colorado

Learning Objectives

- Review anticoagulation medications with an emphasis on relatively new direct oral anticoagulants
- Review the mechanism of action of anticoagulant medications
- Explain the impact on perioperative anesthetic management

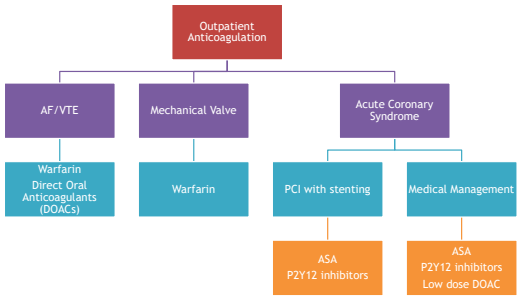
Disclosures

- None

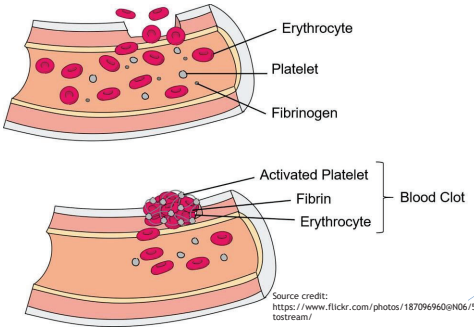


Most Common Indications

- Atrial fibrillation
  - In the US alone, approximately 3-5 million people suffer from AF
  - Approx.. 250,000 patients annually in the US require anticoagulation therapy cessation in order to be considered for surgery
- Prosthetic heart valve
- Recent thromboembolism
- Acute Coronary Syndrome

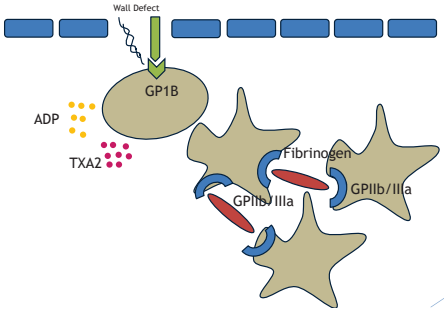


Blood Clot Formation

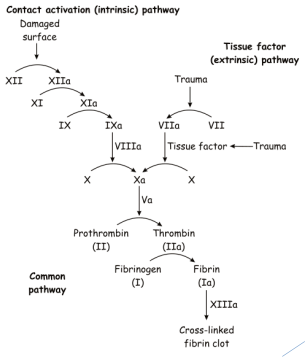


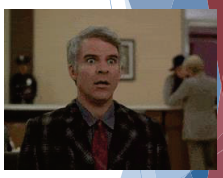
Source credit: https://www.flickr.com/photos/187096960@N06/51173380988/in/photostream/

Primary Hemostasis (Platelet Activation and Aggregation)



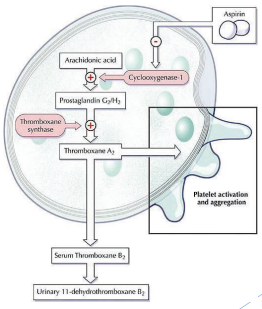
Secondary Hemostasis (Coagulation Cascade)





Aspirin

- MOA: decreases platelet aggregation by irreversibly inhibiting cyclooxygenase (COX) 1 and 2 enzymes
- Duration: half-life 3-6 hours, however lasts 8-9 days due to irreversible action



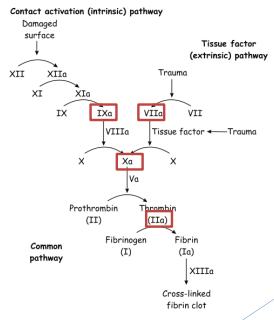
Source credit: https://commons.wikimedia.org/wiki/File:Antiplatelet_effect_aspirin.jpg

P2Y12 Inhibitors

- Thienopyridines (Clopidogrel and Prasugrel)
  - MOA: inhibitors of adenosine diphosphate (ADP) receptor - also called P2Y12 receptor in platelets
  - Prodrugs which metabolites irreversibly affect the platelet function in a time- and dose-dependent fashion
  - Recommended to interrupt these drugs 5-7 days before non-cardiac elective surgery
- Non-thienopyridines (Ticagrelor and Cangrelor)
  - Ticagrelor - reversible, non-competitive ATP analog that binds to a G-protein in the P2Y12 receptor preventing its activation and signaling
  - Cangrelor - direct, reversible inhibitor of P2Y12
    - Intravenous drug

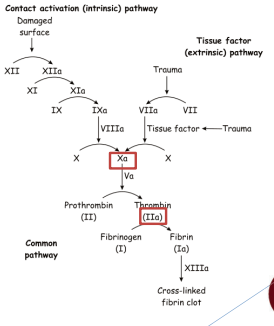
Vitamin K Antagonists (Warfarin)

- Available for more than 50 years
- Major Indications: mechanical heart valves and antiphospholipid syndrome
- Therapeutic window is narrow and dosing is affected by many factors
- MOA: Block the function of vitamin K epoxide reductase complex in the liver



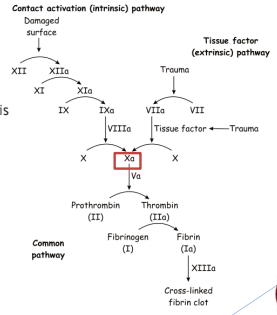
Heparin

- Isolated from porcine or bovine intestines
- MOA: bind to antithrombin receptor to inactivate factors II and Xa
- Risks: Heparin-induced thrombocytopenia
- Monitoring aPTT, anti-Xa



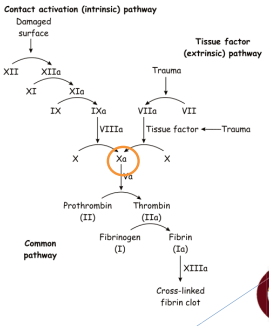
Low Molecular Weight Heparin (LMWH)

- Small fragment of the larger mucopolysaccharide heparin
- Commonly used for VTE prophylaxis
- Longer half-life and dosing can be less frequent



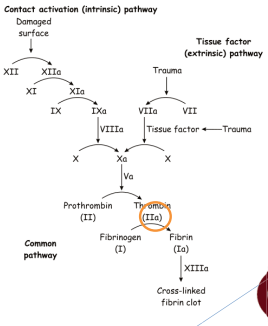
Direct Oral Anticoagulants (DOACs)

- Direct Inhibitors of Factor Xa (Rivaro**xaban**,api**xaban**, endo**xaban**)
  - MOA: bind to the active site of factor Xa inactivating it
  - Short half-life and rapid onset
  - Lower risk of bleeding compared to vitamin K antagonists
  - Pharmacokinetic properties of each DOAC vary according to renal and liver function of the patient



DOACs (cont)

- Direct inhibitors of thrombin (dabigatran)
- First approved in 2010
  - MOA: direct inhibition of thrombin preventing conversion of fibrinogen to fibrin and thus clot formation
  - Half-life is extremely affected by renal function



DOACs and CKD

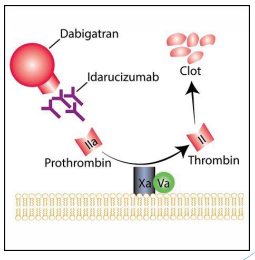
- All are excreted by the kidney to some degree
  - Dabigatran 80-85%
  - Edoxapan - 35 percent
  - Rivaroxaban 35 percent
  - Apixaban - 25 percent
- Concerns over patients with severe CKD in the outpatient setting
- Probably fine in patients with mild - moderate CKD

Advantages of DOACs

- Lower bleeding risk largely decrease in fatal intracranial hemorrhage (PMID 26356595)
- Less laboratory monitoring

Idarucizumab

- Approved in 2015
- Humanized monoclonal antibody binds dabigatran with high affinity removing it from circulation
- Two vials of 2.5mg that can be rapidly infused in 5-10min



Thebloodproject.com

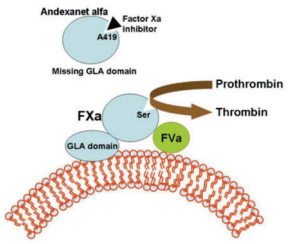
RE-VERSE AD Study (Reversal Effects of Idarucizumab on Active Dabigatran)

- 503 patients treated with idarucizumab to reverse the effect of dabigatran in the setting of urgent procedure (202 patients) or bleeding (301 patients)
- In patients requiring procedure hemostasis was judged to be normal in 93% of patients
  - None were noted to have severely abnormal bleeding
- In patients presenting with bleeding
  - 68% had documented cessation of bleeding within 24 hours
  - Median time to hemostasis was 2.5 hours

Pollack *et al. N Engl J Med.* 2017.

Andexanet Alfa

- Approved in 2018 for the reversal of rivaroxaban and apixaban
- MOA: Recombinant factor Xa acts as a decoy molecule for Xa inhibitors
- Administration depends on dose and time from last dose



Sartori *et al. J Throm Thrombolysis.* 2018.

ANNEXA-4 Study

- Used to treat major bleeding in 352 patients
  - Mean age 77
  - Receiving factor Xa inhibitor for AF or VTE
  - Hemostasis was judged to be excellent in 69% of patients and good in 13% (total 82%)
  - Reduction in anti-factor Xa levels was 92% for apixaban and rivaroxaban
    - No strong correction between anti-factor Xa activity reduction and achievement of hemostasis as determined by blinded adjudicators using pre-specified criteria
  - Adverse events included thromboses (stroke, MI, DVT, PE)
    - 10% of patients within 30 days of follow-up
    - Only 3% were within 5 days of receiving the medication

Connolly *et al. N Engl J Med.* 2019.

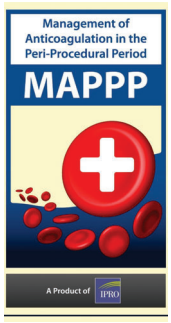
Nonspecific Reversal Agents

- Prothrombin complex concentrates
- Unactivated PCCs
  - 4 factor PCC (Kcentra)
  - 25-50 U/kg or fixed dose of 1500 to 2000units although optimal dosing is unclear)
- Activated PCCs (FEIBA)
  - Contain at least one factor in the activated form (Factor VII)
  - Insufficient evidence comparing 4 factor PCC compared with andexanet

Periprocedural Management

- 1. Estimate the bleeding risk
- 2. Estimate the thromboembolic risk
- 3. Determine the timing of anticoagulation interruption
- 4. Determine whether to use bridging anticoagulation

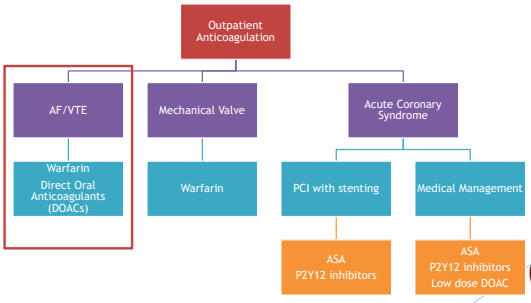
Sample Cognitive Aids



App available
Mappp.ipro.org

Additional Aids:
Thrombosiscanada.ca
Anticoagulationtoolkit.org

Estimating Risks for AF/VTE



Atrial Fibrillation

Letter	Risk factor	Score
C	Congestive heart failure/LV dysfunction	1
H	Hypertension	1
A_2	Age ≥75	2
D	Diabetes mellitus	1
S_2	Stroke/TIA/thrombo-embolism	2
V	Vascular disease*	1
A	Age 65–74	1
S	Sex category (i.e., female sex)	1
	Maximum score	9

Thrombotic Risk

- Low
  - Score < or equal to 4 and no prior stroke, TIA or systemic embolism
  - Risk of recurrent stroke < 5% at 1 year
  - May stop anticoagulation at appropriate interval and resume when hemostasis is adequate
- Moderate
  - Score 5-6 or prior history of ischemic stroke, TIA or systemic embolism
  - If increased bleeding risk, stop
  - If low risk, consider bridge
- High
  - Score 7-9 or recent (within 3 months) ischemic stroke TIE or SE then bridge

Doherty *et al.* J Am Coll Cardiol. 2017.

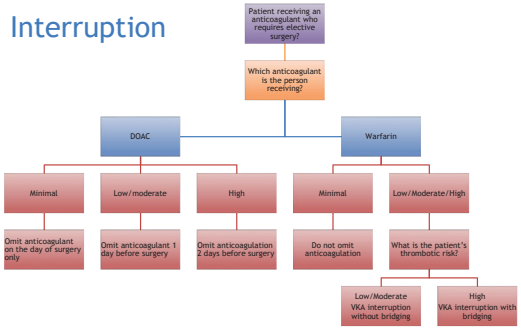
Estimating Procedural Bleeding Risk

- High Risk Procedures
  - Cardiac surgeries
  - Neurosurgical procedures
  - Potential use of neuraxial anesthesia
  - Hip and Knee replacements
- Low Risk Procedures
  - Cholecystectomy
  - Carpal tunnel repair
  - Dental procedures

HAS-BLED Score

	Condition	Points
H	Hypertension	1
A	Abnormal renal or liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (> 65 years)	1
D	Drugs (antiplatelet or NSAIDS) or alcohol (1 point each)	1 or 2

Interruption



Warfarin

- BRIDGE Trial
  - Determined that very few patients with atrial fibrillation required a bridge with LMWH
- Omit for 5 days prior to surgery
  - Does not require preoperative INR
  - Does not increase perioperative bleeding

DOACs

- Shorter prior of interruption due to quick onset and quick offset
- PAUSE study
  - Prospective outcomes in 3007 patients receiving DOAC for AF and undergoing elective procedure
  - Low/moderate risk bleeding – hold one day before and resume done day after (total of 2 day interruption)
  - High risk bleeding – hold DOAC two days prior and resume two days after
  - Recommended for patients taking dabigatran and decreased creatinine clearance to hold one extra day

Shaw *et al*. Blood Adv. 2020

Bridging

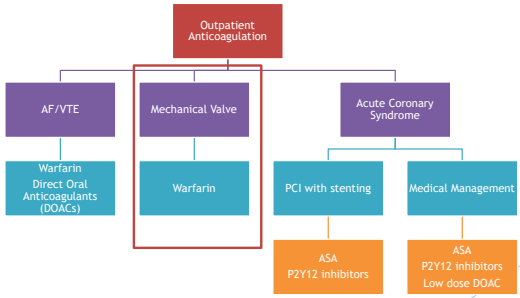
- Intent of bridging is to minimize the time the patient is not anticoagulated and thereby minimizing the risk for perioperative thromboembolism
- May be appropriate during warfarin discontinuation in the following individuals
  - Mechanical valves (exceptions include newer On-X valves or without any additional stroke risk factors)
  - Embolic stroke within the previous three months or very high stroke risk
  - VTE within the previous three months
  - Recent coronary stenting within the previous three months
  - Previous thromboembolism during interruption of chronic anticoagulation

Evidence Against Bridging

- AF
  - 2020 meta-analysis included six randomized trials and 12 cohort studies found that bridging was associated with an increased risk of bleeding with no statistical reduction in thromboembolic risk

Kuo *et al. Clin Cardiol.* 2020

Estimating Risks – Mechanical Valves



Mechanical Heart Valves

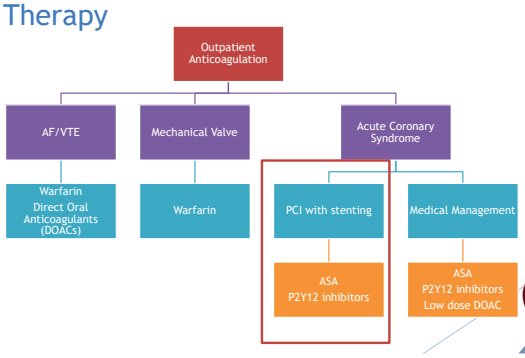
- Minimal-risk procedures (dental cleaning, cataract surgery, minor dermatologic procedures
  - No need to interrupt warfarin
- Non-emergent pacemaker/ICD implant
  - BRUISE CONTROL Trial found increased pocket hematoma in the heparin bridging group
  - INR allowed to be as elevated as 3.5
- Cardiac catheterization
  - Low/moderate risk procedures
    - INR goal lower end of target
  - High risk procedures
    - Hold 4-6 days prior
    - Goal INR < 1.5

Low/Moderate/High Risk Bleeding

- Low/Moderate Thrombosis Risk
  - Current generation mechanical bileaflet aortic valve without additional risk factors for thrombosis can have their VKA interrupted without bridging
  - Stop VKA 3-4 days prior with an INR < 1.5
- High Thromboembolic Risk
  - Mechanical aortic valve plus prior thromboembolism, any mechanical mitral, tricuspid or pulmonary valve
  - Bridging

Otto *et. al. Circulation.* 2021.

Estimating Risks – Dual Antiplatelet Therapy



Surgical Timing After PCI

- Minimum recommended 4-6 weeks after bare-metal stent (BMS) or drug-eluting stent (DES), ideally 6 months
- Increased risk of MI and cardiac death is within the first month after placement
- For procedures with low bleeding risk - anticoagulation does not need to be stopped
- For almost all procedures aspirin may be continued

Medication	Duration Held Before Surgery
Clopidogrel	5 days
Prasugrel	7 days
Ticagrelor	3-5 days

Special Considerations – Urgent Emergent Invasive Procedures

- Warfarin
  - Semi-urgent procedure - Vitamin K
  - Urgent/Emergent - FFP, PCCs
- Dabigatran
  - Idarucizumab
- Direct Xa Inhibitors
  - Andexanet alpha
  - PCCs

Special Considerations – Neuraxial Anesthesia

Anticoagulant	Before	During	After
Heparin SQ or IV	5000u SQ Q8 or 12H: 4-6H 7500u SQ Q8 or 12H: 12H IV infusion: 4-6 hours Verify normal aPTT	May be given, preferred over alternatives	1 hour
Enoxaparin (prophylaxis)	More than 12 hours	Contraindicated	4 hours
Enoxaparin (therapeutic)	More than 24 hours	Contraindicated	4 hours
Apixaban, Rivaroxaban, Betrixaban, Endoxaban	3 days	Contraindicated	6 hours
Dabigatran	CrCl 30-49ml/min: 5 days CrCl 50-79ml/min: 4 days CrCl > 80ml/min: 3 days	Contraindicated	6 hours
Warfarin	4-5 days, verify normal INR	Check INR daily	Remove when INR < 1.5
Clopidogrel	5-7 days	Contraindicated	Without LD: immediate If LD: 6 hours

Pediatrics – Congenital Heart Disease

- Rivaroxaban is the most common as first approved for children for VTE and Fontan thromboprevention
- All 3 anti-Xa inhibitors have shown benefit in this patient population
- Kawasaki disease
  - Risk of coronary artery aneurysms and thrombotic events
  - Patients will present on a combination of medications: including clopidogrel, warfarin, ASA and/or DOACs

Questions/Thank you