Anticoagulation Reversal

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Disclosure

- No relevant commercial relationships to disclose

Objectives:

At the end of this presentation, attendees will be able to:

- Describe the pharmacology of commonly used anticoagulants and how these factors influence reversal
- Match commonly used anticoagulants to their associated reversal agent
- Recall the dosing recommendations for commonly used reversal agents
- Given a patient case, design an appropriate reversal strategy including need and timeline for reversal, agent selection, and dose

Anticoagulation Reversal

General Principles

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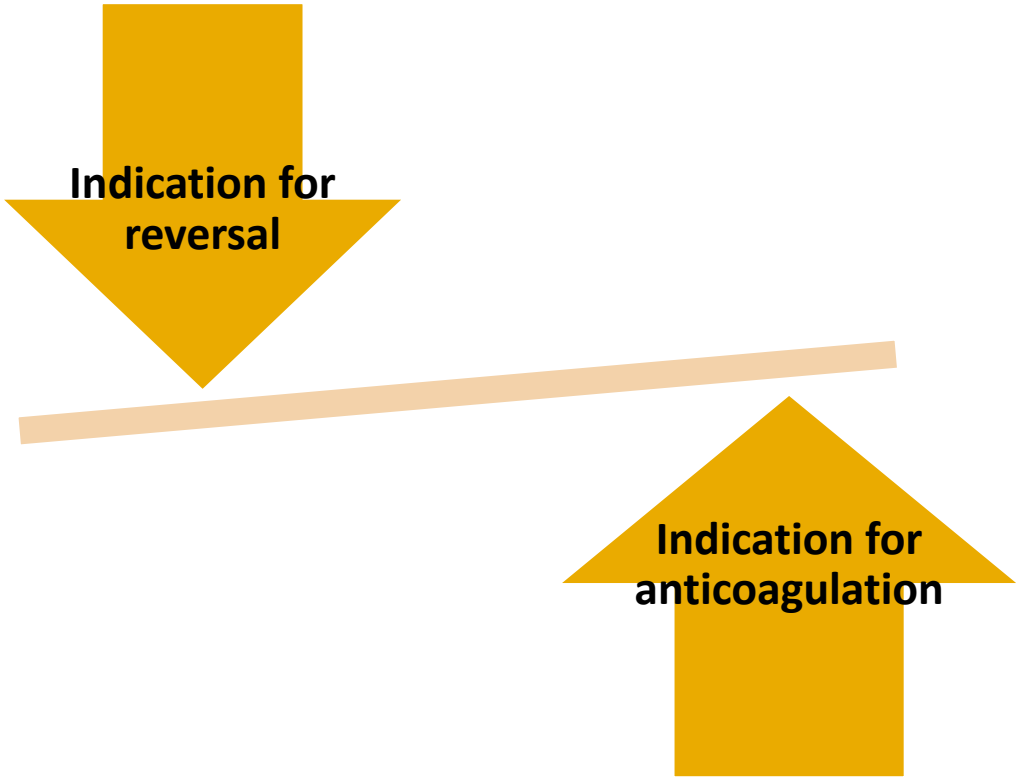
General Principles

- To reverse…or not to reverse…



General Principles

- Consider the indication for anticoagulation
- Consider the indication for reversal
  - Procedural
    - Elective versus urgent or emergent
  - Bleeding
    - Severity
      - Asymptomatic→Symptomatic→Hemorrhagic Shock
    - Location
      - Closed space (intracerebral, joint)
      - Non-compressible site

General Principles

- Pharmacokinetics matters (ADME)
  - Absorption
  - Distribution
  - **Metabolism**
  - Excretion
- Elimination half-life is the most important pharmacokinetic variable related to reversal
  - Half-life = how long it takes for the drug to be metabolized to 50% of the maximum serum concentration
  - By three half lives the remaining drug concentration is 12.5%
  - Five half lives = total elimination

Vitamin K Antagonist (Warfarin) Reversal

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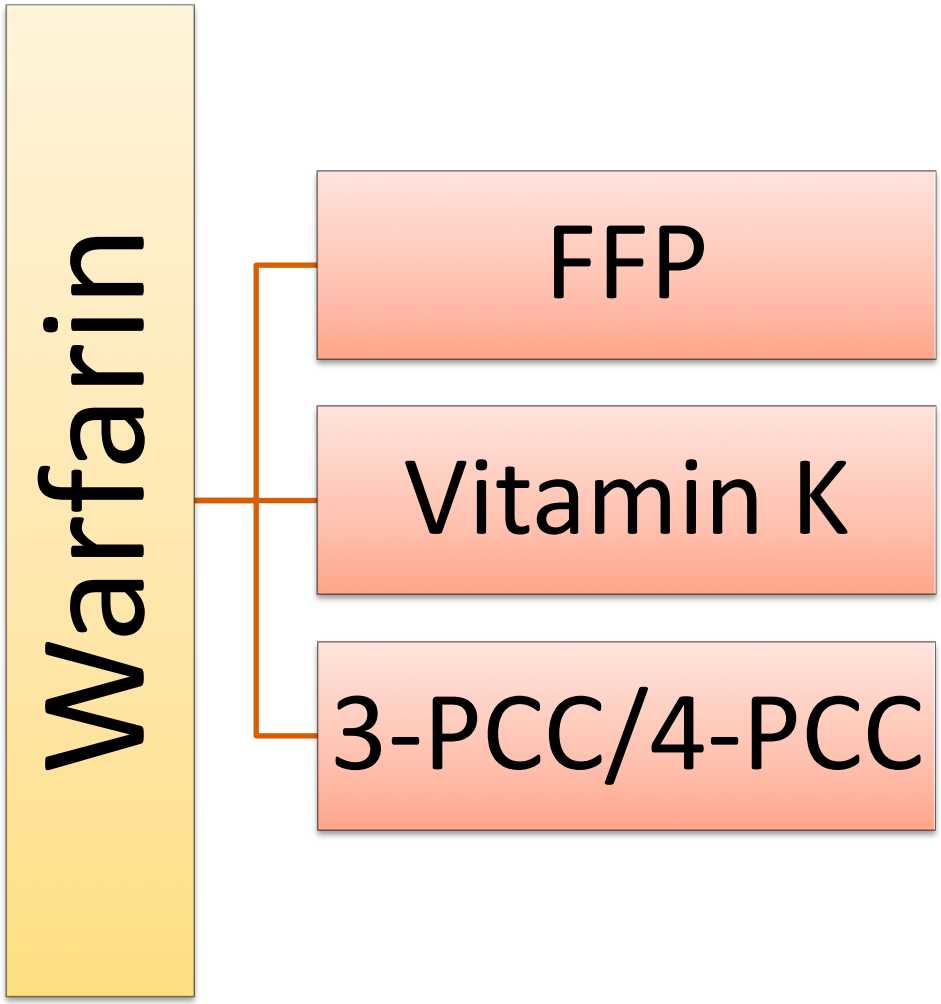
Warfarin pharmacology

Wafarin (Jantoven)	
Mechanism of action	Inhibits hepatic synthesis of vitamin K-dependent clotting factors II, VII, IX, X, and protiens C and S
Absorption	Rapid with onset of anticoagulant effects within 24-72 h and full anticoagulant effects within 5-7 days
Metabolism	Hepatic via CYP2D6
Elimination	Highly variable half-life of 20-60 hours
Laboratory analysis	PT/INR (quantitative)
Perioperative considerations	Hold with or without bridge therapy until INR <1.4, then generally acceptable to proceed

Wafarin. Lexi-Drugs. Lexicomp Wolters Kluwer Health, Inc. Riverwoods IL. Available at http://online.lexi.com. Accessed Aug 2020

Warfarin Reversal



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Tomaselli et al. *J Am Coll* Cardiol. 2020 Aug, 76 (5) 594-622
NCC/SCCM. *Neuro Crit Care*. 2016;24:6

Fresh Frozen Plasma (FFP)

- Only recommended as a 3rd line alternative for reversal in life threatening bleeding
  - 10-15 ml/kg
- Common in various scenarios in clinical practice
- Considerations
  - INR of FFP is 1.4 to 1.7
  - May provide more rapid hemostasis in major bleeding while you wait for the onset of IV Vitamin K
    - No literature to guide dosing
  - No role for FFP if you are giving PCC

Tomaselli et al. *J Am Coll* Cardiol. 2020 Aug, 76 (5) 594-622

Phytonadione (Vitamin K)

- Available as parenteral 10 mg/ml ampule and 5 mg tablets
  - May be compounded into an oral suspension
- IV Vitamin K provides INR reduction within 4 to 6 h
  - Administration as diluted IVPB over 15 to 30 min is recommended to reduce the risk of anaphylaxis
- PO Vitamin K provides INR reduction within 18 to 24 hours
  - Alternative routes are discouraged
    - IM administration is associated with hematoma development
    - SQ absorption is erratic particularly in obese or critically ill

Phytonadione. Lexi-Drugs. Lexicomp Wolters Kluwer Health, Inc. Riverwoods IL. Available at http://online.lexi.com. Accessed Aug 7, 2020

When to use Vitamin K

- Non-bleeding supratherapeutic INR or minor bleeding
  - Oral phytonadione is appropriate
    - Dose of 2 to 5 mg PO x 1, follow INR
- Major but non-life threatening bleeding
  - Intravenous phytonadione is appropriate
    - Dose of 5 to 10 mg IVPB x 1

Tomaselli et al. *J Am Coll C*ardiol. 2020 Aug, 76 (5) 594–622

3-PCC (Profilnine)

- Prothrombin complex concentrate (PCC) that contains
  - Factor II, IX, X
    - Negligible amounts of Factor VII and Protein C and S
- 2nd line option for emergent reversal of warfarin
- Dosing
  - INR 2 to 4: 25 units/kg ideal body weight
  - INR > 4: 50 units/kg ideal body weight
- Administered as IV push
- INR should normalize within 5-15 minutes
- Requires co-administration of Vitamin K for enduring reversal

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3 factor prothrombin complex concentrate (Profilnine). Lexi-Drugs. Lexicomp Wolters Kluwer Health, Inc. Riverwoods IL. Available at http://online.lexi.com. Accessed Aug 7, 2020

4-PCC (Kcentra)

- Prothrombin complex concentrate that contains
  - Factor II, VII, IX, X, Protein C & S
- Agent of choice for emergent reversal of warfarin
  - Dose based on INR, calculated using total body weight
    - INR: 2-4 = 25 units/kg IVPB x 1 (max dose: 2500 units)
    - INR: 4-6 = 35 units/kg IVPB x 1 (max dose: 3500 units)
    - INR: > 6 = 50 units/kg IVPB x 1 (max dose: 5000 units)
  - INR should normalize within 5-15 min after infusion, repeat INR in 15-30 min
- Enduring reversal requires concomitant administration of Vitamin K

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4 factor prothrombin complex concentrate (Kcentra). Lexi-Drugs. Lexicomp Wolte[illegible]luwe[illegible] Health, Inc. Riverwoods IL. Available at http://online.lexi.com. Accessed Aug 7, 2020

Fixed-Dose 4-PCC

- Fixed dose 4-PCC regimens are as effective at normalizing INR as weight/INR based regimens
  - Fixed doses of 1000 units and 1500 units have been studied
- A dose of 4-PCC 1500 units IV x 1 has been shown to effectively reverse warfarin and speed the delivery of reversal agent to the patient
  - The remainder of the weight/INR based dose may be administered if INR normalization was not achieved or if bleeding continues

Tomaselli et al. JACC 2017; 70(24):3042-67

3-PCC versus 4-PCC

- Both agents are effective at decreasing INR
- 4-PCC may be more cost effective
- 4-PCC may be associated with improved mortality
- Differences in thromboembolic events remain unclear

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Mangram et al. J Crit Care 2016;33:[illegible]-256
Voils et al. Thrombosis Res 2015;136:59[illegible]-598
NCC/SCCM. *Neuro Crit Care*. 2016;24:6-46

Direct Oral Anticoagulant (DOAC) Reversal

Apixaban, Rivaroxaban, Dabigatran

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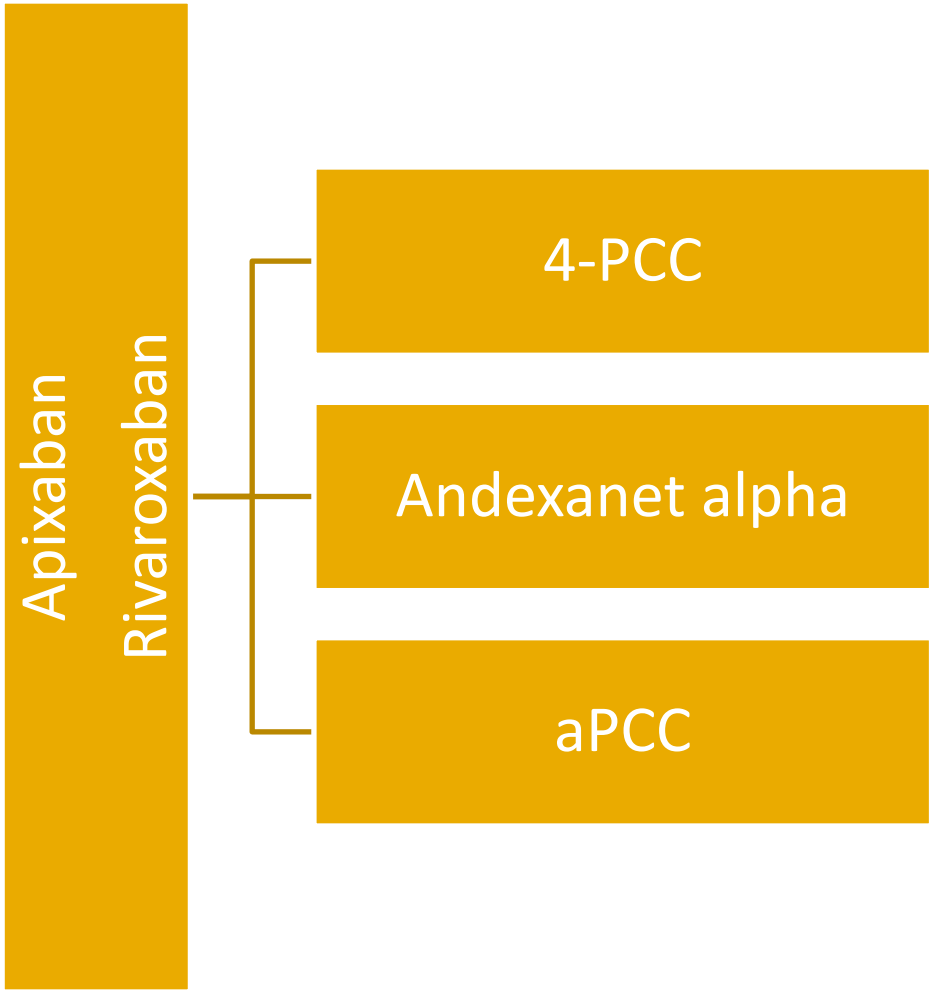
Anti-Xa inhibitor reversal



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NCC/SCCM. *Neuro Crit Care*. 2016;24:6

Anti-Xa Inhibitor Pharmacology

Apixaban (Eliquis)	
Mechanism of action	Inhibits platelet activation and fibrin clot formation by direct, selective and reversible inhibition of both free and clot-bound Factor Xa (inhibits conversion of prothrombin→thrombin)
Absorption	50% bioavailability with onset of full anticoagulant effects within 3-4 hours
Metabolism	Hepatic via CYP3A4, substrate of P-glycoprotein
Elimination	Mean half-life of approximately 12 hours (range 8-15 hours)
Laboratory analysis	PT, aPTT, non-specific Anti-Xa (qualitative), drug specific Anti-Xa (quantitative)
Perioperative considerations	Hold 1 day for low bleeding risk procedure Hold 2 days for high bleeding risk procedure

Apixaban. Lexi-Drugs. Lexicomp Wolters Kluwer Health, Inc. Riverwoods IL. Available at http://online.lexi.com. Accessed Aug 2020
Douketis JD, et al. *JAMA Intern Med*. 2019;179(11):1469-1478

Anti-Xa Inhibitor Pharmacology

Rivaroxaban (Xarelto)	
Mechanism of action	Inhibits platelet activation and fibrin clot formation by direct, selective and reversible inhibition of both free and clot-bound Factor Xa (inhibits conversion of prothrombin→thrombin)
Absorption	Bioavailability 66-100% (increased with food), full anticoagulant effects within 2-4 hours
Metabolism	Hepatic via CYP3A4
Elimination	Half-life of 5-9 hours, increases to 11-13 hours in elderly patients
Laboratory analysis	PT, aPTT, non-specific Anti-Xa (qualitative), drug specific Anti-Xa (quantitative)
Perioperative considerations	Hold 1 day for low bleeding risk procedure Hold 2 days for high bleeding risk procedure

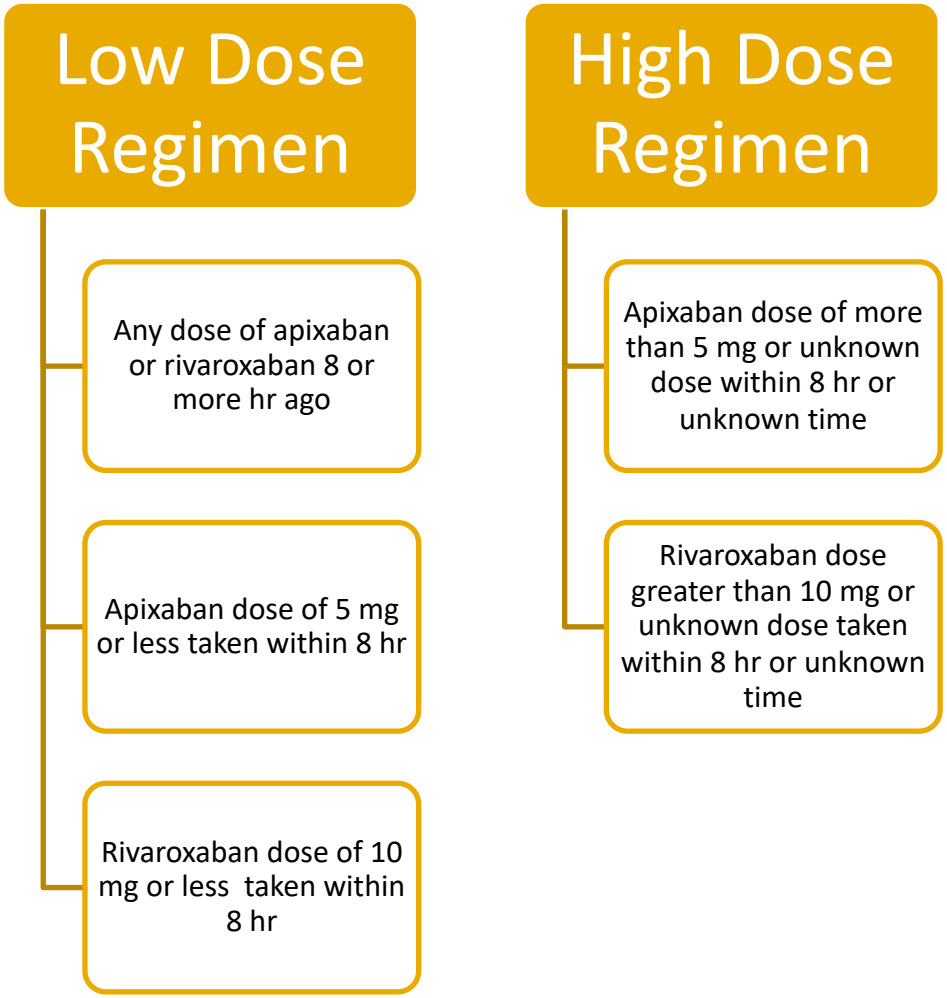
Rivaroxaban. Lexi-Drugs. Lexicomp Wolters Kluwer Health, Inc. Riverwoods IL. Available at http://online.lexi.com. Accessed Aug 2020
Douketis JD, et al. *JAMA Intern Med*. 2019;179(11):1469-1478

Andexanet alpha (Andexxa)

- Relatively new to market Anti-Xa inhibitor (apixaban, rivaroxaban) specific reversal agent
  - Decoy molecule that binds and sequesters apixaban and rivaroxaban
  - Increases thrombin generation through inhibition of Tissue Factor Pathway Inhibitor
    - Rates of thrombosis as high as 18% in approval trials
- Dose based on specific anti-Xa inhibitor taken and time of last dose
  - Low dose = 400 mg IV bolus followed by 4 mg/min infusion for up to 2 hours (total dose 880 mg)
  - High dose = 800 mg IV bolus followed by 8 mg/min infusion for up to 2 hours (total dose = 1760 mg)
- Very short half life may result in rebound anticoagulant (bleeding) effects

Andexanet alpha. Lexi-Drugs. Lexicomp Wolters Kluwer Health, Inc. Riverwoods IL. Available at http://online.lexi.com. Accessed Aug 7, 2020

Andexanet alpha (Andexxa)



Andexanet alpha. Lexi-Drugs. Lexicomp Wolters Kluwer Health, Inc. Riverwoods IL. Available at http://online.lexi.com. Accessed Aug 7, 2020

4-PCC (Kcentra)

- Prothrombin complex concentrate that contains
  - Factor II, VII, IX, X, Protein C & S
- Widely used for anti-Xa reversal prior to the approval of andexanet alpha
- Dose for anti-Xa inhibitor reversal
  - 50 units/kg total body weight IVPB x 1 (max dose: 5000 units)
- No role for vitamin K in anti-Xa inhibitor

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4 factor prothrombin complex concentrate (Kcentra). Lexi-Drugs. Lexicomp Wolte[illegible]luwe[illegible] Health, Inc. Riverwoods IL. Available at http://online.lexi.com. Accessed Aug 7, 2020

Activated PCC (FEIBA)

- FEIBA = Factor VIII inhibitor bypassing activity
- Contains non-activated Factor II, IX and X
- Contains activated Factor VII
- Alternate option for reversal of anti-Xa inhibitors
  - Contraindication to 4-PCC
    - Heparin-induced thrombocytopenia
  - Andexanet alpha or 4-PCC unavailable
- aPCC 50 units/kg ideal body weight IV x 1
- Black Box warning for thromboembolic events

Activated prothrombin complex concentrate (Kcentra). Lexi-Drugs. Lexicomp Wolte[illegible]luwe[illegible] Health, Inc. Riverwoods IL. Available at http://online.lexi.com. Accessed Aug 7, 2020

Andexanet alpha vs 4-PCC

- Controversial FDA approval
- Concerns regarding strict exclusion criteria in ANNEXA-4 and how this may have inflated the reported mortality
- Safety issues
  - Short half life
  - Thrombosis rate
- FDA mandated a head-to-head comparison of andexanet to the standard of care (PCC)
  - Small retrospective comparisons have begun to trickle into the literature
    - Intracerebral hemorrhage
    - Non-intracranial bleeding

Peled, H et al. *Neurocrit Care*. 2020;33:20-24

Patient Case

JW is a 75 yo 88 kg M on warfarin for mechanical mitral valve presents to the ED with refractory epistaxis. Nasal packing placed by ED physician and the patient is admitted to internal medicine service.

BP: 130/66, HR 72 bpm

Hgb: 8.0 gm/dL

INR: 4.23

Design a reversal strategy:

Patient Case

A. Give 4-PCC 3500 units IVBP x 1 and 10 mg IV Vitamin K
B. Give Vitamin K 10 mg IV x 1, no 4PCC
C. Do nothing and observe closely
D. Give Vitamin K 2.5 mg PO x 1

Patient Case

You gave JW 5 mg Vitamin K PO x 1. Two hours later a rapid response is called after JW has a brief loss of consciousness on the toilet and was discovered to have a large volume melena. His BP has dropped to 85/40 with a HR of 115. Repeat Hgb is now 5.8 gm/dL, lactate is 4.4 mmol/L and repeat INR is 2.65

Now what?

Patient Case

A. 4 units of FFP stat

B. 4-PCC 1500 units IVPB x 1 plus Vitamin K 10 mg IV x 1

C. Vitamin K 10 mg PO x 1

D. 4-PCC 2250 unit IVBP x 1 plus Vitamin K 10 mg IV x 1

Direct Thrombin Inhibitor Reversal

Dabigatran

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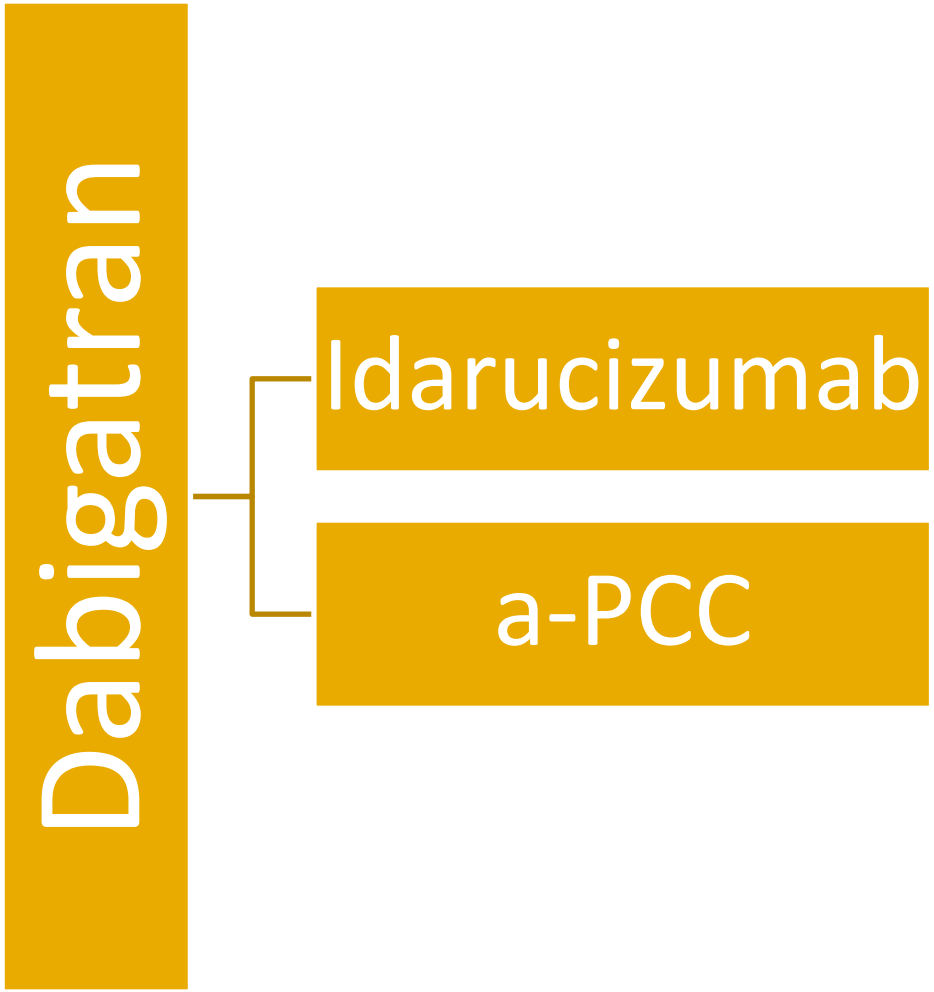
Direct Thrombin Inhibitor Pharmacology

Dabigatran (Pradaxa)	
Mechanism of action	Specific and reversible inhibitor of free and fibrin-bound thrombin. Prevents thrombin mediated effects: platelet aggregation, cleavage of fibrinogen to fibrin, and activation of clotting factors V, VIII, XI, and XIII
Absorption	Prodrug, rapidly absorbed with full anticoagulant effects within 1 hour (2 hours if taken with food)
Metabolism	Hepatic via glucuronidation
Elimination	Half-life of 12-17 hours, increased with renal impairment Severe renal impairment→Half-life = 28 hours
Laboratory analysis	TT, aPTT, PT (qualitative); ECT, dTT (quantitative)
Perioperative considerations	Hold 1 day for low bleeding risk procedure Hold 2 days for high bleeding risk procedure *If CrCl < 50 ml/min double the recommended hold time*

Dabigatran. Lexi-Drugs. Lexicomp Wolters Kluwer Health, Inc. Riverwoods IL. Available at http://online.lexi.com. Accessed Aug 7, 2020
Douketis JD, et al. *JAMA Intern Med*. 2019;179(11):1469-1478

Direct Thrombin Inhibitor Reversal



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Tomaselli et al. *J Am Coll C*ardiol. 2020 Aug, 76 (5) 594-622

NCC/SCCM. *Neuro Crit Care*. 2016;24:6

Idarucizumab (Praxbind)

- Humanized monocolonal antibody fragment (Fab) that binds with very high affinity to dabigatran and its active metabolites
- Idarucizumab is the agent of choice for dabigatran reversal
- Dosing for idarucizumab: 5 g IVPB x 1
  - Supplied as 2.5 g in 50 ml vials
  - Run each vial over 5 min
  - Vials should be infused consecutively, not concurrently
- Need for repeat dosing has been reported
  - Administer another 5 g if hemostasis cannot be achieved

Idarucizumab. Lexi-Drugs. Lexicomp Wolters Kluwer Health, Inc. Riverwoods IL. Available at http://online.lexi.com. Accessed Aug 7, 2020

Activated PCC (FEIBA)

- Review
  - Contains non-activated Factor II, IX and X
  - Contains activated Factor VII
- Alternate option for reversal of dabigatran
  - Icarucizumab unavailable or contraindicated
- aPCC 50 units/kg ideal body weight IV x 1
- Black Box warning for thromboembolic events

Activated prothrombin complex concentrate (Kcentra). Lexi-Drugs. Lexicomp Wolte[illegible]luwe[illegible] Health, Inc. Riverwoods IL. Available at http://online.lexi.com. Accessed Aug 7, 2020

Looking Ahead

- Ciraparantag
  - Small synthetic molecule
  - UNIVERSAL antidote (VKA, FXa, heparin, LMWH, DTI)
  - Still in Phase I development

Antiplatelet Reversal

Aspirin, Clopidogrel, Ticagrelor

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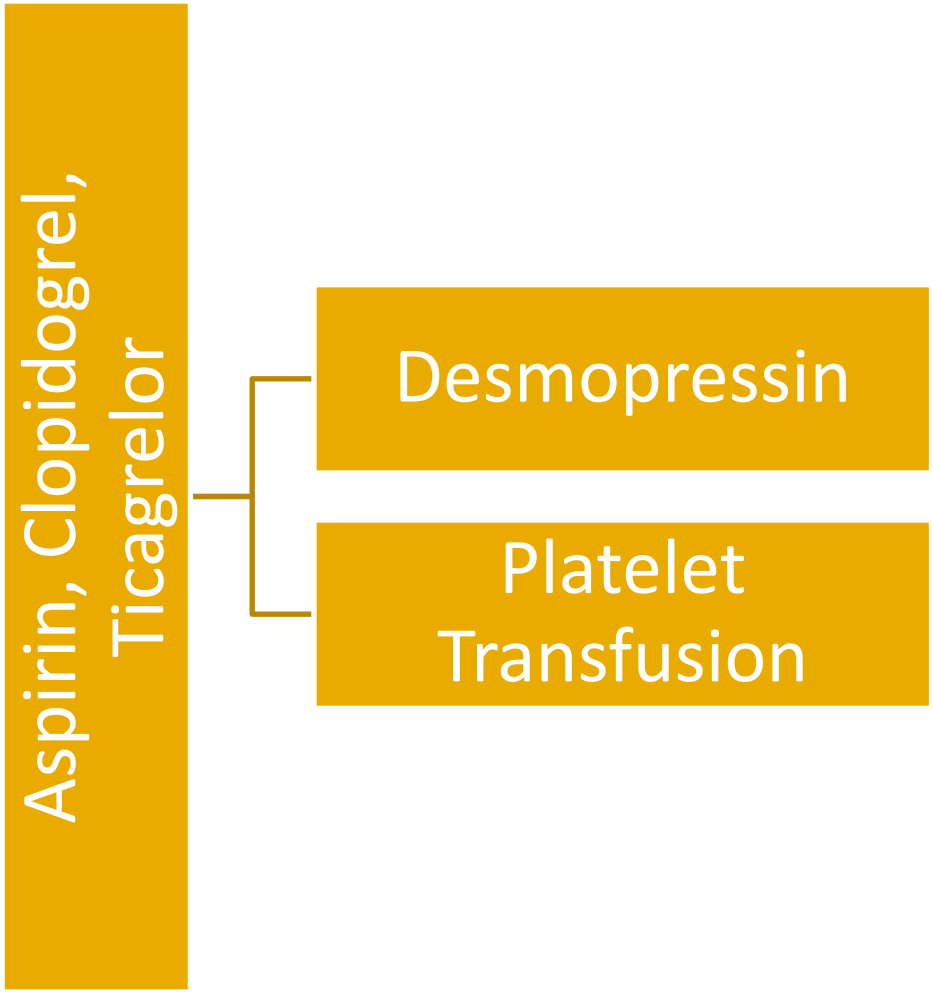
Reversal of Anti-platelet Agents



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Tomaselli et al. *J Am Coll* Cardiol. 2020 Aug, 76 (5) 594-622

NCC/SCCM. *Neuro Crit Care*. 2016;24:6

Antiplatelet Agent Pharmacology

Aspirin	
Mechanism of action	Irreversible inhibition of cyclooxygenase-1 and 2, irreversibly inhibiting formation of thromboxane A_2
Elimination	Parent drug half-life is 15-20 min Active salicylate metabolites half-life is ~ 3 hr
Perioperative considerations	Inhibition of platelet aggregation lasts the lifetime of the platelet, 7-10 days

Aspirin. Lexi-Drugs. Lexicomp Wolters Kluwer Health, Inc. Riverwoods IL. Available at: http://online.lexi.com. Accessed Aug 7, 2020

Antiplatelet Agent Pharmacology

Clopidogrel (Plavix)	
Mechanism of action	Irreversible $P2Y_{12}$ antagonist that reduces platelet aggregation by blocking activation of GPIIb/IIIa receptor complex
Elimination	Parent drug half-life: 6 hours Active metabolite half-life: 30 min
Perioperative considerations	Platelet effects last the lifetime of the platelet, but begin to approach baseline at 5 days after discontinuation
Ticagrelor (Brillinta)	
Mechanism of action	Reversible, noncompetitive $P2Y_{12}$ antagonist that reduces platelet aggregation by blocking activation of GPIIb/IIIa receptor complex
Elimination	Parent drug half-life: 7 hours Active metabolite half-life: 9 hours
Perioperative considerations	Duration of platelet inhibition is affected by serum drug and metabolite concentrations due the reversible inhibition

Clopidogrel (Plavix). Lexi-Drugs. Lexicomp Wolters Kluwer Health, Inc. Riverwoods IL. Available at http://online.lexi.com. Accessed Au 2020

Ticagrelor (Brillinta). Lexi-Drugs. Lexicomp Wolters Kluwer Health, Inc. Riverwoods IL. Available at http://online.lexi.com. Accessed Aug 7, 2020

Desmopressin (DDAVP)

- Synthetic analogue of the antidiuretic hormone arginine vasopressin
  - Increases von Willebrand Factor
  - Increases Factor VIII
  - Increases platelet adhesion to vessel walls
- Desmopressin (DDAVP) 0.3 mcg/kg IVPB x 1, consider dosing on IBW, no need to exceed 30 mcg total dose

Vasopressin. Lexi-Drugs. Lexicomp Wolters Kluwer Health, Inc. Riverwoods IL. Available at: http://online.lexi.com. Accessed Aug 7, 2020

Platelet Transfusion

- Can effectively reverse the effects of aspirin by restoring the ability to synthesize thromboxane A_2
- Transfused platelets may be inhibited by remaining medication in the bloodstream
  - Delaying or repeating platelet transfusion for 12-24 hr in patients on clopidogrel and 24-48 hr for patients on ticagrelor will result in greater restoration of platelet function

Zafar MU, et al. *Circ Cardiovasc interv* 2017 Sep;10(9) [illegible]0028
Theile T, et al. J Thromb Haemost 2012;10:968-71
NCC/SCCM. *Neuro Crit Care*. 2016;24:6-46

Patient Case

VM is a 67 yo 77 kg F who takes apixaban for atrial fibrillation and aspirin 81 mg and clopidogrel for 3 vessel CABG 5 weeks ago. She presents to the ED as a trauma activation after an unhelmeted bicycle crash into a tree trying to avoid a stray kitten. She has an open tib/fib fracture and has a GCS of 12 (E4, V3, M5). Head CT reveals SDH/SAH with 8 mm midline shift.

Design a reversal strategy

Patient Case

- Aspirin
  - Transfuse 1 unit platelets now
- Clopidogrel
  - Desmopressin 23 mcg IV x 1
  - Consider additional unit of platelets if repeat CT scan shows any worsening
- Apixaban
  - Andexanet or 4-PCC or FEIBA
    - Andexanet: high dose regimen 800 mg IV x1 followed by 8 mg/min x 2 hr
    - 4PCC: 50 unit/kg (4000 unit rounded dose) IVPB x 1
    - FEIBA: 50 unit/kg ideal body weight IVPB x 1

Cost comparison

Reversal agent	Cost per unit	Cost per treatment
Vitamin K	10 mg = $42	$42
4PCC	500 unit = $1000	Max dose: $10,000
Idarucizumab	5 gm = $50	$50
Andexanet alpha	200 mg = $5500	High dose: $48,400 Low dose: $24,200
DDAVP	20 mcg = $220	$220
FEIBA	500 unit = $755	$5285 (70-kg patient)

Summary

- Bleeding complications are frequently encountered in patients on anticoagulant and antiplatelet agents
- Reversal strategy selection depends on severity of the bleeding and/or need for invasive procedure and the indication for anticoagulation
- Antidotes such as 4PCC (Kcentra), idarucizumab (Praxbind), and andexanet alpha (Andexxa) should be reserved for life-threatening situations
- Know what agents are available at your institution
- Get to know your pharmacist

Resources

- Tomaselli GF, et al. 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants. *J Am Coll C*ardiol. 2020 Aug, 76 (5) 594-622. DOI: 10.1016/j.jacc.2020.04.053
- NCC/SCCM Guidelines for the reversal of antithrombotics in intracranial hemorrhage. *Neuro Crit Care*. 2016;24:6-46. DOI 10.1007/s12028-015-0222-x

Questions

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