Reversal Options for Direct Oral Anticoagulants

VSSTF Meeting January 24, 2020

Tammie Conway, PharmD, BCPS

Christopher DeMella, PharmD, BCPS

Conflicts of Interest

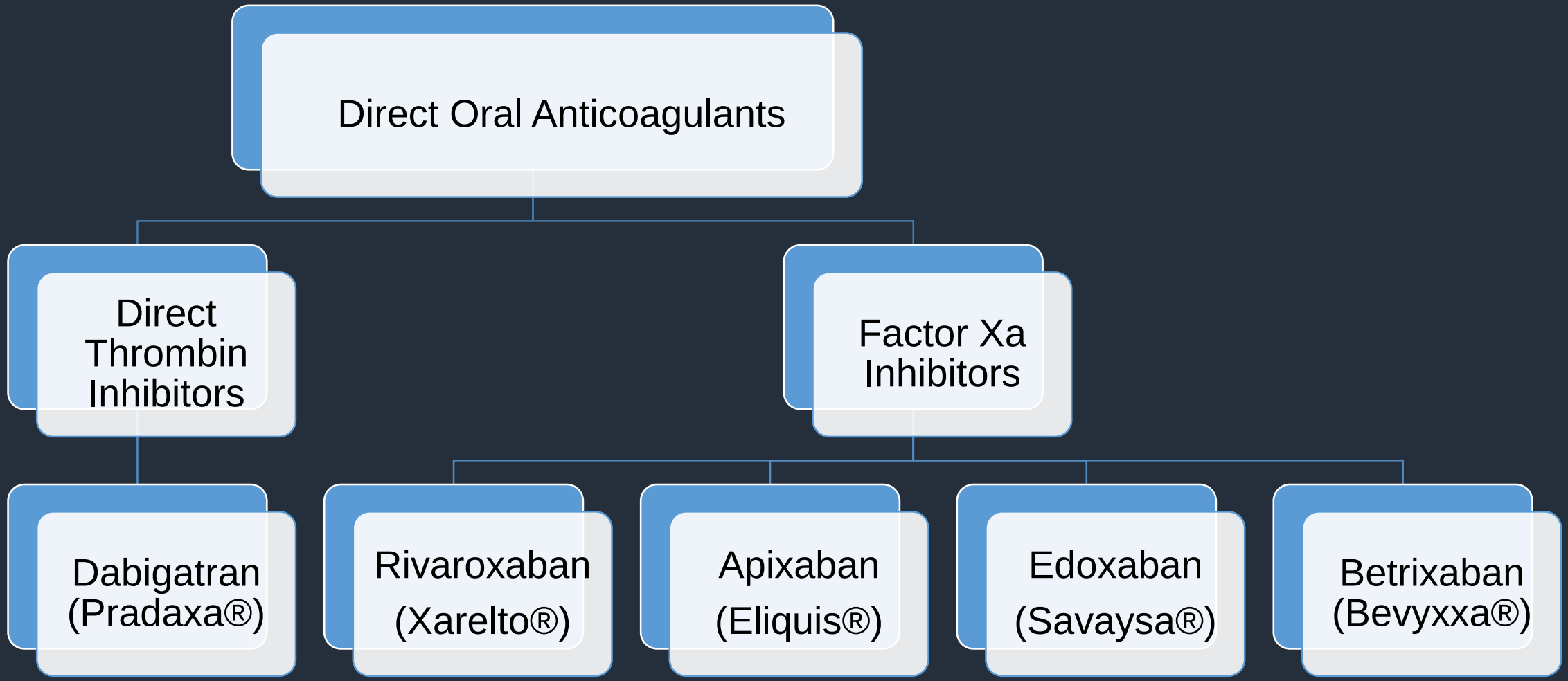
- Tammie Conway, PharmD, BCPS- no financial disclosures
- Christopher DeMella, PharmD, BCPS- no financial disclosures

Objectives

- Identify direct oral anticoagulants (DOAC) currently available and pharmacokinetics of each
- Review the mechanism of action of DOACs within the coagulation cascade
- Discuss reversal agents available for the management of DOAC-associated bleeds
- Analyze management options for DOAC-associated bleeding

Background: Direct Oral Anticoagulant (DOAC)

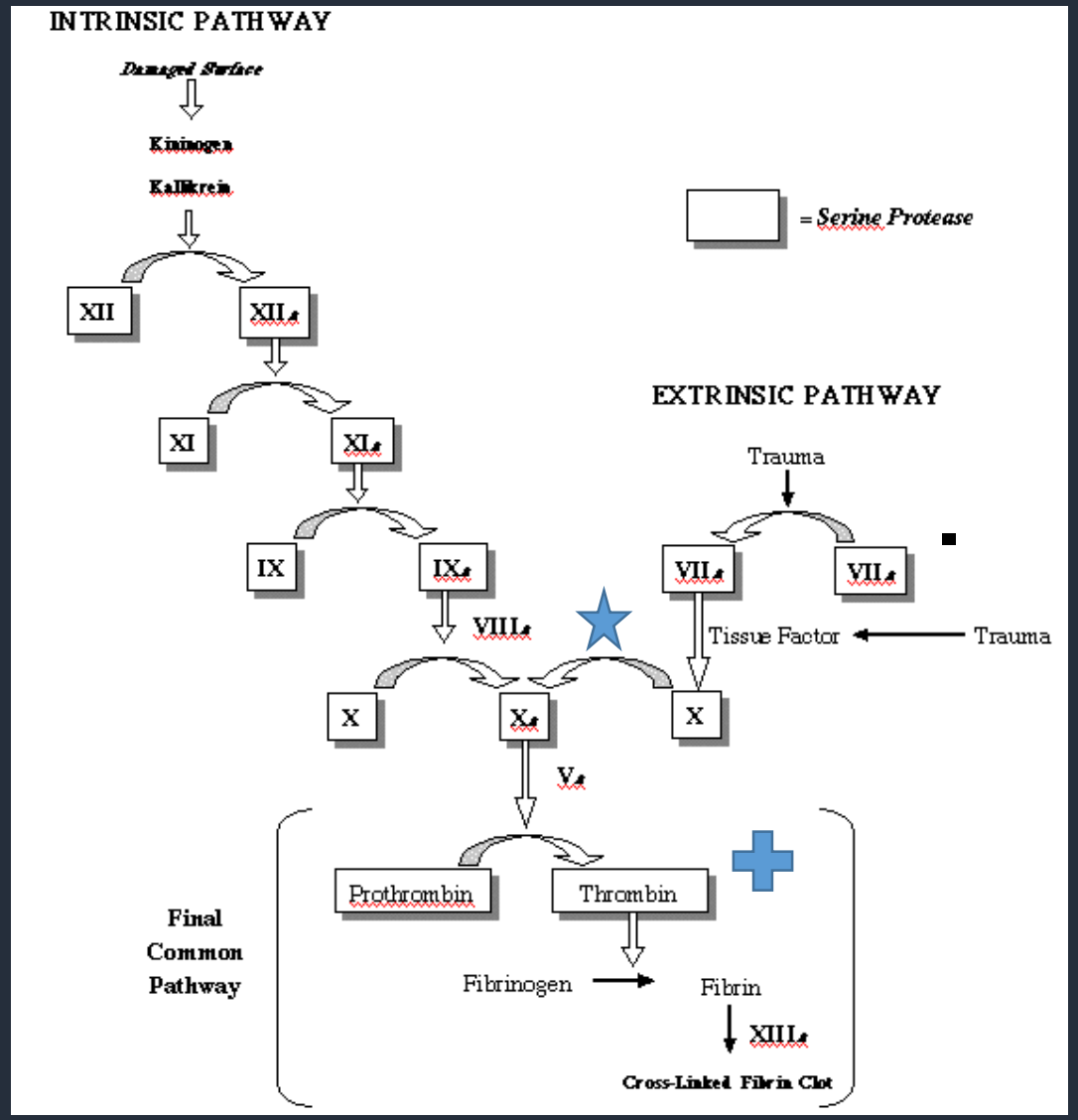
- Formerly known as NOAC
  - Novel Oral Anticoagulant
  - Non-Vitamin K Oral Anticoagulant
  - Concern with errors using term NOAC - interpreted as “no anticoagulation”
- Advantages over warfarin
  - Ease of dosing
  - Rapid, more predictable dose-response
  - Lack of monitoring requirements
  - Less drug-food & drug-drug interactions
  - Lower incidence of intracranial hemorrhage


Direct Oral Anticoagulants
Direct Thrombin Inhibitors
Factor Xa Inhibitors
Dabigatran (Pradaxa®)
Rivaroxaban (Xarelto®)
Apixaban (Eliquis®)
Edoxaban (Savaysa®)
Betrixaban (Bevyxxa®)

Background: Coagulation Cascade

Oral Direct Thrombin Inhibitor = ✚
Dabigatran

Oral Factor Xa Inhibitors = ★
Rivaroxaban
Apixaban
Edoxaban
Betrixaban



http://www.millerandlevine.com/km/evol/DI/clot/Clotting.html

DOAC Characteristics

	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)	Edoxaban (Savaysa)	Betrixaban (Bevyxxa)
MOA	DTI	FXa inhibitor	FXa inhibitor	FXa inhibitor	FXa inhibitor
Time to Peak	1-2 hrs	2-4 hrs	3-4 hrs	1-2 hrs	3-4 hrs
Half-life (hours)	12-17 young 14-17 elderly	5-9 young 11-13 elderly	12 (8-15)	10-14	19-27
95% eliminated	2.5-3.5 days	1-2 days	1.5-3 days	2-3 days	4-5.5 days
Elimination	80% renal	66% renal, 28% fecal	30% renal	50% renal	11% renal, 89% fecal
Dialyzable	Yes	Not likely	Not likely	Minimally	Not likely

MOA=mechanism of action, DTI=direct thrombin inhibitor, FXa inhibitor=factor Xa inhibitor, mg=milligram, QD=daily, BID=twice daily

Dabi A, Koutrouvelis AP. *Crit Care Res Pract.* 2018;2018:4907164.

Your Patient Comes in with a DOAC-associated Bleed…

- Stop anticoagulant, antiplatelet drugs, anti-inflammatory drugs
- Assess patient
  - What specific anticoagulant was used and what was the dose?
  - When was the last dose of anticoagulant?
  - Renal or hepatic disease?
  - Any other medications that could affect drug or hemostasis?
- Obtain labs
- Supportive measures
- Reversal agent

What Are Our Options?

- Non-Specific Reversal Agents
  - Activated Charcoal
  - Prothrombin Complex Concentrate (PCC)
    - Kcentra – 4-factor PCC
    - FEIBA – activated 4-factor PCC
    - ~~Profilnine – 3-factor PCC~~
    - ~~Recombinant factor VIIa~~
- Specific Reversal Agents
  - Idarucizumab (Praxbind®)
  - Andexanet Alfa (Andexxa®)

Non-Specific Reversal Agents

Activated Charcoal

- Activated Charcoal
  - Absorbs substance and inhibits GI absorption
  - Single dose 25 -100 g
  - Only useful if last ingested DOAC < 2-4 hours
  - Avoid in GI bleed or perforation, intestinal obstruction, unprotected airway
  - Risk of aspiration and typically outside window so not used often

Prothrombin Complex Concentrate (PCC)

	Kcentra*	FEIBA
Indication	• Reversal of vitamin K antagonists • DOAC reversal (off-label)	• Hemophilia-related bleeding • DOAC reversal (off-label)
Factors	II, VII, IX, X (all inactive)	II, IX, X (inactive) VII (active)
Dosing	50 U/kg	50 U/kg
Onset	Rapid	15-30 min
Duration	6-8 hours	8-12 hours
Adverse Effects	• Hypersensitivity reactions • Thrombosis (~2%) • Hypotension	• Hypersensitivity reactions • Thrombosis • Hypotension

*Avoid in patients with a history of HITT, product contains heparin

PCC Summary


Guidelines support regardless of lack of FDA approval
Data sources retrospective, clinical experience
Replaces affected clotting factors
Balanced efficacy AND safety outcomes

Specific Reversal Agents

Idarucizumab (Praxbind®)

- Approved in 2015
- Humanized monoclonal antibody fragment
- Restores thrombin activity by binding to with ~350 fold higher affinity than dabigatran to thrombin

Idarucizumab (Praxbind®)

- Onset: effects observed within minutes and hemostasis is restored at median of 11.4 hrs
- Duration: 12 - 24 hrs
- Half-life elimination: 10.3 hrs

Idarucizumab (Praxbind®)

Dosing

- 5 g administered as two separate 2.5 g doses
- Limited data to support additional 5 g dose

Administer

- Undiluted as IV bolus

Rate

- Give 2.5 g infused over 5-10 minutes
- Administer second dose within 15 min of first dose

Idarucizumab (Praxbind®)

- Adverse reactions: headache, constipation, nausea, infusion site reaction
- Warnings:
  - Thromboembolic risk
    - Up to 6-7%
    - Dabigatran can be re-initiated 24hr after administration if appropriate
  - Re-elevation of coagulation parameters (aPTT, TT, or ECT)
  - Hypersensitivity reactions
  - Patients with hereditary fructose intolerance (contains 4 gm sorbitol as excipient)

Pollack CV, et al. *N Engl J Med.* 2017;377(5):431-441.

Management of Dabigatran-Related Bleeds

- Preferred Agent: Idarucizumab 5 g administered as two separate doses 15 minutes apart

- Alternative Agent:
  - Activated 4-factor PCC (FEIBA, 50 units/kg)
  - 4-factor PCC (Kcentra, 50 units/kg)

- Other Potential Agents:
  - Activated charcoal
  - Hemodialysis

Kaide CG, et al. *Journal of Emergency Medicine* 2019
Nestor MA, et al. *Critical Care Nurse* 2019

Andexanet Alfa (Andexxa®)

- Approved in May 2018

- Modified recombinant inactive form of human factor Xa
  - Binds and sequesters factor Xa inhibitor molecules, reducing anti-Xa activity
  - Inhibition is immediate, however anti-Xa activity rises 4 hours after the infusion is complete

Andexanet Alfa (Andexxa®) – Highlights from Package Insert

- Indicated for patients treated with apixaban and rivaroxaban when reversal is needed for life-threatening or uncontrolled bleeding
  - Accelerated approval based on changes in anti-Xa activity in healthy volunteers
  - An improvement in hemostasis has not been proven

Andexanet Alfa – Low or High Dose?

Factor Xa Inhibitor	Factor Xa Last Dose	< 8 hours	> 8 hours
Rivaroxaban	≤ 10 mg	Low Dose	Low Dose
	> 10 mg or unknown	High Dose	
Apixaban	≤ 5 mg	Low Dose	
	> 5 mg or unknown	High Dose	

Dose	Initial IV Bolus	IV Infusion	Total number of 200 mg vials	Total number of 100 mg vials
Low Dose	400 mg at 30 mg/min	480 mg at 4 mg/min (120 minutes)	2 vials bolus + 3 vials infusion (5 vials)	4 vials bolus + 5 vials infusion (9 vials)
High Dose	800 mg at 30 mg/min	960 mg at 8 mg/min (120 minutes)	4 vials bolus + 5 vials infusion (9 vials)	8 vials bolus+ 10 vials infusion (18 vials)

Anexxa-4 Trial

Study Design	Multicenter, prospective, open-label, single-group study*
Study Exclusions	Planned surgery within 12 hours, ICH in a patient with Glasgow score less than 7, estimated hematoma volume of more than 60 mL, expected survival less than 1 month, thrombotic event within previous 2 weeks
Study Outcomes	Percent change in anti-factor Xa activity and percentage of patients with excellent or good hemostasis 12 hours after administration
Safety Outcomes	Death, thrombotic events, antibodies to andexanet alfa
Study Population	Safety Population (n=352), Efficacy Population (n=254)**
Site of Bleeding (Efficacy Population)	GI (24%), ICH (67%), Other (8%)

Connolly SJ, et al. *N Engl J Med* 2019; 380:1326-1335

*Funded by Portola Pharmaceuticals
**Efficacy population: adjudicated to meet bleeding severity

Anexxa-4 Trial

Results	
Hemostasis (n=254)	171 (67%) excellent, 33 (13%) good
Hemostasis based on site	ICH: Excellent or good (80%) GI: Excellent or good (85%)
Safety Outcomes (n=352)**	Thrombotic Events 34 patients within 30 days (10%) 49 died within 30 days (14%) – 35 CV causes, 14 non-CV

Connolly SJ, et al. *N Engl J Med* 2019; 380:1326-1335

Andexanet Alfa – PCC Comparison

	Connolly, et al.	Majeed, et al. (n=84)	Allison, et al. (n=33)	Schulman, et al. (n=66)
Reversal Agent	Andexanet alfa	4-factor PCC	4-factor PCC	4-factor PCC
Patients with ICH (%)	67	70	52	55
Hemostatic Efficacy (%)	Excellent – 67 Good – 13 (n=254)	69	84	76
Mortality (%)	14 (n=352)	32	15	14
Incidence of VTE (%)	10 (n=352)	3.6	0	8

Connolly SJ, et al. *N Engl J Med* 2019; 380:1326-1335
Majeed A, et al. *Blood*. 2017; 130(15):1706-12.
Allison TA, et al. *J Intensive Care Med*. Epub Sept 2018.
Schulman S, et al. *Thromb Haemost*. 2018;118(5):842-51.

Summary
Andexanet alfa (Andexxa®)

Andexanet alfa data has limited clinical applicability

Dosing is cumbersome and prep time is lengthy

High VTE incidence

Nationally and locally, andexanet alfa has not been added to most health systems

Approved by the FDA under accelerated circumstance for apixaban and rivaroxaban reversal

Primary literature is prospective, randomized in nature

Baseline anti-Xa levels showed a statistically significant decrease with andexanet alfa

Andexanet Alfa: Things to Consider

- Follow-up study required by the FDA
- Many hospitals have continued to use Kcentra rather than add Andexanet alfa:
  - VCU
  - Carillion Clinic
  - HCA Capital Division
  - Sentara
  - Bon Secours

Management of Factor Xa Inhibitor-Related Bleeds

- Preferred Agent:
  - 4-factor PCC (50 units/kg)
  - Andexanet alfa (dose dependent) – not appropriate if surgery planned
- Other Potential Agents:
  - Could consider activated charcoal

Reversal Options for Direct Oral Anticoagulants

VSSTF Meeting January 24, 2020

Tammie Conway, PharmD, BCPS

Christopher DeMella, PharmD, BCPS

Cost

- Estimate: 10 patients receive Andexanet alfa (5 low dose, 5 high dose) = $522,500/year
- Andexxa cost per vial
  - 100 mg = $3,300
  - 200 mg = $6,600
- Single high-dose regimen = 1,760 mg = 9 200 mg vials = $59,400