# Anticoagulants: Pharmacology, and Reversal

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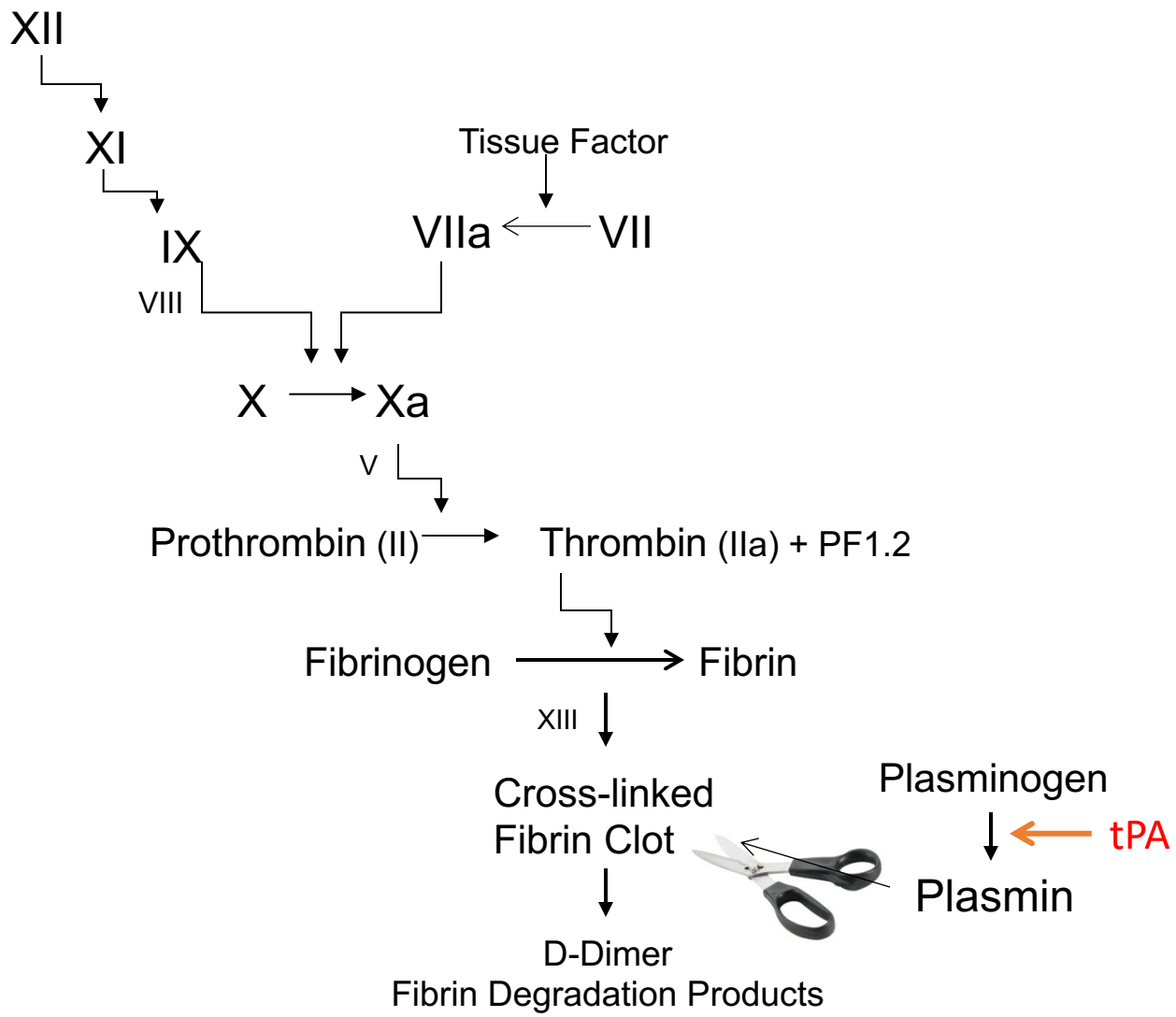
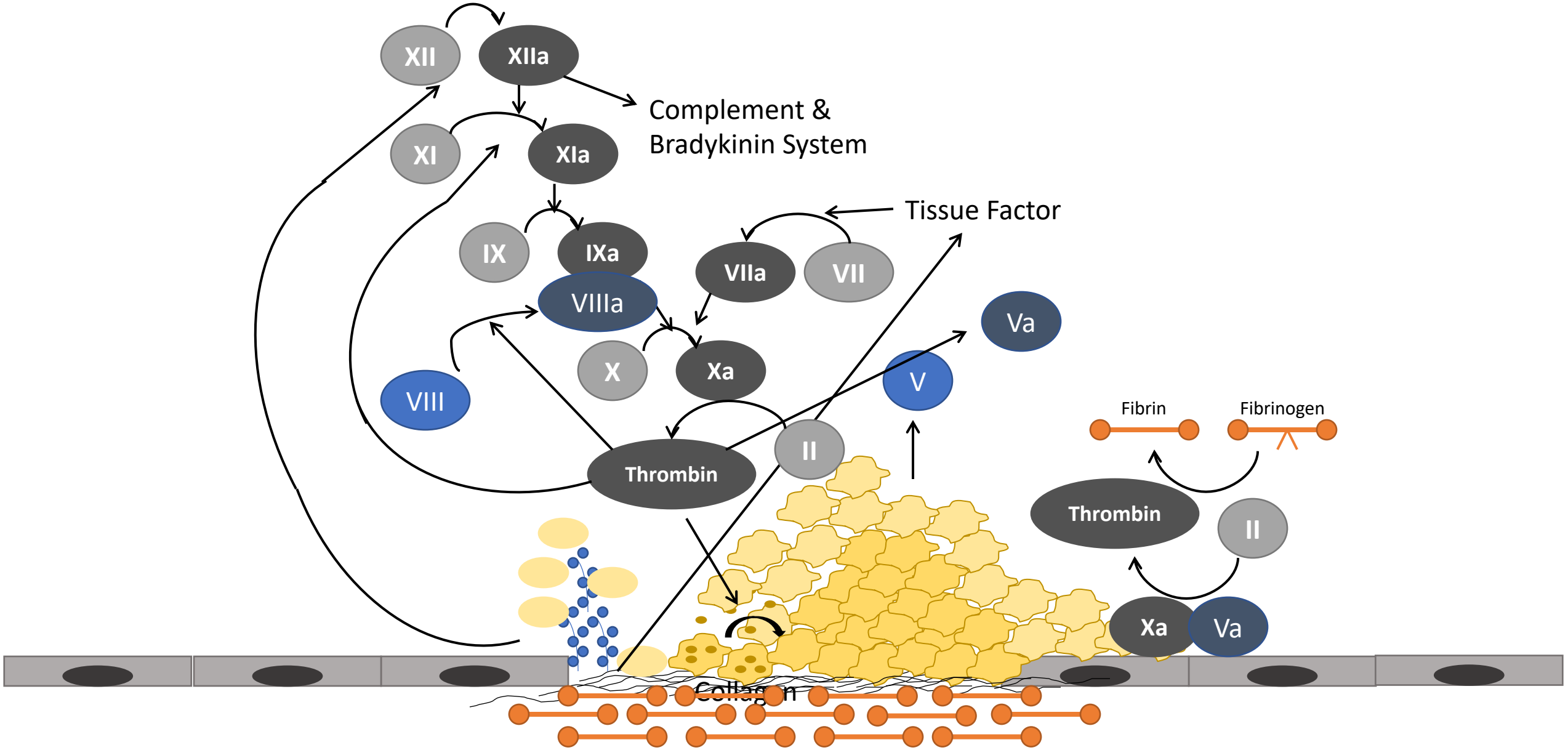
# Outline

- Review of coagulation system
  - Anticoagulant mechanism of action
- DOACs (dabigatran, rivaroxaban, apixaban, edoxaban)
  - Clinical Trial Evidence
  - Hemorrhage Management
- Management of Hemorrhage with warfarin

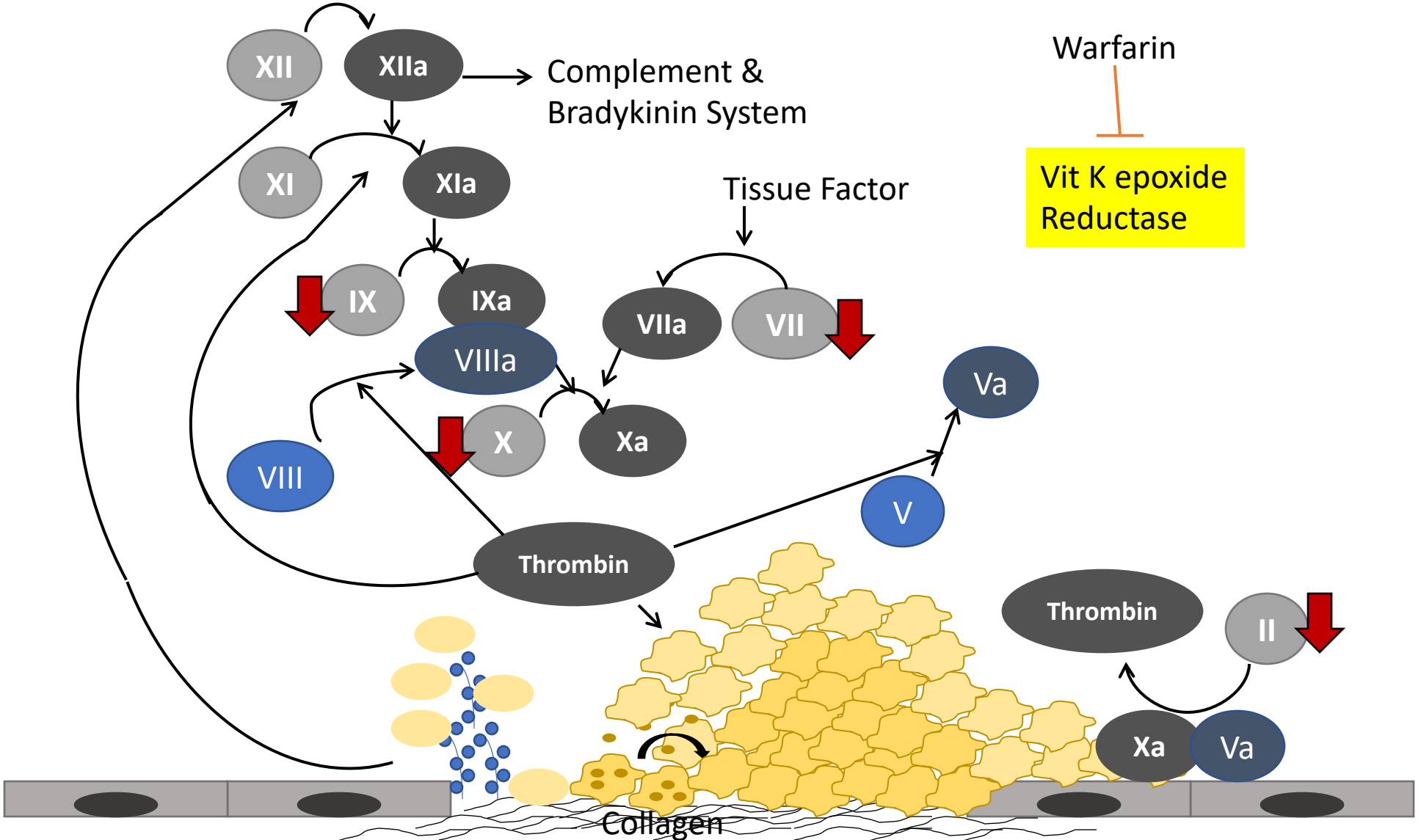
# Coagulation System



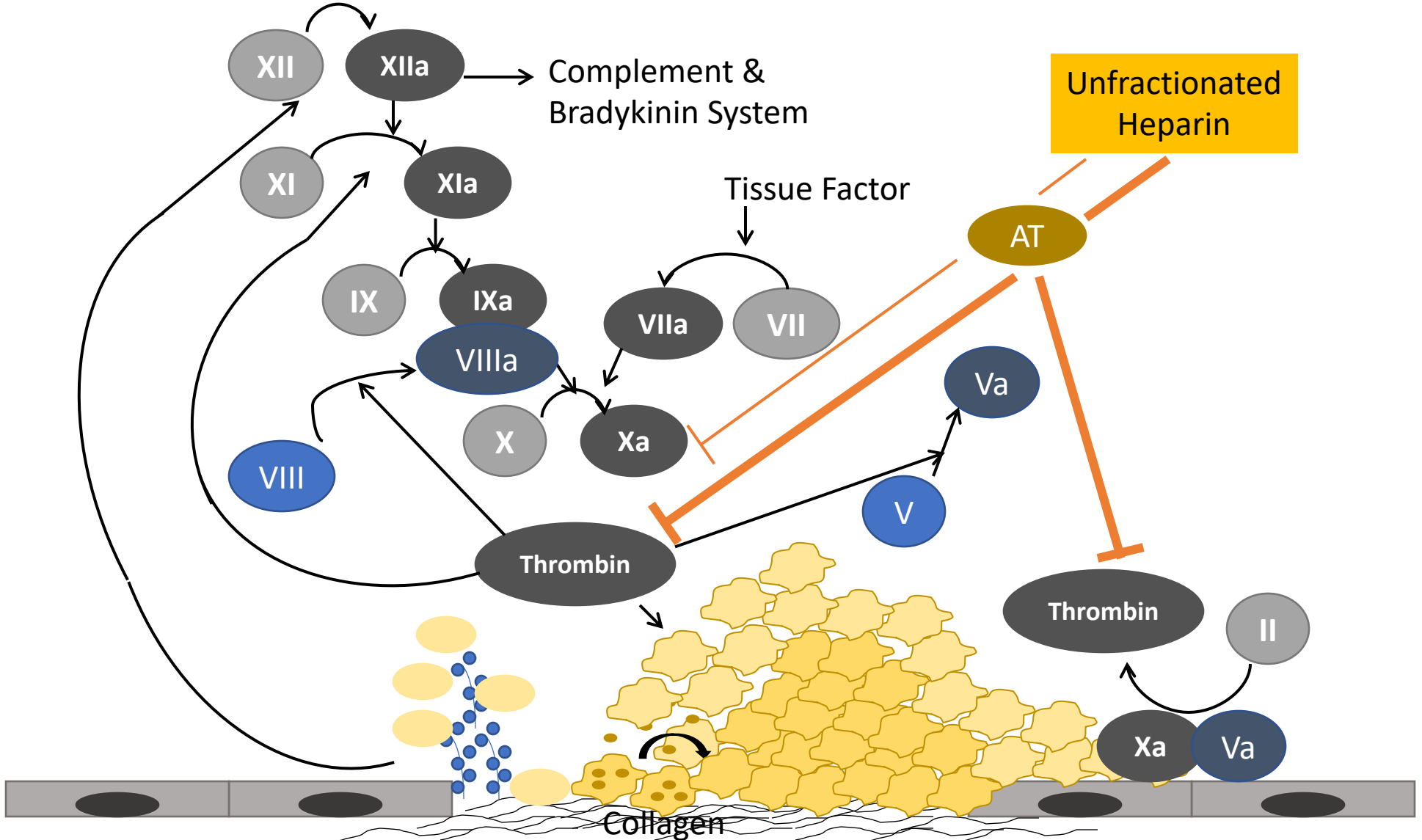
# Coagulation system



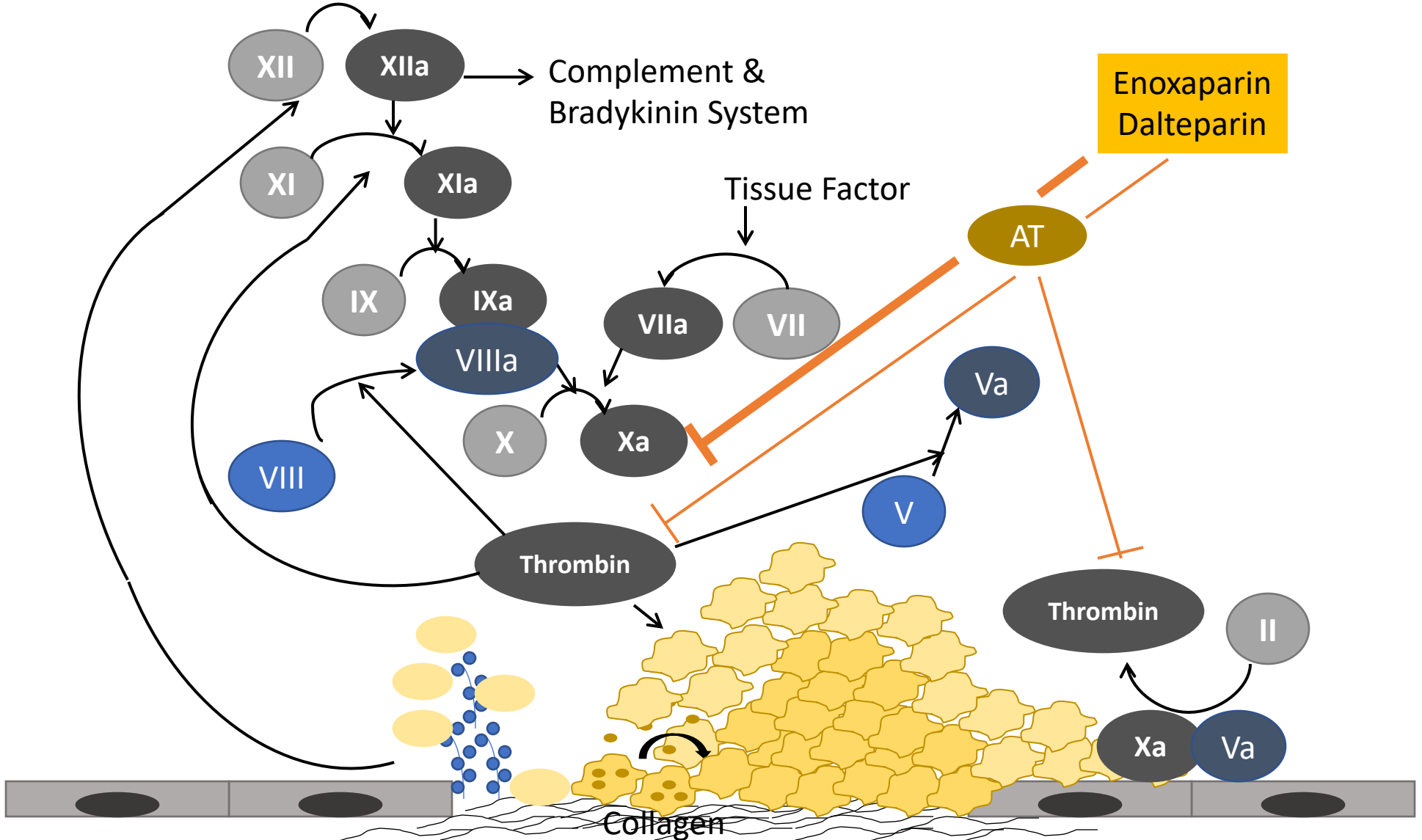
# Warfarin Mechanism of Action



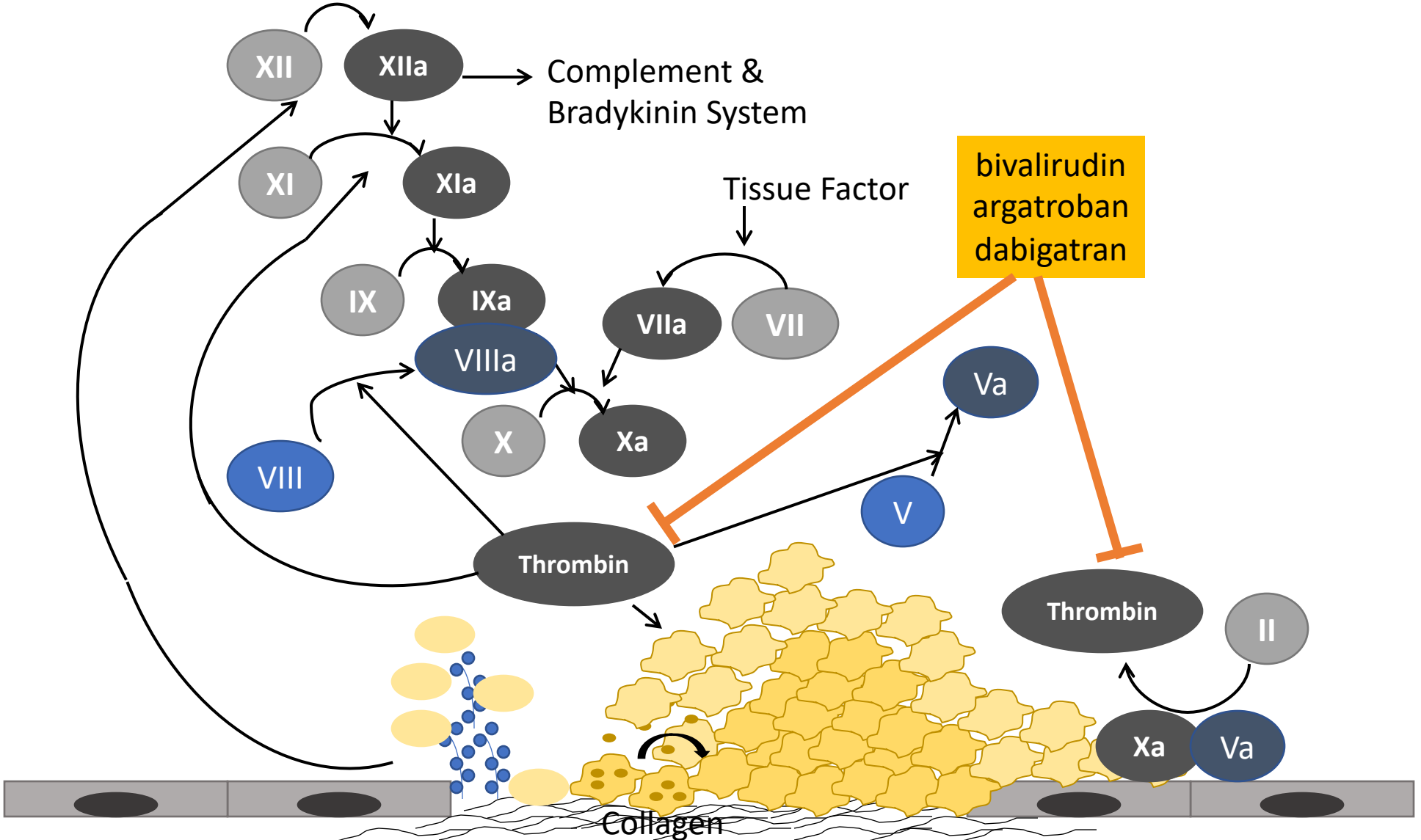
# Heparin Mechanism of Action



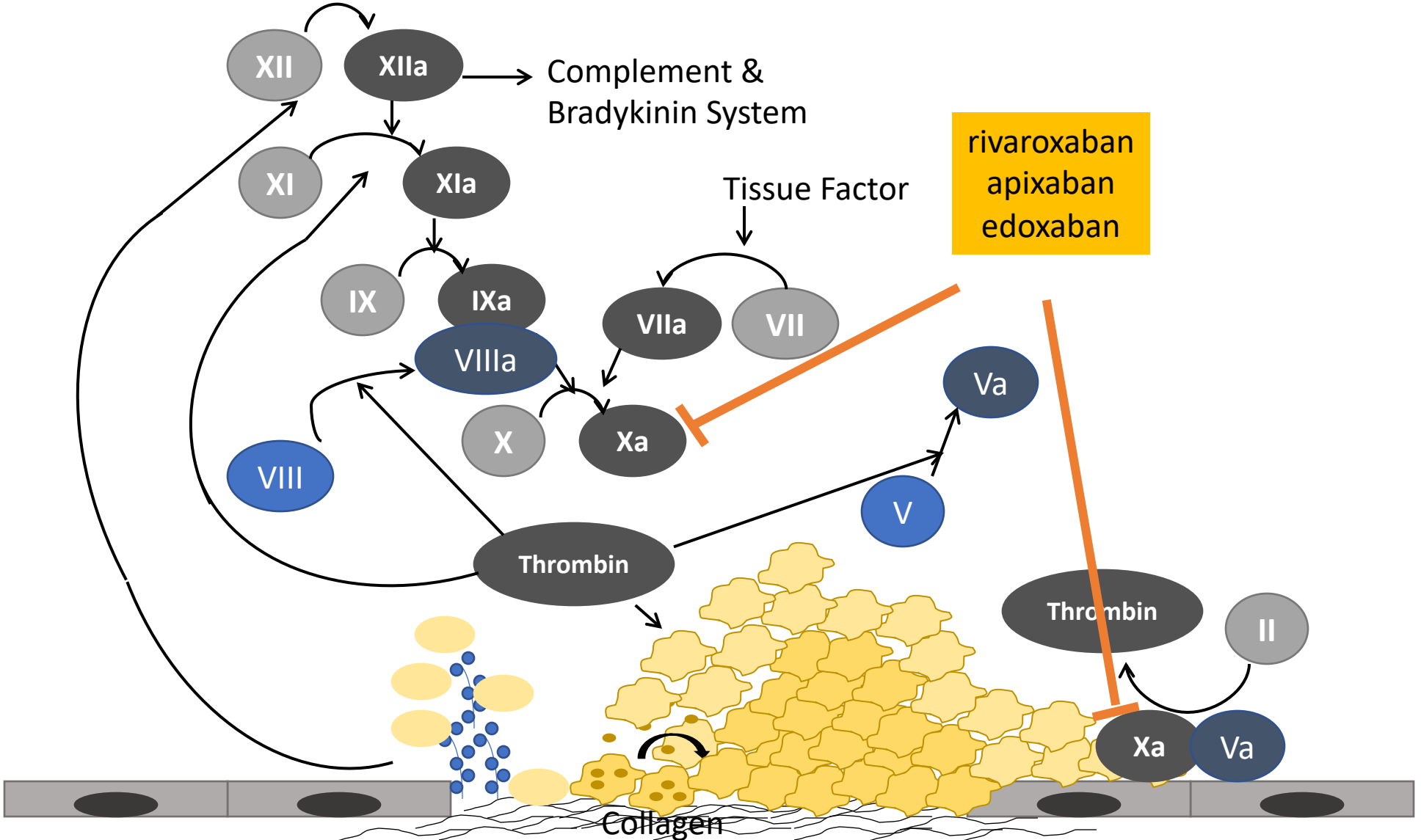
# LMWH Mechanism of Action



# Direct Thrombin Inhibitor Mechanism of Action



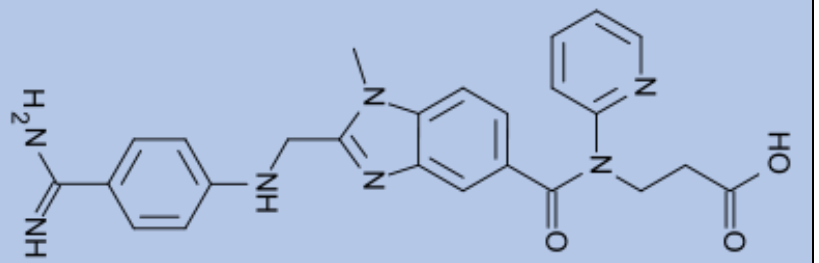
# Direct Oral Anticoagulant Mechanism of Action



# Direct Oral Anticoagulants

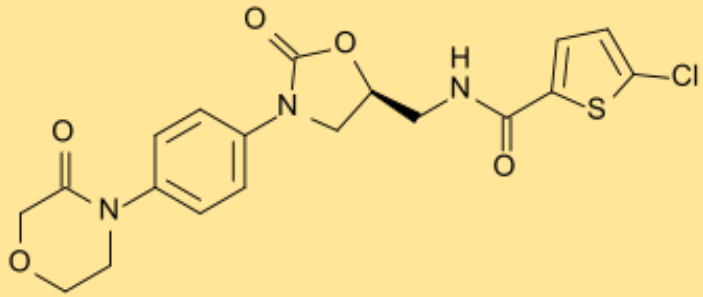
## Dabigatran – *Pradaxa*

*(Boehringer Ingelheim)*



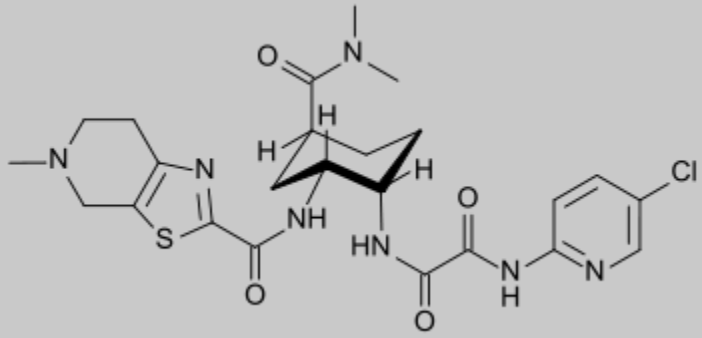
## Rivaroxaban – *Xarelto*

*(Janssen)*



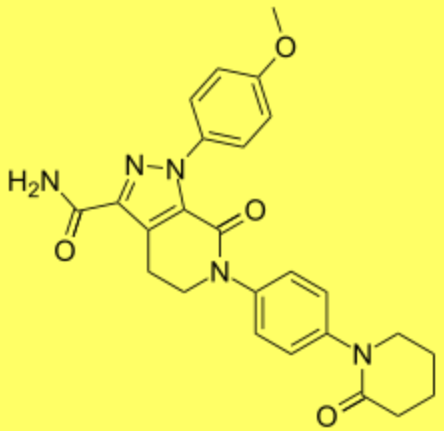
## Edoxaban – *Savaysa*

*(Daiichi Sankyo)*



## Apixaban – *Eliquis*

*(Bristol-Myers Squibb / Pfizer)*



# Pharmacokinetics

| | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|
| Target | Thrombin | Factor Xa | Factor Xa | Factor Xa |
| Peak Effect(h) | 2 – 3 | 2 – 4 | 1-3 | 1-2 |
| Half-life (h) | 12 – 14 | 5 – 13 | 9 – 14 | 6-11 |
| Dosing Frequency | Twice daily | Daily | Twice daily | Daily |
| Clearance | 80% Renal<br>20% Biliary | 66% Renal<br>33% Biliary | 25% Renal<br>75% Biliary | 34% Renal<br>66% Biliary |

Harder & Graff. EJCP 2013; 69: 1617

# DOAC FDA Approved Indications

| | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|
| VTE prophylaxis (THA,TKA) | ✓ 110 mg x 1→220 mg Daily | ✓ 10 mg Daily | ✓ 2.5 mg BID | X |
| Atrial fibrillation | ✓ 150 mg BID | ✓ 20 mg Daily | ✓ 5 mg BID | ✓ 60 mg Daily |
| VTE treatment | ✓ 150 mg BID | ✓ 15 BID→20 mg Daily | ✓ 10 BID→5 mg BID | ✓ 60 mg Daily |

Rivaroxaban (Xarelto®): http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202439s001lbl.pdf
Apixaban (Eliquis®): http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202155s000lbl.pdf
Edoxaban (Savaysa®): http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206316lbl.pdf
Dabigatran (Pradaxa®): http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022512s007lbl.pdf

# Efficacy of DOAC to comparators

**+**: Superior; **NI**: Non-inferior
**-**: Inferior to comparator

| | VTE prophylaxis | VTE treatment | Atrial fibrillation |
|---|---|---|---|
| **Dabigatran** | **NI, −** | **NI** | **+** |
| **Rivaroxaban** | **+** | **NI** | **NI** |
| **Apixaban** | **+ , −** | **NI** | **NI, +** |
| **Edoxaban** | **+** | **NI** | **NI** |

# Bleeding DOAC to comparators

↑: more bleeding; = similar Bleeding; ↓: less bleeding

| | VTE prophylaxis | VTE treatment | Atrial fibrillation |
|---|---|---|---|
| **Dabigatran** | = | = | = |
| **Rivaroxaban** | = | = | = |
| **Apixaban** | =, ↓ | ↓ | =, ↓ |
| **Edoxaban** | = | ↓ | ↓ |

# Intracranial Hemorrhage
# Therapeutic Anticoagulation Trials

| Trial | Warfarin | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|---|
| A Fib | 0.74-0.85%/y | 0.3%/y* | 0.49%/y* | 0.33%/y* | 0.39%/y* |
| VTE | 0.2- 0.4% | 2 (0.1%) | 3 (0.2%)^ | 3 (0.1%) | 5 (0.1%) |

* Statistically significant ^ All critical site bleeding

Rivaroxaban (Xarelto®): http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202439s001lbl.pdf
Apixaban (Eliquis®): http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202155s000lbl.pdf
Edoxaban (Savaysa®): http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206316lbl.pdf
Dabigatran (Pradaxa®): http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022512s007lbl.pdf

# Major bleeding case fatality rates

| | DOAC | Warfarin |
|---|---|---|
| ROCKET AF (rivaroxaban) | 7% | 14% |
| Dabigatran systematic review | 9% | 13% |
| ARISTOTLE (apixaban) | 10% | 12% |
| ENGAGE AF-TIMI 48 (edoxaban) | 8% | 11% |

*Major bleeding with warfarin has a high risk of death unchanged over the last 20 years*

Patel et al. NEJM 2011; Majeed et al. Circ 2013; Granger et al. NEJM 2011; Giugliano et al. NEJM 2013. Adapted from Dr. Deborah Siegal.

# Hemorrhage Management

# Management of Hemorrhage

- Assess severity of Hemorrhage
- Laboratory testing to assess organ function
  - Understand when need to use antidotes
- Activated charcoal if <2-3 hours since ingestion
- Local Control
- Transfusion as needed
  - Massive Transfusion protocols if available

# Pharmacokinetics

| | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|
| Target | Thrombin | Factor Xa | Factor Xa | Factor Xa |
| Peak Effect(h) | 2 – 3 | 2 – 4 | 1-3 | 1-2 |
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| Dosing Frequency | Twice daily | Daily | Twice daily | Daily |
| Metabolism/ Excretion | 80% Renal<br>20% Biliary | 66% Renal<br>33% Biliary | 25% Renal<br>75% Biliary | 34% Renal<br>66% Biliary |

Harder & Graff. EJCP 2013; 69: 1617.

# PAUSE Trial

- 3007 patients with atrial fibrillation taking DOAC undergoing elective procedure
- Last dose of anticoagulant prior to procedure
  - Apixaban and Rivaroxaban : Day -3 High Risk, Day -2 Low risk procedure
  - Dabigatran: Day -2 to -5 based on creatinine clearance & bleeding risk
- 98.8% patients had drug concentration <50 ng/ml
- 30-Day major bleed 0.9-1.9%

Within 36-48 hours, no clinically relevant levels of apixaban or rivaroxaban if normal organ function

JAMA Intern Med. doi:10.1001/jamainternmed.2019.2431

# Antidotes to Anticoagulation Therapy
# When and How to Use?

When→ Hemorrhage or emergent procedure +

Clinically relevant drug concentrations

1. Last dose known & Pharmacokinetics of drug
2. Laboratory testing

# DOACs Coagulation Testing Effect

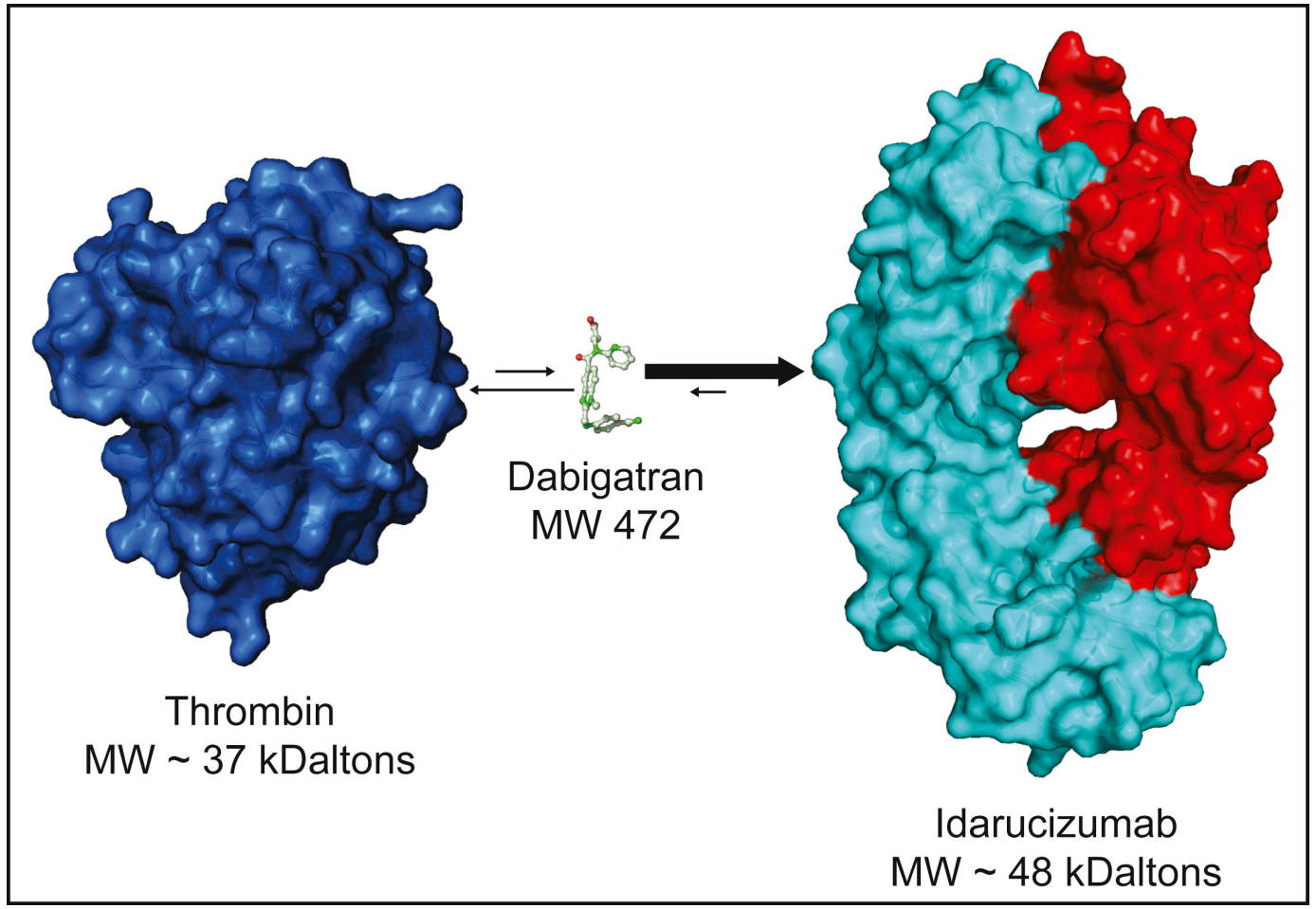
- Dabigatran
  - Peak: aPTT ~2x baseline, Trough: aPTT 1.5x Baseline
  - PT/INR relatively insensitive
  - TT very sensitive
    - If TT normal→ No dabigatran is present
- Xa Inhibitors
  - PT/INR sensitivity varies between labs
  - PTT relatively insensitive
  - Anti-Xa assay can be calibrated

Lindahl TL, et al. *Thromb Haemost* 2011; 105: 371-379; Van Rynn et al. *Thromb Haemost* 2010; 103: 116-1127.
Hillarp A, et al. *J Thromb Haemost* 2011; 9: 133-139.

# DOAC Antidotes

# Idarucizumab

- Humanized monoclonal antibody fragment against dabigatran
- Dabigatran binds idarucizumab with affinity ~350-fold greater than to thrombin

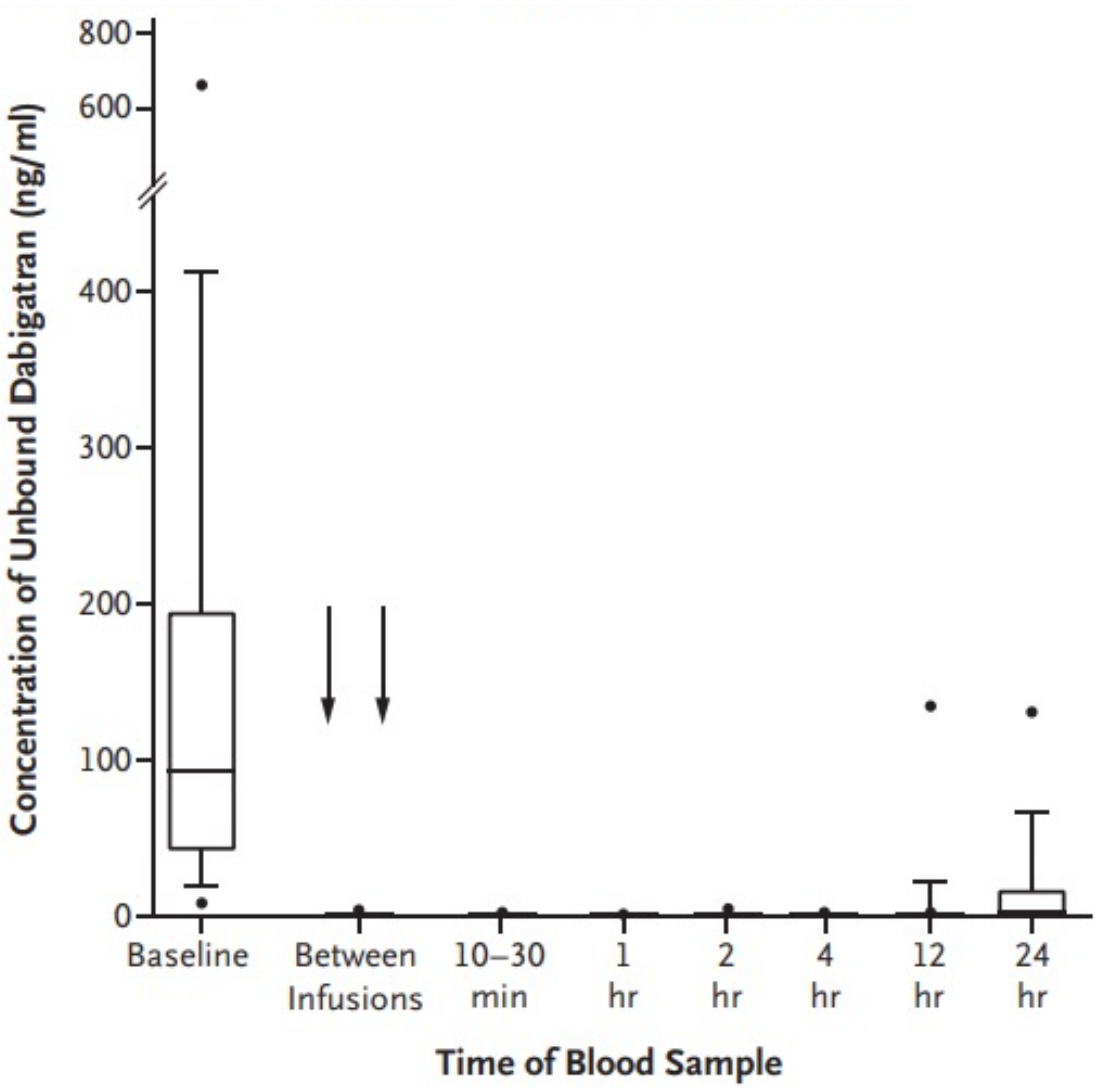



The American Journal of Medicine (2016) 129, S64-S72

# Idarucizumab RE-VERSE AD Phase III Study

- N=301 Bleeding
  - 45% GI Bleed
  - 33% Intracranial Hemorrhage
- N=202 procedure
  - 24% Abdominal
  - 20% Orthopedic
  - 18% Cardiovascular
- 100% Reversal of dabigatran

Concentration of unbound dabigatran




N Engl J Med 2015;373:511-20. N Engl J Med 2017; 377:431-441.

# Idarucizumab RE-VERSE AD Phase III Study

| | **Bleeding (n=301)** | **Procedure (n=202)** |
|---|---|---|
| Efficacy | 2.5 hours median stop hemorrhage<br>(98 ICH excluded;<br>67 unknown) | Normal Hemostasis (93%)<br>Mild Abnormal (5%)<br>Moderate Abnormal (2%) |

- FDA Approved Oct 2015

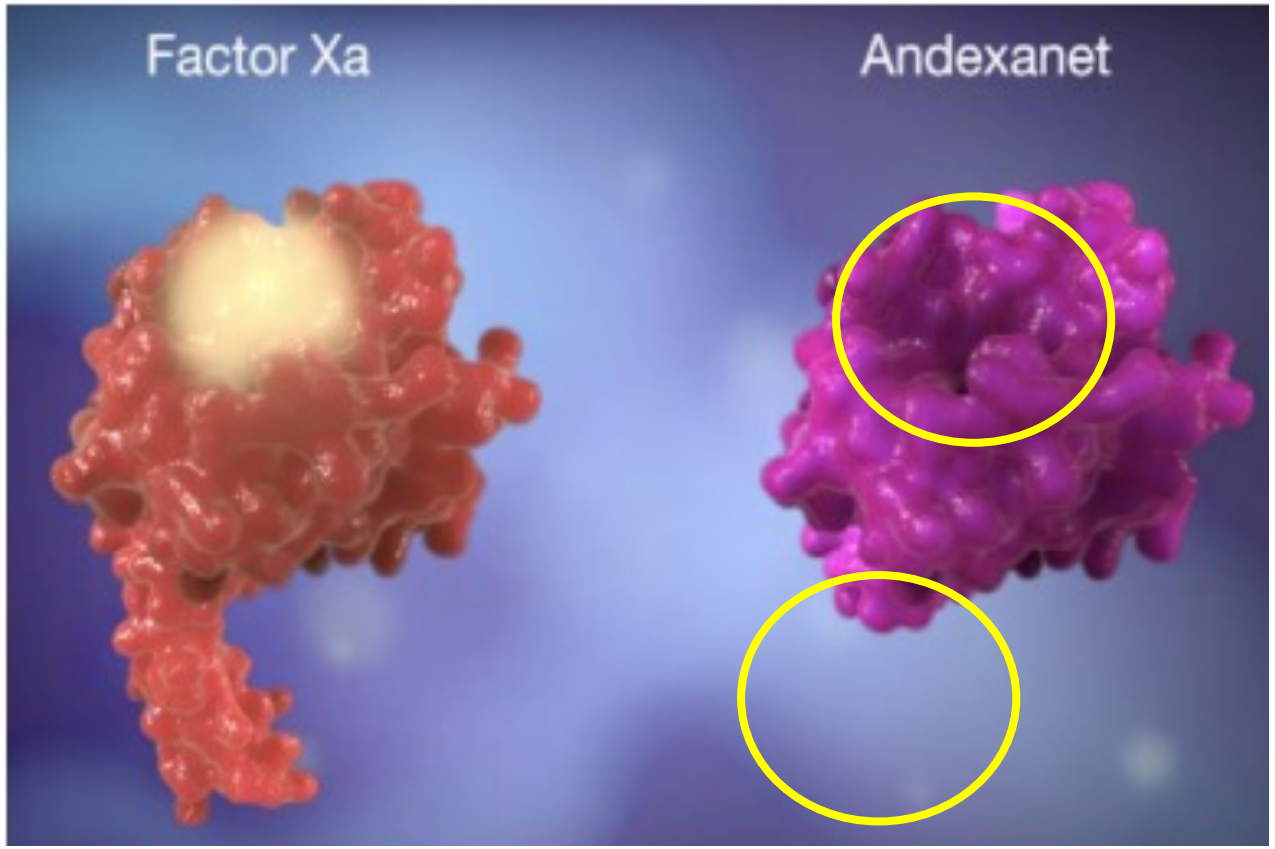
N Engl J Med 2015;373:511-20. N Engl J Med 2017; 377:431-441.

# Idarucizumab Pharmacy Considerations

- Time to Mix: <5 minutes
- Stable exposed to light for 6 hours
- Administer: 2 -2.5 g bolus (infusion or syringe), 15 min apart
- Cost: ~$3500
- Dabigatran can be restarted in 24 hours

# Andexanet Alfa

- A recombinant form of factor Xa
- Lacks catalytic and membrane-binding activity
- Retains the ability to bind factor Xa inhibitors & TFPI



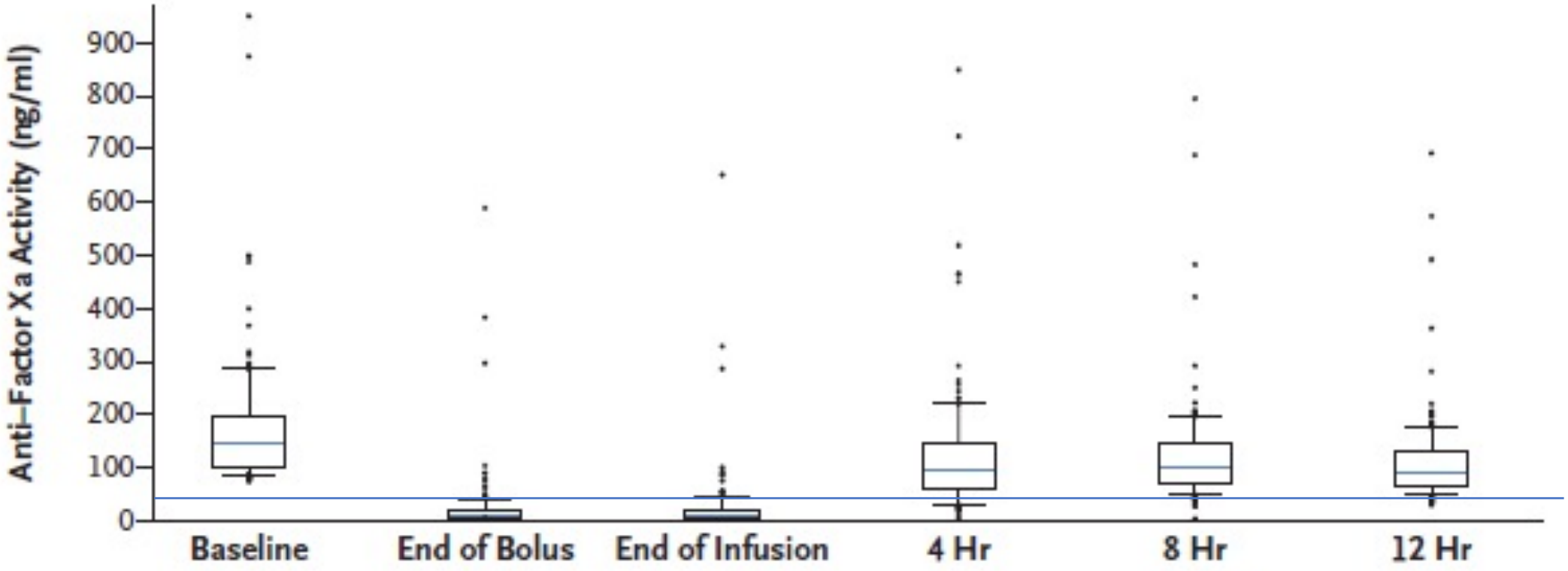

Lu et al. Nat Med 2013 Apr;19(4):446-5. West J Emerg Med. 2016;17(3):264–270. open access at http://escholarship.org/uc/uciem_westjem

# Andexanet Alfa ANNEXA-4 Study

- N=352 Major Hemorrhage
  - 64% Intracranial
  - 26% GI
- Medication
  - Apixaban (n=194, 55%)
  - Rivaroxaban (n=128, 36%)
- Efficacy analysis n=254

N Engl J Med. 2019 Apr 4;380(14):1326-1335

# Reduction in anti-Xa activity apixaban




| | Baseline | End of Bolus | End of Infusion | 4 Hr | 8 Hr | 12 Hr |
|---|---|---|---|---|---|---|
| Median | 149.7 | 11.1 | 11.5 | 97.2 | 104.6 | 91.2 |
| Percent Change (95% CI) | | −92 (−93 to −91) | −92 (−93 to −91) | −32 (−38 to −29) | −34 (−36 to −27) | −38 (−41 to −34) |

Anti-Xa low during andexanet alfa administration & returns by 4 hours

N Engl J Med. 2019 Apr 4;380(14):1326-1335

# Andexanet Alfa ANNEXA-4 Study

| | **Bleeding (n=352)** |
|---|---|
| Efficacy | Excellent or Good Hemostasis: 82% (n=249) |

- FDA Approved May 2018

N Engl J Med. 2019 Apr 4;380(14):1326-1335.

# Andexanet Alfa

- Trial exclusions:
  - Emergent surgery NOT planned within 12 hours
  - Pregnancy, sepsis, or acute thrombosis within previous 2 weeks
  - Administration of prothrombin complex concentrate or recombinant VIIa
- Andexanet alfa will bind heparin or low-molecular weight heparin/AT complex
- No indication for repeat dosing
- Accruing randomized trial  of andexanet alfa vs. standard of care in ICH patients (NCT03661528)- completion 2023

# Andexanet Alfa Pharmacy Considerations

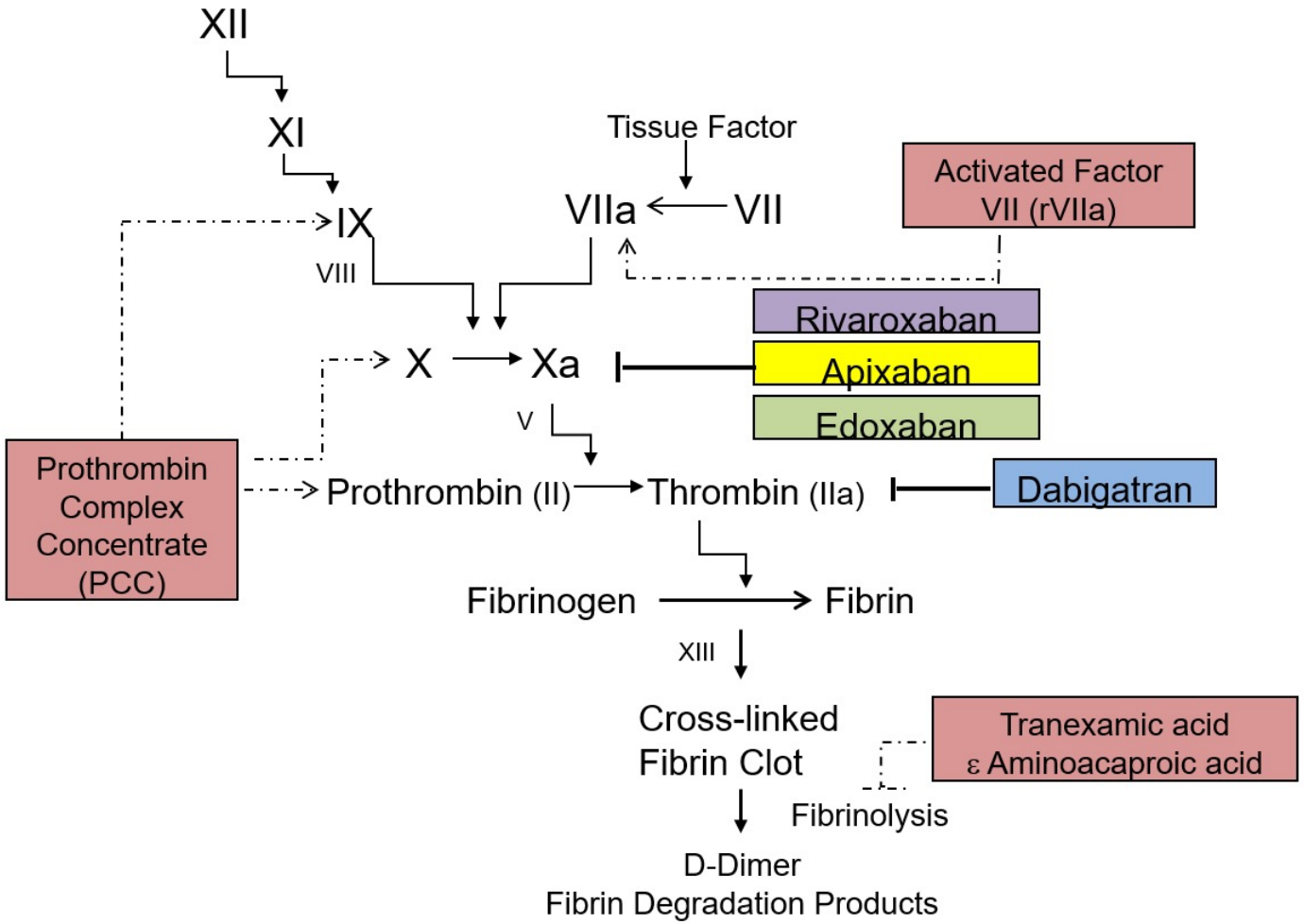
- Bolus + 2-hour infusion

| Time from DOAC | Bolus Dose | Infusion Dose |
|---|---|---|
| > 7 Hours rivaroxaban; apixaban | 400 mg | 480 mg (4 mg/min x 2 hours) |
| <7 hours or unknown timing rivaroxaban | 800 mg | 960 mg (8 mg/min x 2 hours) |

- Andexanet alfa can take >20 minutes to reconstitute
  - 200 mg vials that cannot be shaken
  - 5-9 Vials
  - Recommend single bag if possible
- T code (inpatient) and 340B pricing available (outpatient)

# Prothrombin Complex Concentrates

# Prohemostatic Medications ≠ DOAC Antidote




Significant amount of in-vitro and animal model data using these agents in patients treated with DOAC with inconsistent results

# Prothrombin complex concentrate

## Initial prospective cohort studies

| | **Majeed, et al. (n=84)** | **Schulman, et al. (n=66)** |
|---|---|---|
| Protocol | 25 units/kg (1500-2000 units) | 2000 units |
| Age | 75 (10.9) | 76.9 (10.4) |
| Hemorrhage type | | |
| Intracranial Hemorrhage | 59 (70%) | 36 (55%) |
| GI Bleed | 13 (16%) | 16 (24 %) |
| Number undergoing surgery | 28 (33%) | 10 (29%) |

Blood. 2017 Oct 12;130(15):1706-1712. Thromb Haemost. 2018 May;118(5):842-851.

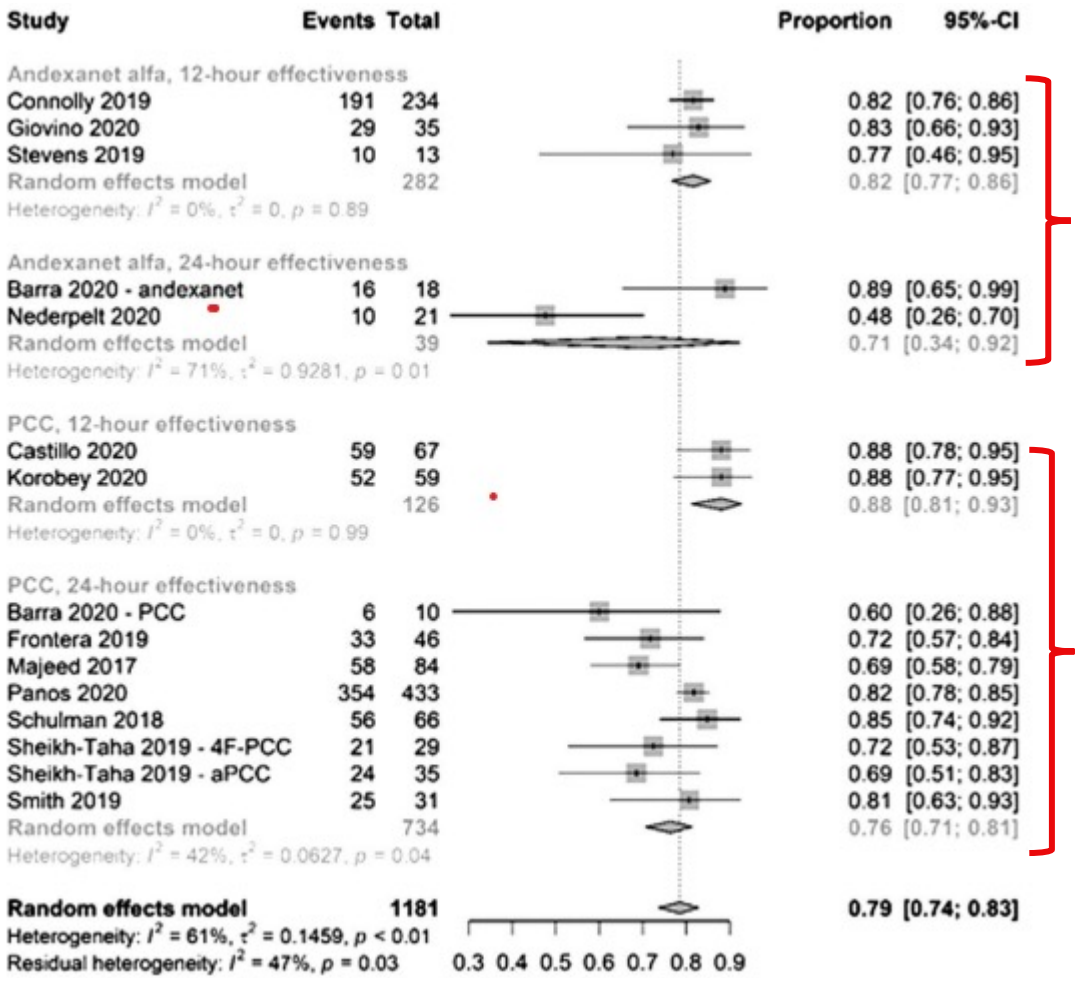
# Prothrombin complex concentrate

## Initial prospective cohort studies

| | Majeed, et al. (n=84) | Schulman, et al. (n=66) |
|---|---|---|
| Effectiveness (Good) | 58 (69%) | 43 (65%) |
| Effectiveness (ISTH criteria for CNS bleeds) | 43 (73%) | 25 (69%) |
| Thromboembolism (30 days) | 3 (4%) | 5 (8%) |
| Death (30 days) | 27 (32%) | 9 (14%) |

Blood. 2017 Oct 12;130(15):1706-1712. Thromb Haemost. 2018 May;118(5):842-851.

# Meta-analysis of Effectiveness of PCC and Andexanet




**Andexanet 82% effective at 12 hours & 71% effective at 24 hours**

**PCC 88% effective at 12 hours & 76% effective at 24 hours**

**Thrombosis 5% with andexanet & 2% with PCC**

**Randomized Control Trials are Needed**



Crit Care Med. 2021 Oct 1;49(10):e1025-e1036. doi: 10.1097/CCM.0000000000005059.

# Prothrombin complex concentrate

## Pharmacy Considerations

- Time to Mix: <5 minutes
- Administer: bolus injection
- Cost: ~$3200 (2000 Units)
- Small amounts of heparin→ contraindicated if history of HIT
- Not FDA approved for DOAC associated hemorrhage management

# Cost Comparison between PCC and Andexanet

- Retrospective review of 2 NYC hospitals over 4 years
- 126 received PCC due to DOAC (most 50 units/kg)
  - 46 would have met ANNEXA-4 criteria
- 70% with ICH

| | **PCC (actual)** | **Andexanet (projected)** |
|---|---|---|
| Total reimbursement | $11,492 (4270-136,567) | |
| Cost | $5670 | $22,120 |
| Projected amount exceeding reimbursement | 0 (0-3643) | $7,604 (0-36,539) |

Journal of Thrombosis and Thrombolysis (2020) 49:121–131

# Warfarin Reversal

# Warfarin Hemorrhage Management

- 4-Factor PCC (Kcentra) approved 4/2013
- Randomized trial 216 acute major hemorrhage

| | 4-Factor PCC | Plasma | Significance |
|---|---|---|---|
| Effective hemostasis | 72% | 65% | NI |
| INR≤ 1.3 at 30 min | 62% | 10% | Superior |
| Thromboembolism | 7.8% | 6.4% | |
| Fluid Overload | 4.9% | 12.8% | |

Sarode, et al. Circulation. 2013 Sep 10;128(11):1234-43

# 4-Factor PCC- Warfarin Reversal

| Pre-Treatment INR | 2- <4 | 4-6 | >6 |
|---|---|---|---|
| Dose (Units of Factor IX)/ kg | 25 U/kg | 35 U/kg | 50 U/kg |
| Max Dose | 2500 U | 3500 U | 5000 U |

- Administered at ~3 Units/kg/min
- Not approved for repeat dosing
  - Give with Vitamin K

Kcentra Prescribing Information. http://labeling.cslbehring.com/PI/US/Kcentra/EN/Kcentra-Prescribing-Information.pdf

# Fixed Dose of PCC for Warfarin reversal

- Meta-analysis of 10 studies, 988 patients
- Fixed dose 500 units-2000 units

| | Fixed dose | Variable dose | RR (95% CI) |
|---|---|---|---|
| Mortality | 12.6% | 19.6% | 0.65 (0.47-0.9) |
| Thrombosis | 2% | 1.5% | 1.1 (0.44-2.8) |
| Goal INR reached | 70% | 81% | 0.87 (0.78-0.96) |
| Baseline INR<4 | | | 0.72 (0.48-1.08) |
| Order to needle time | 68 min | 88 min | -22.5 min (-31to -13) |

Cardiovasc Drugs Ther. 2021 Apr 17. doi: 10.1007/s10557-021-07192-0.

# Antidotes to Anticoagulation Therapy
# When and How to Use

When→ Hemorrhage or emergent procedure +

Clinically relevant drug concentrations

1. Last dose known & PK of drug
2. Laboratory testing

How

Dabigatran→ idarucizumab bolus

Apixaban & Rivaroxaban→ andexanet alfa (bolus, infusion)

Prothrombin complex concentrate (bolus)

Warfarin→ prothrombin complex concentrate

# Summary

- Mechanism of action of anticoagulants differ
- The last dose of DOAC and metabolism will influence management of hemorrhage.
  - Half life ~12 hours
- Identify which laboratory tests can be used to determine if clinically relevant amount of DOACs are present
  - Dabigatran (elevated aPTT or TT); Rivaroxaban or apixaban (anti-Xa)
- Understand available antidotes and prohemostatic medications for management of anticoagulation associated hemorrhage
  - Specific antidotes: idarucizumab (dabigatran) or andexanet alfa (rivaroxaban or apixaban), PCC (warfarin)
  - Prohemostatic medications: prothrombin complex concentrates