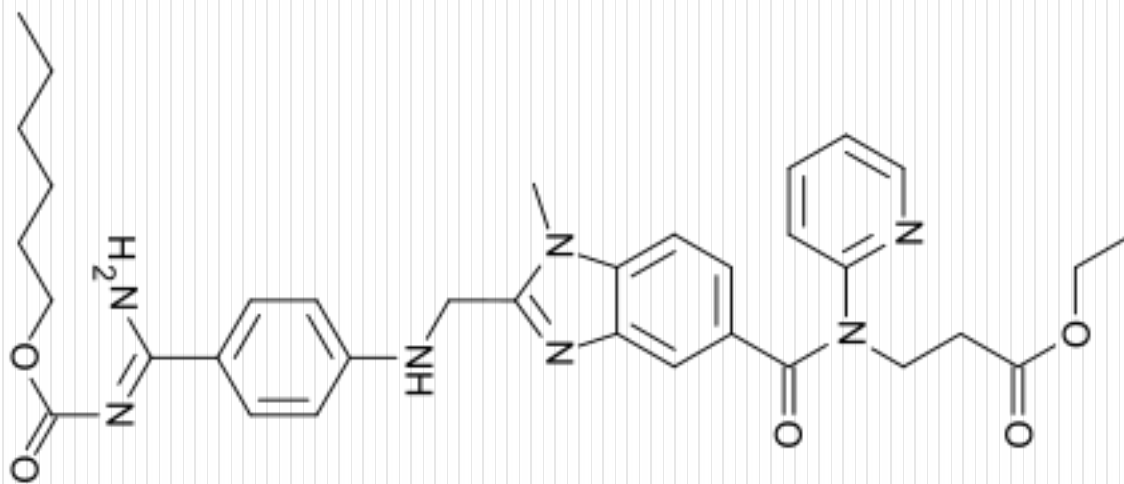


Review of Pharmacology and Management of Bleeding Complications of Novel Oral Anticoagulants



Brent W Morgan MD

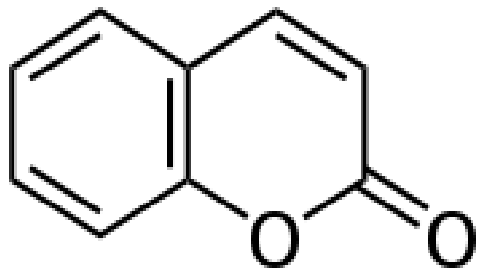
Personal/ Professional Financial Relationships with Industry

External Industry Relationships *	Company Name	Role
Equity, stock, or options in biomedical industry companies or publishers	None	
Board of Directors or officer	None	
Royalties from Emory or from external entity	None	
Industry funds to Emory for my research	None	
Consulting	ECN/Various Law Firms	Reviewer

Case Report

- 70 yo male with a history of a. fib suffers a CHI from falling down 4 steps.
- Per Wife, Medications: Metoprolol, Simvastatin, Dabigatran
- GCS 12, HR 70 RR 14 BP 138/70
- Exam normal except for scalp hematoma
- Head CT reveals an Epidural Hematoma
- Next Steps?

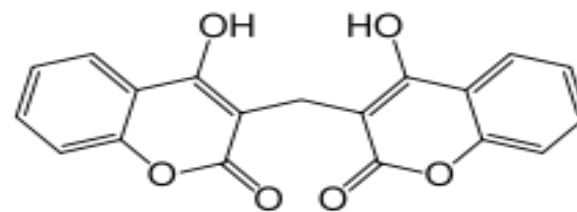




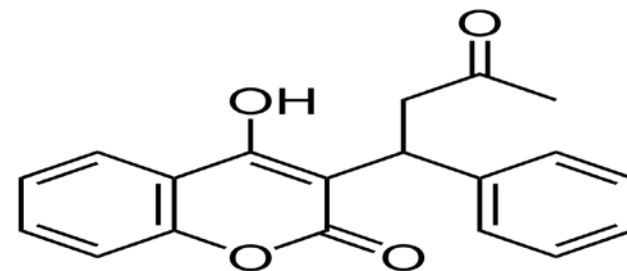
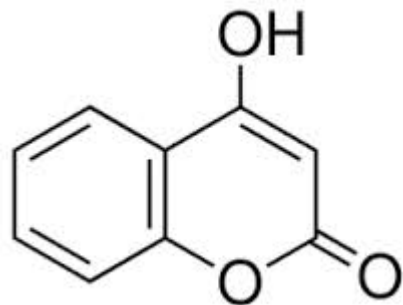
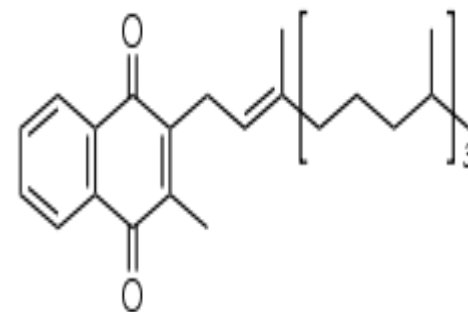
Coumarin



Aspergillus

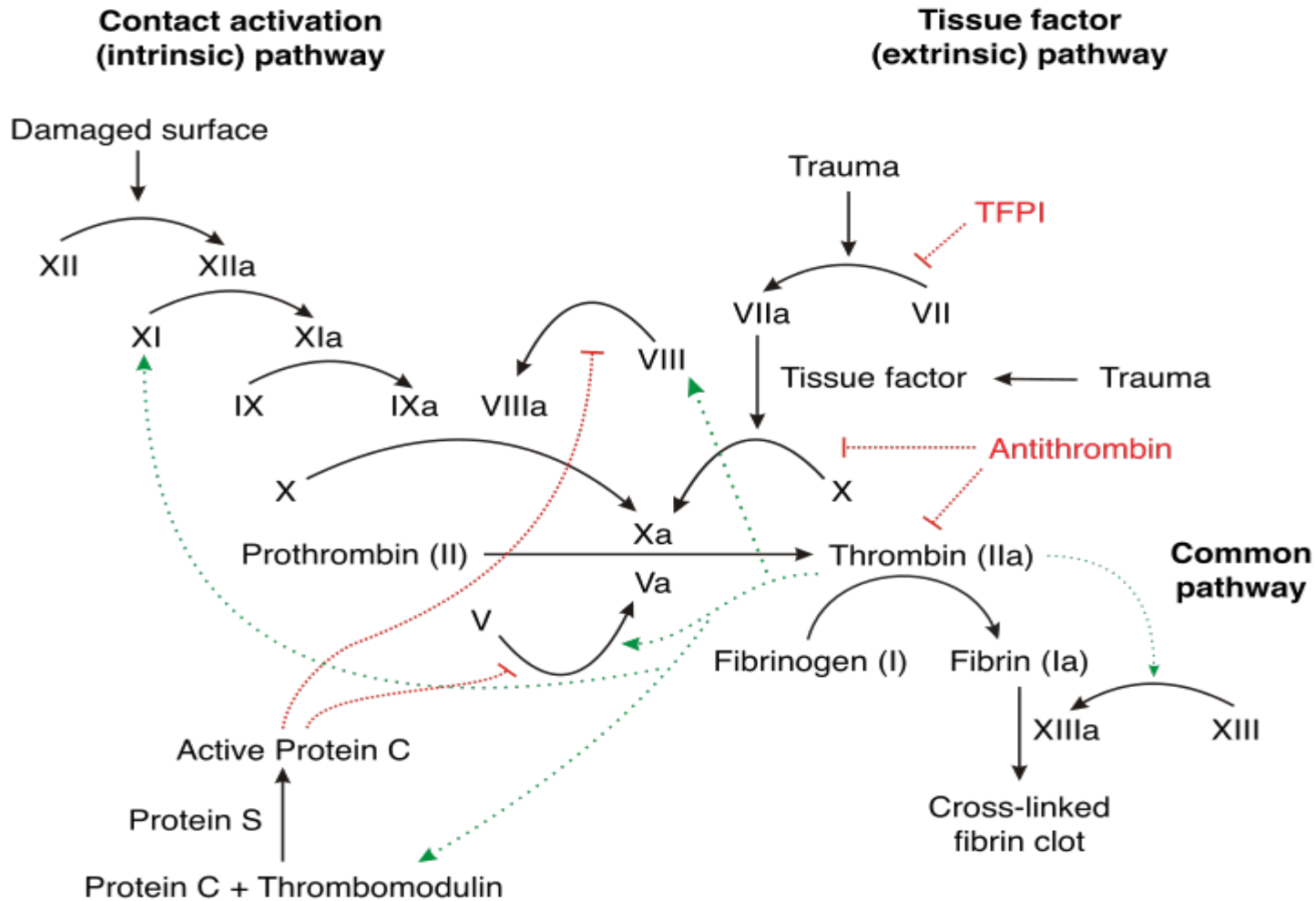


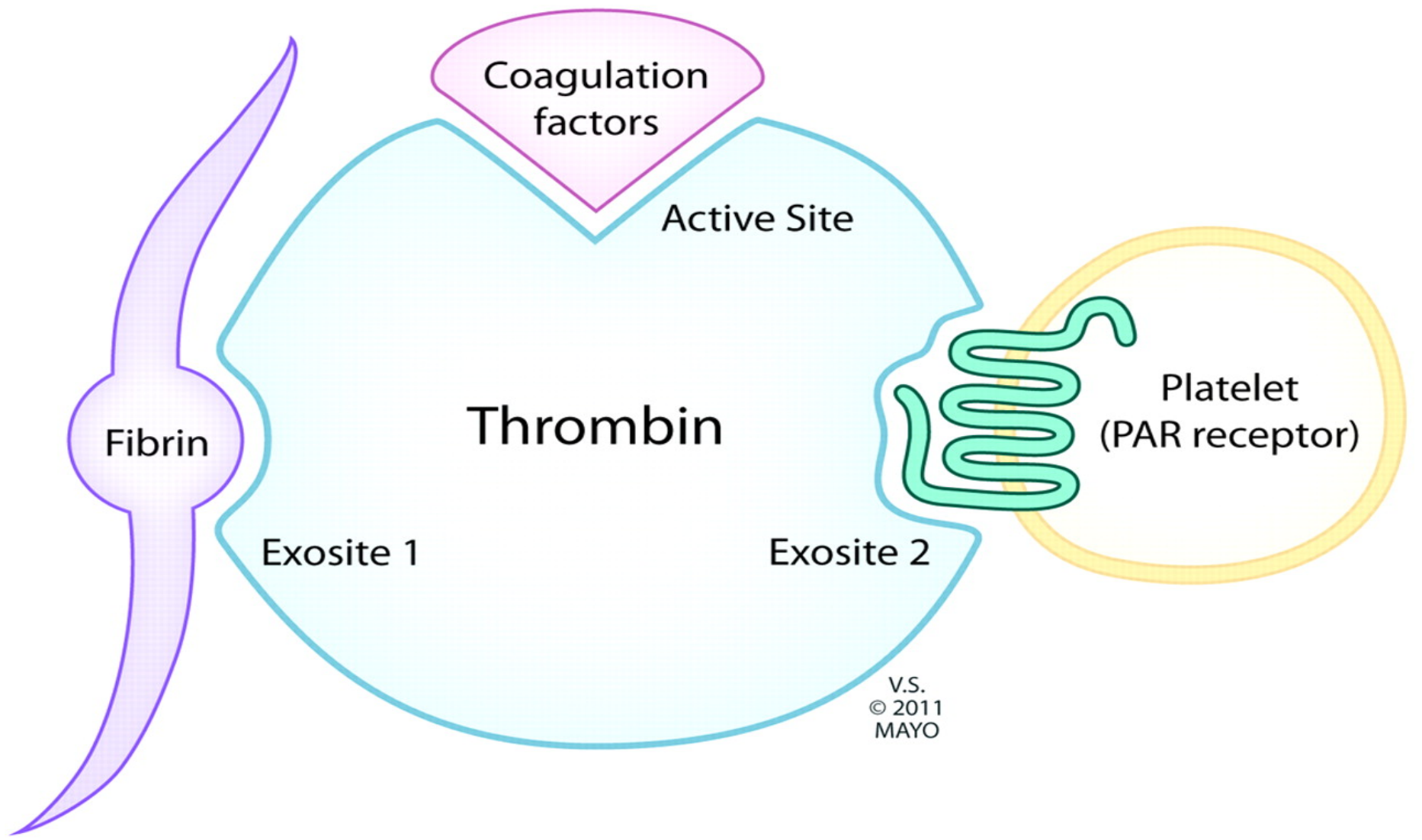
Dicoumarol



The Ideal Anticoagulant

- 1. High efficacy-to-safety index
- 2. Predictable dose response that allows dosing without the need for laboratory monitoring
- 3. Administration by parenteral and oral routes
- 4. Rapid onset of action
- 5. Availability of a safe antidote
- 6. Freedom from non-anticoagulant side effects
- 7. Minimal interaction with other drugs

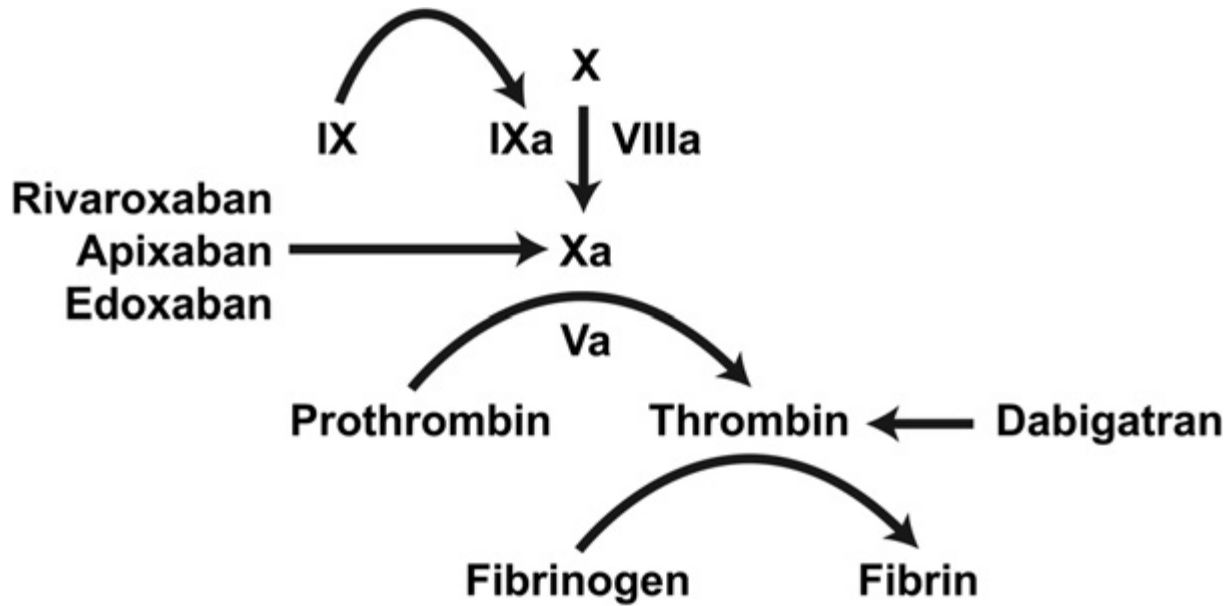




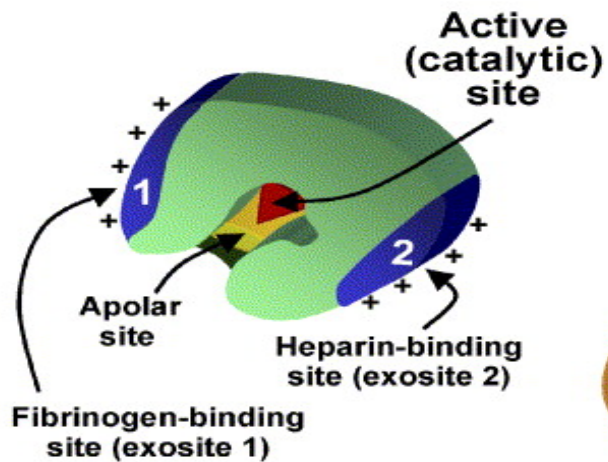
V.S.
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MAYO

Novel Anticoagulants

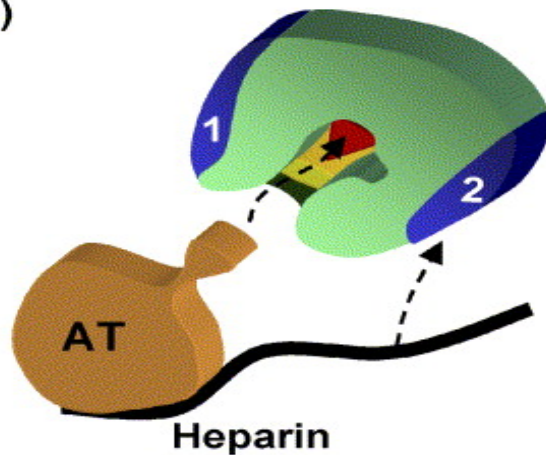
- Thrombin Inhibitors
 - Dabigatran
 - Argatroban (IV)
- Activated factor X (Xa) inhibitor
 - Rivaroxaban
- Hirudin: Thrombin Inhibitors
 - Bivalrudin
 - Lepirudin



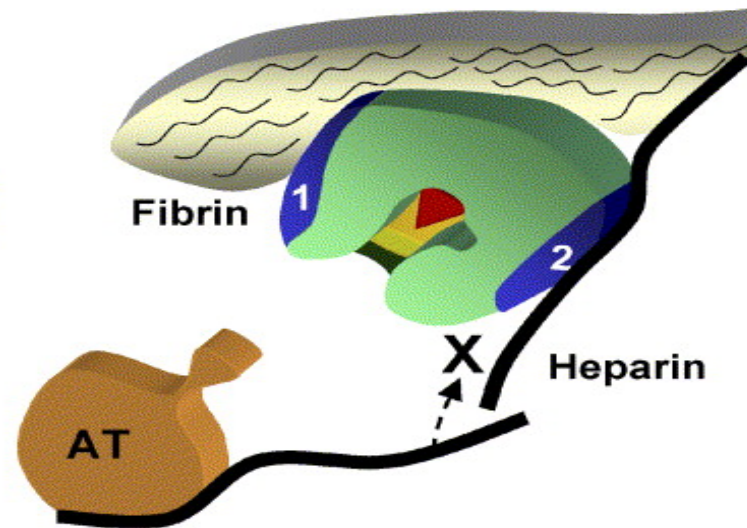
Thrombin



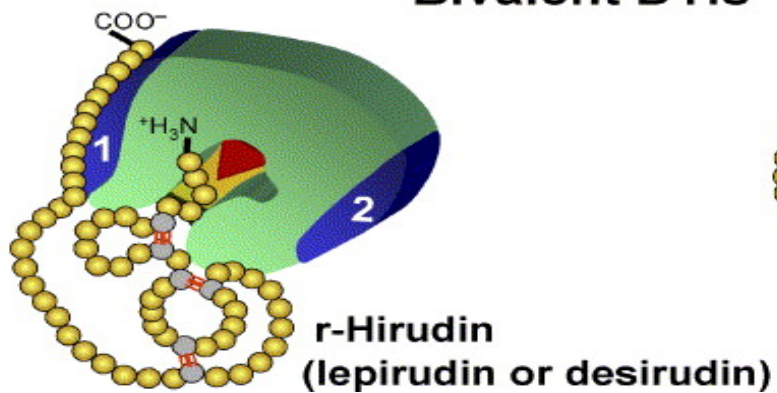
Soluble thrombin



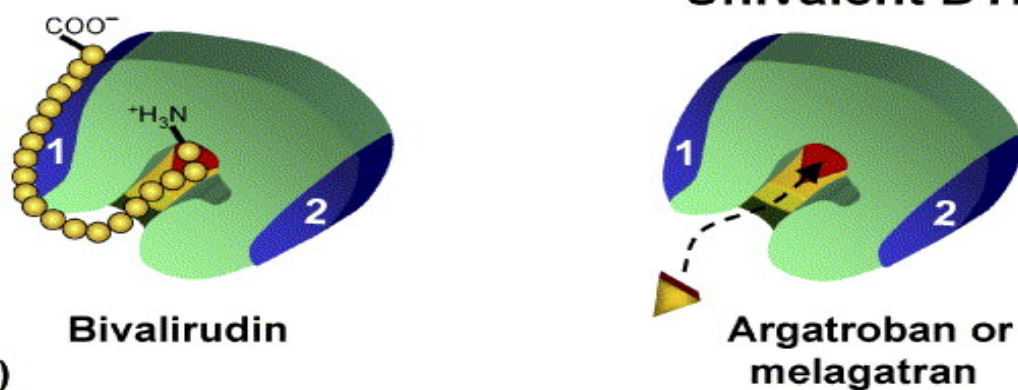
Fibrin-bound thrombin



Bivalent DTIs



Univalent DTIs



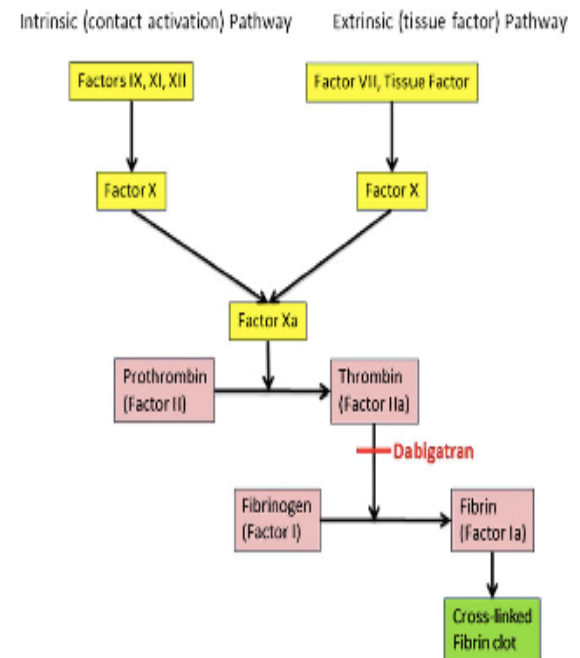
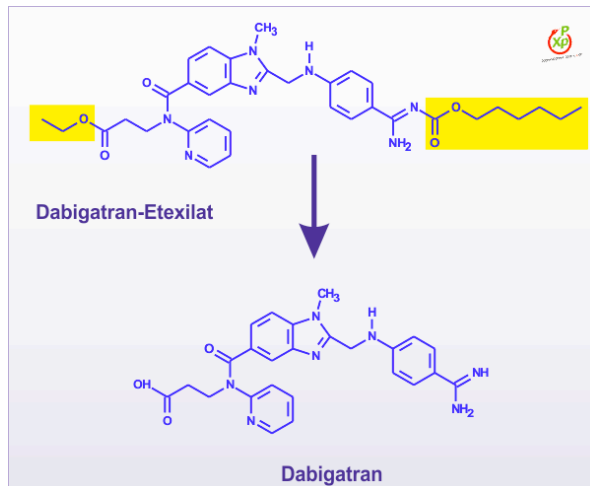
Dabigatran

- Competitive direct thrombin inhibitor
- Approved for stroke prevention
 - Non Valvular Afib
- Predictable anticoagulation response
 - No cyp 450 metabolism
 - Few drug/drug
 - Does not require frequent monitoring
-but no way to reliably reverse hemorrhagic complications, YET



Pharmacology

- Reversible, potent competitive direct thrombin inhibitor
- Heparin binds only free thrombin
- Dabigatran can inhibit both free and clot bound thrombin



Pharmacokinetics

- Administered as a prodrug
- Immediate anticoagulation after hydrolysis into active drug
- Peak plasma level within 2 h (higher peak if pill is cut or chewed, delayed if take with food)
- 35% protein bound
- Metabolized by glucuronidation
 - 10% loss of potency per glucuronide
- $t_{1/2}$ 12-17 hours, renal excretion (dose based on creatinine clearance)
- INR <2.0 when transitioning from warfarin to dabigatran

Rivaroxaban

- **Xarelto**
- **Competitively inhibits free and prothrombinase/clot-associated factor Xa via reversible interactions with active site**
- **Approved for VTE Prophylaxis in patients after hip and knee replacement**
- **Approved for stroke prevention**
 - **Non Valvular Afib**



Pharmacology: Rivaroxaban

- Highly protein bound
- Renal (40%) and Hepatic metabolism CYP3A4,2J2
- Predictable effects; does not require frequent monitoring
- Drug/drug interactions
- Peak plasma 2 to 4 hrs
- T $\frac{1}{2}$ 9-13 hrs

Effects of Coagulation Tests



	PT	aPTT	TCT	Ecarin	Hemoclot assay	Anti-factor Xa Activity
Dabigatran	↑ or no Δ (Linear but not precise)	↑ (non-linear)	↑	↑	↑*	—
Rivaroxaban	↑ or no Δ	↑ or no Δ	—	—	—	↑*

Available Coagulation Test

- Despite their limitations, conventional coagulation assays may provide qualitative information regarding the presence of drug.
- A normal TCT in patients receiving dabigatran, normal PT in patients receiving rivaroxaban suggest very low drug levels and intact haemostatic function.

Dabigatran Clinical Trials

- RE-LY study
 - Vs warfarin in 18113 patients within afib
 - 110 mg bid- same rates of stroke and emboli, lower rate of bleeding
 - 150 mg bid- lower rate of stroke and emboli, similar rate of bleeding
 - Older or renal impaired more likely to bleed
- RE-COVER
 - Vs Warfarin for acute VTE
 - 150 mg BID, no difference in VTE or bleeding
- 5 trials for post orthopedic surgery show non-inferiority vs LMWH

Management of Bleeding

Complications: Factor Replacement

- Current recommendations are not based on evidence or clinical experience
- FFP- theoretical basis
 - Contains prothrombin- ? overcome dabigatran inhibition
 - May replace other factors that may be deficient
- Prothrombin Complex Concentrates (PCC)
 - USA 3-factor II, IX, X
 - Improved clotting times in animal and human IN VITRO studies
 - Thrombogenic- can lead to ischemia



Prothrombin Complex Concentrate

- **Prothrombin Complex Concentrate (PCC)**
 - Three Factor PCC: Non activated II, IX and X small amounts of VII (Profilnine or Bebulin)
 - Activated PCC: Activated VII, II, IX and X (Feiba), during manufacture.

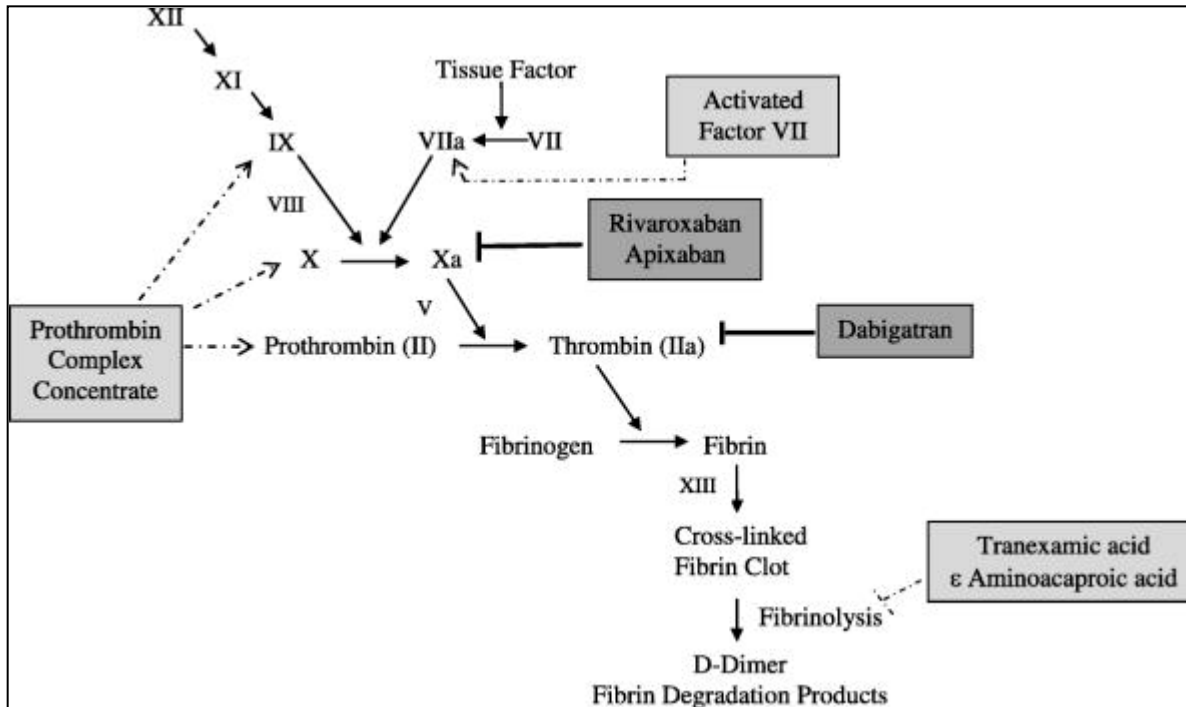
Prohemostatic agents: aPCC

- Activated PCC: Activated VII, II, IX and X (Feiba).
- aPCC has been shown to correct the anticoagulant effect of high dose rivaroxaban in animal models.
- In human plasma incubated with dabigatran, aPCC reduced clot initiation time in vitro.
- aPCC corrected thrombin generation parameters in vitro in plasma from healthy volunteers receiving single doses of rivaroxaban or dabigatran and in blood from healthy volunteers following the addition of apixaban

Prohemostatic agents

- rFVIIa- development to treat hemophilia patients with inhibitors to factors VIII and IX
- Has FDA blackbox warning: arterial thromboembolic events
- No demonstrated efficacy

Figure 1



New anticoagulants: A concise review.
 Baumann Kreuziger, Lisa; Morton, Colleen; Dries, David
 Journal of Trauma and Acute Care Surgery. 73(4):983-992, October 2012.
 DOI: 10.1097/TA.0b013e318265cf9e

Figure 1 . Clotting cascade and location of activity of new oral anticoagulants and hemostatic agents. Proteins are depicted by their zymogen symbols. The new oral anticoagulants are depicted in dark gray boxes with bold inhibition lines. Hemostatic agents are in light gray boxes with dashed lines in the area of activity. The PCC is depicted as containing nonactivated proteins for simplicity but can contain activated proteins and factor VII also depending on the product.

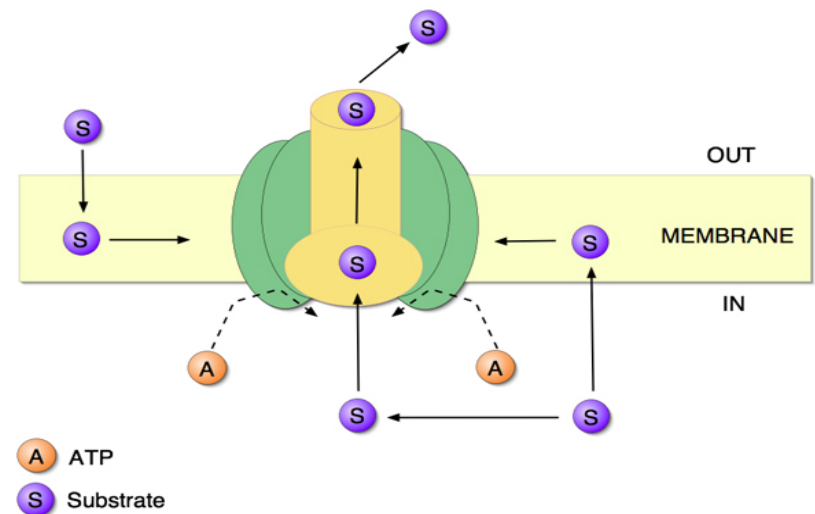
Hemodialysis

- Closed space bleeding
 - GI bleed lasting 12-17 hours ($1 \times \frac{1}{2}$ life) may be tolerated with supportive care
 - Protracted bleeding into intracranial, spinal or pericardial space can be devastating
- No current human data- pharmacokinetic evidence suggests the HD would help
 - Healthy volunteers with ESRD
 - Dialysis removes 62% at 2 H and 68% at 4 h.
- HD can cause fluid shifts, decreased serum osmolality and cerebral edema-problem with ICH

	Dabigatran	Rivaroxaban
FDA Indications	Nonvavular a.fib	Nonvavular a.fib; Ortho Replacement VTE prophylaxis
Mechanism	Inhibits free and clot bound Thrombin (IIa)	Inhibits Factor Xa
Dose	150 mg BID; 75 mg BID	20mg QD; 15 mg QD 10 mg QD
Onset & $\frac{1}{2}$ Life	1.5-3hrs; 14-17 hrs	2-4 hrs; 5-9 hrs
Lab Monitoring	ECT; TT	Anti-Xa assay
Interactions	P-Glycoprotein	P-Glycoprotein & CYP 3A4 inhibitors

P-Glycoproteins

- Efflux transporters
- Using ATP as an energy source, they transport certain hydrophobic substances in the following directions:
- Out of brain, gonads
- Into the gut, urine, bile
- Substrates, Inhibitors, Inducers



Bleeding Management

- Assess severity of bleeding
- Assess severity of anticoagulation
- Additional Labs: CBC, Type and Cross, Creatinine, Transaminases

Mild to Moderate Bleeding

- Risk vs Benefit to hold anticoagulation
- Local Control of Bleeding
- Transfuse Blood Products

Severe Bleeding

- Hold anti-coagulant
- Transfuse blood products (PRBC's, FFP)
- Surgery or Embolization?
- Activated Charcoal ?
- Consider aPCC or PCC
- ? Dialysis for Dabigatran
- Consider antifibrinolytic therapy (tranexamic acid)
- Consider ~~FXIIa~~ FVIIa

On the Horizon

- Monoclonal antibody for Dabigatrin
- Plasma- derived and recombinant factor Xa

Overdose

- No current evidence
- AC absorbs (animal data)
- 2-3 fold elevations well tolerated, accidental ingestions unlikely to have bleeding complications
- In large overdose with severe uncontrolled bleeding, HD should be considered

Procedures

- Discontinue dabigatran & Rivaroxaban 24 hrs (CrCl 50 mL/min or greater) or 48 hrs (CrCl less than 50 mL/min) prior to invasive or surgical procedure if possible due to the increased risk of bleeding;
- Longer times should be considered in patients undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port.
- Anticoagulant therapy should be reinitiated as soon as possible after procedure

Antiplatelet Agents

- Irreversible cyclooxygenase inhibitors
 - Aspirin
- Adenosine diphosphate (ADP) receptor inhibitors
 - Clopidogrel, ticlopidine
- Phosphodiesterase inhibitors
 - Cilostazol (pletal)
- Glycoprotein IIB/IIIa inhibitors (I.V. only)
 - Abciximab, eptifibatide, tirofiban
- Adenosine reuptake inhibitors
 - Dipyridamole (Persantine)

Antiplatelet Agents: Hemorrhage

- Management
 - Discontinuation of antithrombotic drugs
 - Resuscitation with intravenous fluid
 - Packed red cell transfusion
 - Surgical or other procedures to control the bleeding.
 - Platelets (in severe bleeding)
 - No known antidote