Reversal Agents for DOACs

Shriya Sawant and Shivam Gupta, The GTF Group

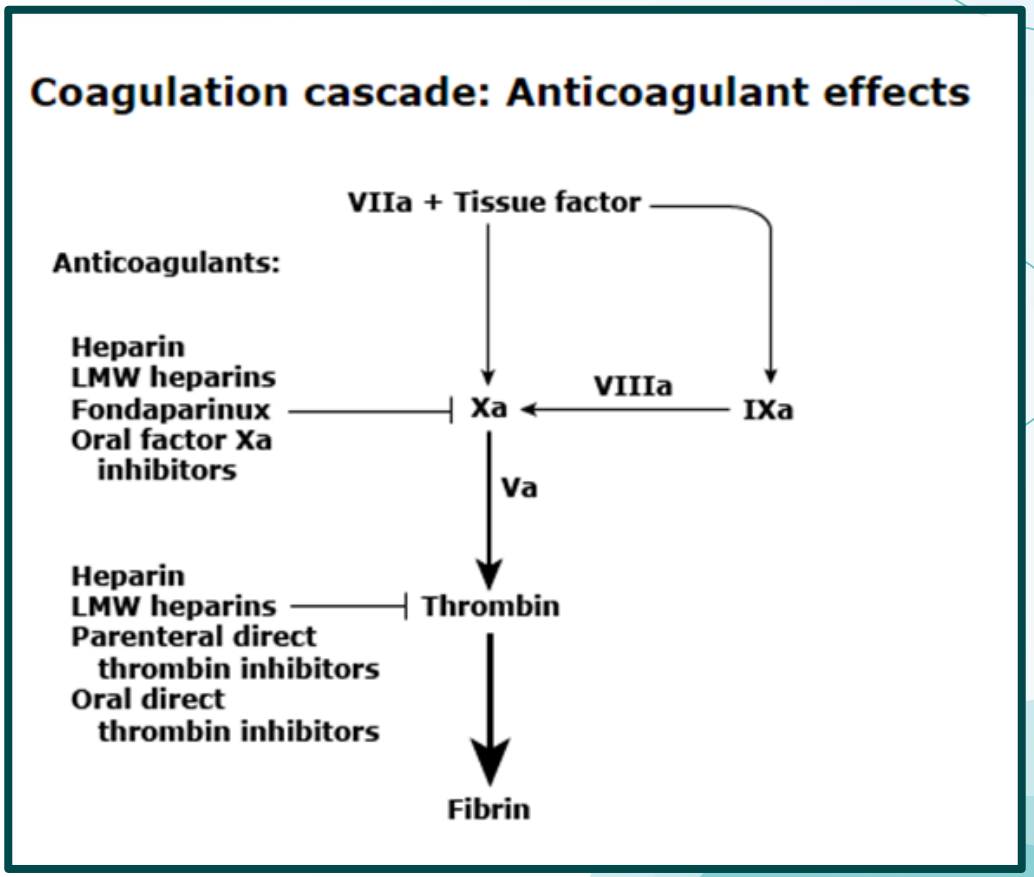
Abstract

- Direct Oral Anticoagulants (DOACs) are widely used to treat conditions such as venous thromboembolism (VTE), atrial fibrillation (AF) and acute coronary syndrome (ACS).
- Bleeding is a major adverse effect of the DOACs.
- We will review the reversal agents used to treat the adverse effects of DOACs.

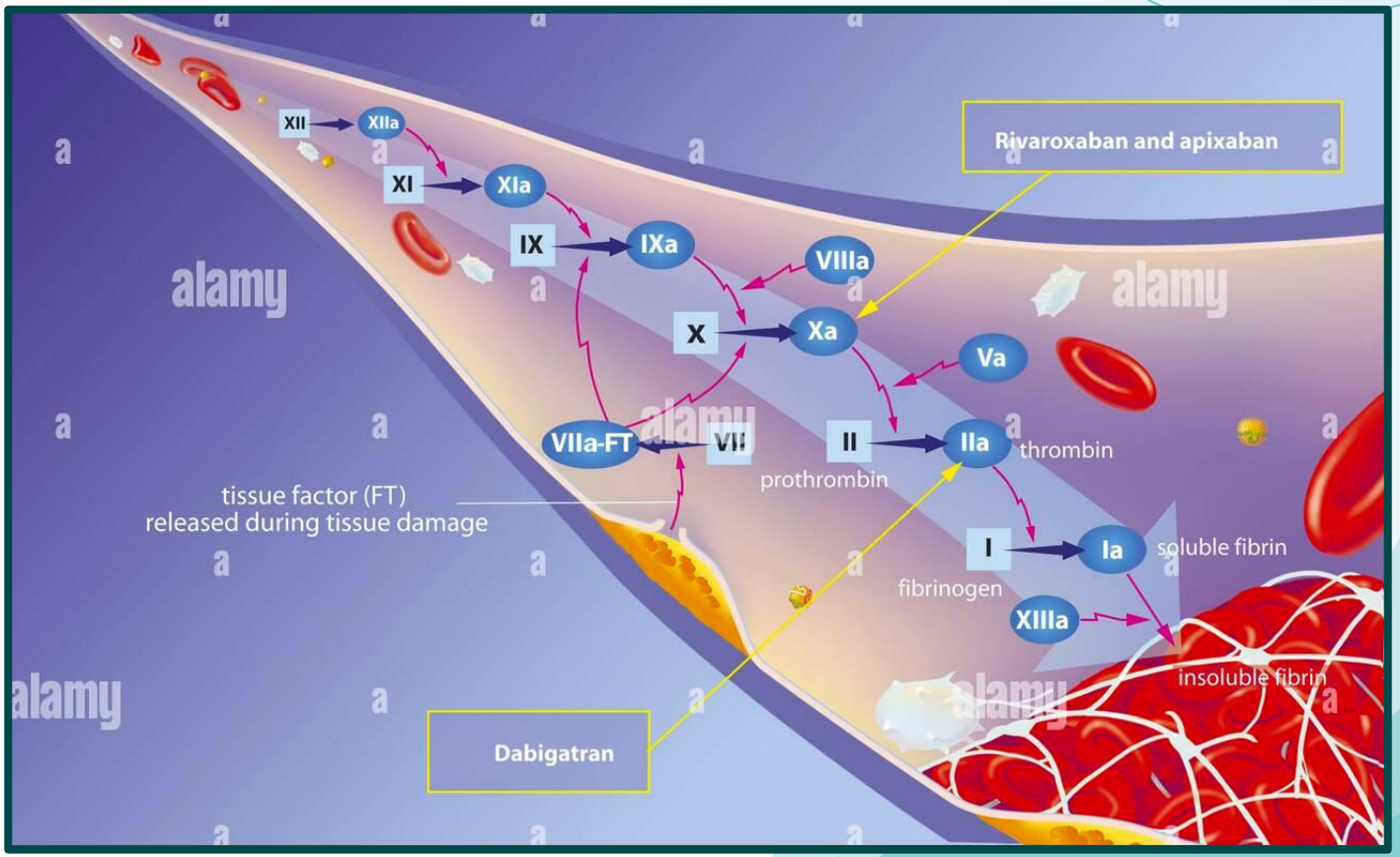
What are DOACs?

- Oral medications that directly inhibit a specific enzyme in the coagulation cascade.
- By blocking the coagulation cascade they prevent formation of a clot and thus they act as blood thinners.

Mechanism of Action



Mechanism of Action (Continued)



Examples of DOACs

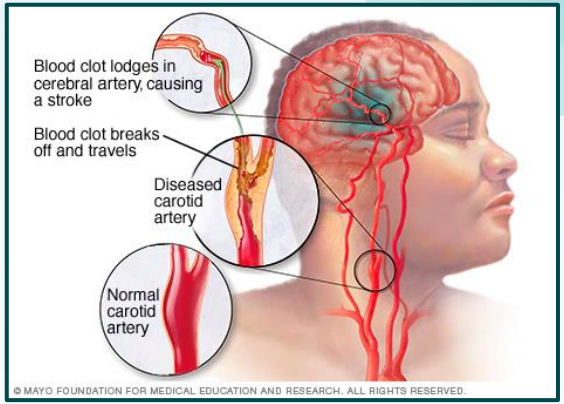
- Thrombin (factor lla) inhibitor: Dabigatran
- Factor Xa inhibitors: Rivaroxaban, Apixaban, Edoxaban, and Betrixaban (discontinued in 2020)
- Milvexian is an investigational direct oral anticoagulant (DOAC) that targets the active form of factor XI.

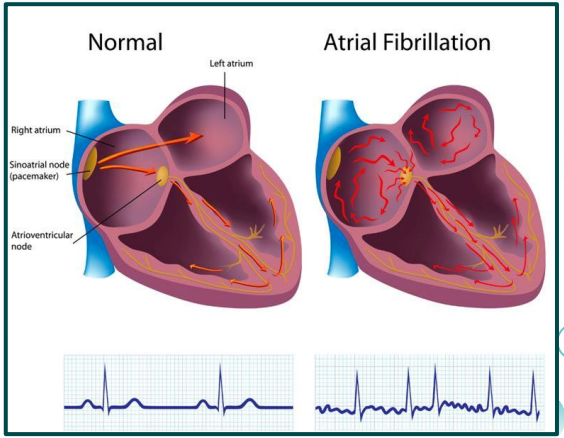
Uses

- Venous thromboembolism (VTE)
  - Used for prevention of VTE in both orthopedic and non-orthopedic patients
  - Used for treatment of VTE in non-cancer and cancer patients, both for initial as well as long term anticoagulation

Uses

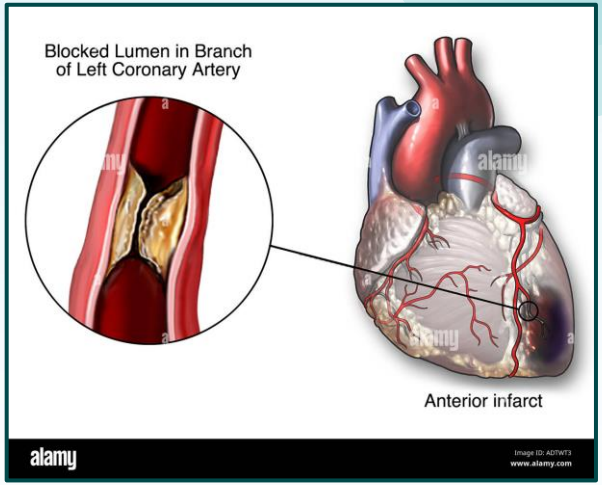
- Atrial Fibrillation
  - Irregular heartbeat which can lead to clot formation
  - Blood clots can travel from the heart and cause ischemic stroke and other embolic events





Uses

- Acute coronary syndrome
- Block in the coronary artery leads to low blood flow to the heart causing heart attack
- DOACs can be used for long term anticoagulation in these patients



Adverse Effects of DOACs: Bleeding

- DOACs prevent the body's natural clotting mechanism. Hence they increase the risk of bleeding
- Such bleeding can range in severity from a minor bleeding to a serious and sometimes life threatening bleeding.
- In cases of serious bleeding, like stomach ulcer bleed or intracranial bleed, patients need to stop the DOAC and get treatment for the bleeding

Anticoagulation Status: Drug Half-Life

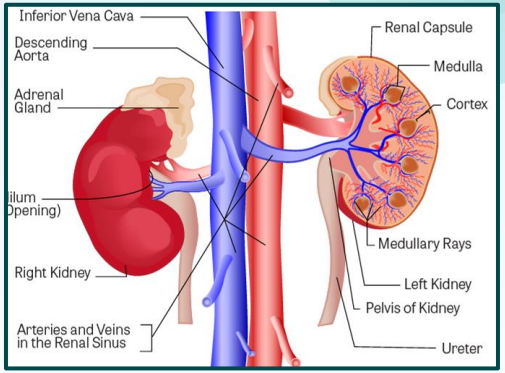
- The half-life of a drug is the amount of time it takes for the body to halven a drug's activity. This time can vary depending on how the body gets rid of it.

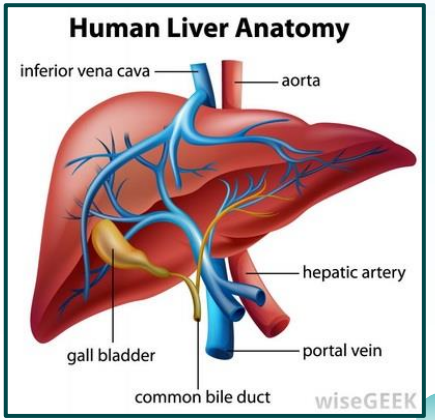
Dabigatran	12-17 hours
Apixaban	8-15 hours
Edoxaban	6-11 hours
Rivaroxaban	5-9 hours

Half-Life of common DOACs in patients with normal renal or hepatic function. Anticoagulation is considered to be resolved after 5 half-lives since the most recent dose.

Renal and Hepatic Excretion

- Renal and Hepatic excretion are two major ways the body gets rides of drugs, the first removed by the kidneys and the latter removed by the liver.
- Renal/hepatic impairment can therefore affect the half-life of a DOAC, possibly having a longer half-life than a patient without that issue.





Does Coagulation Testing Help?

- Prothrombin time (PT), international normalized ratio (INR) and partial thromboplastin time (PTT) are usually used to assess the coagulation status
- DOACs do not significantly affect these tests. Hence these tests cannot be used to assess the degree of anticoagulation achieved with a DOAC.

Initial Assessment

- Severity of bleeding
- Active bleeding vs bleeding in recent past
- Location of bleeding
- Last dose of DOAC
- Use of other blood thinners
- Liver and kidney disease

Reversal Agent for Dabigatran

- Idarucizumab
- Brand Name: Praxbind
- Humanized anti-dabigatran monoclonal antibody fragment

The Mechanism of Action of Idarucizumab

- Idarucizumab binds to the dabigatran with an affinity ≈350-fold higher than the affinity of dabigatran for thrombin
- Once dabigatran is complexed to idarucizumab, the anticoagulant effects of unbound and protein-bound dabigatran and its active metabolites are neutralized.

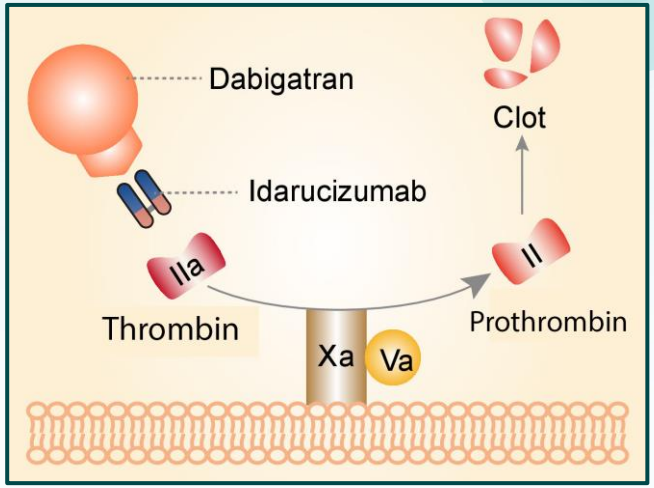
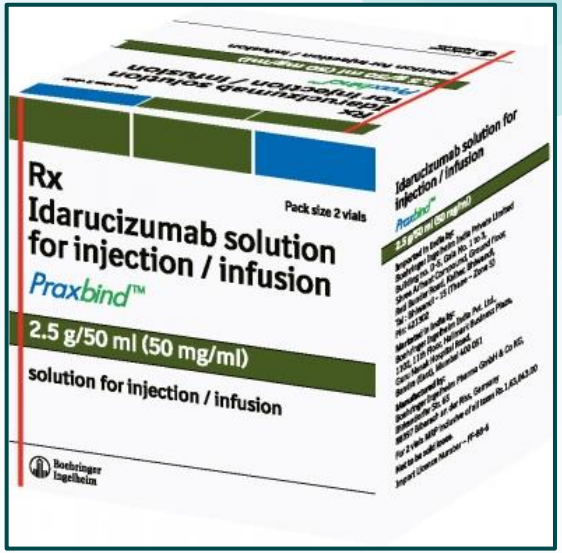


Image from https://www.creativebiolabs.net/idarucizumab-overview.htm

Dose of Idarucizumab

- The dose is 5 grams (two 2.5 g vials), which can be administered either as two consecutive infusions or as a bolus (ie, injecting both vials consecutively via syringe).



Uses of Idarucizumab

- Idarucizumab is used when conservative bleeding management measures have been ineffective
- Patient has life-threatening bleeding
- Patient needs surgery on an urgent/emergency basis

Side Effects of Idarucizumab

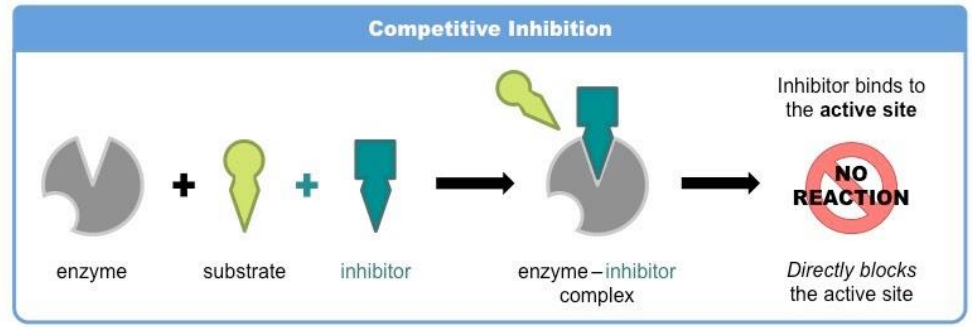
- Thrombosis is a major risk of Idarucizumab
- RE-VERSE AD study: Thrombotic events occurred in approximately 5 percent at one month and 7 percent at three months.

Reversal Agents for factor Xa inhibitors

- Andexanet alfa
- Clotting factor products
  - 4-factor PCC (Prothrombin complex concentrate) both activated and unactivated
  - Recombinant activated factor VII
  - Plasma products
- Activated charcoal

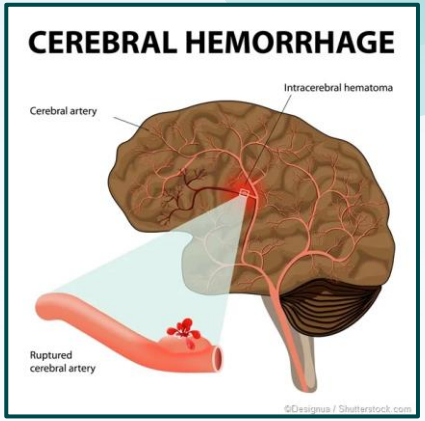
Andexanet Alfa

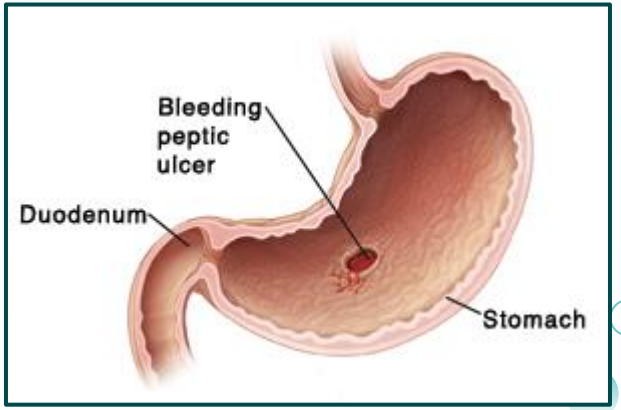
- Recombinant modified human Factor Xa protein that is catalytically inactive
  - Binds and sequesters Factor Xa inhibitors and native Factor Xa
  - Competitive inhibitor



Use of Andexanet Alfa

- Life-threatening bleeding where conservative management strategies have failed
- Surgery is required on an urgent basis





Unactivated and Activated PCC

- Prothrombin Complex Concentrates
- Types:
  - 4-factor PCC contains unactivated forms of factors II, VII, IX and X
  - 3-factor PCC contains unactivated forms of factors II, IX and X
- Activated and inactivated form
- Factor VIII inhibitor activity bypassing agent (FEIBA) is the only aPCC available in USA

Side Effects of Reversal Agents

- Thrombosis is a major risk
- Little evidence to estimate the risk of thrombosis
- Andexanet alpha ANNEXA-4 study: Adverse events included thromboses in 34 of 352 patients (10 percent), distributed across the 30 days of follow-up.

Acknowledgments

We are thankful to:

- The board of directors of GTF for giving us this opportunity
- Our parents for their support
- Our mentor Dr. Garud for his time guiding us for this project

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