DIRECT ACTING ORAL ANTICOAGULANTS

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Direct Acting Oral Anticoagulants (DOACs) | MOA , Indications, Adverse Reactions, Contraindications

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OUTLINE

I) MECHANISM OF ACTION

(A) FACTOR IIa (THROMBIN) INHIBITORS

1) **Argatroban (IV)**
   - Alternative for patients that cannot take heparin
     - Heparin Induced Thrombocytopenia (HIT)
     - Allergic to Heparin
2) **Bivalirudin (IV)**
   - Alternative for patients that cannot take heparin
     - HIT
     - Allergy
3) **Dabigatran (PO)**

Review Coagulation Cascade

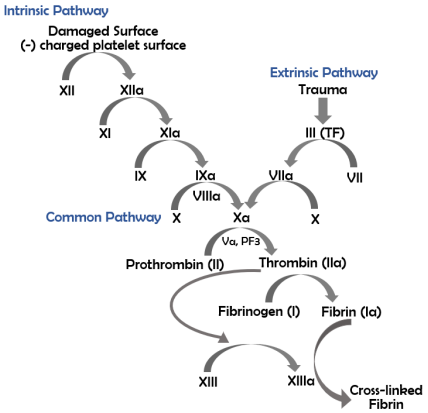

Figure 1. Coagulation Cascade

- **Intrinsic Pathway**
  - Platelet plug forms negatively charged surface on platelet that activates Factor XII
  - Factor XIIa activates Factor XI
  - Factor XIa activates Factor IX
  - Factor IXa and VIIIa activate Factor X
- **Common Pathway**
  - Factor X is activated via the clotting factors produced by the extrinsic or intrinsic pathway
  - Factor Xa combine with Factor Va and Platelet Factor3 (PF3) to convert Factor II (Prothrombin) into the activated Thrombin (Factor IIa)
  - **Thrombin**
    - Activates Factor V and VIII
    - Activates soluble fibrinogen (Factor I) into the insoluble fibrin (Factor Ia)
    - Activates Factor XIII into XIIIa that crosslinks fibrin strands producing fibrin mesh that stabilize platelet plug

Mechanism of Action

- **Inhibit thrombin**
  → inhibit clotting process
  → ↓clot formation progression

(B) FACTOR Xa INHIBITORS

- Potent, **higher bleeding risk**
- Good alternatives to warfarin
- all are in PO (per orem)/ oral form

1) **Rivaroxaban**
2) **Apixaban**
3) **Edoxaban**

Mechanism of Action:

- **Inhibit Factor Xa**
  → inhibit activation of prothrombin to thrombin
- **Higher bleeding risk** since Factor Xa activates multiple thrombins that activate multiple fibrinogens
- Inhibiting Factor Xa would have more profound effect on the downstream cascade as compared to inhibiting thrombin
- Inhibiting factors higher up in the coagulation cascade will have a more amplified effect on anticoagulation
- Inhibition of Factor Xa will inhibit activation of multiple thrombins
  → ↑bleeding risk

Important to Remember:
Direct Factor IIa Inhibitors: alternative to **Heparin**
Direct Factor Xa Inhibitors: alternative to **Warfarin**

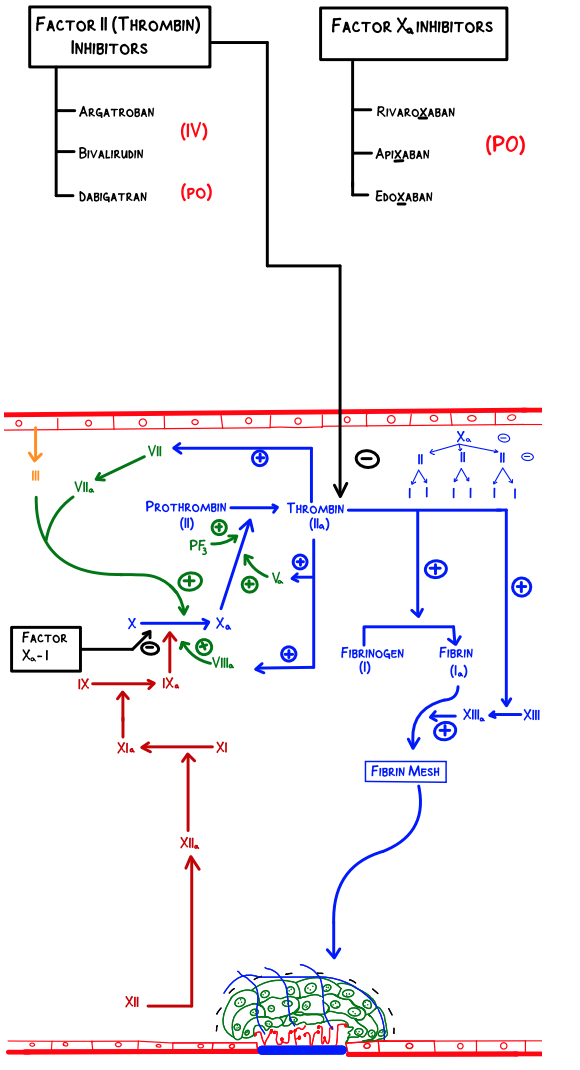

Figure 2. Mechanism of Action of Factor II Inhibitors and Factor X_a Inhibitors

II) INDICATIONS

- **Similar to Heparin**

(A) ACUTE DEEP VEIN THROMBOSIS (DVT)/ ACUTE PULMONARY EMBOLISM (PE)

- Patients that cannot take heparin (i.e. HIT, allergy)
- **Factor IIa Inhibitors (IV)**
  - **Argatroban**
  - **Bivalirudin**

(B) PROPHYLAXIS OF DVT/ PE

- Conditions that ↑risk of clotting
  - surgery
  - hypercoagulable conditions
  - malignancies
- Warfarin-like effect
- **Dabigatran (PO)**: LMWH-like effect
- **Factor Xa Inhibitors (PO)**
  - **Rivaroxaban**
  - **Apixaban**
  - **Edoxaban**

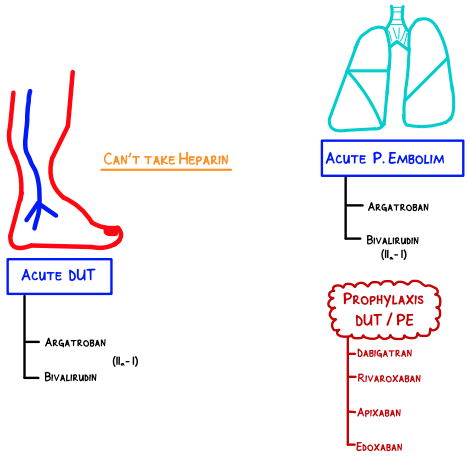

Figure 3. Role of Direct Acting Anticoagulants on DVT and PE Management

(C) NON-VALVULAR ATRIAL FIBRILLATION

- Management of patients that cannot take heparin

Pathophysiology

- Not caused by a problem with a heart valve
  - No mitral valve disease
  - No mitral stenosis
  - No rheumatic fever that can cause inflammation in mitral stenosis
  - No senile cardiac valve fibrosis
- Possible causes
  - Catecholamine
  - Methamphetamine overdose
  - Hypothyroidism
  - Hypoxic due to lung disease
  - Electrolyte Imbalances that can alter atrial circuitry but not affect valve
- Clots form in the heart due to blood stasis when atria have multiple ectopic foci and fire at different areas
- Contractions not powerful enough to push blood from atria to ventricles

Treatment Strategy

1) **Rate Control**
2) If rate control fails, try **Rhythm Control**
   - **Cardioversion** (shock)
   - **Prior to cardioversion**
     - Conduct **transesophageal ECG**
     - Make sure that there is no thrombus in atria before cardioversion
     - If there is a **thrombus**, give **Heparin**
     - Cardioversion will result to reverting the atria to the normal circuitry
       → normal contractions
       → thrombi can break off and travel to different parts of the body
       → embolism
   - **After cardioversion**
     - **Anticoagulate with heparin**
       - prevent thrombi from breaking off or prevent formation of new thrombi since cardioversion will improve the contraction of atria
     - If patient has **HIT or allergic to heparin**, give:
       - **Argatroban and Bivalirudin (IV)**
         - Acute treatment (if w/ thromboembolism)
       - **Rivaroxaban, Apixaban, Edoxaban** (Factor Xa Inh) **(PO)**
         - contraindicated in patients with prosthetic heart valve/ mechanical heart valve
         - studies show that giving Factor Xa Inhibitors still increase thrombogenic potential in these patients

Recall: Valvular AFib, give **Warfarin**

- Preventing embolism due to AFib will prevent:
  - Cerebrovascular accident (CVA): clot in brain circulation
  - Renal infarct: renal circulation
  - Splenic infarct: splenic circulation
  - Mesenteric ischemia: Superior mesenteric artery
  - Ischemic colitis: Inferior Mesenteric Artery
  - Limb gangrene: necrosis due to blocked artery in leg

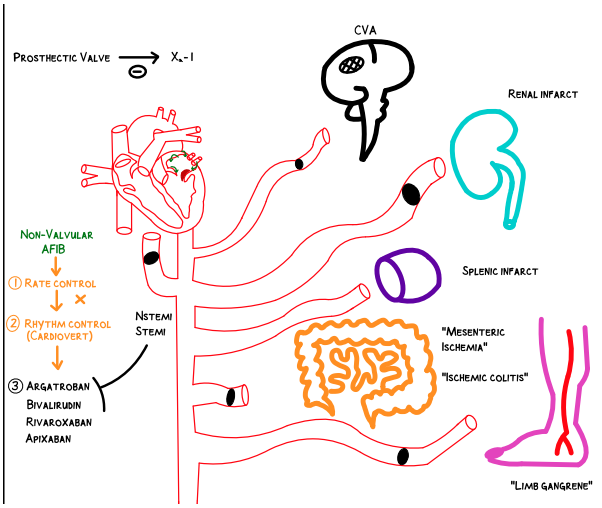

Figure 4. Role of Direct Acting Anticoagulants on the Management of Non-valcular AFib and Prevention of Embolism

(D) NSTEMI/ STEMI

- Alternative to Heparin
  - **Argatroban & Bivalirudin**

III) ADVERSE DRUG REACTIONS

(A) BLEEDING

- Anticoagulants → ↑bleeding risk since they are thinning the blood to prevent clot formation or progression of clot formation

1) **Gingival Bleeding**
2) **Anterior Epistaxis** – nosebleed
3) **Rectal bleeding**
   a. **Melena** – upper GI bleed – dark or black feces
   b. **Hematochezia** – lower GI bleed – bright red stool
4) **Hematemesis** – vomiting blood
5) **Iron Deficiency Anemia**
   - Fecal occult blood test: to check unseen GI bleed
   - CBC
6) **Hematuria** – blood in urine
7) **Excessive Vaginal bleeding or menstrual bleeding**

8) **Bleeding indications on skin**
   a. **Petechiae** – pinpoint hemorrhage on skin
   b. **Purpura** – larger pinpoint hemorrhaging
   c. **Ecchymosis** – large bruising

Antidote for Dabigatran
- Idarucizumab
  - *Monoclonal antibody* that will bind to dabigatran and inactivate it

Antidote for Factor Xa Inhibitors (Apixaban, Rivaroxapan)
- Andexanet alfa

Treatment for ↑↑ Bivalirudin and Argatroban
- No antidote
- Prothrombin Complex Concentrate (PCC) to replace clotting factors and reverse severe bleeding
  - Factor II (thrombin), VII, IX, X: procoagulant
  - Protein C, S: anticoagulant (opposing effect)
  - AT III: anticoagulant (opposing effect)

Important!
- **Do not suddenly stop** these medications since there is an increased risk of clotting if they are abruptly withdrawn

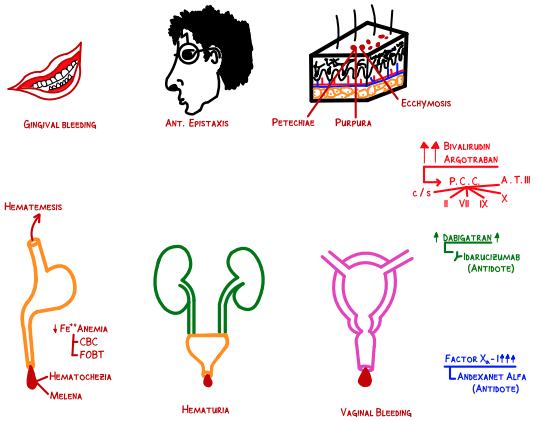

Figure 5. Adverse Drug Reactions caused by Direct Acting Anticoagulants and their Antidotes

IV) CONTRAINDICATIONS

(A) BLEEDING RISKS

(1) Uncontrollable bleeding

- Stop anticoagulants

(2) Recent CVA

- Giving anticoagulants can convert ischemic stroke to hemorrhagic transformation

(3) Uncontrolled ↑BP

- Increased risk of aortic dissection (smokers)
- Increases risk of aortic aneurysm (old patients, thinner aortic walls)

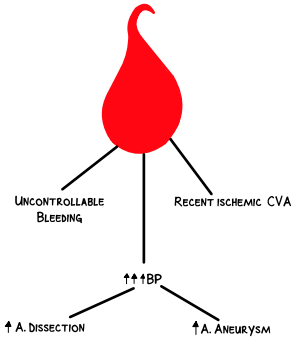

Figure 6. Direct Acting Anticoagulants are Contraindicated in Patients that have an Increased Risk of Bleeding

Summary
- **Factor IIa Inhibitors**
  - Bivalirudin, Argatroban, Dabigatran
  - Used when patients cannot take heparin
    - HIT
    - allergic to heparin
    - renal failure
- **Factor Xa Inhibitors**
  - Rivaroxaban, Apixaban, Edoxaban
  - Used in place of Warfarin
  - Disadvantages of Warfarin:
    - Many drug interactions (Recall: CYP450 Inhibitors "O DEVICES" and Inducers "CP BARS")
    - Monitor PT-INR constantly to make sure that warfarin dose is correct (no risk of clotting or bleeding)- can affect patient compliance
    - Takes a long time to kick in (vs. Factor Xa Inhibitors: quick onset)
  - Due to the disadvantages of Warfarin, Factor Xa inhibitors are now becoming more commonly used (except for Valvular AFib), but they are more expensive.

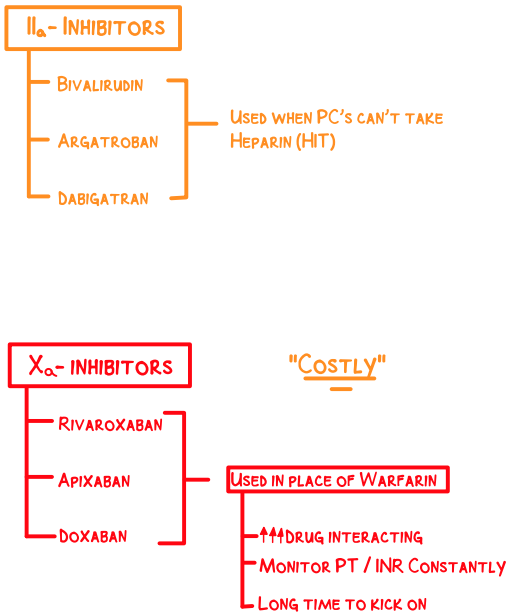

Figure 7. Summary of Uses of Factor II Inhibitors and Factor X_a Inhibitors

V) REVIEW QUESTIONS

1) **Factor IIa Inhibitor that is in PO form:**
   a. Rivaroxaban
   b. Dabigatran
   c. Bivalirudin
   d. Apixaban

2) **Antidote for Dabigatran:**
   a. Idarucizumab
   b. Andexanet alfa
   c. PCC
   d. Vitamin K

3) **What is used as an alternative if patients cannot tolerate heparin?**
   a. Factor Xa Inhibitors
   b. Factor IIa Inhibitors
   c. Warfarin
   d. Apixaban

4) **True or False: Factor IIa Inhibitors can be given in Valvular AFib.**
   a. True
   b. False

5) **True or False: Factor IIa Inhibitors have higher risk of bleeding than Factor Xa Inhibitors.**
   a. True
   b. False

CHECK YOUR ANSWERS

VI) REFERENCES

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