SNAPSHOT OF ANTITHROMBOTIC THERAPY WITH A FOCUS ON THE PERIOPERATIVE PERIOD
A PHARMACIST’S PERSPECTIVE

Katie Cinnamon, PharmD, BCPS
Clinical Pharmacist

DISCLOSURE
- The content of this presentation is based on my professional views as a pharmacist and has no association or conflicts with any other organizations or employers.

OBJECTIVES
- Review the basics of clot formation
- Discuss the basic pharmacology of anticoagulants (Coumadin, Heparin, Lovenox, Aristixtra, Pradaxa, and Xarelto)
- Understand how to manage these medications during the perioperative period
How Does Blood Clot?

NORMAL PHYSIOLOGY OF THE VASCULAR SYSTEM

Under normal circumstances, as blood flows through the blood vessels, the endothelial cells on the vessel wall maintain blood flow by producing substances that inhibit platelet adherence, prevent the activation of the coagulation cascade, and facilitate fibrinolysis.

PATHOLOGIC CLOT FORMATION

Virchow's Triad
- Vascular injury or trauma
- Venous stasis or "blood pooling"
- Hypercoagulable states

Alterations in any one of these elements may lead to pathologic clot formation.
**VIRCHOW’S TRIAD**
- Cancer
- High estrogen states
- Family history
- Inflammatory Bowel
- Nephrotic Syndrome
- Blood transfusions
- Thrombophilia
- Surgery
- Prior DVT or PE
- Central venous access
- Trauma
- Chemotherapy

**PATHOLOGIC CLOT FORMATION**
- If vascular injury occurs, this can expose the subendothelial cells, in which platelets readily adhere to. This results in **platelet aggregation**. Tissue factor is released from the damaged vessel, which results in activation of the extrinsic pathway of the **coagulation cascade**.

**“RED CLOTS” vs. “WHITE CLOTS”**
- To simplify the different types of clots in order to determine the appropriate treatment, the type of clot can be categorized as either a **“red clot”** or a **“white clot”**.
- Remember that most clots will have both platelet aggregation AND involvement of the coagulation cascade (fibrin). However, one usually predominates, which helps us determine the most appropriate treatment.
“WHITE CLOTS”

- "White Clot": The primary mechanism of clot formation is platelet aggregation because the blood has a fast flow.
- Antiplatelet agents are preferred for treatment.
  Think of fast blood flow = arteries.
- Examples: Noncardioembolic ischemic stroke, peripheral occlusive arterial disease, coronary artery disease.

**ANTIPLATELETS**

- Aspirin
- Aggrenox (aspirin/dipyridamole)
- Plavix (clopidogrel)
- Effient (prasugrel)
- Brilinta (ticagrelor)
- Ticlid (ticlopidine)

**Please Note:** This list is not all inclusive.
**“Red Clots”**

- **Red Clot**: The primary mechanism of clot formation is slowed blood flow or "pooling" of the blood. Because the blood flow is slow, clotting factors predominate, because there generally is more time for the coagulation cascade to become activated.
- **Agents that inhibit the coagulation cascade (anticoagulants)** are preferred for treatment. Think of **slow blood flow=veins**.
- **Examples**: DVT, PE, atrial fibrillation and heart valve replacement

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**ANTICOAGULANTS**

- Coumadin (warfarin)
- Heparin
- Lovenox (enoxaparin)
- Arixtra (fondaparinux)
- Pradaxa (dabigatran)
- Xarelto (rivaroxaban)
- Argatroban

**Please Note**: This list is not all inclusive.
Pharmacology of Anticoagulants

Coumadin® (Warfarin Sodium)

Mechanism of Action

Vitamin K

Synthesis of Functional Clotting Factors
MECHANISM OF ACTION

- Inhibits enzyme in the Vitamin K conversion pathway
- **End result:** Diminished coagulant activity of clotting factors II, VII, IX, and X since they depend on vitamin K to become activated

COAGULATION CASCADE

COUMADIN

**Indications:**
- DVT/PE (treatment and prophylaxis)
- Atrial fibrillation
- MI
- Cardioembolic stroke
- Prosthetic heart valves

**Dose:**
- Individualized for each patient
FACTORS AFFECTING COUMADIN

Patient Characteristics
- Lower albumin concentrations/malnutrition
- Drug interactions
- Multiple disease states (fever, infection, heart failure exacerbation, ascites/liver cirrhosis)

Diet
- Foods high in vitamin K
  - Green leafy vegetables
  - Beef liver
  - Green tea

ADVERSE EFFECTS

Bleeding

Skin necrosis
- Uncommon
- Usually associated with protein C deficiency
- Usually observed between the 3rd and 8th days of therapy

Purple-toe syndrome
- Occurs 3 to 8 weeks after initiation
- Causes pain and discoloration
- Caused by cholesterol emboli from atheromatous plaques with bleeding into plaque

CONTRAINDICATIONS/PRECAUTIONS

- Pregnancy (especially 1st trimester)
- Active bleeding
- Invasive surgery
- History of skin necrosis from Coumadin
**Monitoring**
- PT/INR
- CBC
- Signs of bleeding/bruising

**Drug Interactions**

**Increased Coumadin Effect**
- Amiodarone
- ‘Azole’ Antifungals
- Cimetidine
- Fluoroquinolones
- Macrolides
- Metronidazole
- Sulfamethoxazole/trimethoprim

**Decreased Coumadin Effect**
- Phenobarbital
- Nafcillin
- Rifampin
- Phenytoin
- Carbamazepine
- Cholestyramine
DRUG INTERACTIONS
INCREASED RISK OF BLEEDING

Aspirin

NSAIDs

Heparin

Mechanism of Action:
- Binds to and enhances antithrombin (a natural anticoagulant)
- Inhibits clotting factors IIa (thrombin) and Xa
- End result = Inhibits fibrin production
**Heparin**

- **Indications:**
  - DVT/PE (treatment and prophylaxis)
  - Atrial fibrillation
  - MI
  - Cardioembolic stroke
  - Prosthetic heart valves
  - Disseminated Intravascular Coagulation
  - Maintain patency of indwelling catheters

- **Dose:**
  - **DVT Prophylaxis** — 5000 units SQ q8h or q12h
  - **Treatment** — Based on weight and indication
    - DVT/PE — 80 units per kg bolus then 12 units per kg per hr initial infusion rate
    - Cardiac — 60 units per kg bolus then 12 units per kg per hr initial infusion rate
    - Cardioembolic Stroke — NO BOLUS then 12 units per kg per hr initial infusion rate
HEPARIN

- **Adverse Effects:**
  - Bleeding
  - Hypersensitivity reactions
  - HAT/HIT
  - Long-term - alopecia, priapism, hyperkalemia, elevated ALT/AST, and osteoporosis

- **Contraindications/Precautions:**
  - Active bleeding
  - Severe thrombocytopenia
  - Previous hypersensitivity reaction to heparin
  - History of HIT (especially if recent)

- **Drug Interactions:**
  - Other antithrombotic agents

- **Monitoring:**
  - PTT
  - CBC
  - Signs of bleeding/bruising

LOVENOX® (ENOXAPARIN)

**LOVENOX (ENOXAPARIN)**

- **Mechanism of Action:**
  - Derived from heparin
    - Low molecular weight heparin
    - More predictable response
    - Longer plasma half-life
    - Lower incidence of HIT
    - Lower risk of osteopenia
  - Binds to and enhances antithrombin
    - Binds to and enhances antithrombin
    - Inhibits clotting factors IIa (thrombin) and Xa
    - End result = Inhibits fibrin production

**Indications:**
- DVT/PE (treatment and prophylaxis)
- MI
- “Bridging”
<table>
<thead>
<tr>
<th><strong>LOVENOX® (ENOXAPARIN)</strong></th>
<th><strong>LOVENOX® (ENOXAPARIN)</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Dose:</strong></td>
<td><strong>Dose:</strong></td>
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<tr>
<td>- <strong>Prophylaxis:</strong></td>
<td>- <strong>Prophylaxis:</strong></td>
</tr>
<tr>
<td>40 mg SQ q24h</td>
<td>30 mg SQ q12h</td>
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<tr>
<td>30 mg SQ q12h</td>
<td>Renal Impairment – 30 mg SQ q24h</td>
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<tr>
<td>Morbid Obesity – 40 mg SQ q12h</td>
<td>Morbid Obesity – 40 mg SQ q12h</td>
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<tr>
<td><strong>Treatment:</strong></td>
<td><strong>Treatment:</strong></td>
</tr>
<tr>
<td>- DVT/PE – 1 mg per kg SQ q12h or 1.5 mg per kg SQ q24h</td>
<td>- STEMI –</td>
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<tr>
<td>- STEMI –</td>
<td>Age &lt; 75: 30 mg IV bolus then 1 mg per kg SQ q12h</td>
</tr>
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<td>Age ≥ 75: 0.75 mg per kg SQ q12h (no bolus)</td>
<td>NSTEMI – 1 mg per kg SQ q12h</td>
</tr>
<tr>
<td>Renal Impairment – 1 mg per kg SQ q24h</td>
<td>Renal Impairment – 1 mg per kg SQ q24h</td>
</tr>
<tr>
<td><strong>Adverse Effects:</strong></td>
<td><strong>Contraindications/Precautions:</strong></td>
</tr>
<tr>
<td>Bleeding</td>
<td>Active bleeding</td>
</tr>
<tr>
<td>HIT (less common than with heparin)</td>
<td>Lumbar puncture/Indwelling Epidural Catheter</td>
</tr>
<tr>
<td><strong>Contraindications/Precautions:</strong></td>
<td>HIT</td>
</tr>
</tbody>
</table>
LOVENOX® (ENOXAPARIN)

○ Drug Interactions:
  - Other antithrombotic agents

○ Monitoring:
  - CBC
  - Signs of bleeding/bruising
  - Serum creatinine/renal function

ARIXTRA® (FONDAPARINUX SODIUM)

○ Mechanism of Action:
  - Inhibits clotting factor Xa

  ![Fondaparinux Mechanism of Action Diagram]

  *Image source: [https://www.proprofs.com/flashcards/upload/q3422408.jpg](https://www.proprofs.com/flashcards/upload/q3422408.jpg)*
Indications:
- DVT/PE prophylaxis after orthopedic surgery and abdominal surgery
- Acute DVT/PE treatment

Dose:
- **DVT/PE Prophylaxis:**
  - 2.5 mg SQ q24h
- **DVT/PE Treatment:**
  - Weight <50 kg = 5 mg SQ q24h
  - Weight 50-100 kg = 7.5 mg SQ q24h
  - Weight > 100 kg = 10 mg SQ q24h

ARIIXTRA® (FONDAPARINUX SODIUM)
ARIIXTRA® (FONDAPARINUX SODIUM)

- **Adverse Effects:**
  - Bleeding

- **Contraindications/Precautions:**
  - Weight < 50 kg for prophylaxis
  - Renal Impairment (CrCl < 30 mL/min)
  - Active bleeding

ARIIXTRA® (FONDAPARINUX SODIUM)

- **Drug Interactions:**
  - Other antithrombotic agents

- **Monitoring:**
  - CBC
  - Signs of bleeding/bruising
  - Serum creatinine/renal function

**MECHANISM OF ACTION**

HEPARIN, LOVENOX, AND ARIXTRA

- Heparin
- Lovenox
- Arixtra

10/1/12
PRADAXA® (DABIGATRAN ETEXILATE)

- FDA Approved on October 19th, 2010
- Route of Administration = Oral

PRADAXA® (DABIGATRAN ETEXILATE)

- Mechanism of Action:
  - Direct thrombin (Factor IIa) inhibitor
  - End result: Inhibits fibrin production

- FDA-Approved Indication:
  - Non-valvular Atrial fibrillation
**COAGULATION CASCADE**

**PRADAXA® (DABIGATRAN ETEXILATE)**

- **Dose:**
  - **CrCl > 30 mL/min**: 150 mg PO bid
  - **CrCl 15-30 mL/min**: 75 mg PO bid
  - **CrCl < 15 mL/min & dialysis**: Cautions

- **Adverse Effects:**
  - Bleeding
  - Dyspepsia

- **Contraindications/Precautions:**
  - Active bleeding
  - Hypersensitivity reaction to Pradaxa
  - Renal impairment
**PRADAXA® (DABIGATRAN ETEXILATE)**

- **Drug Interactions:**
  - Other antithrombotic agents
  - Rifampin

- **Monitoring:**
  - CBC
  - Signs of bleeding/bruising
  - Serum creatinine/renal function
  - Do NOT administer via feeding tube

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**XARELTO® (RIVAROXABAN)**

- **Mechanism of action**
  - Direct Factor Xa Inhibitor
  - End result: Inhibits fibrin production

- **Indication**
  - DVT prophylaxis s/p hip and knee replacement surgery
  - Non-valvular A.fib – reduce the risk of stroke and systemic embolism
XARELTO® (RIVAROXABAN)

- **Dose**
  - DVT Prophylaxis:
    - 10 mg PO once daily with or without food
    - Initial Dose: at least 6-10 hours after surgery
  - Recommended Duration:
    - Hip Replacement – 35 days
    - Knee Replacement – 12 days

- **A.fib:**
  - 20 mg PO daily with evening meal
XARELTO® (RIVAROXABAN)

Dose Adjustments:
- DVT Prophylaxis:
  - CrCl < 30 ml per min = AVOID
  - CrCl 30 – 49 ml per min –
  - Child-Pugh B/C or Hepatic Disease with Coagulopathy = AVOID
- A.fib:
  - CrCl 15 – 50 ml per min – 15 mg PO daily with evening meal
  - CrCl < 15 ml per min - AVOID

Adverse Effects
- Bleeding

Contraindications/Precautions
- Active bleeding
- Allergy to Xarelto or its product ingredients

Drug Interactions
- Other antithrombotic agents
- Combined P-gp and Strong CYP3A4 Inhibitors
  - i.e. Ketoconazole, Itraconazole, Clarithromycin, Ritonavir, Lopinavir/ Ritonavir, Indinavir/Ritonavir, Conivaptan
- Combined P-gp and Strong CYP3A4 Inducers
  - i.e. Carbamazepine, Phenytoin, Rifampin, St. John's Wort
**Xarelto® (Rivaroxaban)**

**Monitoring**
- CBC
- Signs of bleeding/bruising
- Serum creatinine/renal function
- Hepatic function
- Avoid administration via a method that could deposit the drug directly into the small intestine (e.g., J-tube)

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**PERIOPERATIVE MANAGEMENT**

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**Risk vs. Benefit**

- Bleeding
- Thromboembolism
ASSESSING RISK FOR THROMBOEMBOLISM

- **Indication for Antithrombotic Therapy**
  - Patients on antithrombotic agent prior to procedure
  - Patients receiving antithrombotic agent post-operatively (i.e. DVT prophylaxis)

- **Risk Stratification**
  - High risk: > 10% annual risk for thromboembolism
  - Moderate risk: 5-10% annual risk for thromboembolism
  - Low risk: < 5% annual risk for thromboembolism
  - Based on indirect evidence from studies outside of the perioperative setting
  - Individual patient factors may override classification

- **Surgery Type**

ASSESSING RISK FOR THROMBOEMBOLISM

**Atrial Fibrillation**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>CHADS2 Score</th>
</tr>
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<tbody>
<tr>
<td>HIGH</td>
<td>5 or 6</td>
</tr>
<tr>
<td></td>
<td>Recent stroke or TIA (within 3 months)</td>
</tr>
<tr>
<td></td>
<td>Rheumatic valvular heart disease</td>
</tr>
<tr>
<td>MODERATE</td>
<td>3 or 4</td>
</tr>
<tr>
<td>LOW</td>
<td>0, 1, or 2 and no prior stroke or TIA</td>
</tr>
</tbody>
</table>

*CHADS2 = CHF, HTN, Age ≥75, Diabetes mellitus, Stroke/TIA

CHEST 2012; 141 (2) (Suppl): e330S.

ASSESSING RISK FOR THROMBOEMBOLISM

**Mechanical Heart Valves**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Details</th>
</tr>
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<tbody>
<tr>
<td>HIGH</td>
<td>Any mitral valve prosthesis</td>
</tr>
<tr>
<td></td>
<td>Caged-ball or tilting disc aortic valve prosthesis</td>
</tr>
<tr>
<td></td>
<td>Recent (within 6 months) stroke or TIA</td>
</tr>
<tr>
<td>MODERATE</td>
<td>Bileaflet aortic valve prosthesis and one or more:</td>
</tr>
<tr>
<td></td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td></td>
<td>Prior stroke/TIA</td>
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<tr>
<td></td>
<td>HTN</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
</tr>
<tr>
<td></td>
<td>Age &gt;75</td>
</tr>
<tr>
<td>LOW</td>
<td>Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke</td>
</tr>
</tbody>
</table>

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ASSESSING RISK FOR THROMBOEMBOLISM
VENOUS THROMBOEMBOLISM (VTE)

HIGH
- Recent (within 3 months) VTE
- Severe thrombophilia (i.e. protein C/S/AT deficiency, antiphospholipid antibodies, or multiple abnormalities)

MODERATE
- VTE within the past 3 to 12 months
- Non-severe thrombophilia (i.e. heterozygous factor V Leiden or prothrombin gene mutation)
- Recurrent VTE
- Active cancer (treated within 6 months or palliative)

LOW
- Single VTE event > 12 months ago and no other risk factors

GUIDELINES FOR PERIOPERATIVE BRIDGING

Definition of “Bridging”: Administration of short-acting anticoagulant (i.e. SQ LMWH; IV UFH) during interruption of warfarin therapy when the INR is below therapeutic range

Risk of Thromboembolism (Mechanical Heart Valve, A.fib, or VTE):
- High-risk: Bridging
- Moderate-risk: Bridging or No Bridging approach
- Low-risk: No bridging

Risk of Bleeding
- Lack of validation for use of bleeding risk stratification schemes with the perioperative use of antithrombotic agents
- Dose
  - High-dose/Therapeutic-dose
  - Low-dose/Prophylactic-dose
Assessing Risk for Bleeding

- Surgeries associated with increased bleeding risk during perioperative antithrombotic drug administration
  - Urologic surgery (TURP, bladder resection, tumor ablation, nephrectomy, kidney biopsy)
  - Pacemaker or ICD implantation
  - Colon polyp resection (i.e., > 1-2 cm long)
  - Highly vascular organs (kidney, liver, spleen)
  - Bowel resection
  - Major surgery with extensive tissue injury
    - Cancer surgery
    - Joint arthroplasty
    - Reconstructive plastic surgery
  - Cardiac surgery
  - Intracranial and spinal surgery

Guidelines for Pre-operative Management of Antithrombotic Agents

- For patients who require temporary interruption of antithrombotic agents before surgery:
  - Stop warfarin ~ 5 days before surgery
  - Stop IV Heparin 4-6 hours before surgery
  - Stop therapeutic-dose SQ LMWH 24 hours before surgery (last dose recommended to be half of the total daily dose)
  - May need to stop Arixtra up to 5 days before surgery to allow full clearance of the drug
  - Stop Pradaxa 1-2 days (if CrCl ≥ 50 ml per min) or 3-5 days (if CrCl < 50 ml/min) before surgery
  - Stop Xarelto at least 24 hours before surgery
  - Stop clopidogrel (Plavix) and prasugrel (Effient) 5 days before surgery
  - Some minor procedures (minor dental procedures or cataract surgery) may not require interruption of antithrombotic therapy
  - These are GUIDELINES ONLY and must be individualized for each patient
  - Keep renal function in mind

Guidelines for Post-operative Management of Antithrombotic Agents

- Resume warfarin ~ 12-24 hours after surgery and when there is adequate hemostasis
- After consideration of anticipated bleeding risk and when adequate hemostasis has been achieved, therapeutic-dose IV heparin or LMWH may be resumed 48-72 hours after surgery
- For all antithrombotic agents, the risks of bleeding and the risks of thromboembolism must be weighed to determine when to start the medication post-operatively
- These are GUIDELINES ONLY and must be individualized for each patient
REFERENCES

- Xarelto® [package insert].
- www.medscape.com