LEARNING OBJECTIVES

- Know what factors anticoagulant medications work on in the clotting cascade or in platelet aggregation
- Understands the basic principals of the clotting cascade and platelet aggregation
- Know which drug belongs to the antiplatelet or anticoagulant
- Know difference between white clot and red clot
- Know warfarin
- Know heparin associated thrombocytopenia (HAT) and heparin induced thrombocytopenia (HIT)
- Know how to calculate protamine dose for heparin reversal
CLOTTING CASCADE

- All factors with an “a” have been activated
  12a was just 12 before it was activated
- Factor 2a is Thrombin
  - Comes from Prothrombin that was activated
- Factor 1a is Fibrin
  - Comes from fibrinogen that was activated
- Everything in red required vitamin K in order to be produced in the liver
- Everything surrounded by yellow needs calcium to be activated from ?? To ??a
PLATELET AGGREGATION

Release:
1. ADP
2. Thromboxane A2
3. Thrombin (2a)

Fibrin

Adhesion
THROMBOEMBOLIC

White Clots

Platelet rich

Form in areas of fast blood flow

Formed where damaged or abnormal endothelia surface

Red clots form over top

Treated with:
- Aspirin
- Clopidogrel
- Dipyridamole
- Prasugrel

Red Clots

Erythrocyte (RBC) rich

Form in areas of slow blood flow

No cell damage necessary

Treated with:
- Warfarin
- Heparins
- Direct thrombin inhibitors
  - Dabigatran
- Factor 10 a inhibitors
  - Rivaroxiban
  - Apixaban
Aspirin – CVD prevention

MOA: Irreversibly inhibits the formation of thromboxane A2 by irreversibly inhibiting cyclooxygenase through acetylation

Dosage forms for antiplatelet: Usually oral tablet or chewable tablet

Dosing: 81 mg effective for prophylaxis / 325 mg used depending on risk vs benefit, take with food to protect stomach

ADRs: Increased risk of bleeding, stomach upset – ulceration, hypertension, asthma, bronchospasm, hyperglycemia, and many more

Interactions: Any antiplatelet or anticoagulant, antihypertensives, antidiabetic medication

Monitoring: Signs and symptoms of bleeding, difficulty breathing, platelets, CBC,

Cl: Active bleeding, hemophilia

Antidote: None / supportive therapy

DC: 5 days prior to surgery
ANTIPLATELET

Clopidogrel (Plavix) – MI prophylaxis & thromboembolic stroke, intolerant of ASA

MOA: Prevents activation of platelet receptors by irreversibly blocking ADP receptors

Dosage forms: Oral tablet

Dosing: 75 mg / 300 mg

Kinetics: Prodrug CYP2C19, cleared by the kidneys and liver equally

ADRs: Increased risk of bleeding, GI distress (recurrent ulcer – may need a PPI), headache, anxiety, dizziness, weakness, constipation, many more

Interactions: Any antiplatelet or anticoagulant, inhibitors or inducers of CYP3A4

Monitoring: Signs and symptoms of bleeding, CBC, blood pressure, HR

Antidote: None – supportive therapy, stop prior to surgery (at least 5 days)
**ANTIPLATELET**

Ticagrelor (Brilinta) – MI treatment/prophylaxis & thromboembolic stroke

**MOA:** Prevents activation of platelet receptors by reversibly blocking P2Y 12 ADP receptors

**Dosage forms:** Oral tablet – taken with or without food

**Dosing:** 60 mg / 90 mg – must be taken with 100 mg or less of aspirin

**Kinetics:** Metabolized by CYP3A4, cleared mostly by the liver

**ADRs:** Increased risk of bleeding, dyspnea, (contraindicated in ICH, hypersensitivity, and active bleeding)

**Interactions:** Any antiplatelet or anticoagulant, inhibitors or inducers of CYP3A4

**Monitoring:** Signs and symptoms of bleeding, CBC, blood pressure, HR

**Antidote:** None – supportive therapy (PRP), stop prior to surgery (at least 5 days)
Dipyridamole – Decrease thrombosis after valve replacement, stroke prevention (off label)

MOA: Inhibit thromboxane A2, phosphodiesterase inhibitor, adenosine uptake (platelet aggregation inhibitor)

Dosage forms: IV and tablet

Kinetics: Peak concentrations in 75 minutes, highly protein bound, metabolized in liver and excreted in the bile, dosed 4 times per day

ADRs: Increased risk of bleeding, hypotension, headache, tachycardia, dizziness, abdominal upset, and rash

Interactions: Any antiplatelet or anticoagulant, theophylline (should be held 48 hours prior to dipyridamole use)

Monitoring: Signs and symptoms of bleeding, blood pressure, HR

Antidote: Aminophylline can reverse vasodilatory effects
Prasugrel (Effient) – Acute coronary syndrome (ASC) managed with percutaneous intervention (PCI) *CI in stroke/TIA

MOA: Irreversibly blocks a component of the ADP receptor on the platelet – reduce platelet activation and aggregation

Dosage forms: Oral tablet

Dosing: 10 mg daily combined with ASA

Kinetics: Prodrug activated by CYP450 enzymes (including 3A4), excretion 68% (urine) and 27% (feces)

ADRs: Increased risk of bleeding, hypertension, headache, hyperlipidemia, epistaxis, dyspnea

Interactions: Any antiplatelet or anticoagulant, CYP enzyme inhibitors or inducers (monitor)

Monitoring: Signs and symptoms of bleeding, CBC

Antidote: None – platelet return to normal after 5-9 days, supportive fresh frozen plasma (FFP) or cryoprecipitate
ANTICOAGULANTS - HEPARINS

Heparin – Clot prophylaxis, ok in pregnancy, rapid acting
MOA: Inactivates factors IXa, Xa, XIa, XIIa
Dosage forms: IV, subQ
Dosing: Based on weight or indication
Kinetics: Highly protein bound, metabolized in the liver, excreted in the kidneys
ADRs: Increased risk of bleed, HAT & HIT
Interactions: Any antiplatelet/anticoagulant
Monitoring: Signs & symptoms of bleeding, PTT, CBC, platelets!
Antidote: Protamine

Low molecular weight heparin (Lovenox) – Clot prophylaxis, DVT treatment, ASC
MOA: Mainly inactivates factor Xa
Dosage forms: SubQ
Dosing: Treatment DVT/ACT = 1 mg/kg Q 12 or 1.5 mg/kg Q24 or prophylaxis 30 mg/kg BID or 40 mg/kg daily 7-14 days
Kinetics: SubQ (protein binding does not effect predictability) effects decreased in obese & increased in kidney failure
ADRs: Increased risk of bleeding, pain @ injection site, bruising, hematoma (avoid in lumbar puncture)
Interactions: Any antiplatelet/anticoagulant
Monitoring: Signs & symptoms of bleeding, PTT, CBC, platelets, factor Xa (especially for obese or kidney compromise)
Antidote: None, hold medication supportive therapy
Heparins

**HIT**

- Heparin-induced thrombocytopenia
- The PT and aPTT are prolonged, and the platelet count is decreased
- A systemic hypercoagulable state
- Characterized by venous and arterial thrombosis
- Related to the immune response to heparin
- Treatment: to discontinue heparin and administer DTI or Fondaparinux

**HAT**

Mild and transient drop in platelets
Fondaparinux (Arixtra) – clot prophylaxis, used in patients who experience HAT or HIT

**MOA:** Factor Xa inhibitor

**Dosage forms:** SubQ

**Dosing:** Weight based

**Kinetics:** Highly protein bound, prolonged half life in renal impairment and elderly, excreted up to 77% unchanged in urine

**ADRs:** Increased risk of bleeding, anemia, hypotension, insomnia, thrombocytopenia

**Interactions:** Any antiplatelet/anticoagulant

**Monitoring:** Signs & symptoms of bleeding, PT, aPPT, CBC

**Antidote:** None, hold dose - FFP
Warfarin (Coumadin) – Treatment and prophylaxis of DVT and VTE & anticoagulation in afib

**MOA:** Inhibit the synthesis of vitamin K dependent clotting factors VII, IX, X, 2, as well as protein C & S

**Dosage forms:** Oral tablet

**Dosing:** Wide range of dosages available (1mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, & 10 mg) dosed daily

**Kinetics:** Metabolized by CYP2C9 and 3A4, slow onset 2-3 days (peak 5-7 days) **CONVERSION IN HIGH RISK**, excretion in urine 92% as metabolites

**ADRs:** Increased risk of bleeding, skin necrosis (purple toe syndrome), nausea, vomiting, diarrhea – **TERATOGENIC**

**Interactions:** Any antiplatelet/anticoagulant, vitamin K, alcohol, BARs, herbal medications, many, many, many interactions!!! - **BE CONSISTENT!!!!!**

**Monitoring:** PT/INR (target INR depends on indication – afib 2-3), CBC, signs and symptoms of bleeding

**Antidote:** Vitamin K (oral or IV depending on INR)
ANTICOAGULANTS – DIRECT THROMBIN INHIBITORS

Dabigatran (Pradaxa) – DVT & VTE treatment and prophylaxis, afib (non-valvular)

MOA: Direct thrombin inhibitor that in return inhibits factors V, VIII, XIII, & XII

Dosage forms: Oral capsule

Kinetics: Prodrug metabolized to active form by hepatic and plasma esterases, moderately protein bound, half life effected by renal impairment, excreted 80% in urine

Dosing: BID - CI in serum creatinine less than 30 mL/min

ADRs: Increased risk of bleeding, dyspepsia, gastritis, hematuria, anemia

Interactions: Any antiplatelet/anticoagulant, amiodarone, antacids, some vitamins, many drug interactions

Monitoring: Signs & symptoms of bleeding, CBC, aTTP, thrombin time, renal function

Antidote: None – supportive therapy (FFP)
Apixaban (Eliquis) – Non-valvular afib, DVT, PE
  MOA: Selective and reversible inhibition of factor Xa
  Dosage forms: Oral tablet
  Dosing: BID
  Kinetics: Metabolized by CYP3A4, 1A2, 2C9, 2C19…, moderately protein bound, excreted in urine and feces, half life about 12 hours
  ADRs: Increased risk of bleeding, anemia
  Interactions: Any antiplatelet/anticoagulant, Inducers & inhibitors of CYP3A4, some vitamins, herbs, many
  Monitoring: Signs & symptoms of bleeding, antifactor Xa levels
  Antidote: None – supportive therapy (FFP)

Rivaroxaban (Xarelto) – Non-valvular afib, DVT & PE treatment & 2ndary prevention
  MOA: Selective and reversible inhibition of factor Xa
  Dosage forms: Oral tablet
  Dosing: BID – adjusted in kidney impairment
  Kinetics: Metabolized by CYP3A4, excreted in urine and feces, half life 5-9 hours (increased in elderly)
  ADRs: Increased risk of bleeding, wound secretion, back pain
  Interactions: Any antiplatelet/anticoagulation, enzyme inducers & inhibitors, many
  Monitoring: Signs & symptoms of bleeding, antifactor Xa, PT
  Antidote: None – supportive therapy (FFP)
SIGNS AND SYMPTOMS OF BLEEDING

All contraindicated in active bleed

Major bleeds:
- Blood in urine or stool – Red, tan, black tarry
- Bleed in brain – Major/severe headache
- Blood in vomit – Coffee ground emesis

Minor bleeds:
- Bruising
- Bloody nose
- Bloody gums

Tell all doctors/dentists on anticoagulant

Protect your body & be safe

FFP and supportive therapy if no antidote
QUESTIONS