VTE (Venous thromboembolism)

What is thrombosis:

- Thrombosis: process that occurs when inappropriate, or over-activation of hemostasis in an uninjured or slightly injured blood vessel, which results in a thrombus, or "blood clot"
    - Primary hemostasis: damaged blood vessel → collagen and vWF interact on platelet surface → glycoprotein 1a/1b receptors form a plug → platelets connected to sub-endothelium through receptor complexes → activates to secrete ADP, TXA2, 5-HT → recruits other platelets to site of damage → glycoprotein 2a/2b link platelets together to form a larger plug
    - Secondary hemostasis: endothelium disrupted → tissue factor released into circulation → activate extrinsic pathway of coagulation cascade → activates thrombin (factor 2) → recruit more platelets, amplify coagulation cascade → more thrombin → convert fibrinogen to fibrin → clot is more stable
- Could be arterial thrombi or venous thrombi

What is VTE:

- Results from thrombus formation in the venous system (most cases of PE start in deep veins of leg)
    - Proximal deep veins have higher risk of thrombus embolization (common iliac vein, internal iliac vein, external iliac vein, common femoral vein, great saphenous vein, deep femoral vein, femoral vein, popliteal vein)
    - Distal deep veins have lower risk of thrombus embolization
    - Superficial veins of leg have least risk of thrombus embolism
- Consists of DVT (deep vein thrombosis) and PI (pulmonary embolism)

Diagnosis:

- Virchow's triad
    - Stasis (laminar flow becomes disturbed flow – slow and turbulent rate of blood flow)
    - Vessel wall injury
    - Hyper-coagulability (Protein C/S deficiency, prothrombin gene mutation, anti-phospholipid antibodies, anti-thrombin deficiency, factor V Leiden, pregnancy, estrogen therapy, malignancy)
- Risk factors:
    - Strong (OR – odds ratio > 10) – involvement of all 3 factors (hip/leg fracture, major surgery)
    - Moderate (OR 2 – 9) – involvement of ~2 factors (malignancy, hormone replacement, chemo)
    - Weak (OR < 2) – involvement of 1 factor (bed rest 3 days, ↑ age, obesity, pregnancy, varicose)
- Signs, symptoms, labs
    - Non-specific
        - DVT: unilateral swelling, dilated superficial veins, palpable cord
            - Labs: ↑ D-dimer, ↑ erythrocyte sedimentation rate, ↑ WBC count
        - PE: cough, shortness of breath, light-headedness, tachypnea, tachycardia, hypoxemia, fever, ECG changes (↑ right ventricle pressure)
            - Labs: ↑ D-dimer, ↑ erythrocyte sedimentation rate, ↑ WBC count
    - Diagnosis requires testing and scoring systems (ex. Well's criteria, D-dimer test which is not specific, but sensitive)
        - DVT diagnosis: compression ultrasonography (ultrasound transducer applied to 1. femoral artery near groin, and 2. popliteal artery behind knee)
        - PE diagnosis: spiral computed tomography (CT), ventilation/perfusion (V/Q) scan

Laboratory monitoring tests (clinical biochemistry, need to monitor labs for most medications)

- Prothrombin tests: PT/INR
    - Prothrombin Time (PT): measures extrinsic and common coagulation cascades (monitor warfarin)
        - Decalcified plasma + Tissue Factor (thromboplastin) + calcium

        - PT: time it takes from the addition of calcium for the plasma to clot (↑ PT, longer it takes to clot)
        - Depends on thromboplastin used → PT varies significantly
    - INR (international normalized ratio): developed to standardize PT values from different labs
        - Sensitivity of thromboplastin is compared to WHO's reference sensitivity (ISI)
        - Inaccurate results due to: lupus anticoagulants (falsely ↑ INR), first few days of warfarin therapy (INR due to ↓ clotting factor 7 with shortest half-life), also if reading is > 4.5 there is less certainty
- aPTT: measures intrinsic and common coagulation cascades (monitor UFH)
    - Decalcified plasma + phospholipid + contact activator (kaolin) + calcium
    - aPTT: time it takes from addition of calcium until plasma clots (↑ aPTT, longer it takes to clot)
- Anti-factor Xa assay: indirectly measures concentration of anticoagulants that inhibit factor Xa (monitor LMWH (pregnancy, renal impairment), UFH, in special circumstances DOACs with anti-Xa activity)

VTE Prophylaxis

- Individual based approach (use prophylaxis 0-2 hours preoperatively, 0-12 hours after surgery, and if high risk VTE, should take at least until discharge from hospital:
    - Estimate individual's risk of developing VTE
        - Use a statistically validated risk stratification tool (like Caprini model – for novice)
        - Clinical gestalt (pattern recognition – for experienced clinicians)
    - Estimate individual's risk of bleeding
        - Assess major bleeding risk for all surgical patients (absolute and relative CI)
        - Absolute CI: active, clinically-important bleeding, platelets <30 x 10^9/L, major bleeding disorder
    - Determine the appropriate mix of prophylactic methods
        - Early ambulation (reduce immobility, however risk of falls)
        - Mechanical (IPC – intermittent pneumatic compression, GCS – graduated compression stockings)
        - Pharmacological (UFH, LMWH, fondaparinux) – LMWH preferred usually, but UFH preferred when CrCl < 20-30 mL/min (renal impairment), and fondaparinux preferred if patient had HIT
- Group based approach (encouraged by Canadian Patient Safety Initiative – CPSI):
    - Use a standardized order set for all patients within a particular group or "service"
    - Easy to do and systematic, but may cause overtreatment of low risk patients
- Non-hospitalized approach:
    - Long-term care/nursing home: chronically ill – don't use prophylaxis
    - Cancer-related: high-risk can use apixaban, rivaroxaban, LMWH
    - Long-distance air travel: can use GCS (if worried about bleed) or prophylactic LMWH (if worried about another PE) for > 4 h travel

Acute VTE treatment (initiation: first 5-7 days after diagnosis)

- Diagnosis of VTE
- Determine clinical stability of patient (candidate for surgery or thrombolysis)
    - Removal of thrombus (by pharmacological thrombolysis or surgery) can be considered if:
        - Pulmonary embolism with risk factors for poor prognosis: bradycardia (< 40 bpm) and shock (low BP with organ failure), hypotension (systolic BP < 90 mmHg), myocardial injury
        - Massive DVT plus limb gangrene
- Determine if inferior vena cava filer (IVC) is required – only if have absolute CI to anticoagulants
- Inpatient or outpatient treatment: is patient hemodynamically stable?

- Hypotension, hypoxemia, tachycardia = hospital admission
- Outpatient treatment must have caregiver support and daily patient contact with HCP

- Selection of anticoagulant regimen (all patients must have rapid-acting anticoagulant (almost always parenteral, and rapid-acting anticoagulant must be continued for 5 days + 2 INRs that are > 2.0 if warfarin is chronic anticoagulant)
  - UFH (IV + monitoring, SC + with/without monitoring)
    - Initial bolus 80-100 units/kg, initial infusion of 17-20 units/kg/hour
    - May experience major bleeding or thrombocytopenia/HIT, osteoporosis (extra-long chain)
    - IV can be stopped, antidote – protamine sulfate 100% efficacy, adjust based on aPTT q 4-6 h
    - Inexpensive drug, expensive administration (IV)
    - Must monitor CBC + platelets, aPTT
  - LMWH (SC + no monitoring)
    - Dalteparin (200 units/kg QD; if > 100 kg, 100 units/kg BID), tinzaparin (175 units/kg QD), enoxaparin
    - Depends on body weight dosing (if above threshold, unsure about efficacy/safety)
    - May experience major bleeding (rare thrombocytopenia/HIT, osteoporosis)
    - Antidote – protamine sulfate can be used but difficult to dose, and 60% efficacy
    - Cleared by the kidney, avoid in CrCl < 30 mL/min (accumulation)
    - Biggest advantage: convenience (QD, ideal for outpatient, don't require monitor)
    - CBC (q 5-10 days during first 2 weeks) + platelets, PT/INR, aPTT, sCr
    - Not expensive due to lack of monitoring

  - Fondaparinux (SC + no monitoring)
    - 7.5 mg SC QD (may change if > 100 kg, or < 50 kg)
    - Similar efficacy to LMWH, but no antidote
    - No concerns about thrombocytopenia (can be used to treat HIT), cleared by kidney, CI when CrCl < 30 mL/min
  - Rivaroxaban and apixaban (oral + no monitoring) – DOACs (direct-acting oral anticoagulants)
    - Rivaroxaban: 15 mg BID for 21 days, change dose to 20 mg QD on day 22
      - No approved antidote, no valid monitoring test (could use anti-factor Xa assay)
      - Biggest advantage: doesn't require monitoring
      - Rivaroxaban – 3 months of treatment covered by ODB, supplemental insurance
    - Apixaban: BID, can be used without LMWH overlap
    - Edoxaban, dabigatran (requires overlap with LMWH)
- Warfarin for acute VTE
  - Start with first dose of rapid-acting anti-thrombotic (except if surgery or fibrinolytic)
  - Dose for balance of thrombosis and risk of bleeding, target INR 2.5
  - Antidote: vitamin K, fresh frozen plasma, or recombinant clotting factors
  - 10mg initiation nomogram (for young patients) or 5mg initiation nomogram (older patients > 70 y/o), or ⩽4 mg for 85+ y/o
- Non-pharmacological treatment
  - PTS (post-thrombotic syndrome) – common complication of DVT, no good treatment options
  - Elastic Compression Stockings (ECS) – measured to provide 30-40 mmHg ankle pressure
    - Don't use for PTS prevention, but can use for PTS treatment

Chronic warfarin therapy (maintenance)

- From initiation to maintenance: INR QD, at least 5 days of rapid-acting anti-thrombotic (UFH/LMWH) and INR > 2.0 for 2 consecutive days
    - Afterwards, length of time between INR tests depends on stability of INR readings/risk factors (⩾ 2x/week for first 2-3 weeks of outpatient therapy)
- What does INR too high or low mean
    - If INR ↑, risk of bleeding, needs less warfarin
    - If INR ↓, risk of clotting, needs more warfarin
- Warfarin dose adjustments (if INR out of range)
    - Try to figure out why (non-adherence, changes in medications, acute illnesses)
    - Determine patient's risk of thrombosis
        - 0-1 month since diagnosis: 40% risk per month (> 1%/day)
        - 1-3 months: 10% per 2 months (> 0.15%/day)
        - Recurrent VTE (secondary prevention), clot > 3 months ago: 15%/year (> 0.04%.day)
    - Consider how far INR is out of range
        - If isolated INR < 0.5 units outside of 2-3, repeat INR in 1-2 weeks, don't adjust warfarin dose (unless patient is within first 3 months of therapy, then risk of thrombosis)
    - Consider alternatives:
        - No changes, repeat INR sooner (< 0.5 units out of range)
        - One-time adjustment dose, then resume maintenance dose
            - If patient is within 0-3 months of diagnosis, see in 2 days for INR
            - For non-adherence, give double dose that they missed
        - Change maintenance dose (change based on percentage of patient's weekly dose)
            - If INR ⩽0.5 units out of range, 5-10% of weekly dose
            - If INR > 0.5 units out of range, 10-20% of weekly dose
            - Try and keep same tablet strengths, can make some days higher
            - Takes a few weeks to see full effect of changes made to maintenance dose
        - If excessive INR (> 4.0), withhold a dose or two of warfarin, repeat INR daily until < 4.0
            - > 6.0 can administer a small dose of vitamin K (1-2.5 mg PO)
- Drug interactions with warfarin
    - Inhibition of platelet function [ASA, clopidogrel, NSAIDS] – doesn't affect INR
    - Reduced synthesis of vitamin K by gastrointestinal flora [antibiotics] – increases INR
    - Alteration of warfarin metabolism [Inhibitors/inducers of CYP 2C9 – cotrimoxazole, amiodarone] – changes INR
    - Injury to gastrointestinal mucosa [NSAIDS] – doesn't affect INR
    - Interference with vitamin K epoxide-reductase [acetaminophen] – increases INR

Chronic DOAC therapy (maintenance)

- DOACs (direct-acting oral anticoagulants) – targets factor Xa, interacts with inhibitors of PGP and CYP 3A4
    - Rivaroxaban: BID, then 3 weeks later, QD; Apixaban: BID
- Pros (vs. warfarin): quick onset, don't need to overlap with parenteral anticoagulant, no need for monitoring (predictable PK/PD, convenient), fewer interactions
- Cons (vs. warfarin): renal elimination (CI if CrCl < 25-30 mL/min), some BID, inability to accurately measure drug effect (no accepted therapeutic range, and needs to be calibrated by lab), bleeding management (no reversal agent or antidote), cost (max duration 3 months of ODB, no insurance coverage)

Maintenance of oral anticoagulation therapy for acute VTE

- Minimum duration: 3 months
    - After 3 months, patients with unprovoked VTE may:
        - Continue warfarin, target INR 2.5
        - ASA 100 mg QD
        - DOAC
- Possibly use indefinitely: patients with a first episode of unprovoked VTE, especially PE)
- Likely use indefinitely: patients with a second episode of unprovoked VTE