VENOUS THROMBOEMBOLISM

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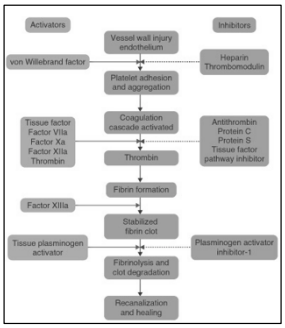
Definitions

- DVT and PE
- Provoked vs. unprovoked
- Risk factors: surgery, trauma, hx VTE, hypercoagulable D/O, age, immobility, major surgery, malignancy, pregnancy, estrogen, HIT, critical illness
- Caused by imbalance between thrombogenic and antithrombotic forces

Homeostasis and Thrombosis



Source: DiPiro J *et al.* Pharmacotherapy Principles and Practice, 2nd Ed. 2010

Epidemiology

- 1/3 of pts with symptomatic VTE have PE
- > 50% have silent VTE
- 1 month mortality
  - DVT = 6%, PE = 12%
- In pts post-trauma or post-orthopedic surgery to lower limbs, VTE risk > 50% w/o prophylaxis

Signs, Symptoms, Diagnosis

- DVT
  - Most likely to form in lower extremity
  - Leg pain, swelling, cyanosis, pain, warmth
  - D-Dimer, doppler ultrasonography, and clinical exam used to diagnose DVT
- PE
  - SOB, tachypnea, tachycardia, hemoptysis
  - D-Dimer, CT scan, Wells Criteria, and clinical exam used to diagnose PE

VTE Complications

- Post-Thrombotic Syndrome (PTS)
  - 2/2 vein damage from thrombosis, resulting in chronic venous insufficiency
  - S/S: pain, swelling, skin discoloration, ulceration
- Recurrent VTE
- DVT progression to PE
- Death

VTE Prevention

- CHEST guidelines!
- Identify pts at risk for VTE, classify risk
- Non-pharmacologic
  - Graduated Compression Stockings (GCS)
  - Intermittent Pneumatic Compression (IPC)
  - Early mobilization post surgery
  - Inferior vena cava filter (IVCF)

VTE Prevention

- Pharmacologic Prophylaxis
  - SQ: LMWH, Fondaparinux, UFH
  - PO: warfarin, dabigatran, apixaban, rivaroxiban
  - THA/TKA
    - 1st line: LMWH
    - 2nd line: fondaparinux, UFH, dabigatran, apixaban, rivaroxiban
    - 3rd line: ASA, warfarin
  - All other pts: LMWH or UFH as 1st line
  - Factors to consider: pt preference, compliance, dose frequency, price, availability..

VTE Treatment

- CHEST guidelines!
- Goals of therapy
  - Prevent progression of thrombus, embolization, death
  - Prevent long-term complications of VTE/recurrence
- Principles of therapy
  - Minimal symptoms and low risk for extension (i.e., superficial vein thrombosis): monitor, no need for AC
  - PE with hemodynamic instability: consider lytics
  - PE without hemodynamic instability, or DVT: initiate parenteral AC
  - Transition to oral therapy for long-term treatment
  - Stop AC when clot resolves and per guideline recommendations

VTE Treatment
DVT/Hemodynamically Stable PE

1. Initiate parenteral AC ASAP, continue ≥ 5d
   - LMWH and fondaparinux preferred over UFH
   - LMWH: enoxaparin 1.5 mg/kg SQ QD or 1 mg/kg BID
   - Fondaparinux: 7.5 mg SQ QD, with dose adjustment required for pt weight
   - UFH: SQ or IV infusion to target therapeutic aPTT
2. Initiate PO warfarin as early as possible
   - Usual starting dose 5 mg/d, unless confounding factors (see warfarin section)

VTE Treatment
DVT/Hemodynamically Stable PE

3. Stop parenteral AC once INR >2 x24h, *and* after at least 5d of parenteral AC
4. Continue warfarin for 3 mo for most pts, with careful monitoring
5. Some pts require > 3 mo of warfarin (i.e. based on risk for recurrence or bleeding)
6. In patients with cancer and VTE, LMWH is *preferred over warfarin* for the entire duration of treatment

VTE Treatment
Hemodynamically Unstable PE

- In pts with PE associated with HoTN (i.e. SBP < 90 mmHg) with low bleeding risk, thrombolytic therapy is recommended
- Once thrombolytic therapy is complete, treat as hemodynamically-stable PE

VTE Treatment
Pharmacotherapy: UFH

- IV continuous infusion for VTE dosed per wt, although also available in IV bolus and SQ
- Dose is adjusted per aPTT
- Generally, aPTT is measured a baseline, 6h after initiation, and 6h after any dose change
- No renal adjustment necessary
- Major AEs: bleeding (aPTT-related), HIT (non-aPTT-related)
- C/I: active bleeding, history of HIT
- Antidote: protamine sulfate
- Monitoring: PLT, aPTT, INR, Hg

Heparin-Induced Thrombocytopenia

- Immune-mediated reaction resulting in thrombocytopenia and possible thrombosis at the same time
- Not related to AC intensity
- 4 Ts: Thrombocytopenia, Thrombosis, Timing, other causes for Thrombocytopenia
- PLT drop > 50% of baseline or < 100,000
- Onset: 5-14 d
- Compare with HAT

Heparin-Induced Thrombocytopenia
Management

- D/C all sources of heparin, do not re-challenge
- Initiate alternative AC immediately unless C/I (lepirudin, argatroban..) and regardless of thrombosis presence
- Initiate warfarin once PLT > 150,000 /mL
  - Otherwise high risk for venous limb gangrene and warfarin induced skin necrosis
  - Reverse warfarin if already started
- Avoid PLT transfusion unless actively bleeding
- For px in pts with HIT, fondaparinux can be used

VTE Treatment
Anticoagulants

- General principles:
  - AC do not lyse a clot, they only stop its growth and propagation
  - Labs that you'll need to monitor at baseline and periodically after: Hg, PLT, INR, aPTT, Cr with certain drugs

VTE Treatment
Pharmacotherapy: LMWH

- Enoxaparin, dalterparin, tinzaparin
- Smaller heparin fragments than UFH
- Given SQ
- At least as safe and effective as UFH for VTE, more effective in THA/TKA surgeries
- Enoxaparin
  - Prophylaxis: 40 mg QD or 30 mg BID
  - Treatment: 1.5 mg/kg QD or 1 mg/kg BID
  - Requires renal adjustment CrCl < 30 mL/min

VTE Treatment
Pharmacotherapy: LMWH

- No therapeutic monitoring required except in special populations (large or small size, CKD..)
- Cr should be checked at baseline
- Can be safely used at home- convenient
- AEs: HIT (10x less likely than UFH), bleeding
- C/I: HIT, active bleeding
- Antidote: protamine sulfate (partial efficacy)

VTE Treatment
Pharmacotherapy: Factor Xa Inhibitors

- Fondaparinux, rivaroxaban, apixaban
- Only fondaparinux and rivaroxaban approved by FDA for treatment of VTE
- Synthetic, do not cross-react with heparins, ideal in pts with HIT history or heparin allergy
- No therapeutic monitoring required
- Not reversed by protamine
- Fondaparinux dosing: (SQ)
  - Prophylaxis: 2.5 mg QD
  - Treatment: < 50 kg: 5 mg QD; 50-100 kg: 7.5 mg QD; > 100 kg: 10 mg QD

VTE Treatment
Pharmacotherapy: DTIs

- Dabigatran (PO), lepirudin (IVI), bivalirudin (IVI), argatroban (IVI), desirudin (SQ)
- Dabigatran is the only PO DTI, requires no therapeutic monitoring, and has quick onset
  - Requires at least 5d of parenteral anticoagulation before initiation
- Lepirudin is cleared renally, argatroban hepatically. Both used in pts with HIT
- Bivalirudin is used in PCI
- Desirudin is used SQ for VTE Px after THA
- DTIs have no antidote and falsely elevate INR

VTE Treatment
Pharmacotherapy: Warfarin

- Inhibitor of Vitamin K-dependent coagulation factors (II, VII, IX, X, protein C, protein S)
- No effect on existing factors- anticoagulation will start when factors eliminated (5-10 d)
- Metabolized by CYP450 2C9
- Dosed to target INR which takes several doses to reach
- Acute drop in protein C before depletion of clotting factors results in paradoxical hypercoagulable state in the first few days of therapy

VTE Treatment
Pharmacotherapy: Warfarin

- Dosing and bleeding risk depends on environmental and genetic factors
  - Age, nutritional status, liver disease, pt wt, hyperthyroidism, genetic polymorphisms, prior used doses, FAMES (Fluconazole, Fluoroquinolones, Amiodarone, Metronidazole, Erythromycin, Sulfas), rifampin, phenobarbital, phenytoin, vitamin K, NSAIDs/antiplatelets/ anticoagulants, gut flora modifiers, general health status, infections..

VTE Treatment
Pharmacotherapy: Warfarin

- Dosing strategy:
  1. Obtain baseline labs (CBC, INR, aPTT)
  2. Initiate 5 mg PO QD for most pts
     - Avoid loading dose
     - Initiate at lower or higher doses according to your pt evaluation
  3. Obtain INR more frequently during initial dosing, less frequently once therapeutic on stable dose
     - Example for initial phase: QD if in hospital setting; twice a week if in outpatient setting
     - Example for late phase: every other day if in hospital setting; every 2-4 wks if in outpatient setting

VTE Treatment
Pharmacotherapy: Warfarin

- Dosing strategy/Cont:
  4. Make dose adjustments in small increments (0.5-1 mg per adjustment) until INR becomes therapeutic
     - Normal pace to achieve therapeutic INR is 5-7d
     - If INR starts rising too fast, lower dose
  5. Pick a chronic dose, follow-up on INR less frequently, adjust dose if necessary
  6. Educate pt on importance of diet consistency, need to avoid drug interactions, avoiding injuries and bleeding risks, ways to recognize bleeding..

VTE Treatment
Pharmacotherapy: Warfarin

- DTIs falsely elevate INR
- AEs
  - Warfarin-induced skin necrosis and venous limb gangrene
  - Bleeding
  - Teratogenicity (Category X)
- Antidote:
  - Vitamin K (1-10 mg IV/PO x1)
    - SQ/IV: peaks in 12h, given in urgent cases with bleeding
    - PO: peaks in 24h, given in less urgent cases
    - No reversal necessary if INR < 10 with no bleeding

VTE Treatment
Pharmacotherapy: Thrombolytics

- Can be used in pts with PE and hemodynamic instability
- High bleeding risk- careful pt selection needed
- Streptokinase, urokinase, t-PA are FDA-approved for PE treatment
- All are equally efficacious, t-PA has shortest infusion time