Pulmonary Embolism & Deep Vein Thrombosis

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Definitions
- **DVT** - blood clot in venous circulation composed of erythrocytes, leukocytes, fibrin
  - Primarily in the proximal large veins of lower extremities/thighs, calf veins (primarily), or knee veins or in venous segments exposed to direct trauma
  - 20% of calf vein thrombi extend into proximal venous system
- **PE** - thrombus from the venous system that lodges in the pulmonary vasculature
  - Majority from proximal leg veins
  - Less commonly from deep pelvic or renal veins, IVC, the right heart or axillary veins

Epidemiology
- Annual incidence 48 per 100,000 for DVT and 69 per 100,000 for PE (with or without DVT)
- 600,000 patients in US are hospitalized for venous thromboembolism (VTE) annually; up to 200,000 die from PE.
  - Of the fatal PE cases, half have potentially curable illness.
  - VTE kills more people than AIDS, breast cancer, and highway fatalities combined.
  - Overall incidence has not changed over 30 years.
- More common in men than women
- Increases with age
  - Higher 1-year mortality rate associated with DVT or PE among the elderly.

Venous Thrombosis Facts
- **DVT**
  - 2 Million
- **Silent PE**
  - 1 Million
- **PE**
  - 600,000
- **Silent PE**
  - 10%
- **Death**
  - 50,000
- **Pulmonary Hypertension**
  - 30,000

VTE: $1.5 billion / year

Virchow’s Triad

**Factors that predispose patients to deep venous thrombosis:** interactions between the elements of Virchow’s triad

- **Stasis**
  - Inactivity
  - Immobility
  - Venous injury (deep vein thrombosis, arterial injury, surgery)

- **Hypercoagulability**
  - Hemostatic defects
  - Inherited disorders (factor V Leiden, prothrombin 20210A)
  - Acquired disorders (cancer, pregnancy, oral contraceptives)

- **Endothelial Injury**
  - Inflammation
  - Trauma
  - Hypertension
  - Rheumatoid arthritis
  - Hypothyroidism

*Figure 1*
Pathophysiology: Virchow’s Triad

- Venous Stasis
  - Decreased or abnormal blood flow
  - Pooling of blood in venous sinuses or valve cusps
  - Concentration of activated clotting factors
- Vascular Wall Injury/Endothelial Damage
  - Mechanical trauma or chemical trauma
  - Inflammatory response (phlebitis)
  - Increased ADP -> platelet adhesion and release of collagen -> activation and aggregation of platelets -> increased coagulation and formation of intraluminal thrombus

- Hypercoagulability
  - Imbalance between clotting and fibrinolytic systems
  - Inherited conditions: APC resistance, ATIII, Protein C or S deficiencies, anti-phospholipid antibody syndrome, Lupus anticoagulant
  - Acquired: Estrogen therapy, certain malignancies

Risk Assessment

**Intrinsic factors**
- Family history/past history of VTE
- Advanced age
- Obesity
- Varicose veins
- Venous insufficiency
- Thrombophilia

**Extrinsic factors**
- Pregnancy/puerperium
- Immobilization
- Paralysis
- Intravascular catheter
- Previous or current malignancy
- Chronic heart failure
- Chronic respiratory failure
- Inflammatory bowel disease

**Molecular risk factors**
- Factor V Leiden mutation
- Activated protein C resistance
- Deficiencies: anti-thrombin, antiphospholipid antibodies, protein C, protein S, lupus anticoagulant
- Prothrombin gene mutation
- Methylenetetrahydrofolate reductase mutation

**Primary Risk Factors for VTE**

- Major surgery
- Acute MI
- Major trauma
- Paralytic stroke
- Cancer
- Spinal cord injury
- Pelvic fracture

**Secondary Risk Factors for VTE**

- Congestive heart failure
- Previous VTE
- Immobilization
- Obesity
- Chronic respiratory failure
- Increasing age
- Hematological disorders
- Central venous catheter
- Varicose veins
- Pregnancy
- Estrogen treatment
- Hospitalization

Clinical Presentation

- **DVT**
  - Unilateral pain/tenderness, discoloration/cyanosis
  - Swelling, edema, palpable cord, warmth
  - Homan’s sign
  - 75% with clinically suspected DVT do not have clot
- **PE**
  - Dyspnea*, tachypnea*, pleuritic chest pain*
  - Tachycardia, hemoptysis, cough
  - Apprehension, fever
  - Pleural effusions, widened P(A-a)O2 gradient
  - Massive hypoxemia, right ventricular failure
Differential Diagnosis

- **DVT**
  - Muscle strain/trauma
  - Arterial insufficiency, varicose veins
  - Postphlebitic syndrome
  - Lymphedema

- **PE**
  - Pneumonia, bronchitis, CHF, atelectasis
  - Pneumothorax, pulmonary edema, pericarditis, AMI

Diagnosis: DVT

- Ultrasonography-Doppler, Real-time B-Mode, Duplex
  - Extremely sensitive for proximal vein thrombosis, less so for calf or non-occlusive thrombosis
  - Serial testing over 10-14 days if non-diagnostic lung scan for PE and adequate cardiopulmonary reserve

- Impedance Plethysmography (compression US)
  - Measures obstruction in venous outflow after deflation of a pneumatic thigh cuff
  - Sensitive and specific for proximal not calf or non-occlusive DVT; false + if disorders in flow
  - Inferior to doppler

Diagnosis: DVT

- Venography
  - Gold standard- most sensitive and specific
  - Invasive, $, risk of hypersensitivity reactions and nephrotoxicity due to radiocontrast dye

- MRI
  - Very sensitive and specific
  - $, testing equipment
Diagnosis: DVT
- D-Dimer
  - Degradation product of fibrin from clot dissolution
  - If a sensitive assay is used- elevated levels are highly sensitive but low specificity for DVT/PE (most useful for negative predictive value)
    - ELISA Test with value < 500 very low probability of VTE
  - May be beneficial in combination with noninvasive testing

Diagnosis: PE
- Clinical Suspicion
- Ventilation/Perfusion (V/Q) Scan
  - Main screening test but often nondiagnostic
  - Estimates probability of PE based upon patterns of inhaled and injected radioactive dyes
  - High probability- reliable confirmation
  - Intermediate or low probability- further testing may be necessary
  - Normal V/Q- excludes PE

Diagnosis: PE
- Pulmonary Angiography
  - Invasive, risks
  - Reserved for patients with poor cardiorespiratory reserve
  - Confirmatory test
- Spiral Computed Tomography (CT)
  - Increased vascular contrast and visualization of filling defects using IV contrast
    - Can also scan through pelvis, diagnose other abnormalities
  - Sensitivity 96-100%, specificity 96%
  - Availability in hospital settings may be limited

Treatment Goals: Venous Thrombosis
- Prevent development of PE
- Reduce mortality and morbidity of PE
  - 80% of deaths from PE within 2 hours of symptoms
- Reduce morbidity from DVT
  - Significant recurrence in < 5% proximal DVT during 5-7 days of heparin and in 2% during 3 months of warfarin
- Achieve above with minimal ADRs and costs (direct and indirect)

Postphlebitic Syndrome
- Incidence 22.8% after 2 yrs, 28% after 5 yrs, and 29.1% after 8 yrs
- Venous valve destruction by clots causes venous hypertension and direction of blood from deep venous system into superficial system → edema and impaired viability of tissue → venous ulceration
- Symptoms of calf pain, pigmentation and induration of ankle and lower leg areas, and ulceration
Treatment: Unfractionated Heparin (UH)

**Mechanism of Action**
- Binds and catalyzes ATIII accelerating the neutralization of IX, X, XI, XII, plasmin, kallikrein, and thrombin
- Prevents the further growth of the thrombus

**Dose**
- LD 75-100 (80) U/kg then 15-25 (18) U/kg/hr IV infusion adjusted to goal aPTT 1.5-2.5 times control (institution specific range must correspond to specific UH conc)
- Alternative: Adjusted-dose SQ (17,500 U SQ BID) to aPTT 1.5 times control

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**Goal**
- Controversy whether therapeutic PTT in 24 hrs is predictor of recurrence

**Monitor**
- aPTT 6 hr after bolus or change in infusion rate and then QD once stable
- Platelets, Hgb, bleeding


**Duration**
- DC - warfarin therapeutic (stable INR > 2) X 2 days

**ADRs**
- Hemorrhage (5% clinically significant)
- Thrombocytopenia (HIT I/HAT and HIT II)
  - HAT: incidence 25%, mild, transient, nonimmune, decrease in 1-4 days, platelets > 100,000/mm³; return to normal despite heparin, nonthrombogenic
  - HIT II: Incid 1-3%, immunoglobulin mediated, platelets decrease > 50% to < 150/mm³ (nadir 59) in 5-14 days, 30-75% thrombosis, must DC heparin
  - Use lepirudin, argatroban, bivalirudin, or danaparoid
  - Check platelets q 2 days until day 14 or DC

**Osteoporosis (doses > 20,000 U/day for > 6 months)**

**Reversal**
- Mild: DC UH and recheck aPTT in 4-6 hr
- Severe
  - Protamine 1 mg IV neutralizes 100 U UH
  - Fresh Frozen Plasma, Whole Blood

**Clinical Experience**
- At least as effective as UH for DVT treatment
  - Convenience, lack of frequent aPTT monitoring
  - May need anti-Xa levels to optimize dosing, prevent bleeding

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Treatment: Low Molecular Weight Heparins

**Mechanism of Action**
- Greater factor Xa to IIa (thrombin) ratio than UH
- Longer t 1/2
- Lower protein binding

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**Initial treatment with LMWH SC QD or BID over UFH as an outpatient if possible (Grade 1C) and as an inpatient as necessary (Grade 1A)**

**Patients with acute nonmassive PE: LMWH over UFH (Grade 1A)**

Buller HR et al. Chest 2004;126:401S-428S.
Treatment: Low Molecular Weight Heparins

- **Dosing (for treatment)**
  - Enoxaparin (Lovenox®) 1 mg/kg SQ BID (Outpatient DVT) or 1.5 mg/kg SQ QD (Inpatient DVT with or without PE)
  - Dalteparin (Fragmin®) 100 U/Kg SQ BID or 200 U/Kg SQ QD - Not FDA approved
  - Tinzaparin (Innohep®) 175 U/kg QD

- **Duration**
  - At least 5 days or until warfarin therapeutic > 2 days

- **ADRs**
  - Hemorrhage, thrombocytopenia

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**Treatment: Fondaparinux (Arixtra®)**

- **Mechanism of action**
  - Pentasaccharide, selectively binds to antithrombin III and inactivates Xa, interrupting the coag cascade and inhibiting thrombin formation without inactivating thrombin (factor II).
  - Given SQ, peak in 2 hrs, t1/2 13-17 hrs
  - Cautions - bleeding (major bleeds dose-related)
  - Adjust dosage in renal failure (50% renal elim)
  - Monitor anti-factor Xa activity
  - No cross-reactivity with heparin-PF4 antibodies nor elicits HIT II antibodies
  - Good alternative in acute HIT II

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**DVT Treatment with LMWH: Exclusions**

- Thrombocytopenia, HIT II (High cross reactivity in-vitro)
- Severe renal or hepatic failure
- PE with hemodynamic instability or multiple DVTs
- Pregnancy
- Catheter related DVT
- Obesity (> 30% over IBW)
- Severe HTN
- Active bleeding, hypercoagulable state, malignancy

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**Treatment: Warfarin**

- **Mechanism of Action**
  - Anticoagulant and antithrombotic
  - Inhibition of the reduction of Vit K leading to partially active or inactive clotting factors II, VII, IX, X and also limits the carboxylation of proteins C and S
  - Due to t 1/2s of clotting factors (VII shortest with 4-6 hrs and II longest with 42-72 hrs), may not have full antithrombotic effects for 2-7 days post initiation
  - S-warfarin three times more potent vs R-warfarin

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**Treatment: Fondaparinux (Arixtra®)**

- **FDA Approval**
  - Prophylaxis of DVT in hip and knee surgery
    - Dosage 2.5 mg SQ QD
    - Cost approx $31-35/day
  - Treatment of DVT and PE
    - Dosage 5 mg (wt < 50 kg), 7.5 mg (wt 50-100 kg) or 10 mg (wt > 100 kg) SQ QD

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Treatment: Warfarin

- **Dosing**
  - 2-10 mg PO daily (lower in elderly or very small patients, higher if ATIII or protein C/S deficiencies, or Lupus anticoagulant)
  - Generally 5 mg daily PO
  - No rationale for loading
  - Initiated within 24 hrs of heparin ideally and overlap for 4-5 days or until INR therapeutic
  - Adjust by 5-20% daily

- **Duration**
  - Calf vein thrombosis \(\rightarrow\) 6 weeks to 3 months
  - Proximal vein thrombosis/1st event \(\rightarrow\) 3-6 months
  - PE or idiopathic etiology of DVT and 1st event \(\rightarrow\) Therapeutic dilemma-at least 3-6 months vs indefinite
  - Recurrent thrombus \(\rightarrow\) 12 months to lifelong
  - 1st event with unresolved cancer, protein C resistance, antiphospholipid antibody syndrome, deficiency of antithrombin/protein C or S \(\rightarrow\) 12 months to lifelong, or as long as risk factor is present

- **Monitoring**
  - INR 2.0-3.0 goal
  - 3.0-4.5 if recurrent, mechanical valves, or antiphospholipid syndrome

- **ADRs**
  - Hemorrhage, skin necrosis, purple-toe syndrome, fetal malformation

- **Reversal**
  - Minor- Hold warfarin
  - Serious- Vitamin K PO, SQ, or IV 1-10 mg FFP

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Treatment: Thrombolysis

- Thrombolitics are indicated for pts with acute massive PE who are hemodynamically unstable and not prone to severe bleeding.
- Thrombolitics provide more rapid improvement of abnormal hemodynamic status, clot resolution and reperfusion in PE vs heparin alone but no difference in short term mortality, increased bleeding incidence, and $$$. They may potentially decrease long-term complications.
- Goals of lytics in DVT are to reduce incidence of post-phlebitic syndrome.

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Thrombolytics in PE & DVT

<table>
<thead>
<tr>
<th>Lytic</th>
<th>LD</th>
<th>MD</th>
<th>Duration (PE)</th>
<th>Duration (DVT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SK</td>
<td>250,000 IU</td>
<td>100,000 IU/hr</td>
<td>24 hr</td>
<td>48-72 hr</td>
</tr>
<tr>
<td>UK</td>
<td>4,400 IU/Kg</td>
<td>4,400 IU/kg/hr</td>
<td>12 hr</td>
<td>48-72 hr</td>
</tr>
<tr>
<td>t-PA</td>
<td>NA</td>
<td>100 mg over 2 hr</td>
<td>2 hr</td>
<td>Not approved</td>
</tr>
</tbody>
</table>

- **Administration**
  - Stop heparin infusion and begin thrombolytic when aPTT is \(\leq\) 1.5 times control
  - Initiate heparin (no load) post lytic when aPTT is back to 1.5-2 times control and then transition to warfarin
- **Monitoring**
  - Coagulation tests not necessary
- **Catheter-directed instillation of lytic into DVT clot**
  - Less bleeding, being studied for limb salvage
Treatment: Surgical Procedures

- **IVC Filters (Greenfield, Birds’ Nest filters)**
  - For pts with contraindication to or complication of anticoagulation or with recurrent thromboembolism despite adequate anticoagulation
- **Pulmonary Embolectomy**
  - For massive PE with hemodynamic instability and lytic failure or contraindication
- **Venous Thrombectomy (clot removal)**
  - If severe limb ischemia
  - May prevent postphlebitic syndrome

Prophylaxis

- **Necessity of use dependent upon**
  - Type of surgery (general, hip/knee, neurosurgery)
  - Medical conditions (multi trauma, spinal cord injury, ischemic stroke, AMI, degree of immobility)
  - Number of risk factors
- **Graduated compression stockings (GCS or Teds hose)**
- **Intermittent Pneumatic Compression (Pneumoboots, Plexipulse)**

Prophylaxis

- **Unfractionated Heparin**
  - 5000 u SQ BID or TID
  - 7500 u SQ BID
- **Low Molecular Weight Heparin**
  - Enoxaparin 30 mg SQ BID (Hip/knee replacements) or 40 mg SQ QD (Hip, Gyne, Abdominal surgery, general medicine)
  - Dalteparin 2500-5000 IU SQ QD (Hip or abdominal surgery)
  - Ardeparin (Normiflo®) 50 anti-Xa U/Kg SQ q 12 hr (Knee)

Prophylaxis

- **Fondaparinux 2.5 mg SQ QD**
- **Warfarin (INR 2.0-3.0)**

Prophylaxis

- **VTED Risk in Surgical Patients**
  - **Low-Risk Patient**
    - Level of Risk Example
      - Age under 40 years
      - Minor surgery
      - No other risk factors
    - VTE Event Rate
      - Calf DVT: 2.0%
      - Proximal DVT: 0.4%
      - Clinical PE: 0.2%
      - Fatal PE: <0.01
    - Recommended Regimen: No specific measures, Aggressive mobilization

- **Moderate-Risk Patient**
  - Level of Risk Example
    - Minor surgery in patients with additional risk factors
    - Surgery in patients 40-60 yr with no additional risk factors
  - VTE Event Rate
    - Calf DVT: 10-20%
    - Proximal DVT: 2-4%
    - Clinical PE: 1-2%
    - Fatal PE: 0.1-0.4%
  - Recommended Regimen: LMWH (<3,400 IU daily), LDUH q12h, GCS, IPC

### VTED Risk in Surgical Patients

#### High-Risk Patient

<table>
<thead>
<tr>
<th>Level of Risk Example</th>
<th>VTE Event Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery in patients &gt;60 yr.</td>
<td>Calf DVT 20-40%</td>
</tr>
<tr>
<td>Surgery in patients 40-60 with additional risk factors (prior VTE, cancer, molecular hypercoagulability)</td>
<td>Proximal DVT 4-8%</td>
</tr>
<tr>
<td></td>
<td>Clinical PE 2-4%</td>
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<tr>
<td></td>
<td>Fatal PE 0.4-1.0%</td>
</tr>
</tbody>
</table>

**Recommended Regimens:**
- LMWH > 3,400 U daily
- LDH 48h
- IPC

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### VTED Risk in Surgical Patients

#### Highest-Risk Patient

<table>
<thead>
<tr>
<th>Level of Risk Example</th>
<th>VTE Event Rate</th>
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<tbody>
<tr>
<td>Surgery in patients with multiple risk factors (&gt;40 yr, prior VTE, or cancer)</td>
<td>Calf DVT 40-80%</td>
</tr>
<tr>
<td>Hip or knee arthroplasty, hip fracture surgery</td>
<td>Proximal DVT 10-20%</td>
</tr>
<tr>
<td>Major trauma</td>
<td>Clinical PE 4-10%</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>Fatal PE 0.2-5%</td>
</tr>
</tbody>
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**Recommended Regimens:**
- LMWH (> 3,400 U daily)
- Fondaparinux
- Oral VKAs (INR 2-3)
- IPC/GCS + LDH/LMWH

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### ACCP Recommendations

#### DVT Prophylaxis

- ACCP grade 1A treatment options for DVT prophylaxis in general medical patients with clinical risk factors for VTE (including active cancer, bed rest, heart failure, severe lung disease, previous VTE, sepsis, acute neurologic disease, or IBD)
  - Low-molecular-weight heparin
  - Low-dose UFH

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