VENOUS THROMBOEMBOLISM (VTE)

American College of Surgeons SCC Review Course
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Epidemiology (***CDC***, *Beckman, Am J Prev Med, 2010*)

- ●Includes deep venous thrombosis (DVT) and pulmonary embolism (PE) and affects more than 300,000 to 600,000 patients annually with 60,000-100,000 deaths (some estimates as high as 300,000); AHRQ estimates 2 million affected per year and 200,000 deaths; 50% develop during admission or within 30 days after hospitalization
- ●***PE remains most common preventable cause of in-hospital mortality and a leading cause of maternal mortality in the U.S.; fatal PE is the 3rd most common cause of death in trauma patients who survive the first 24 hours***
- ●Incidence of 1-2/1000 of general population; as high as 1/100 in those >80 years of age; likelihood of developing a VTE doubles with each decade of life after 40
- ●2/3rd of VTE present as DVT, 1/3rd PE (+/- DVT); 50% are idiopathic; 60% are occult; sudden death is the first symptom in 25% of people who have a PE; in fatal PE, 2/3rd die within 1 hour; 10 to 30% of people will die within one month of diagnosis; 1/3rd of people with DVT/PE will have a recurrence within 10 years
  - ◇3 month mortality 17% increased to 31% to 52% if associated with hemodyamic instability; PE contributed to cause of death in 63-91% (MAPPET and ICOPER studies)
- ●Outcome of PE dependent on size of embolus and patient's underlying cardiopulmonary status
- ●Among people who have had a DVT, 1/3 develop post-thrombotic syndrome
- ●Approximately 5 to 8 percent of the U.S. population has one of several genetic risk factors in which a genetic defect can be identified that increases the risk for thrombosis
- ●20% of calf DVTs propagate to thigh; 50% of proximal DVTs embolize to the lungs; 90% of PEs come from lower extremity DVTs)
- ●Autopsy studies in trauma patients – 65% incidence of DVT and 16% PE (*Sevitt, BMJ, 1961*)
- ●Autopsy studies in critically ill patients find that PE was cause of death in 45% of patients and was not suspected
- ●**Incidence in the absence of (appropriate) prophylaxis** -
  - ◇General surgery – 20-30% incidence of DVT, proximal 7%, fatal PE 0.1 to 0.8% (18% if untreated)
  - ◇Trauma – 58% incidence of DVT, proximal DVT 18%, PE in 2-22%, fatal PE 1% (*Geerts, NEJM, 1994*)
  - ◇Fractured hip – 50% incidence of DVT, proximal DVT 20%, 4 to 7% risk of fatal PE
  - ◇SCI – 90% incidence of DVT
  - ◇Medical
    - ▪DVT FREE Registry Study – 50% of inpatients who developed VTE were nonsurgical
    - ▪ 17-34% MI, 20-40% CHF, 11-75% stroke, 25-42% MICU
- ●**Numerous initiatives to increase prophylaxis**
  - ◇Thrombophylaxis not being offered (or not appropriate method) despite numerous guidelines – only 60% of at-risk surgical patients received American College of Chest Physicians (ACCP)-recommended prophylaxis (ENDORSE Study)
  - ◇Agency for Health Care Research and Quality (AHRQ) - **#1 strategy to improve patient safety in hospitals is prevention of VTE**
  - ◇Surgical Care Improvement Project – *CMS considering appropriate VTE prophylaxis to be a pay-for-performance quality measure for specific procedures*

Risk Factors ***Virchow's Triad – venous stasis, endothelial injury/trauma, hypercoagulability***

- ●**Acquired** – increasing age, cancer, trauma/surgery, immobility, OCPs/hormone replacement therapy, obesity, HX of VTE, CA
  - ◇**Risk factors for lower extremity DVT** – mechanical ventilation, NMBs, CVL (CVL with increased relative risk of 1.04 for each day catheter is in place)
  - ◇**Risk factors for upper extremity DVT** – CVL and CA; 30% idiopathic (inherited thrombophilia, prothrombin G20210A mutation, anticoagulant protein deficiency)
    - ▪CVL-induced upper extremity DVT → PICC > CVL, 3 months anticoagulation, *catheter may be left in place if functional and needed*
  - ◇**Increased risk after surgery** – increasing age, type (chest, abdominopelvic, and lower extremity) and extent of surgery, duration of hospital stay, HX of VTE or CA (includes family members), immobility, pregnancy/post-partum, sepsis, CVL, obesity, presence of inherited or hypercoagulable conditions, medical co-morbidities (stroke, CAD, infection, inflammation)
  - ◇**Increased risk after trauma** –older age, increasing ISS, blood transfusion, surgery, long bone fractures, pelvic fractures, TBI/SCI, spinal fractures, CVL
    - ▪Femoral CVL – 12 to 22% increase risk of ipsilateral iliofemoral DVT (2% with subclavian site)
    - ▪Independent predictors of DVT
      - ◦Age, blood transfusion, surgery, fracture of femur or tibia, SCI (*Geerts, NEJM, 1994*)
      - ◦Age ≥ 40, lower extremity fracture with AIS ≥ 3, ventilator days ≥ 3 days, head injury with AIS ≥ 3, venous injury, major operation (*Knudson, Ann Surg, 2004*)
      - ◦Risk assessment profile developed by Greenfield (*J Trauma 1997*) and supported by Gearhart (*Surgery, 2000*)
        - -RAP score ≥ 5 → 3X more likely to develop VTE

-2 points → obesity, CA, abnormal coagulation, femoral CVL, transfusion > 4U's, operation > 2 hrs, chest AIS > 2, abdomen AIS > 2, head AIS > 2, age ≥ 40 and ‹60
-3 points → HX of VTE, major venous repair, spinal fractures, GCS < 8, age ≥ 60 and ‹75
-4 points → severe LE fx, pelvic fx, SCI, age ≥ 75

◇**Independent risk factors for VTE** – multivariate analysis in med-surg ICU patients revealed platelet transfusion and use of vasopressors

◇***Two most powerful patient-related risk factors are HX of VTE and CA***

●**Genetic** – deficiencies of protein C and S, antithrombin; factor V Leiden and prothrombin 20210A mutations; blood group non-O; hyperhomocysteinemia; dysfibrinogenemia; elevated levels of factors II, V, VII, VIII, IX, X, and XI (VIII, IX, and XI most common); elevated plasminogen activator inhibitor (PAI-1); myeloproliferative disorders

◇Factor V Leiden deficiency results in 10-65% of patients with DVT attributable to genetic causes and is the most common inheritable blood coagulation disorder (present in 5% of population); resists degradation by protein C → hypercoagulable; long-term anticoagulation not recommended for those heterozygous for the mutation

●**Hematologic** – heparin-induced thrombocytopenia and thrombosis (HITTS), DIC, antiphospholipid antibody syndrome (cardiolipin or lupus anticoagulant), TTP, HUS

◇Antiphospholipid antibody syndrome → thrombosis + persistent antibody titer on two separate occasions 12 weeks apart; high recurrence rates after discontinuation of anticoagulation → indefinite treatment; may interfere with standard assays → may need to follow factor II and X assays

Pathophysiology ***Virchow's Triad – venous stasis, endothelial injury/trauma, hypercoagulability***

●Thrombogenic platelet nidus in venous valves (most in calf) → platelets adhere to exposed subendothelium via vWF or fibrinogen →PMNs and platelets activate and release procoagulant and inflammatory mediators → thrombus composed of platelets, leukocytes, and fibrin → thrombotic and inflammatory process

◇PE develops when thrombus detaches from endothelium and migrates into pulmonary system

◇Can organize and grow into endothelium → venous incompetency → post-thrombotic syndrome

●**Coagulation pathway**

◇Extrinsic– tissue factor released as result of mechanical injury or trauma

◇Intrinsic– involves circulating plasma factors

◇Both pathways converge at factor X, activate to form Xa → promotes conversion of prothrombin to thrombin (factor II) → fibrin clot from fibrinogen

◇Fibrinolysins restore normal blood flow by lysing fibrin clot → plasmin digests fibrin and inactivates clotting factors V, VIII, and fibrinogen

●**Pulmonary Embolism**

◇Thrombogenic platelets in clot release serotonin, ADP, and thrombin → PA vasconstriction → increased pressure load → RV decompensation and decreased RV output → decreased LV preload → decreased CO and decreased MAP

◇PE increases RVEDP and the RV perfusion pressure is difference between MAP and RVEDP

▪Increased RV pressure load → decompensation → increased RVEDP → increased RV myocardial oxygen demand → further RV decompensation → RV ischemia and decreased CO

◦Increased RV pressure load also → RV wall stress and ischemia

▪RV volume increased by Starling mechanism to help compensate → left shift of interventricular septum → decreased LV preload →decreased LV output → hemodynamic instability/shock

▪Failure of compensation to maintain forward flow and resultant instability → thrombolytics

◇Gas exchange abnormalities related to size of embolus and patient's cardiopulmonary status; hemodynamic instability may be secondary to a large PE in a patient with a normal cardiopulmonary status, or a smaller PE in a patient with no cardiopulmonary reserve

▪Hypoxia – increase in alveolar dead space, V/Q abnormalities, right-to-left shunting

◦Low mixed venous 02 with cardiogenic shock

▪Low V/Q → hypoxia

◦Redistribution of blood flow away from area of embolism → increased perfusion in unembolized lung and reperfusion of atelectatic areas of clot

▪Desaturation with as little as 13% pulmonary vascular obstruction (25-30% obstruction → pulmonary HTN develops)

◦Normal mean pulmonary artery pressure = 20 mm Hg; no HX of cardiopulmonary disease and patient unable to reach/generate PAP > 40 mm Hg (maximal pressure a healthy RV can generate)

◦Obstructions greater than 50% with PAP > 40 mm Hg → RV failure in patients without cardiopulmonary disease

▪No underlying cardiopulmonary disease

◦Increased PAP in PE → signifies severe obstruction

◦PAP can be increased without decreased CO

◦***Decreased CO without increased PAP → search for alternative diagnosis***

▪HX of cardiopulmonary disease → greater cardiovascular compromise with less obstruction

◦90% presenting in shock had cardiac HX (*European Pulm Embolism Trial*)

◦Underlying cardiopulmonary process dominates presentation

◇70% of patients with cardiac arrest will die; 30% will survive

Diagnosis of DVT (*gold standard is venography*)

- **Clinical evaluation** – 50% of patients may be asymptomatic at presentation (exam unreliable)
  - ◇Extremity pain, swelling (most common finding), or erythema; calf pain on dorsiflexion of the foot (Homan's sign – 50%); palpable cord
  - ◇Massive iliofemoral DVT with obstruction of venous drainage of the extremity
    - ▪Phlegmasia alba dolens – thrombosis of deep veins only, sparing collaterals to allow for some venous drainage; underlying CA in 20-40% as precipitating event; white, edematous extremity
    - ▪Phlegmasia cerulea dolens – thrombosis of deep veins and collaterals, resulting in no venous drainage → impaired arterial inflow; blue, edematous extremity
      - ◦Venous gangrene may occur if arterial inflow obstructs due to increasing venous hypertension; preceded by phlegmasia cerulea dolens; amputation rates 20-50%, PE 12-40%, mortality 20-40%
  - ◇Upper extremity DVT – less than 5% of all DVTs; associated with PE in 10-36%
    - ▪Primary axillary/subclavian thrombosis – Paget-von Schrotter syndrome
      - ◦Muscular athletes; hypercoagulable states
    - ▪Secondary – mediastinal tumors, CHF, nephritic syndrome
    - ▪Symptoms – arm pain/edema/cyanosis; superficial vein distention over extremity and anterior chest wall
- **Compression duplex ultrasound** – most common method of detecting DVT; > 90% sensitivity and specificity in detecting femoral and popliteal DVT but only 50% of calf DVT (poor visualization of pelvic veins); preferred diagnostic method as least invasive, reproducible, and more sensitive than impedance plethysmography; nearly 100% PPV
  - ◇B-mode image (2-D image) and Doppler flow pattern
  - ◇Negative duplex that is technically adequate (all venous segments evaluated) – accurate enough to withhold anticoagulation
  - ◇May be used to diagnose symptomatic trauma patients with suspected DVT without venography (*Level I EAST recommendation, 2002*); not as accurate in asymptomatic patients for screening
    - ▪Proximal symptomatic DVT 97% vs. proximal asymptomatic DVT 62%
    - ▪Distal symptomatic DVT 73% vs. distal asymptomatic 53%
  - ◇If indeterminant → biomarkers (d-dimer), re-duplex in 24-48 hours
  - ◇Serial duplex U/S in high risk, asymptomatic trauma patients for screening may be cost-effective and decrease incidence of PE (*Level III EAST recommendation, 2002*) ***CONTROVERSIAL***
- **Impedance plethysmography** – noninvasive, measurements of venous capacitance and outflow obtained by inflating and deflating a cuff around the thigh to infer presence of a DVT; poor sensitivity and specificity
- **Fibrinogen leg scanning** – iodine 125 to measure local fibrinogen activity to detect a newly formed thrombus; poor sensitivity and specificity
- **Venography** – gold standard for diagnosis of DVT; required with strong clinical suspicion and negative or equivocal studies
  - ◇Time-consuming, invasive, risk of contrast-induced nephrotoxicity, transport out of ICU
  - ◇CT venography – of pelvic veins and lower extremities; may becombined with CTA pulmonary arteries
    - ▪PIOPED reported equivalent to compression ultrasound
  - ◇MR venography – diagnosis of acute DVT in proximal extremity or pelvis
- **Hypercoagulable workup** – idiopathic, recurrent, family HX, or unusual location
  - ◇PT/INR, PTT (mixing studies if PTT elevated), platelet count, platelet aggregation studies
  - ◇APC resistance/factor V Leiden deficiency; prothrombin 20210A; homocysteine level; protein C and S and antithrombin III antigen; antiphospholipd/anticardiolipin antibody; factors II, V, VII, VIII, IX, X, and XI levels; functional plasminogen; heparin antibodies if indicated
- **D-dimer** – if positive and clinical suspicion, associated with DVT in 70%; ***negative – no VTE***
  - ◇Degradation product of cross-linked fibrin formed after clots degraded by plasmin
  - ◇Reflects systemic activation of clot as well as degradation
  - ◇NPV high → no VTE; poor specificity, poor PPV
  - ◇***Useful predictor of recurrence of VTE; if still elevated after discontinuing anticoagulation → should be restarted***
- **P-selectin** – cell adhesion molecule important in clot formation; stored in platelets and endothelial cells; marker under investigation

Diagnosis of PE (*gold standard pulmonary angiography*)

- **Clinical evaluation** – MS changes, dyspnea, hypoxia, pleuritic CP, cough, hemoptysis, tachycardia, ***tachypnea most common sign***, elevated RAP, increases second heart sound and RV S3
  - ◇Massive PE – syncope, CV collapse, resp failure
  - ◇Postop – dyspnea, hypoxia, tachycardia, dysrhythmia
  - ◇Wells scoring system (based on clinical suspicion) – active cancer, paralysis/paresis, recent plaster immobilization, localized tenderness along deep venous system, swollen leg, bedridden for 3 or more days, calf swelling 3 cm larger that uninvolved side, pitting edema, and HX of DVT
  - ◇Revised Geneva scoring system (objective)– age > 65, previous surgery requiring general anesthesia within 1 month, HX of VTE, active CA, hemoptysis, HR > 75 BPM, unilateral extremity pain or pain with deep palpation
  - ◇Pretest probability is very important (high pretest probability and high probability scan → confirm diagnosis; other combinations require further studies)
    - ▪Discordant pretest and angiography → consider repeat CTA, CTA + CTV, pulmonary angiogram, serial duplex ultrasound
- **EKG**
  - ◇Normal ECG uncommon (14-30% in UPET and PIOPED); S1Q3T3 – classic sign, but uncommon

◇Afib, aflutter, 1st, 2nd, and 3rd degree heart blocks all uncommon as presenting sign of PE
◇Non-specific ST or T-wave changes most common (UPET and PIOPED)
▪Anterior T-wave inversion most common (68%); appears early in course → marker of severity
◦Effective thrombolytics → T-wave normalization

●**ABG**
◇Pa02 < 80 mm Hg (> than 80 seen in nearly 20%), elevated A-a gradient, respiratory alkalosis
◇Desaturation requiring escalating FIO2 → R/O PE

●**CXR** – normal unusual (16% - 34% in PIOPED and UPET; usually atelectasis, pleural effusions, infiltrates)
◇Prominent central pulmonary artery with decreased pulmonary vascularity (Westermark's sign)
◇Abrupt cutoff of PA

●**Contrast-enhanced spiral CT of the chest** – sensitivity 70-90% (> 90% when clinical assessment added and even higher with Duplex of lower extremities); comparable to pulmonary angiography; pretest probability important in diagnosis
◇Evaluate other pulmonary abnormalities (effusions, infiltrates)
◇PIOPED II – concordant CT and clinical exam → therapies safely recommended ; discordant → further studies
▪96% NPV if low pretest probability and negative CTA → no treatment
▪58% PPV if low pretest probability and positive CTA
◦97% PPV if lobar embolus, 68% segmental, and 25% if subsegmental
▪60% NPV if high pretest probability and negative CTA
◇Can be combined with CTA of pelvis and deep thigh veins to detect DVT as well
◇Can identify RV dilation in those with massive PE
▪RV:LV ratio > 0.9 → increased risk of sudden death and 30 day mortality; NPV 92%
◇Has replaced V/Q scan (radionucleotide ventilation and perfusion lung imaging)

●**V/Q scan** – indicated when CT chest PE protocol contraindicated (renal failure); difficult to interpret in pre-existing lung disease
◇PIOPED I – 98% sensitive, 10% specific; combine clinical factors and sensitivity and specificity >95%
◇High probability strongly suggests PE; with 2 risk factors → sensitivity 97%; one risk factors → 84%; no risk factors → 82%
◇Intermediate probability – noted in more than 50% of patients and thus need for further testing
▪More than 25% of these patients have a PE, therefore need further evaluation or empiric anticoagulation/treatment
◇Low probability + low-likelihood assessment = no PE

●**Echocardiography** – risk stratification by identifying PE and assessing cardiac function and hemodynamics; ***ideal in hemodynamically unstable patient***; assess for other etiologies like MI, aortic dissection, tamponade
◇***RV dysfunction = increased mortality***
◇Trans-thoracic echo (TTE) – ***RV strain/dysfunction as surrogate for PE***(associated with PE but not specific), RV and pulmonary artery dilation, increased RV/LV diameter, right-sided thrombus, hypokinesis, TR, abnormal motion of interventricular septum and bowing into the LV, lack of collapse of IVC during inspiration
◇Trans-esophageal echo (TEE) – direct visualization of PE; sensitive for central PE (loses accuracy in periphery secondary to left mainstem bronchus interference)
◇Without cardiopulmonary disease, echo may approximate degree of embolic burden
▪HX of cardiopulmonary disease, frequently RV dilatation and echo not effective in evaluation
◇***Absence of RV dilatation in unstable patient excludes PE as cause of shock***

●**Pulmonary angiography** – gold standard; pursue when diagnosis uncertain, being considered for IVC interruption, when planning thrombolysis or pulmonary embolectomy, or confirmation in patients at high risk of complications from anticoagulation

●**MRI** – evaluating central pelvic vein and IVC thromboses; PIOPED III found MRI angiogram inadequate in 25%; if adequate, sensitivity 78% and specificity 99%; limited role

●**Biomarkers**
◇If hemodynamically stable and normal/low BNP and troponin (cTnT and cTnI) → low mortality
▪If elevated BNP and troponin → higher mortality
▪BNP and NT-proBNP indicators of cardiac wall stress and hypoxia

Prophylaxis

●**Primary prophylaxis –** methods effective at preventing DVT (chemical, mechanical) **versus**
◇Secondary prevention – early detection by screening postoperative/posttraumatic patients
▪Primary prophylaxis contraindicated or ineffective
▪Serial duplex U/S in high risk, asymptomatic trauma patients for screening may be cost-effective and decrease incidence of PE (*Level III EAST recommendation, 2002*)
◦Not an effective strategy; cost prohibitive
◦Possibly in patient whom anticoagulation is delayed (trauma, TBI)
◦2008 and 2012 ACCP guidelines → routine screening with duplex not effective in prevention and prohibitive cost

●**Prophylaxis preoperatively in patients undergoing major procedures because of venous stasis and relative hypercoagulability during the operation *(CONTROVERSIAL)***
◇**Major bleeding as defined by International Society for Thrombosis and Hemostasis**
▪Fatal bleeding**,** symptomatic bleeding in a critical area/organ, or decrease in Hb ≥ 2 g/dL or leading to transfusion of 2 or more units of blood
◇Orthopedic surgery (hip replacement/arthroplasty) – large risk reduction in DVT when LMW given at half dose in proximity (two hours before surgery or 4-6 hours after); *two hours before surgery with increased risk of major bleeding*

- ACCP → values and preferences started in 2004
- In PE, typically prevention of death >> low bleeding risk from anticoagulation
- Ortho → avoidance of bleeding from anticoagulation >> prevention of death from PE
  - LMWH 18-24 hours postop
  - Warfarin common even with delayed onset of anticoagulation
  - No role for UFH

● **Increased risk after surgery** – increasing age, type (chest, abdominopelvic, and lower extremity) and extent of surgery, duration of hospital stay, HX of VTE or CA (includes family members), immobility, In pregnancy/post-partum, sepsis, CVL, obesity, presence of inherited or hypercoagulable conditions, medical co-morbidities (stroke, CAD, infection, inflammation)

● **Types of prophylaxis**

◇Mechanical – patients at high risk of bleeding; placed preoperatively until discharge; consider chemo-prophylaxis as soon as bleeding risk becomes acceptable; reduce vein lumen → increase venous flow velocity;

◇***Mechanical prophylaxis alone not likely to be effective in ICU patients unless bleeding a great concern***

- Intermittent pneumatic compression – enhance blood flow in deep venous system of extremities → decrease venous stasis; upregulates thrombomodulin and fibrinolysin, reduced plasminogen activator inhibitor (PAI-1) increasing fibrinolysis
  - Alternative in at-risk patients at significant bleeding risk with anticoagulation
  - Contraindicated in patients with peripheral ischemia (PVD)
  - Prolonged bedrest may be at risk for dislodging clot with IPC
  - Incidence of VTE may be less when combined with chemoprophylaxis
  - Cochrane review – effective in preventing DVT in surgery patients but more effective with chemical agent
  - Remove if a DVT is found to prevent embolization
  - Trauma
    - -comparable to LDUH (*Velmahos, J Trauma, 2000; Fisher, J Ortho Trauma, 1995*)
    - -similar DVT rate with SCD, LDUH, or combination (*Velmahos, JACS, 1998*)
    - -meta-analysis showed no benefit over no prophylaxis (*Velmahos, J Trauma, 2000*)
    - -GCS or IPCs provide suboptimal protection; combine with LMWH, or with contraindication to chemoprophylaxis
    - -2002 EAST guidelines → level III recommendation as may be of benefit in TBI
  - SCI – IPC + UFH less effective than LMWH alone in pRCT
- Graduated compression stockings – less convincing evidence; limb measured accurately to prevent incorrect pressure gradients which can occur in up to 50%
  - Mechanism – reduces venous diameter and increasing venous flow
  - Reduce DVT in hospitalized patients (*Sachdeva, Cochrane, 2010*)
  - GCS + LDUH more effective than LDUH (*Br J Surg 1985*)
  - 2008 ACCP guidelines do not differentiate between IPCs and GCS
  - Incorrect sizing/application → reverse flow → greater proximal pressure → increase DVT
  - Not complementary with IPCs as IPCs empty deep venous syste
- Venous foot pumps – less convincing evidence for their use; increased venous blood flow in popliteal vein 250
  - Higher rates of DVT (trauma)
  - Combine with chemoprophylaxis (trauma)
    - -2002 EAST guidelines → level III recommendation as substitute for IPCs
- IVCFs
  - ***Not recommended (ACCP) as prophylaxis***
    - -2002 EAST guidelines → level III evidence in favor of
    - -prophylactic placement in very high risk trauma patients who are unable to receive chemoprophylaxis because of bleeding risk and who are immobilized
  - More commonly placed for prophylaxis than for treatment (*Knudson, Ann Surg, 2004*)
  - Classic indications include: placement in patients with proximal DVT or PE with contraindication to anticoagulation, including bleeding or recurrent VTE; adjunct to anticoagulation in patients unable to withstand another VTE event
  - Alternative to chemoprophylaxis or mechanical prophylaxis in trauma, spine, neuro-surgical, and bariatric patients despite conclusive data that PE and death are reduced
  - NTDB review → 6282 patients received IVCF of which 86% placed prophylactically (*Shackford, J Trauma 2007*)
    - -meta-analysis → lower PE in IVCF group (*Velmahos, J Trauma 2000*)
  - May increase risk of DVT; recurrent PE 2-4%
    - -data lacking on decreasing fatal PE (*Ku, Thromb Haemost, 2005*)
  - Placement
    - -using fluoroscopy or ultrasound
    - -bedside (transabdominal or intravascular)
      - *intravascular → abdominal wounds, spine injury with turning limitations, morbidly obese
      - *multisystem trauma patient (*Rosenthal, J Cardiovasc Surg, 2005)*
  - Newer devices → optimal flow dynamics, maximal clot-trapping capabilities, potentially

retrievable
-Bird's nest filter large enough to accommodate an IVC with a diameter > 30mm
◦Retrievable
-retrieval rates 20-60%
*59% with a dedicated filter registry (*Rogers, J Trauma, 2012*)
*15.5% to 31.5% with registry (*Kalina, Am Surg, 2012*)
*trauma 55% compared to non-trauma 19% (*O'Keeffe, Am Surg, 2011*)
-protection from PE during the "at-risk" period
-bedside placement
-Cherry (*J Trauma, 2008*) → 1.6% PE, low complication rate (0.1%)
*retrieval 59%
◦Systematic review in trauma patients (*Kidane, Injury, 2012*)
-24 studies met inclusion criteria; lack of high quality literature
-supports use of prophylactic IVCFs in high-risk, polytrauma patients with contraindications to chemoprophylaxis
-limited data support a decrease in PE and fatal PE
-increasing use of retrievable filters
-retrieving after longer periods of time
-*Rajasekhar, J Thromb Thrombolysis, 2011*
*review of seven non-randomized studies in trauma showed pooled PE rates were 79% lower in filter group compared with historical controls
-*Girard, Thromb Res, 2003*
*review of 16 case series showed pooled risks of PE after IVCF: PE 0.6%, DVT 9.3%
◦Bariatric surgery
-*Vaziri, Obes Surg, 2011*
*high risk patients undergoing bariatric surgery
*5% DVT with IVCF + chemoprophylaxis
*67% of filters retrieved
-*Vaziri, Surg Endosc, 2009*
*HX of previous VTE, undergoing bariatric surgery
*IVCF + chemoprophylaxis
*21% with recurrent DVT after IVCF placement; 15% IVC thrombosis
*No PE
-*Trigilio-Black, Surg Obes Relat Dis, 2007*
*protocol for placement in all super morbidly obese
*no PE
*limited series with one death due to rhabdomyolysis from prolonged placement procedure

◇Chemical –
▪LDUH – 5000 U's SQ q12 or q8
◦Major abdominal or thoracic surgery → meta-analyses reduced all DVT and proximal DVT, and PE and fatal PE; reduce incidence of DVT 20-40%
-two hours before abdominal surgery (*Collins, NEJM, 1998*)
◦Inexpensive, easy administration, no monitoring
◦Complication includes HIT in 4%
◦2002 EAST guidelines
-no support for LDUH (level II recommendation)
◦Ruiz (Am J Surg 1991) – inadequate protection in trauma patients with ISS > 10
◦Knudson (*J Trauma 1994*) – no protection over SCDs
◦Geerts (*NEJM 1996*) – LDUH 5000 q12 insufficient in trauma patients
◦***Arnold (Am Surg 2010) – LDUH 5000 q8 may be as effective as enoxaparin (trauma)***
◦RCT of LDUH versus placebo in medical-surgical ICU patients reduced DVT from 29% to 13%
▪LWMH
◦Derived from chemical depolymerization of UFH → reduces size (5 kDa), charge, weight
-greater activity toward factor Xa; less activity for thrombin inhibition
◦Greater bioavailability, longer half life, more predictable dose-response curves, better safety profiles (less bleeding), outpatient management
-less endothelial cell binding and protein binding
-less osteoporosis
-less interference with protein C and complement activation
◦Renal clearance
◦Once daily or twice daily dosing, no monitoring
-standard dosing leads to low anti-Xa levels → increased DVT in SICU (*Malinoski, J Trauma 2010*)
◦Reduced incidence of HIT; ? decreased incidence of PTS
◦Treatment of choice in trauma (Geerts); equal to LDUH in general surgery patients
-2002 EAST guidelines → pelvic fx's, complex LE fx's, SCI, ISS > 9
◦Green (*Ann Int Med 1990*) – SCI, safe and effective for VTE prevention; superior to LDUH

◦2008 ACCP guidelines recommend LMWH for major trauma patients
◦Dalteparin once-daily in high risk trauma patients (*Cothren, World J Surg, 2007*)
-safe to operate through prophylaxis
-DVT 3.9%, PE 0.8%

▪Fondaparinux
◦Synthetic pentasaccharide; factor Xa inhibitor; blocks thrombin generation by accelerating rate of factor IIa, VIIa, IXa, Xa, XIA, and XIIA inactivation by antithrombin
◦Once daily dosing → improve compliance; renal clearance
◦No HIT; no antidote; long half life (17 hours); no endothelial or protein binding
◦Ortho, general surgery, medical patients
◦Superior to LMWH (enoxaparin) in ortho (TKR, THR, hip fracture) patients
-increased bleeding but did not lead to death, reoperation, or bleeding into a critical organ
-risk reduction of 56% in hip fracture patients (*Eriksson, NEJM, 2001*)
-incidence of DVT 1.4% (*Eriksson, J Arthoplasty, 2004*)
◦One study on elective THR → compared with enoxaparin, no advantage
◦Equal to dalteparin (LMWH) in patients undergoing major abdominal surgery (*PEGASUS*)
-dalteparin given 2 hours before surgery and 12 hours after first dose compared to fondaparinux 6 hours postoperative
-postop fondaparinux non-inferior to periop dalteparin
-Agnelli, Br J Surg, 2005
◦Pilot study in trauma patients → 1.2% DVT vs. 4.6% overall (*Lu, JACS, 2009*)
-no PE, HIT, or bleeding in fondaparinux group
-small study; no control group

▪Vitamin K antagonists (coumadin or acenocoumarol)
◦Takes 3-4 days to become therapeutic so may not prevent small thrombi from forming
◦Delayed onset of action + bleeding rates similar to LMWH → popular with Ortho

▪Aspirin
◦No benefit against VTE prophylaxis for any medical or surgical group (ACCP 2008)
◦***2012 ACCP → when UFH or LMWH contraindicated (2C)***

▪Direct thrombin inhibitors
◦Alternative in which heparin contraindicated (HIT)
◦Argatroban
◦Lepirudin, hirudin, desirudin, bivalirudin

◇***Oral*** antithrombotic agents
▪Rivaroxaban – factor X inhibitor, excellent bioavailability, half life = 9 hours, renal excretion
◦Contraindicated in renal failure, severe liver disease, and > 65 yo (dose reduction)
◦Compared to enoxaparin in THR/TKR → decreased symptomatic VTE and mortality

▪Dabigatran – direct thrombin inhibitor active against free and clot-bound thrombin; directed against conversion of fibrinogen to fibrin but also inhibits platelet activation by thrombin and the activation of clotting factors V, VIII, and XI by antithrombin
◦Given 12 hours preop and compared to enoxaparin in THR/TKR → non-inferior
◦Meta-analyses → symptomatic VTE and mortality similar with enoxaparin in THR/TKR

●Heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia + thrombosis (HITTS)
◇1-30% of patients
◇Begins 3-14 days after exposure to heparin products, although sooner if previously exposed
▪Heparin-coated pulmonary artery catheters, arterial lines
◇Heparin-dependent antibody that binds to platelet factor 4 → activates platelets → thrombocytopenia +/- thrombosis (arterial or venous)
◇UFH (4%) > LMWH (thrombosis less with LMWH)
▪Diagnosis
◦50% drop or greater in platelet count
◦Platelet count drops below 100,000/microL
◦Thrombosis during anticoagulation
◦Fondaparinux induces HIT antibody but does not cause disease
◦ELISA – highly sensitive, poorly specific
◦Serotonin release assay – more specific, less sensitive than ELISA
◇Once diagnosed, stop heparin
◇Warfarin only when platelets > 150,000/microL and alternative anticoagulant given to prevent paradoxical thrombosis or warfarin skin necrosis
◇High cross-reactivity of LMWH with UFH, therefore cannot substitute
◇Mortality 15%; amputation rate 6%
◇Alternatives
▪Direct thrombin inhibitors – lepirudin, argatroban
▪Fondaparinux – not FDA approved for this indication
▪Continue until thrombosis improves and platelet count increases

●2008 ACCP guidelines for patients undergoing surgery – low, moderate, and high risk groups
◇Low risk - < 40yo, no adverse patient- or surgery-related factors, require GETA < 30 minutes
▪Minor abdominal, thoracic, vascular, gynecology (laparoscopy as well)
▪Proximal DVT without prophylaxis 0.4%; fatal PE less than 0.01%

- ▪RCTs lacking
- ▪Early and frequent ambulation

◊Moderate risk – minor surgery with additional risk factors or age 40-60, GETA > 30 minutes, no additional adverse patient- or surgery-related risk factors (as in CA)
- ▪Urology, minor gynecologic, thoracic, neurosurgical procedures, arthroscopic knee surgery
- ▪Proximal DVT without prophylaxis 2-4%; fatal PE 0.1-0.4%
- ▪LMWH or LDUH or fondaparinux**;** LWMH for arthoscopy

◊High risk - > 60yo, major surgery or ages 40-60 with additional adverse patient- or surgery-related risk factors
- ▪Orthopedic surgery (trauma, elective), SCI, major trauma, CA, colorectal, vascular, major gynecologic, major abdomen
  - ◦Major gyn for benign disease without additional risk factors → LMWH, LDUH or IPC started preop
- ▪Proximal DVT 4-8%; fatal PE 0.4-1.0%
- ▪LMWH or LDUH q8 or fondaparinux

◊Highest risk – any patient with multiple risk factors
- ▪Proximal DVT 10-20%; fatal PE 0.2-5%
- ▪LMWH or LDUH q8 or fondaparinux + mechanical
  - ◦Major gyn for CA and/or additional risk factors → LMWH or LDUH q8 or IPC preop, or LMWH or LDUH q8 + GCS/IPC, or fondaparinux

●2012 ACCP guidelines (9th edition) for patients undergoing general and abdominopelvic surgery

◊Rogers score – low risk (<7; VTE risk 0.1%); medium risk (7-10; VTE 0.5%); high risk (>10; VTE 1.5%)

◊Caprini score
- ▪Low risk – 0 to 1; DVT < 10%; early ambulation
- ▪Moderate risk – 2; DVT 10-20%; elastic stockings, IPC, LDUH 5000U q12, or LMWH
- ▪High risk – 3 to 4; DVT 20-40%; IPC, LDUH 5000U q8, or LMWH
- ▪Highest risk – 5 or more; DVT 40-80%; mortality 1-5%; LDUH, LMWH, warfarin, or factor Xa inhibitor alone or in combination with elastic stockings or IPC

◊Very low risk – VTE < 0.5%, Rogers score <7, Caprini score 0 → early ambulation

◊Low risk – VTE 1.5%, Rogers score 7-10, Caprini score 1-2 → IPC

◊Moderate risk – VTE 3%, Rogers score >10, Caprini 3-4, not at high risk for major bleeding → LMWH or LDUH or IPC
- ▪Moderate risk at high risk for bleeding →IPC

◊High risk – VTE 6%, Caprini ≥5, not at risk for bleeding → LMWH or LDUH + ES or IPC
- ▪CA → 4 weeks LMWH
- ▪Contraindication to LMWH or UFH (?HIT) → ***low dose ASA*** (2C) or fondaparinux or IPC
  - ◦Subgroup analysis of Antiplatelet Trialists Collaborative in general surgery patients showed 37% risk reduction in asymptomatic proximal and distal DVT; 71% reduction in clinical PE
  - ◦Re-evaluation of data by ACCP found that ASA reduced risk of asymptomatic proximal or distal DVT by 48%, proximal DVT by 59%, and PE by 57%
  - ◦Data with moderate heterogeneity, no blinding in two studies, inconsistent outcomes, imprecision in RR of bleeding, six studies used fibrinogen uptake scanning for surveillance

◊IVCF not used for primary VTE prevention

◊Periodic surveillance with DUS not beneficial

●2012 ACCP guidelines for trauma patients

◊***LDUH*** or LMWH or IPC (2C)
- ◦Low quality evidence in support of ***asymptomatic*** proximal DVT which is reduced by 58% with LMWH and by 90% with LDUH plus continuous passive motion (ortho trauma and skeletal trauma

◊Major trauma patients at high risk for VTE (SCI, TBI, spinal surgery for trauma) → add IPC (2C)

◊Major trauma patients in whom LMWH and LDUH contraindicated → IPC
- ▪Add chemoprophylaxis when risk of bleeding diminishes

◊IVCF not used for primary VTE prevention and no periodic surveillance for DVT
- ▪No RCTs for either of these groups

●Trauma

◊Methods of prophylaxis effective in non-trauma/general surgical population are ineffective in trauma patients
- ▪Factors leading to thrombosis develop immediately after injury – or soon after
- ▪Contraindications due to bleeding limit prophylaxis options
- ▪Limited RCTs → controversy as to optimal method in severely injured and timing in TBI

◊**Increased risk after trauma** –older age, increasing ISS, blood transfusion, surgery, long bone fractures, pelvic fractures, TBI/SCI, spinal fractures, CVL

◊**In the presence of (appropriate) prophylaxis**
- ▪Enoxaparin 30mg SQ q12 vs. heparin 5000 U's SQ q12 in major trauma patients (*Geerts, NEJM, 1996*)
  - ◦Rates of overall DVT 31% in enoxaparin vs. 44% in heparin group
    -relative risk reduction with enoxaparin – 30%
  - ◦Rates of proximal DVT 6% in enoxaparin vs. 15% in heparin group
    -relative risk reduction with enoxaparin – 58%
- ▪UFH 5000 U's SQ q8 vs. enoxaparin 30mg SQ q12 (*Arnold, Am Surg, 2010*)
  - ◦UFH as effective, no increase in bleeding, decreased cost
  - ◦Retrospective, protocol change mid-year from enoxaparin to UFH

◇EAST recommendations 2002
▪LDUH – little evidence to support use (level II)
▪LMWH – indicated in pelvic and complex LE fx's and SCI (level II); ISS >9 (level III)
◦With Geerts, LMWH to a level I recommendation
◇Spinal cord injury
▪2008 ACCP recommendations
◦LMWH
◦LMWH + mechanical, LDUH + mechanical
◦Contraindication to chemoprophylaxis → mechanical
◦***IVCFs not routinely recommended (under any circumstances)***
◦Rehab after SCI → LMWH or VKA; 2012 ACCP → 3 months
▪DETECT (*J Trauma 2007*) – dalteparin 5000 U's SQ daily vs. enoxaparin 30mg SQ q12
◦Retrospective, cohort study in SCI and major orthopedic trauma patients
◦May not be clinically non-inferior
◦Enoxaparin remains supported by level I evidence

◇Traumatic brain injury ***TIMING CONTROVERSIAL***
▪Incidence of VTE 3-5% when prophylaxis started within 24-48hrs, up to 15% when delayed beyond 48 hours (*Kim, Neurocrit Care, 2009; Reiff, J Trauma, 2009; Nathens, J Trauma, 2007*)
◦LMWH within 48 hours in 525 TBI patients → progressive hemorrhagic changes on CT in 3.4% and change in management or outcome in 1.1%; 0.5% required craniotomy (*Norwood, J Trauma, 2008*)
◦LMWH (enoxaparin and dalteparin) within 48-72 hours, retrospective
-proximal DVT in 3.1%, no differences between LMWHs
-only one patient had symptomatic expansion of ICH
-Dudley, J Neurotrauma, 2010
◦Enoxaparin within 72 hours in 268 TBI patients, retrospective (*Koehler, J Trauma, 2011*)
-no difference in outcomes compared with >72 hours
◦Chemoprophylaxis (LDUH, heparin, LMWH) in 169 TBI patients within 48 hours and 242 within 72 hours (*Scudday, JACS, 2011*)
-VTE in chemoprophylaxis group of 1% vs. 3% in no prophylaxis group and lower rates of injury progression (although not significant)
◦LMWH in 158 TBI patients compared with LDUH in 171 TBI patients (*Minshall, J Trauma, 2011*)
-VTE higher in LDUH group; ICH progression higher in LDUH group
◦**Brain Trauma Foundation** (*Stratton, J Neurotrauma, 2007*)
-Level III recommendation for LMWH or LDUH + mechanical with insufficient evidence to support preferred agent, dose, or timing

●**Colorectal/general surgery** (**ASCRS**, *Stahl, Dis Colon Rectum 2006*)
◇Anorectal procedures < 40 yo and no additional risk factors → no prophylaxis
◇Anorectal procedures > 40 yo and/or have additional risk factors considered for prophylaxis case-by-case
◇Moderate- to high-risk patients undergoing abdominal surgery → LDUH (moderate q12; high q8) or LMWH
▪At risk of bleeding → mechanical prophylaxis
▪Grade A recommendation supported by Level I evidence (*McLeod, Ann Surg 2001*)
◇Highest risk should receive both mechanical and LDUH prophylaxis
▪Grade A recommendation supported by Level I evidence (??? *Cochrane Library, 2004*)
◇Laparoscopic surgery same prophylaxis as in open procedure

●**Bariatric**
◇21% incidence of VTE → some studies recommend higher doses of LMWH or LDUH
◇VTE after laparoscopic bariatric surgery (Becattini, Surg Obes Relat Dis, 2012)- a meta-analysis
▪Weight-based chemoprophylaxis regimens equivalent to standard regimens with increase in major bleeding

●**THR/TKR**
◇LMWH, fondaparinux, VKA, rivaroxaban
◇American Academy of Orthopedic Surgeons 2009 guidelines for VTE prophylaxis

PE Risk	Bleeding Risk	Recommendation
Baseline	Baseline	Any of: 1. ASA 325 bid starting the day of surgery and continuing for 6 wks 2. LMWH starting 12 to 24 hrs postop for 7 to 12 days, dosed per package insert. 3. A synthetic pentasaccharide starting 12 to 24 hrs postop for 7 to 12 days, dosed per package insert. 4. Warfarin starting the night before surgery at a dose sufficient to obtain an INR $\leq$ 2.0 for 2-6 weeks.
Baseline	Increased	Any of: 1. ASA 325 bid starting the day of surgery and continuing for 6 wks 2. Warfarin starting the night before surgery at a dose sufficient to obtain an INR $\leq$ 2.0 for 2-6 weeks. 3. No Prophylaxis
		Any of:

Increased	Baseline	1. LMWH starting 12 to 24 hrs postop for 7 to 12 days, dosed per package insert. 2. A synthetic pentasaccharide starting 12 to 24 hrs postop for 7 to 12 days, dosed per package insert. 3. Warfarin starting the night before surgery at a dose sufficient to obtain an INR $\leq$ 2.0 for 2-6 weeks.
Increased	Increased	Any of: 1. ASA 325 bid starting the day of surgery and continuing for 6 wks 2. Warfarin starting the night before surgery at a dose sufficient to obtain an INR $\leq$ 2.0 for 2-6 weeks. 3. No Prophylaxis

- **Burns**
  - ◇Additional risk factors including advanced age, morbid obesity, extensive burns, LE burns, LE trauma, femoral CVL, and/or prolonged immobility → LMWH or LDUH (grade 1C 2008)
- **Pregnancy**
  - ◇***Leading cause of death in industrialized countries is VTE***
  - ◇Risk factors- hypercoagulability, hormonal-induced decrease in venous capacitance, decreased venous outflow from pelvis, decreased mobility
  - ◇Increased incidence throughout pregnancy (generalized hypercoagulable state)
  - ◇Pelvic vein thromboses account for about 10% of VTE in pregnancy
  - ◇More proximal and massive compared to general population; L > R due to longer course of left common iliac vein
  - ◇30% of DVTs and 50% of PEs occur post-partum
  - ◇In general, no prophylaxis during pregnancy as risks of anticoagulation > risk of VTE except:
    - ▪HX of thrombosis in which anticoagulation will also decrease risk of sAb
      - ◦Single prior episode of VTE plus a higher risk thrombophilia
      - ◦Multiple prior episodes of VTE
    - ▪Antithrombin deficiency
    - ▪Regimens include LMWH > LDUH, no coumadin
  - ◇Post-partum anticoagulation
    - ▪One or more episodes of VTE
    - ▪HX of thrombophilia
    - ▪Regimens include LMWH> LDUH, coumadin (patients not wanting SQ injections)
- **Epidural catheters and LMWH**
  - ◇2002 American Society of Regional Anesthesia and Pain Management consensus guidelines
    - ▪Monitoring of anti-Xa levels not recommended as not predictive of risk of bleeding
    - ▪Return of blood during placement requires that LMWH be delayed 24 hours
    - ▪Catheters can be placed safely 12 hours after a prophylactic dose
    - ▪Catheters can be safely placed 24 hours after a therapeutic dose
    - ▪May start LMWH two hours after catheter removal

- **Extended prophylaxis** – result of shortened hospital LOS
  - ◇Following total hip replacement/hip fracture surgery
    - ▪28 to 35 days with LMWH
    - ▪Coumadin effective but with higher incidence of major bleeding (*Samama, Arch Int Med, 2002*)
    - ▪Hip fracture patients received additional fondaparinux for 3 weeks and compared to placebo → decreased asymptomatic and symptomatic VTE
  - ◇Patients who have undergone major abdominal/cancer surgery may benefit from post-discharge prophylaxis with LMWH
    - ▪ASCRS, 2-3 weeks after discharge, maybe 4
    - ▪Four weeks of dalteparin 5000 IU daily compared with 1 week (*Rasmussen, J Thromb Haemost, 2006*)
      - ◦pRCT, multicenter, reduced venographically-confirmed DVT from 16.3% to 7.3%
    - ▪LMWH for 1 month after major abdominal or pelvic surgery reduced DVT from 14.3% to 6.1% (*Rasmussen, Cochrane, 2009*)
  - ◇SCI
    - ▪2012 ACCP guidelines → 3 months (>90% of all VTE occurred within first 91 days)
      - ◦*Knudson, Ann Surg, 2004; Ploumis, Spine J, 2009*

Treatment

- Primary goal of treatment for VTE is to reduce risk of PE, reduce extension of thrombus, and reduce recurrence.
  - ◇Recurrence rate is higher if anticoagulation not therapeutic within 24 hours
    - ▪Higher doses of UFH may be required in PE than DVT as heparin cleared more rapidly from plasma
    - ▪Early and sufficient dosing rather than slowly escalating
    - ▪Rare that anticoagulation completely contraindicated (ICH, uncontrolled bleeding)
      - ◦IVCF and embolectomy if unable to anticoagulate
      - ◦Start anticoagulation once contraindication abates
        - -consider no bolus and lower intensity
  - ◇Recurrence in 30% at 8-10 years even with anticoagulation
  - ◇Early and frequent ambulation (grade 1A, 2008 ACCP)
  - ◇GCS with ankle pressure gradient of 30-40mm Hg

- ▪Compression therapy continued for 2 years

- May require intubation. Catecholamine surge may be blunted with intubation, further worsening hemodynamics
  - ◇Alveolar overdistention (excessive bagging) may further increase pulmonary vascular resistance
- RV resuscitation
  - ◇PE may impair RV dysfunction → decreased CO
    - ▪Myocardial ischemia due to poor coronary perfusion and diastolic overdistention
  - ◇Enlarged right-sided chambers → push septae left → limit diastolic filling and impairing systolic contractility
  - ◇Gentle volume administration in PE patients with decreased preload (normotensive without evidence of RV dysfunction/dilatation) may improve CO
    - ▪Aggressive volume → RV overdistention → impair coronary perfusion and LV filling → decreased CO
      - ◦Volume in setting of RV dysfunction → increased wall stress, ischemia
  - ◇Once "tank" is full (follow by echo), add dobutamine and norepinephrine as needed
    - ▪Consider vasopressors early if RV pressures high or RV dysfunction
    - ▪Norepinephrine → may improve RV dysfunction through vasoconstriction (improves MAP and perfusion pressure to RV subendocardium)
- Pulmonary vasodilators
  - ◇Nitric oxide – lowers pulmonary artery pressures to unload RV and allow time to recover in pressor-dependent RV dysfunction
  - ◇Inhaled prostacyclin – may increase CO, decrease PAPs, improve gas exchange
  - ◇Sildenafil – PDE inhibitor increases cAMP → PA vasodilation, lowers mean PAPs
- Anticoagulants – UFH, LMWH, or fondaparinux for at least 5 days and until INR is > 2.0 for 24 hrs (grade 1C, 2008 ACCP)
  - ◇Heparin – UFH
    - ▪***All patients suspected of PE should receive anticoagulation during their evaluation unless a contraindication***
    - ▪IV UFH preferable in critically ill (variability of absorption of SQ LMWH in shock, potential for bleeding complications that can be reversed with protamine, shorter half-life)
    - ▪Weight based; monitor PTT → q4-6 hours
      - ◦80U/kg bolus then 18U/kg/hr to maintain PTT that corresponds to plasma heparin levels of 0.3 to 0.7 IU/mL anti-Xa activity (2008 ACCP)
      - ◦SC UFH initial dose 17,500U or 250U/kg BID
    - ▪Warfarin started once therapeutic in UFH (2008 ACCP says start on day 1)
    - ▪UFH stopped once INR therapeutic (for 2 days ??)
    - ▪Heparin resistance – failure to achieve therapeutic PTT despite higher than usual dose
      - ◦Bleeding risk increased
      - ◦Consider monitoring using anti-Xa levels
  - ◇LMWH – no monitoring except morbid obesity, pregnancy, or renal insufficiency
    - ▪ACCP – no routine indication to follow anti-Xa levels
    - ▪Weight-based; SQ q12 (1mg/kg) or 24 hours (1.5mg/kg)
    - ▪Preferred over UFH for initial treatment of VTE unless severe renal failure
  - ◇Warfarin – together with LMWH, UFH, or fondaparinux on first treatment day rather than delaying initiation of VKA (grade 1A, 2008 ACCP) **versus** starting after therapeutic anticoagulation (overlap 5 days as takes this long for intrinsic clotting pathway to be suppressed)
    - ▪Warfarin impairs production of vitamin K-dependent clotting factors
    - ▪Depletes protein C and S (anticoagulants) before factors II, VII (half life 5-7 hours) IX, and X (procoagulant) → transiently hypercoagulable → skin necrosis
    - ▪Stop IV/SQ anticoagulation after INR therapeutic (2.0-3.0)
    - ▪Duration depends on thrombogenic risk factors, type of thrombosis (idiopathic), recurrence, and D-dimer one month after warfarin therapy stops
      - ◦After first episode
        - -3 months if transient/reversible risk factor
        - -calf thrombi maybe 6 weeks to 3 months (if treated)
      - ◦After second episode, lifelong unless very young or fall risk → ICH
      - ◦Unprovoked, at least 3 months and re-evaluation for risk-benefit of long-term tx
        - -first unprovoked + proximal + no risk factors for bleeding + adequate monitor → long-term treatment
        - -second unprovoked → long-term
        - -unprovoked, distal DVT → 3 months
      - ◦DVT + CA → 3-6 months of LMWH
        - -followed by warfarin or LMWH indefinitely or until CA is resolved
    - ▪Recurrence increased with homozygous factor V Leiden and prothrombin 20210A mutations, protein C and S and antithrombin deficiencies, and antiphospholipid antibodies, and CA until remission
      - ◦Long-term warfarin
      - ◦Heterozygous factor V Leiden and prothrombin 20210A mutations → shorter duration
    - ▪Continuing warfarin with INR 1.5-2.0 superior to placebo with 64% risk reduction for recurrent DVT after completion of 6 months standard treatment
    - ▪Continuing warfarin with INR 2.0-3.0 superior to low dose warfarin with no increase in bleeding
  - ◇Fondaparinux
    - ▪Known DVT compared with LMWH (*Ann Intern Med 2004*), and known PE compared with LDUH (*NEJM 2003*)- equivalent safety and effectiveness

- ▪Weight based
  - ◦5mg if < 50kg, 7.5mg if 50-100kg, 10mg if > 100kg
  - ◦Anti-Xa assays may overestimate dose
- ◇Lepirudin (irreversible DTI)
  - ▪Approved in HIT; PTT 1.5-2.5X normal (possibly less as increased risk of bleeding)
  - ▪0.1 mg/kg/hr
  - ▪Renal clearance → in patients with liver disease
  - ▪Antibodies develop after 5 days → enhance anticoagulation effects
- ◇Argatroban (reversible DTI)
  - ▪Approved in HIT; PTT 1.5-3.0X normal; 2microgm/kg/min
  - ▪With transition to warfarin, target INR 3-4 (not 2-3)
  - ▪Hepatic elimination although renal insufficiency increases bleeding risk

● Drugs being tested
- ◇Oral heparin
- ◇Oral lepirudin and argatroban
- ◇Ancrod (defibrinating agent)
- ◇P-selectin inhibitors (anti-inflammatory that limits thrombus without anticoagulating)
- ◇Factor VIIa inhibitors
- ◇TF inhibitor
- ◇APC

● Bleeding from anticoagulation
- ◇Heparin – 10% in first 5 days
- ◇Warfarin – 6% per year (fatal bleeding in < 2%)
  - ▪Meta-analysis → 9.1% if anticoagulated beyond 3 months
  - ▪Essential to monitor INR in outpatient setting
- ◇Surveillance key to prevent/decrease serious complications
- ◇Treatment
  - ▪Frequent Hb/coags monitoring
  - ▪Control of bleeding site if able
  - ▪Blood component therapy (FFP, pRBCs, platelets)
  - ▪Volume expansion
  - ▪Discontinue anticoagulant
  - ▪Antidote if appropriate
    - ◦Protamine for UFH → hypotension, pulm HTN, decreased CO; 1mg per 100 Us of UFH
    - ◦Protamine for LMWH → less useful as reverses 40% (<70%???) of anti-Xa activity; 1mg per 1mg or 100 Us of LMWH
    - ◦Desmopressin → analog of vasopressin without pressor activity; longer duration of action (6-24 hours); IV infusion at 0.3micrograms/kg body weight; increases factor VIII and vWF 4x normal within 1 hour; tachyphylaxis after 3-4 doses; improves platelet aggregation and reduces blood loss in impaired hemostasis (renal insufficiency, cardiac surgery, non-cardiac surgery)
    - ◦Recombinant activated factor VII → increased risk of thrombosis; expensive; approved for hemophiliacs; expanded use with trauma and ICH; 90-200 micrograms/kg, repeated in 2 hours; partially reverse fondaparinux
    - ◦Prothrombin complex concentrates → vitamin K antagonists and bleeding; accompanied by FFP and vitamin K

● D-dimer
- ◇Positive and clinical assessment associated with VTE in 70%; negative – no VTE
- ◇Degradation product of cross-linked fibrin formed after clots degraded by plasmin
- ◇Reflects systemic activation of clot as well as degradation
- ◇NPV high → no VTE; poor specificity, poor PPV
- ◇Useful predictor of recurrence of VTE; if still elevated after discontinuing (1 month after) anticoagulation → should be restarted

● **IVCF/caval interruption**
- ◇Caval interruption suggested by Trousseau in 1868 and performed by Bottini in 1893 for DVT
- ◇Indications – routine use of IVCF for DVT not recommended (2008 and 2012 ACCP)
  - ▪VTE with contraindications to anticoagulants (bleeding risk) in proximal DVT
  - ▪VTE with complications of anticoagulation (bleeding) in proximal DVT
  - ▪VTE with failure of anticoagulation (recurrent VTE) in proximal DVT
  - ▪Free-floating iliofemoral/caval thrombus (controversial) > 5cm (???)
  - ▪Relative
    - ◦HX of pulmonary hypertension or poor cardiopulmonary reserve and patient unable to withstand another embolic event
    - ◦Massive PE resulting in hemodynamic instability and inability to withstand a second event
    - ◦Morbid obesity with BMI > 55 undergoing gastric bypass
- ◇Only RCT of IVCFs in proximal DVT to prevent PE (*Decousus, NEJM, 1998 and PREPIC, Circulation, 2005)*
  - ▪400 patients with proximal DVT at risk for PE, randomized to permanent filter or no filter and to LMWH or LDUH
  - ▪Initial *reduction in PE* (not significant) and at 8 years (63% risk reduction), but no change in mortality
    - ◦Cumulative risk decreased from 15 to 6%

▪At 2 years and 8 years → *increased DVT*, no change in mortality, PTS similar
▪LMWH = LDUH

◇***Short-term and long-term anticoagulation in setting of IVCFs (once safe) to decrease recurrent DVT, IVC thrombosis, and PTS***
◇Usually infrarenal, but may consider suprarenal if: high-lying clot, pregnancy, clot-filled previously placed filter, renal vein thrombosis, IVC thrombus extending above renal veins
◇Not routine in UE DVT treatment (contraindication to anticoagulation)
◇***Beneficial in patients undergoing surgical embolectomy (Aklog, Circulation, 2002)***
◇Complications of IVCF placement
▪Mortality low (0.12%); major complications (0.3%)
▪Complications include: hematoma at insertion site, DVT at insertion site, IVC thrombosis, filter migration, filter erosion through IVC, filter embolization, and strut fragmentation

●**Thrombolytics →** activate plasminogen to form plasmin → accelerates clot lysis
◇Systemic thrombolysis (?improvement in mortality or decreased recurrent VTE over anticoagulation alone)
◇DVT
▪Not routinely recommended secondary to bleeding potential and inability to predict complete lysis
▪Goals → restore venous flow, preserve valve function, decrease incidence of PE/DVT
◦Phlegmasia → venous gangrene
▪National registry of urokinase and catheter-directed thrombolysis
◦Completely thrombolysis in 31%; partial in 52%
-complete more likely if: acute iliofemoral DVT, no previous HX, popliteal vein access
-patency at 12 months 79% if lysis complete vs. 32% if lysis < 50%
◦Major bleeding requiring transfusion in 11%; minor in 16%
◦Mortality 0.4%; ICH 0.2%
▪Anticoagulation after thrombolytics reduce PTS and maintain venous patency after DVT compared to anticoagulation (*Watson, Cochrane, 2004*)
▪Post-thrombotic syndrome
◦Thromboses damage deep venous valves → incompetent → venous reflux and venous hypertension →can affect segments of veins and valves not originally involved
◦Incidence as high as 50% in proximal DVT
◦Pain, heaviness, edema; worse with standing and ambulating
◦Progresses to SQ atrophy, hyperpigmentation, ulceration (10%)
◦Anticoagulation and GCS and early ambulation → reduce frequency
◦GCS after DVT → reduces PTS (*Lancet 1997, Ann Intern Med 2004*)
◦Catheter-directed thrombolysis may reduce incidence by recanalizing
-maintain valvular competence → avoid venous hypertension
▪Catheter-directed thrombolytics → may reduce bleeding risks; may reduce PTS and maintain valve function greater than systemic thrombolysis
◦ 2008 ACCP recommendations
-low risk of bleeding
-life expectancy > 1 year
-good functional status
-extensive iliofemoral thrombosis
-present within 14 days of symptoms
-plus thrombus fragmentation and/or aspiration over CDT alone
-follow with anticoagulation therapy
-if CDT not available, use systemic thrombolysis
◦ATTRaCT Study → randomize patients with iliofemoral or femoropopliteal DVT to catheter-directed thrombolytics and anticoagulation or anticoagulation alone to determine primary outcome of PTS over 24 months
◇PE – ***indicated in hemodynamically unstable (SBP < 90 mm Hg) patient without major contraindication to bleeding***; the majority of patients with PE do not require thrombolytics
▪Successful (restore hemodynamics) but with higher bleeding rates (retroperitoneal and intracranial)
◦Combined with successful embolectomy, mortality 0% compared to 30% with failed thrombolytics
◦Improvements in end-tidal C02 → success of thrombolytics
◦Not successful in 8%
-survival benefit to embolectomy, versus repeating thrombolysis (mortality 7% vs. 38%); recurrent PE higher in repeat thrombolysis group (and cause of death)
▪International Cooperative Pulmonary Embolism Registry
◦Thrombolytics uncommonly used
◦Recurrent PE at 90 days and death similar to those who did not receive thrombolytics
◦Major bleeding (22% vs. 9%) and ICH bleeding higher (3% vs. 0.3%)
▪Peripherally as not superior to locally in PA (*Verstraete, Circulation, 1998*)
▪Clot-directed (CDT) may be superior (*Uflacker, J Vasc Interv Radiol, 2001*)
◦Clot fragments better with decreased bleeding???
▪Compared to heparin, greater percentage of clot resolution/lysis with thrombolytics by 7 days
◦After 7 days, no difference
▪***Not indicated in treatment of PE in hypotensive <u>surgical</u> patients because of risk of hemorrhage***

◦Angiographically-proven → percutaneous or surgical embolectomy
▪Do not delay as irreversible cardiogenic shock may ensue
▪Recurrence rates and mortality unchanged
▪Thrombolytics followed by anticoagulation
▪Best if young, embolus less than 48 hours, and embolus is large
▪All agents equally effective (streptokinase, tPA, urokinase)
▪Most beneficial in patients with massive PE at risk for death within first hour (10%)
▪RV dysfunction without instability may benefit; ***possibly*** also-
◦Severe hypoxemia
◦Large perfusion defect on ventilation-perfusion scans
◦Extensive embolic burden on computed tomography (CT)
◦Free-floating right atrial or ventricular thrombus
◦Patent foramen ovale
◦Cardiopulmonary resuscitation
▪Contraindication to thrombolytics or failure of thrombolysis → embolectomy
▪Outcome from PE related to embolism size and underlying cardiopulmonary function
▪Cardiac arrest from embolism size and cardiopulmonary status → mortality 70%
◦30% will survive → continue resuscitation and chest compressions to fracture embolism
▪Thrombolysis or embolectomy should be considered even without definitive diagnosis when PE suspected (???)
▪Mortality ≤ 1% if RV is not dilated from embolism size and cardiopulmonary function AND therapeutic anticoagulation is achieved
▪Outcomes after thrombolytics
◦Mortality 8%; major bleeding 9.6% (heparin 6%); nonmajor bleeding 23% versus 10% with heparin (significant); recurrent PE 7.6%
◦RV dysfunction reversible in 80% within 48 hours
◦Predictors of poor outcomes → hemodynamic instability, paradoxical septal motion on echo, and pulmonary artery obstruction > 70%
◦Long-term death → older age, pulmonary artery obstruction persistently > 30%

▪***RV dysfunction/strain in hemodynamically stable patients with PE***
◦Controversial treatment
◦Biomarkers may allow stratification
◦Troponin → indicates myocardial ischemia from increased wall tension secondary to PE
◦BNP → indicates RV stress and dilatation
◦No elevation → excellent outcomes (discharged or brief observation)
◦Elevations → higher mortality → possibly thrombolytics
◦Syncope and emboli-in-transit associated with higher mortality

◊Contraindications to thrombolytics- active internal bleeding, HX of ICH, intracranial/spinal surgery within 3 months, intracranial tumor, AVM, or aneurysm, bleeding diathesis, severe uncontrolled HTN, CVA within 2 months

◊Reversal of agent for bleeding
▪FFP and cryoprecipitate
▪Protamine if heparinized

Shock or hemodynamic instability/decompensation with proven PE → trans-catheter embolectomy + thrombolytics or surgical embolectomy

Patients without cardiopulmonary disease + hemodynamically unstable + RV dilatation + high probability of PE → consider thrombolysis and/or embolectomy without confirmation

●**Embolectomy**
◊DVT
▪Rescue therapy for failed systemic thrombolysis or high risk of bleeding and to prevent venous gangrene
▪Mechanical clearing of clot → recurrence rates less than 20% reported
▪Successful in 42 to 93%
▪Maintain patency but decline in valve competence
▪Embolectomy + anticoagulation compared to anticoagulation alone
◦Iliofemoral and femoropopliteal patency better
◦Patency at 10 years better
◦Less popliteal reflux
◦2008 ACCP guidelines recommend against percutaneous/trans-catheter embolectomy alone

◊PE
▪Surgical embolectomy with massive, central PE and hypotension on vasopressors (thrombolytics usually not successful)

- Expand indications to include all patients with hemodynamic instability and not necessarily in those with a large clot burden
  - High morbidity and mortality (historically 30%, recently 20% - *Stein, Am J Cardiol, 2007*)
  - Failed trans-catheter embolectomy or thrombolytics
  - Improved outcomes (operative death 6%, 83-92% 3 year survival)
    - -performed prior to cardiogenic shock/cardiac arrest
    - -performed on warm, beating heart without cross-clamping, cardioplegia, or fibrillation
    - -***routinely placing IVCF***
    - -not operating on patients with out-of-hospital arrest without restoring spontaneous circulation
    - -not operating on elderly (>80yo)
  - Requires preop localization with CT (not always) and echo showing RV dysfunction
  - Still a role for the unstable patient who has failed thrombolytics or percutaneous embolectomy
- Percutaneous trans-catheter embolectomy
  - Aspirates thrombus after destroying it with high-pressure saline
  - Successful in 87% with major procedural complications in 8%
  - Majority did not receive thrombolytics
  - Consider as first line therapy
  - *Kutcher, Chest, 2007* and *Kuo, J Vasc Interv Radiol, 2009*
- Complications → severe hemolysis, anemia, pancreatitis