VENOUS THROMBOEMBOLISM (VTE)

American College of Surgeons SCC Review Course
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- 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 hemodynamic 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
  - Numerous initiatives to increase prophylaxis
    - Thromboprophylaxis 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
Virechow’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 comorbidities (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
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 vasocostriction → 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 → thrombolitics
- 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%
  - Indeterminate → 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
  - May be used for other diagnostic workup
  - CT venography – of pelvic veins and lower extremities; may be combined with CTA pulmonary arteries
  - PICOPE 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; antiphospholipid/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, hemoptyis, tachycardia, **tachyypnea 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, hemoptyis, 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); STQ3T3 → classic sign, but uncommon
\*Afib, aflutter, 1\*st, 2\*nd, and 3\*rd 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

\*Antiocoagulation / treatment when planning thrombolysis or pulmonary embolectomy, or confirmation in patients at high risk of complications from antiocoagulation

\*Absolute hemorrhagic or relative hypercoagulability during the operation

\*ABG
  \*PaO\textsubscript{2} < 80 mm Hg (> than 80 seen in nearly 20\%); elevated A-a gradient, respiratory alkalosis
  \*Desaturation requiring escalating FIO\textsubscript{2} ⇒ 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 CT

\*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

\*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

\*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

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\*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 \*(CONTRIVERSAL)

\*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
anticoagulation in patients unable to withstand another VTE event

contraindication to anticoagulation, including bleeding or recurrent VTE; adjunct to receive chemoprophylaxis because of bleeding risk and who are immobilized

propylatic placement in very high risk trauma patients who are unable to withstand another VTE event

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 chemoprophylactic 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


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
- Bird's nest filter large enough to accommodate an IVC with a diameter > 30mm

- Retrieval rates 20-60%
  * 59% with a dedicated 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

  * 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 Endose, 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 LDH (level II recommendation)
  - Knudson (J Trauma 1994) – no protection over SCDs
  - Geerts (NEJM 1996) – LDH 5000 q12 insufficient in trauma patients

- Arnold (Am Surg 2010) – LDH 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, Xla, 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)
- One study on elective THR → compared with enoxaparin, no advantage
  - DVT 1.4% (Eriksson, J Arthroplasty, 2004)

- 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
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- Heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia + thrombosis (HITTS)
  - 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%

- 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%
- 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 without fondaparinux; LMWH for arthroscopy
  - 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 \(\rightarrow\) LMWH, LDUH or IPC
    - 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 \(\rightarrow\) LMWH or LDUH q8 or IPC

\[\text{2012 ACCP guidelines (9th edition) for patients undergoing general and abdominopelvic surgery}\]
- 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, LMWH 5000U q12, or LMWH
  - High risk – 3 to 4; DVT 20-40%; IPC, LMWH 5000U q8, or LMWH
  - Highest risk – 5 or more; DVT 40-80%; mortality 1-5%; 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 \(\rightarrow\) early ambulation
- Low risk – VTE 1-5%, Rogers score 7-10, Caprini score 1-2 \(\rightarrow\) IPC
- Moderate risk – VTE 5%, Rogers score >10, Caprini score 3-4, not at high risk for major bleeding \(\rightarrow\) LMWH or LDUH or IPC
  - Moderate risk at high risk for bleeding \(\rightarrow\) IPC
- High risk – VTE 6%, Caprini ≥5, not at risk for bleeding \(\rightarrow\) LMWH or LDUH + ES or IPC
  - CA \(\rightarrow\) 4 weeks LMWH
- Contraindication to LMWH or UFH (3HT) \(\rightarrow\) 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

\[\text{2012 ACCP guidelines for trauma patients}\]
- 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) \(\rightarrow\) add IPC (2C)
- Major trauma patients in whom LMWH and LDUH contraindicated \(\rightarrow\) 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

\[\text{Trauma}\]
- 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 \(\rightarrow\) controversy as to optimal method in severely injured and timing in TBI

\[\text{Increased risk after trauma}\]
  - Older age, increasing ISS, blood transfusion, surgery, long bone fractures, pelvic fractures, TBI/SCI, spinal fractures, CVL

\[\text{In the presence of (appropriate) prophylaxis}\]
  - 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

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<tr>
<th>PE Risk</th>
<th>Bleeding Risk</th>
<th>Recommendation</th>
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| 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 < 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 < 2.0 for 2-6 weeks.  
3. No Prophylaxis |
| Baseline | | Any of: |
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 ≤ 2.0 for 2-6 weeks.

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 ≤ 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)

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 embolotomy 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 overdistension (excess bagging) may further increase pulmonary vascular resistance

RV resuscitation
- RV dysfunction/dilatation may improve CO
- RV perfusion pressure to RV subendocardium
- RV resuscitation
  - May require intubation. Catecholamine surge may be blunted with intubation, further worsening hemodynamics
  - Alveolar overdistension (excess bagging) may further increase pulmonary vascular resistance
- RV pressure gradient due to poor coronary perfusion and diastolic overdistention
- RV perfusion pressure to RV subendocardium
- Gentle volume administration in PE patients with decreased preload (normotensive without evidence of RV dysfunction/dilatation) may improve CO
- Aggressive volume management to RV overdistention → impaired 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
- 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, 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 may be 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; 2 microgm/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 0.3 micrograms/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 hemophilic; 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

- Cava interruption suggested by Trousseau in 1858 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 = IDUH

○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

  • Phleegmasia → 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 thrombolysis 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


    • Catheter-directed thrombolysis may reduce incidence by recanalizing

    • -maintain valvular competence → avoid venous hypertension

  • Catheter-directed thrombolysis → 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 Co2 → 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 surgical 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 embolus size and cardiopulmonary status → mortality 70%
- 30% will survive → continue resuscitation and chest compressions to fracture embolism
- Thrombosis 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 (thrombolitics 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
  ◦ Complications ➔ severe hemolysis, anemia, pancreatitis