Daria C. Ruffolo DNP APRN ACNP-BC CCRN

Assistant Professor

Loyola Marcella Niehoff Graduate School

ACNP Department of Anesthesia

Loyola University Medical Center

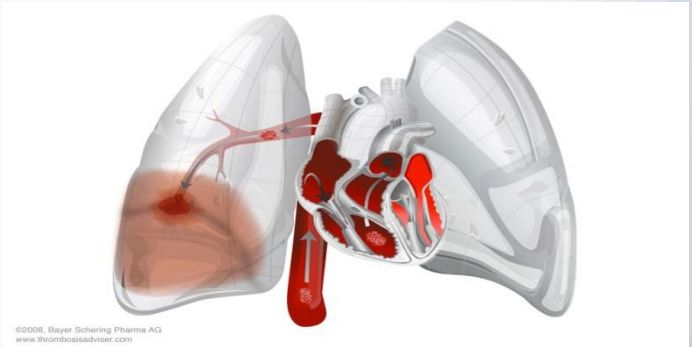
druffol@luc.edu

Learner Objectives

- Review risk factors, symptoms and subgroups of VTE
- Recognize medications utilized to treat VTE, indications and contraindications
- Utilize most current evidence-based guidelines for prevention and duration of treatment therapy

Pulmonary Embolism

- **Thrombosis (VTE)** that originates in the venous system and embolizes to the pulmonary arterial circulation
  - DVT in veins of leg above the knee (>90%)
  - DVT elsewhere (pelvic, arm, calf veins, etc.)
  - Cardiac thrombi
- **Air embolism.**
- **Fat embolism.**



Epidemiology

- Third most common acute cardiovascular disease
  - After coronary ischemia and stroke
  - Rate is 98 (nonfatal) and 107 (fatal) events per 100,000 persons in USA (650,000 yr)
  - Over 300,000 hospitalizations and 50,000 deaths per year

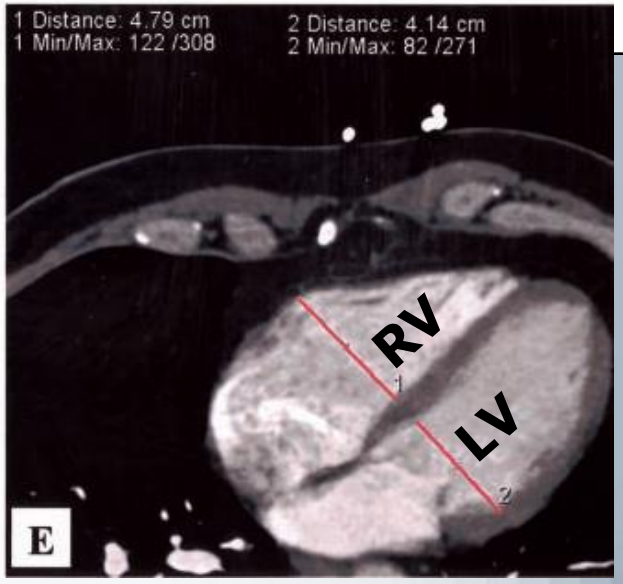
- Mortality increases with age and male sex
- 40% (idiopathic PE's) have increased incidence of developing overt cancer
- 10-20% of persons with PE have genetic thrombophilic disorders
- Patients with PE are at increased risk (>1.5X) of death within 6 months of diagnosis

Definitions

Massive PE	Submassive PE	Minor/Nonmassive PE
High risk	**Moderate/intermediate risk**	**Low risk**
• Sustained hypotension (systolic BP <90 mmHg for ≥15 min) • Inotropic support • Pulseless • Persistent profound bradycardia (HR <40 bpm with signs or symptoms of shock)	• Systemically normotensive (systolic BP ≥90 mmHg) • **RV dysfunction** • Myocardial necrosis	• Systemically normotensive (systolic BP ≥90 mmHg) • No RV dysfunction • No myocardial necrosis

RV dysfunction

- RV/LV ratio > 0.9 or RV systolic dysfunction on echo
- RV/LV ratio > 0.9 on CT
- Elevation of BNP (>90 pg/mL)
- Elevation of NTpro-BNP (>500 pg/mL)
- ECG changes:
  - new complete or incomplete RBBB
  - anteroseptal ST elevation or depression
  - anteroseptal T-wave inversion



Jaff et al. Circulation 2017;123(16):1788-1830.

Predisposing Factors

- History of DVT, Concurrent DVT >95% of patients with PE; PE occurs in >50% of cases with confirmed DVT
- Obesity ~40%
- Cancer ~30%
- Heart Failure ~35%
- Surgery - ~20% (> 60 minutes)
- Fracture ~20% (pelvic/femur)
- Smoking (> 25 cigarettes/day)
- Shock
- Air Travel - particularly >3100 miles

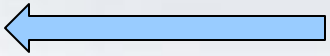
Predisposing Factors- con't.

- **Intake of (high doses of) Estrogen**
  - Especially in smokers on OCP
  - Estrogen replacement therapy (ERT): increase risk ~1.2-2X in current users
  - Factor V Leiden patients on OCPs may have >30X increased risk of thromboembolism
- **Trauma**
- **Pregnancy: peri- and post-partum**

Predisposing Factors- con't.

- **Hypercoagulable States**
  - Factor V Leiden - Resistance to Activated Protein C (~12% of PE cases)
  - Factor II (Prothrombin) 20210A mutation - (~10% of PE cases) It was discovered in 1996 that a specific change in the genetic code causes the body to produce an excess of the prothrombin protein.
  - Protein C, S or Antithrombin III Deficiency
  - Low levels of tissue factor pathway inhibitor (TFPI)

High Risk for Fatal Outcome

- Cancer
- Heart Failure
- Chronic underlying lung disease
- Recurrent PE 
- Elevated troponin (T or I)
- Pulmonary Hypertension (P-HTN)
- BNP elevated brain natriuretic peptide or N-terminal pro-brain natriuretic peptide (NT-proBNP) predicts RV dysfunction and mortality
- RV thrombus -have a higher 14-day mortality and three-month mortality
- ***Overall, few patients have recurrent emboli, particularly after initiation of therapy***

Pathogenesis

- **Clot forms at distal site, usually in distal veins in the leg or in pelvic veins**
- **Clots migrate to pulmonary vasculature**
  - Most clots lodge in pulmonary arterioles or segmental arteries
  - Lodging at pulmonary artery bifurcation leads to "saddle" embolism
- **Lodged thrombi release vasoconstrictors**
  - Serotonin
  - Thrombin
  - Endothelin

Pathogenesis – con't.

- **Release of these vasoconstrictors causes diffuse pulmonary vascular constriction**
  - P-HTN follows and can cause right heart failure, JVD not sensitive in acute P-HTN
- **Alveolar Dead Space**
  - Vascular blockade (full or partial) leads to unperfused areas of lung
  - These areas are called dead space (ventilated but not perfused)
  - Alveolar dead space increases in PE in proportion to severity of vascular blockade

Clinical Presentation

- Symptoms are non-specific, not very sensitive; high suspicion must be maintained
- Pleuritic chest pain in absence of dyspnea is common first presentation
- Dyspnea 77% (A-a gradient)
- Tachypnea 70%
- Chest Pain 55% (usually pleuritic)
- Tachycardia 43%
- Cyanosis 18%
- Hemoptysis 13%
- Syncope 10%

Symptoms – con't.

- Cough 43%
- Leg Swelling 33%
- Leg Pain 30%
- Palpitations 12%
- Wheezing 10%
- Angina-like pain 5%
- Sudden cardiac arrest with pulseless electrical activity
- Some have NO SYMPTOMS

Differential Diagnosis

- Myocardial Infarction
- Pneumonia
- Pulmonary Edema / Heart Failure
- Asthma, COPD Exacerbation
- Pneumothorax/rib fracture
- Musculoskeletal Pain, Costochondritis
- Dissecting Thoracic Aneurysm
- Anxiety / Panic Attack

Pulmonary Embolism Prediction Rules

- **Suspicion should be high if ANY risk factors or symptoms/signs are present**
  - >70% of patients who die of PE are not suspected of having it
  - Only ~35% of patients suspected of having PE actually have it
  - PE testing is less reliable in older persons than in younger persons
  - Age is a major risk factor, particularly with underlying predisposing conditions

Wells' Score

Clinical symptoms of DVT (leg swelling, pain with palpation)	3.0
Other diagnosis less likely than pulmonary embolism	3.0
Heart rate >100	1.5
Immobilization (≥3 days) or surgery in the previous four weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1.0
Malignancy	1.0

Traditional clinical probability assessment (Wells criteria)	
High	>6.0
Moderate	2.0 to 6.0
Low	<2.0
Simplified clinical probability assessment (Modified Wells criteria)	
PE likely	>4.0
PE unlikely	≤4.0

Diagnostic Evaluation

- Low clinical probability: high sensitivity D-dimer (level <500µg/L) to rule out PE
- Lower extremity venous ultrasound (US) to rule in DVT
- Helical CT angiography or V/Q scanning
- Contrast angiography
- MRA

Routine Laboratory Tests

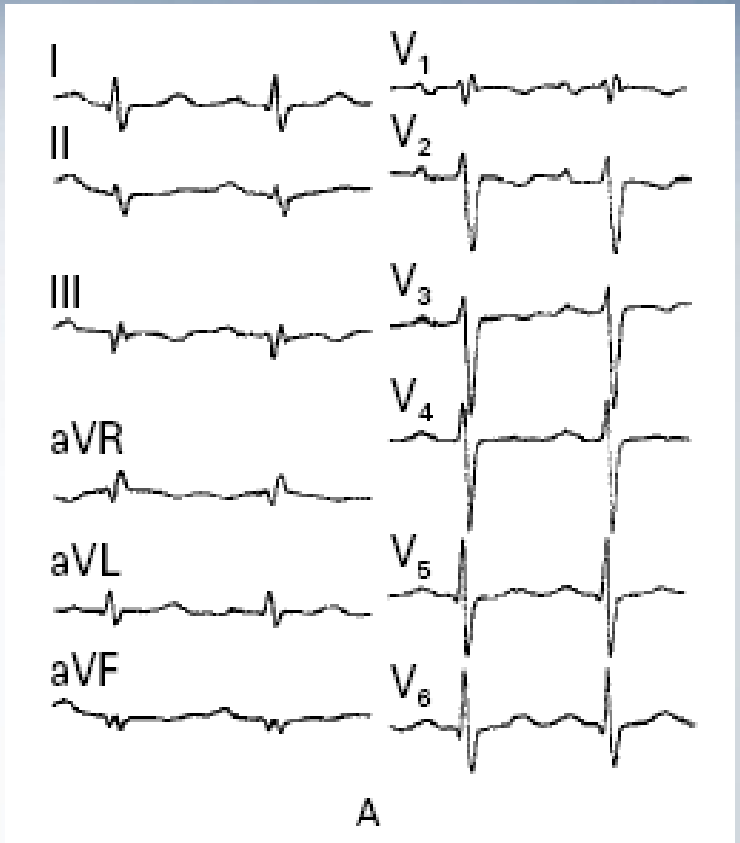
- Electrolytes, complete blood count, coagulation parameters (PT, aPTT)
- ECG with right sided leads
- All patients should have an Arterial Blood Gas (ABG, preferably on room air)
- A PaO2 between 85 and 105 mmHg exists in approximately 18 percent of patients with PE
- Normal A-a gradient found in <6% of patients with PE
- High Sensitivity D-Dimer Test
- Lower extremity venous US with doppler measurements

D-Dimer Artifact

- Arterial thrombosis
- DVT/PE
- MI
- CAD
- CVA
- Malignancy
- Pregnancy
- Surgery
- Trauma
- DIC
- Afib
- Limb ischemia
- Renal failure
- Liver disease
- SIRS/Sepsis
- Sickle Cell

ECG Changes

- Most common ECG is normal sinus rhythm:
- Sinus Tachycardia extremely common
- Right Axis Deviation; Q in III, inverted T in III
- Right sided leads should be evaluated



Ventilation-Perfusion (V/Q) Scans

- High probability scans identify only ~50% of patients with PE overall
- About 60% of V/Q scans will be indeterminant (intermediate + low probability)
- Of intermediate probability scans, ~33% occur with angiographically proven PE
- Conclude: normal test rules out PE in ~98% of cases
- Note that low probability test still has ~15-25% chance of PE
- However, there were no deaths due to PE within 6 months in a study of 536 patients with low probability scans

Lower Extremity Doppler US

- To evaluate for DVT as possible cause of PE or to help rule in PE
- Up to 40% of patients with DVT without PE symptoms will HAVE a PE by angiography
- Pelvis blinded area
- A positive US with abnormal V/Q rules IN a PE

Helical (Spiral) Computed Tomography

- Helical CT scanning produces volumetric two-dimensional image of lung
- This is accomplished by giving IV contrast agent and rotating detector around the patient
- PE appears as a filling defect that may be central, eccentric or mural
- The embolism may completely or partially occlude the vessel

Helical (Spiral) Computed Tomography (CT)

- Reported sensitivity 83% in PIOPED II specificity 96% in PIOPED II N Engl J Med. 2006 Jun 1;354(22):2317-27.
- Test is very quick, requires IV contrast and careful interpretation and is costly
- Helical CT increases the diagnosis of PE and reduce angiography

Pulmonary Angiography

- This has been the gold standard for diagnosis but it is highly invasive May be morbid with worsening shortness of breath, artery perforation
- The pulmonary catheter may also be used therapeutically (angioplasty)
- Positive result is a filling defect or sharp cutoff in a pulmonary artery branch
- Angiography can be avoided in most patients by using other tests

Magnetic Resonance Angiography (MRA)

- Techniques for use of MRA for diagnosing PE are evolving rapidly
- Estimated sensitivity ~80% (~100% for larger emboli), specificity 95%
- Non-invasive with little morbidity
- Dynamic gadolinium enhancement is used, allowing high quality images
- Strongly consider prior to standard invasive pulmonary angiography

Prevention of VTE in Non Surgical Patient

- Increased risk of thrombosis (scoring systems), LMWH, LDUH, BID/TID (Grade 1B)
- Low risk of thrombosis, no use of pharm or mech prophylaxis (Grade 1B)
- None for patient who are bleeding or high risk for bleeding (Grade 1B)

Critically Ill Patients

- No need for US screening (2C)
- Suggest use of LMWH/LDUH over none (2B)
- Bleeding or risk of bleeding suggest mech (2C)
- When bleeding risk decreases, suggest that pharm be started (2C)

Prevention of VTE Non-orthopedic Surgery

- Very low risk for VTE-no need for pharm (1B) or mech (2C) use early mobility
- Low risk, mech over pharm (2C)
- Mod risk for VTE and not at risk for bleeding, LMWH/LDUH (2B), mech (2C) over no use
- Mod risk VTE and high risk for bleeding, mech over pharm (2C)

- High risk for VTE not at risk for bleeding, LMWH/LDUH over none (1B) and mech (2C)
- High risk for VTE, risk for major bleeding, mech and then start pharm when risk over (2C)
- IVC should not be used for primary prevention (2C)
- No serial US screen (2C)

Case

A 44-year-old man is evaluated in follow-up for an episode of unprovoked left proximal leg deep venous thrombosis 3 months ago. Following initial anticoagulation with low-molecular-weight heparin, he began treatment with warfarin. INR testing done every 3 to 4 weeks has shown a stable therapeutic INR. He has mild left leg discomfort after a long day of standing, but it does not limit his activity level. He tolerates warfarin well. Family history is unremarkable, and he takes no other medications.

Which of the following is the most appropriate management?

A. Continue anticoagulation indefinitely
B. Discontinue warfarin in another 3 months
C. Discontinue warfarin now
D. Discontinue warfarin and perform thrombophilia testing

Objectives

- Recognize subgroups of VTE
- Review medications for VTE anticoagulation
- Learn guidelines for duration of therapy
- Understand differences in therapy based on type of VTE

Subgroups of VTE

- Cancer-associated vs No cancer
- Provoked vs Unprovoked
- Proximal vs Distal DVT
- Upper extremity vs Lower extremity DVT

VTE and No Cancer

- Use NOAC – preferred! (Grade 2B)
  - Rivaroxaban, apixaban
    - No bridging needed
  - Dabigatran, edoxaban
    - Start with parenteral anticoagulation x5 days
- If contraindications to NOAC, then use VKA therapy (warfarin) (Grade 2C)
  - Overlap with parenteral anticoagulation x5 days,
  - And INR >2 for 24 hours

NOACs and VTE

Historical result summary

- **DOACs were non-inferior to warfarin**
- **DOACs have similar to less bleeding than warfarin**
  - Dabigtran has similar major bleeding
  - Rivaroxaban had less CNS bleeding
  - Apixaban had less overall bleeding
- **DOACs are approved for VTE treatment**
  - Favored over warfarin if CrCl and liver ok
  - Warfarin is preferred for pts with renal dysfunction
  - Cost issues
  - Patient concern over short follow-up of data

Contraindications to NOACs

- Extreme BMI (>40)
- CrCl <30
- Patient who doesn't like idea of "no known reversal agent/strategy" (except apixaban (Eliquis), rivaroxaban (Xarelto))
- Significant increased risk of bleeding

Cancer-Associated Thrombosis

- Use LMWH (Grade 2C)
  - Enoxaparin 1 mg/kg/dose BID

Coming changes???

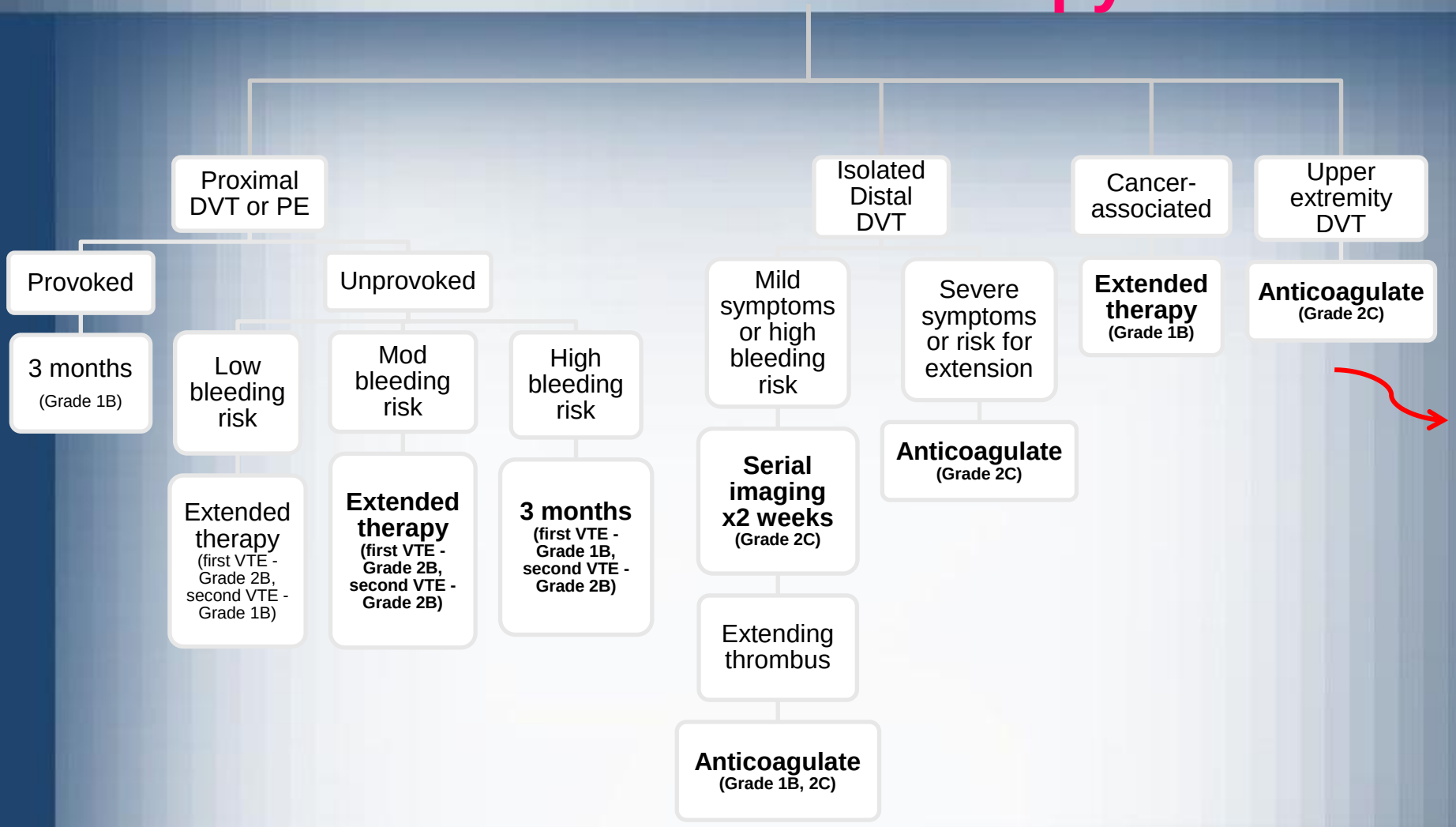
Provoking Transient Risk Factors for VTE

- Surgery
- Estrogen therapy
- Pregnancy
- Leg injury
- Flight >8h

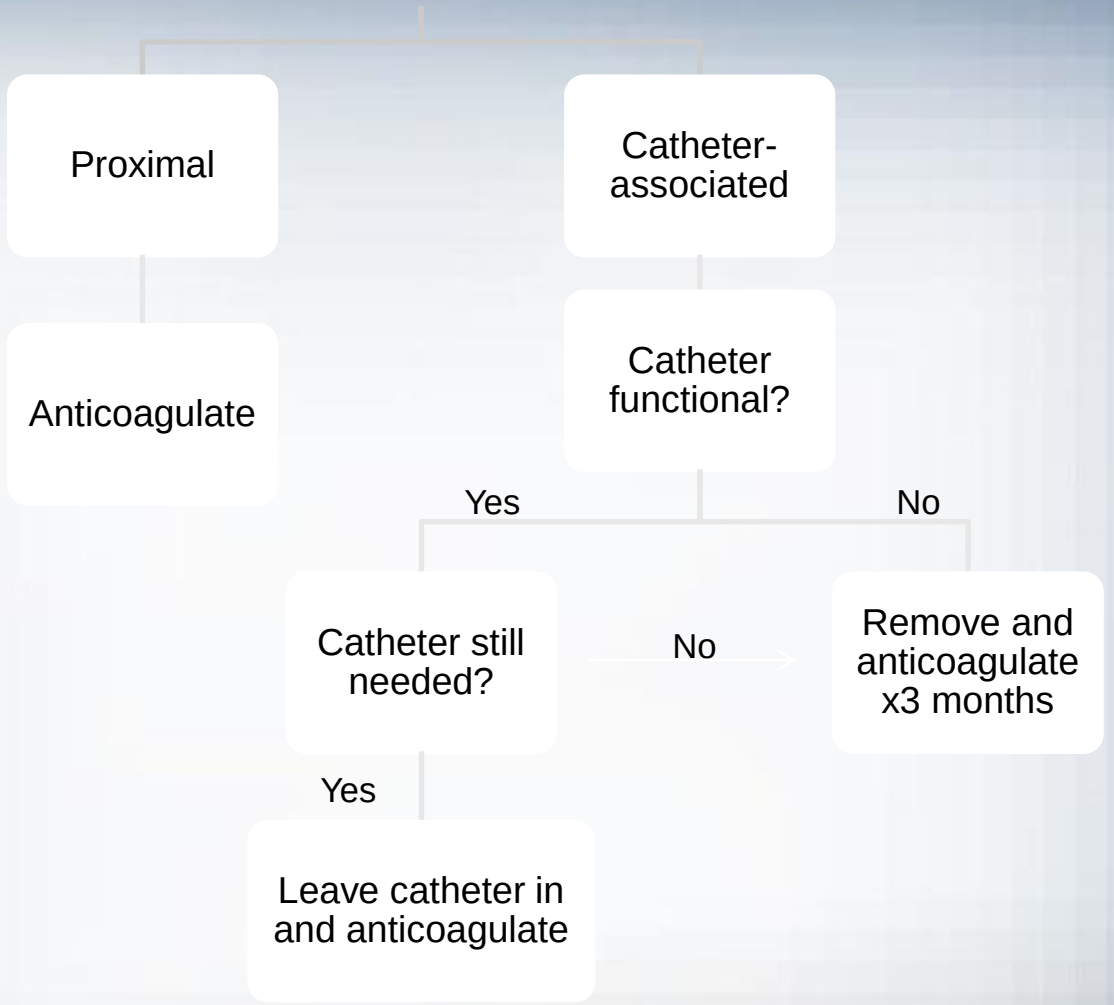
Location of VTE

- Lower extremity DVT
  - Proximal – Popliteal or more proximal veins
  - Distal – Calf veins
- Upper extremity DVT
  - Proximal – Axillary or more proximal veins
  - Catheter-associated

Duration of Therapy



Special Considerations for Upper Extremity DVT



Risk Factors for Extension of Distal DVT

- Positive D-dimer
- Extensive thrombus
  - >5cm long, involves multiple veins, >7mm diameter
- Thrombus close to proximal veins
- No reversible provoking factor
- Active cancer
- History of VTE

What if my patient stops anticoagulation?

- Aspirin is NOT a reasonable alternative to anticoagulation for extended therapy
  - Much less effective at preventing recurrent VTE
- However, aspirin is better than nothing (Grade 2B)

Recurrent DVT on Anticoagulation

- If on therapeutic warfarin or NOAC, then switch to enoxaparin temporarily (minimum 1 month) (Grade 2C)
  - Is this really recurrent VTE?
  - Is my patient compliant with therapy?
  - Is there underlying malignancy?
- If on enoxaparin and compliant, then increase the dose by 25-33% (Grade 2C)

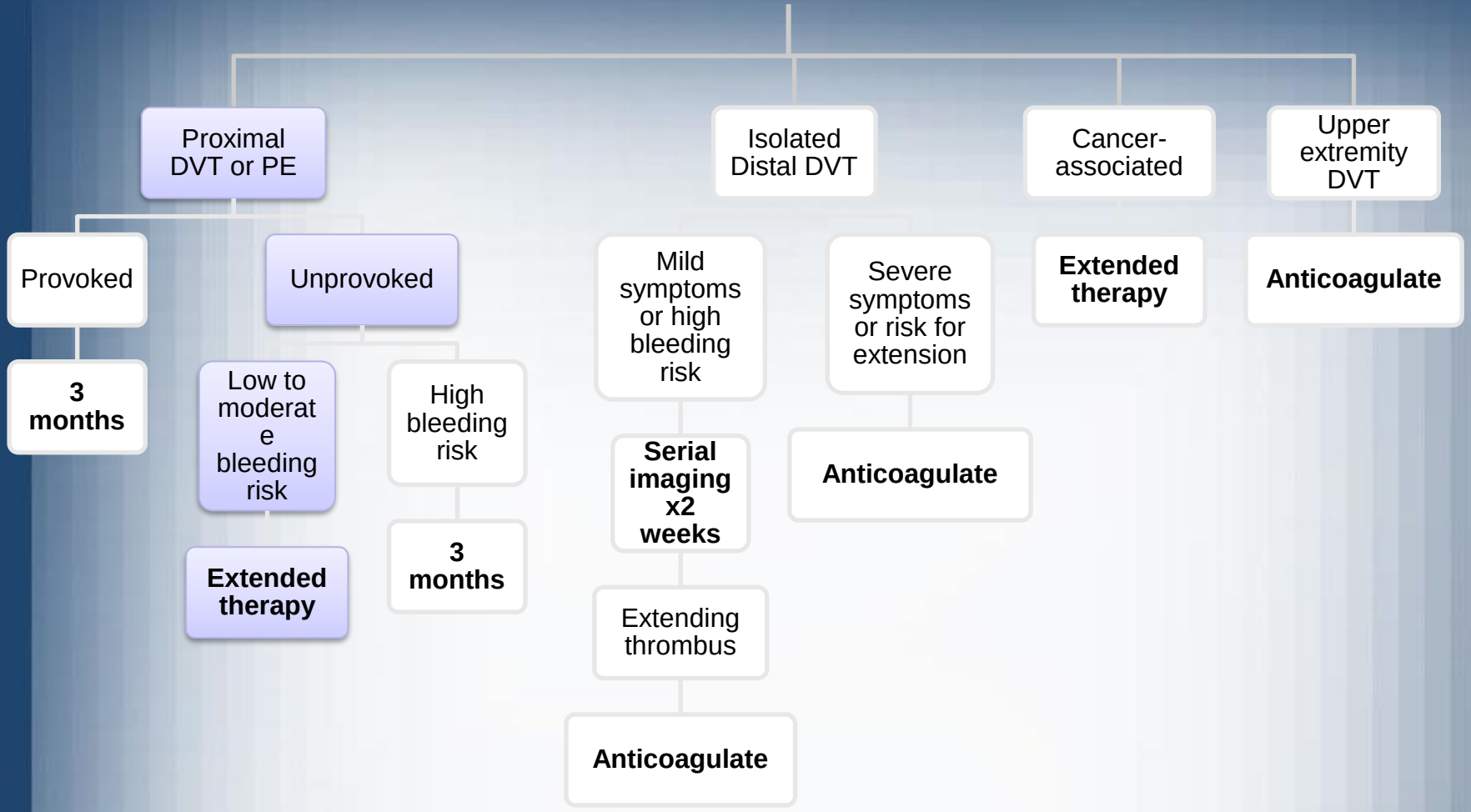
Case Revisited

A 44-year-old man is evaluated in follow-up for an episode of unprovoked left proximal leg deep venous thrombosis 3 months ago. Following initial anticoagulation with low-molecular-weight heparin, he began treatment with warfarin. INR testing done every 3 to 4 weeks has shown a stable therapeutic INR. He has mild left leg discomfort after a long day of standing, but it does not limit his activity level. He tolerates warfarin well. Family history is unremarkable, and he takes no other medications.

Which of the following is the most appropriate management?

A. Continue anticoagulation indefinitely
B. Discontinue warfarin in another 3 months
C. Discontinue warfarin now
D. Discontinue warfarin and perform thrombophilia testing

Duration of Therapy



Case Revisited

A 44-year-old man is evaluated in follow-up for an episode of unprovoked left proximal leg deep venous thrombosis 3 months ago. Following initial anticoagulation with low-molecular-weight heparin, he began treatment with warfarin. INR testing done every 3 to 4 weeks has shown a stable therapeutic INR. He has mild left leg discomfort after a long day of standing, but it does not limit his activity level. He tolerates warfarin well. Family history is unremarkable, and he takes no other medications.

Which of the following is the most appropriate management?

A. Continue anticoagulation indefinitely
B. Discontinue warfarin in another 3 months
C. Discontinue warfarin now
D. Discontinue warfarin and perform thrombophilia testing

Summary

- NOACs are preferred over warfarin for anticoagulation
- Except if VTE is cancer-associated, then use enoxaparin
- Duration of therapy is usually 3 months, with extended therapy based on risk factors for recurrent VTE

Betrixaban 2018!!!

- First oral approved VTE prophylaxis in adult patients hospitalized for an acute medical illness who are at risk due to moderate or severe restricted mobility and other risk factors for VTE.
- Efficacy was measured in 7,441
- Fewer events were observed in patients receiving betrixaban (4.4%) compared with enoxaparin (6%)
- The most common adverse reactions (≥5%) with betrixaban were related to bleeding.

- 54% of patients receiving betrixaban experienced at least one adverse reaction compared with 52% taking enoxaparin.
- The frequency of patients reporting serious adverse reactions was similar between betrixaban (18%) and enoxaparin (17%).
- The most frequent reason for treatment discontinuation was bleeding, with an incidence rate for all bleeding episodes of 2.4% and 1.2% for betrixaban and enoxaparin, respectively.
- The incidence rate for major bleeding episodes was 0.67% and 0.57% for betrixaban and enoxaparin, respectively.

HESTIA Criteria-Don't Leave Home Without it

- Hemodynamically unstable
- Thrombolysis or embolectomy needed
- Active risk or significant risk of bleeding
- Oxygen required to keep saturation > 94% for > 24 hours
- Pulmonary embolism during anticoagulation therapy
- IV pain medications within the last 24 hours
- Medical or social issues that require in-hospital stay
- Creatinine clearance < 30 ml/min
- Severe liver dysfunction
- Pregnancy
- History of HIT

If any question illicits a **YES** the patient cannot be treated as an outpatient

Thrombolytic Therapy

- Usually given to patients with echocardiographic evidence of right heart strain / failure Massive PE
- Fibrin-specific agents, which include alteplase (tPA), reteplase and tenecteplase
- Non–fibrin-specific agent - streptokinase is not widely used in the United States but is still used elsewhere because of its lower cost.

Thrombectomy

- Surgical thrombectomy only in very selective cases
- Perioperative mortality is 25-50%
- Massive pulmonary embolism where thrombolysis contraindicated

"In acute diseases,,, coldness of the extremities,, is a very bad sign."

IVC Filter Placement

- Generally reserved for patients with recurrent PE on anti-coagulation
- May also be used for patients in whom anti-coagulation is contraindicated
- Can be used as adjunct in massive PE where thrombolysis is not an option
- IVC filters are being used for PE prophylaxis in select groups of patients

IVC Filter Placement

Complications — rare but include

- Complications related to the insertion process (eg, bleeding, venous thrombosis at the insertion site).
- Filter misplacement.
- Filter migration.
- Filter erosion and perforation of the IVC wall.
- IVC obstruction due to filter thrombosis.

VTE in Children

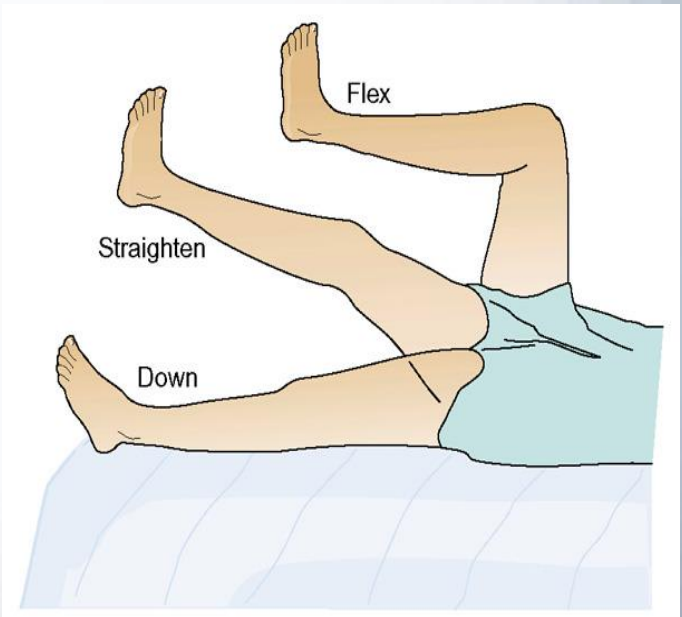
Epidemiology

- Not until 1990's was there serious study in children
- 2001 34 cases/10,000 by 2007 70% increase
- Incidence peaks in < 1 year and then very low rates until early adolescence

Cause

- Thrombin inhibitors are low until 6 m
- Arterial caths (prophylactic heparin decreases incidence from 40% to < 8%)
- Central lines can account for 45% of VTE
- Surgery and immobilization (though very low)
- Malignancy (and associate central cath)
- Inherited clotting disorders
- Congenital heart disease-prosthetic valves

- 60 sec cycles
- 22% effective solo therapy
- 53% effective with dual therapy
- Most effective on surgical, cancer patients
- 35% misused
- 75% patient compliance
- Legs exercises and ambulation more effective
- ***EARLY MOBILITY !!!!!***



VTE and Covid

- Studies reveal that 10-40% of Covid patients have VTE
- D-dimer is useless as it will be abnormal
- Best screening is with US of LE and POCUS ECHO
- Not all VTE needs to be treated in the ICU/intubated-Henry Ford treated nearly 70% outside of the ICU

What is Causing VTE in Covid Patients?

- Found to have an autoimmune AB in > 90% of cases
- Same AB as seen in APLS
- It causes apoptosis, destroys the intravascular lining and contributes to clot formation
- It causes a self-amplifying cycle of **"Inflammation and Clotting"**

Thoughts?

- Find out what is driving this AB formation
- Would this be a place for the convalescent plasma?
- Use of plasmaphresis?
- We know that LMWH carries with it anti-inflammatory action-use this empirically on all Covid patients that “crash”-desat, hemodynamically unstable, RH strain, elevated CVP

Studies in the works

- DICER-RCT looking at the use of Dipyridamole as a clot reducing agent in Covid patients
- International Society of Thrombosis and Hemostasis (ISTH)-suggesting the use of LMWH on **ALL** Covid positive hospitalized patients
- Austrian study-looking at the use of statin to stabilize the vascular wall

Conclusions

- VTE is common among all patient populations
- Assessment of VTE and bleeding risk should be done on all patients
- Mechanical and pharm regimens have been proven to be effective for prophylaxis
- NOACs have changed VTE management
- There will always be a role for warfarin
- Get patients moving!!!!