VENOUS THROMBOEMBOLISM

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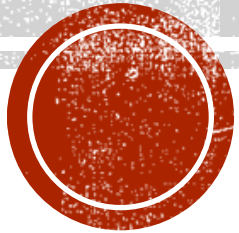
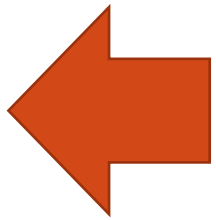


LEARNING OBJECTIVES

- **Define** venous thromboembolism (**VTE**)
- Discuss the **epidemiology, pathophysiology, and risk factors** for VTE
- Describe the **clinical presentation** of VTE
- Analyze the **pretest probability** for deep venous thrombosis (**DVT**) and **likelihood** of pulmonary embolism (**PE**) using **Wells Criteria**
- Describe the **diagnostic work-up** for VTE
- Define the **PERC Criteria** and know how it is appropriately used
- Create a **treatment strategy** for VTE
- Describe the strategy for the **work-up of an underlying thrombophilia**
- Demonstrate appropriate **prophylactic** measures to prevent VTE

VENOUS THROMBOEMBOLISM (VTE):

- Most common presentations of venous thrombosis (**clot**):
  - **Deep venous thrombosis (DVT)**
    - Typically, of the lower extremity
  - **Pulmonary embolism (PE)**



2 manifestations of same disorder

VTE – EPIDEMIOLOGY

- Estimated up to **900,000 cases** of deep vein thrombosis (**DVT**) and pulmonary emboli (**PE**) per year
  - Resulting in **up to 100,000 deaths**
    - Many of these are sudden deaths (25%)
      - 10-30% of people die within 3 months of diagnosis

- **Most of these deaths are considered preventable (~70%)!!!**

Goal should be to prevent VTE or treat VTE before morbid consequence!

https://www.cdc.gov/blood-clots/?CDC_AAref_Val=https://www.cdc.gov/ncbddd/dvt/data.html

VTE – EPIDEMIOLOGY & ECONOMICS

- **~1/3** of persons who survive the first occurrence of VTE **develop another VTE within 10 years**
- **~1/3** develop long term complications
  - Swelling, pain, discoloration (post-thrombotic syndrome)
- **$10 billion or more spent annually** on the care of patient's with VTE

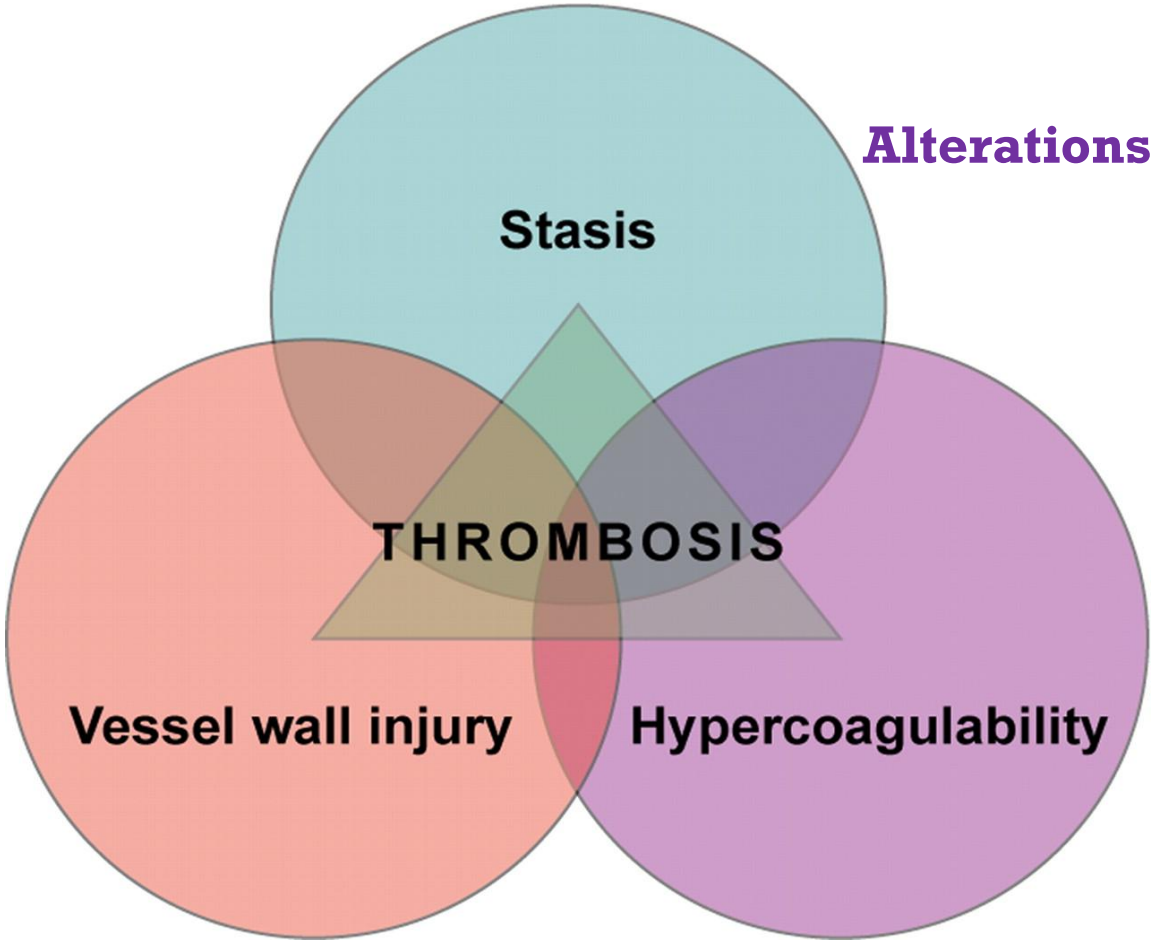
- **BIG DEAL?????**

https://www.cdc.gov/blood-clots/?CDC_AAref_Val=https://www.cdc.gov/ncbddd/dvt/data.html

ETIOLOGY OF VTE

- **Causes** of venous thrombosis can be divided into 2 groups:
  - **Hereditary**
  - **Acquired**
    - These are **often multiple and overlap** in a given patient

VTE PATHOGENESIS: VIRCHOW'S TRIAD



Alterations in blood flow

Vascular endothelial injury

Alterations in the constituents of the blood (inherited or acquired hypercoagulable state)

RISK FACTORS FOR VTE

- In **over 80%** of the patients with VTE **a risk factor can be identified**
- In fact, most patients with VTE **fulfill most or all of Virchow's triad**
  - **50%** of thrombotic events in patient with **inherited thrombophilia** are associated with the **additional presence of an acquired risk factor** (e.g., surgery, prolonged bed rest, pregnancy, oral contraceptives)
- **Previous thrombotic event** is associated with **MAJOR** risk for **recurrent VTE**

Risk factors (causes) for the development of venous thrombosis

Inherited thrombophilia
Factor V Leiden mutation
Prothrombin G20210A mutation
Protein S deficiency
Protein C deficiency
Antithrombin deficiency
Other disorders and risk factors
Presence of a central venous catheter
Malignancy
Surgery, especially orthopedic
Trauma
Immobilization
Pregnancy
Oral contraceptives
Hormone replacement therapy
Certain cancer therapies (eg, tamoxifen, thalidomide, lenalidomide, asparaginase)
Heart failure
Congenital heart disease
Antiphospholipid syndrome
Older age (≥65 years)
Obesity
Severe liver disease
Myeloproliferative neoplasms
Polycythemia vera
Essential thrombocythemia
Paroxysmal nocturnal hemoglobinuria
Inflammatory bowel disease
Nephrotic syndrome

ACQUIRED RISK FACTORS BY CATEGORY

Chronic Conditions	Transient States	Female specific factors
Chronic diseases (CHF, inflammatory bowel disease, nephrotic syndrome)	**Surgery** - recent (especially orthopedic)	**Pregnancy**
Malignancy	**Trauma**	Post-partum
Obesity	**Immobilization**	**Hormonal contraceptives**
Antiphospholipid antibody syndrome	Presence of a central venous catheter	Hormone replacement therapy
Advanced age	**Hospitalization**	
Smoking	Infections	
Myeloproliferative disorders	Extended travel	

Red = Most common

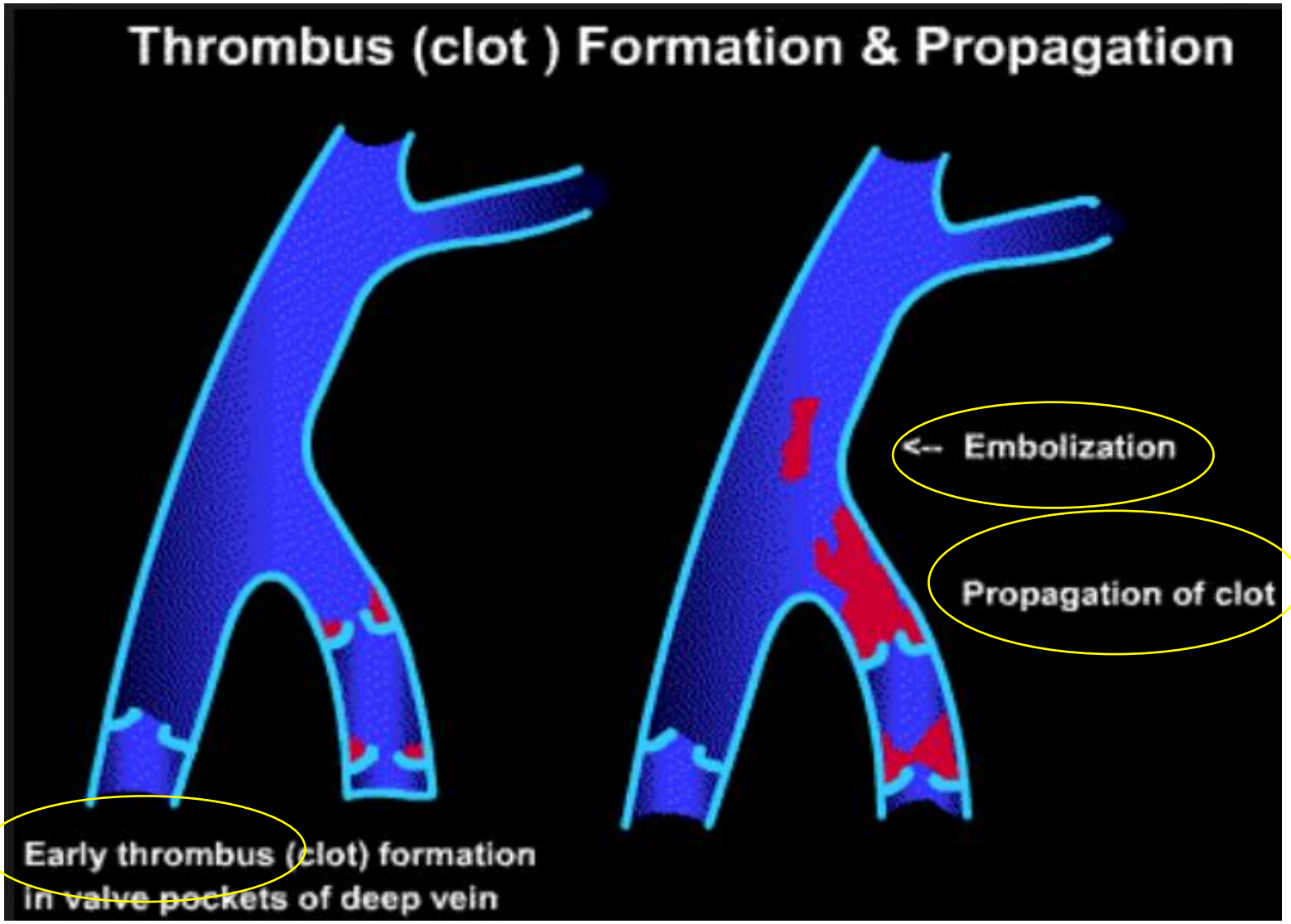
INHERITED RISK FACTORS – "INHERITED THROMBOPHILIA"

- **Factor V Leiden mutation**
- **Prothrombin gene mutation**
- Protein S deficiency
- Protein C deficiency
- Antithrombin deficiency

Most Common (50-60% of cases)

Also known as Prothrombin G20210A

THE WRATH OF A DVT



DVT – HISTORICAL FEATURES

- Elicit a good **family history**
- Obtain a thorough **history for risk factors** (see previous discussion)
  - Obtain complete OB/GYN history in women
  - Think about occult malignancy
  - Choose a pretest probability scoring system

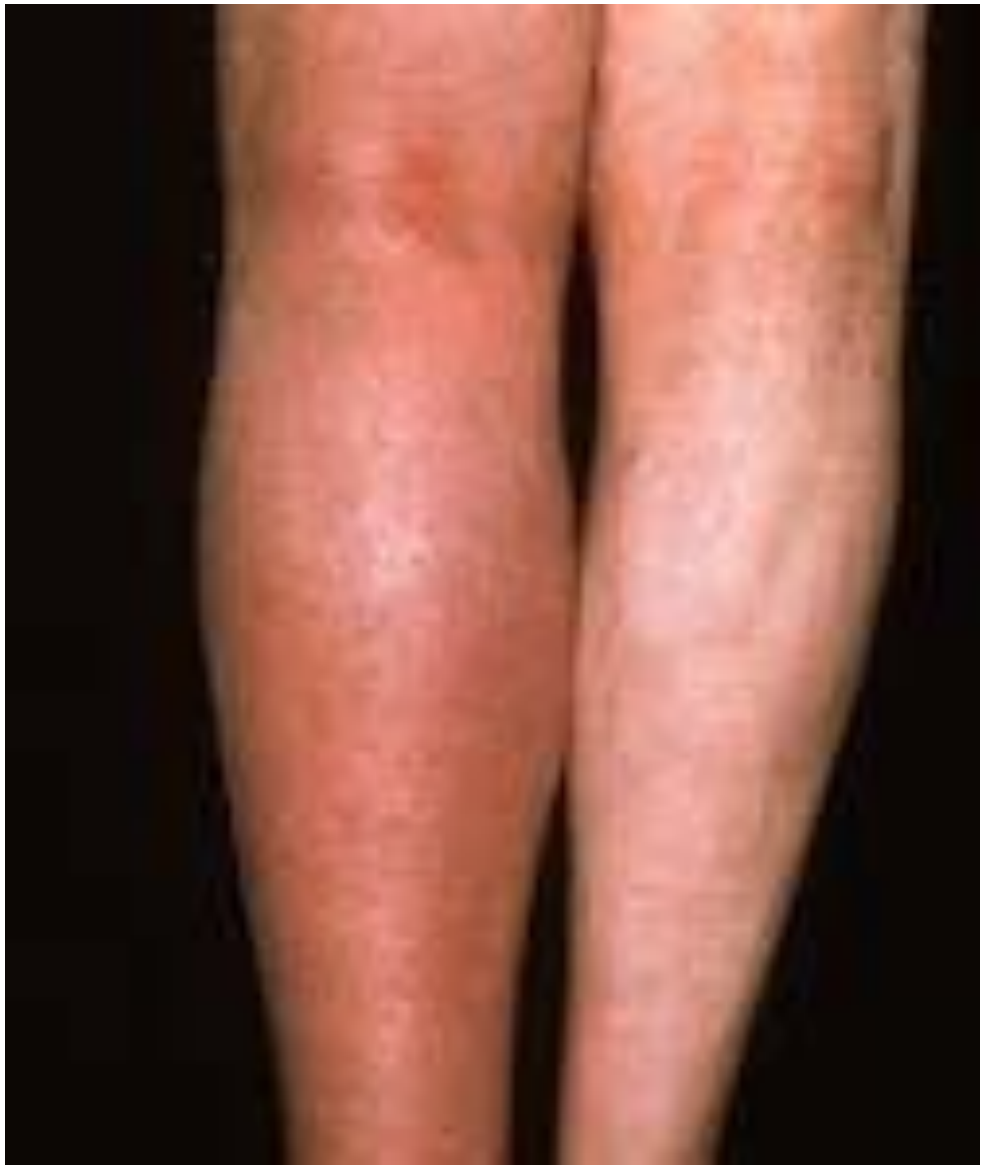
SYMPTOMATOLOGY OF DVT

- Classic symptoms of DVT include **swelling**, **pain**, **warmth** and **erythema of the involved extremity**
  - Not necessarily a correlation between the location of symptoms and the site of thrombosis
  - Symptoms are confined to the calf in patients with isolated distal DVT, while patients with proximal DVT may have calf or whole leg symptoms
  - Symptoms are usually unilateral

CLINICAL PRESENTATION OF DVT

- **Often asymptomatic**
- Affected area may have:
  - **Swelling**
  - Pain
  - Warmth
  - Redness or discoloration
  - Palpable cord (reflecting a thrombosed vein)

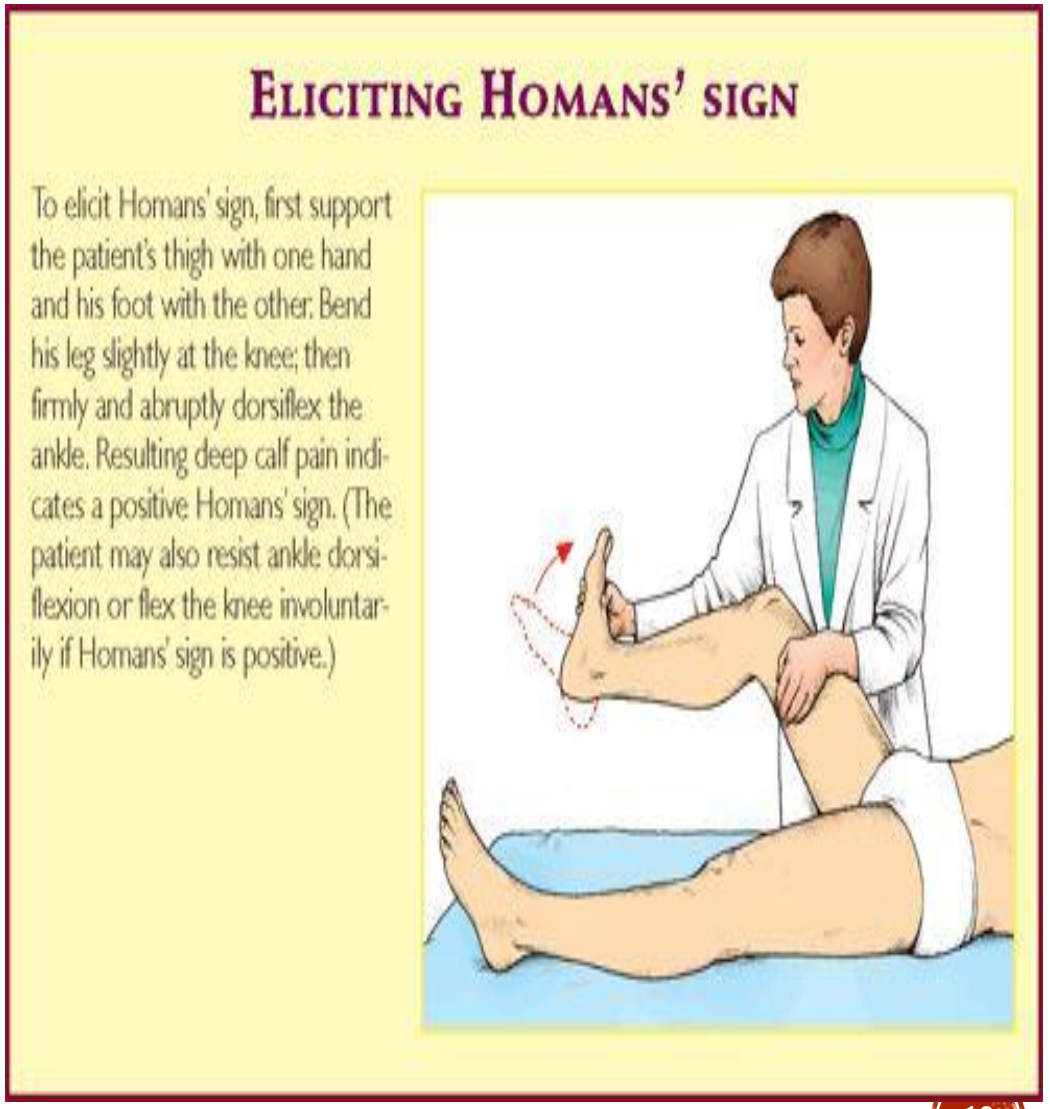
A larger calf diameter is a very useful finding



http://theveincarecentre.co.uk/blog/wp-content/uploads/DVT.jpg

DVT – PHYSICAL EXAM – HOMANS' SIGN

- Named for the American physician John Homans
- A **positive** sign is present when there is **pain in the calf** on forceful and abrupt **dorsiflexion** of the patient's foot at the ankle while the knee is extended
- Test has **fallen out of favor**
  - **Low sensitivity and specificity**



Simplified Charlotte Rule

Geneva and modified Geneva Score

Padua Predication Score

Pisa Model

CLINICAL SCORING SYSTEMS CONUNDRUM

NONE OF THE PTP SYSTEMS ARE FOOLPROOF & NONE HAVE DEFINITIVELY PROVEN SUPERIOR OVER ANOTHER

Villalta Score

IMPROVE RAM Model

Khorana Score

Caprini Risk Score

PESI – Pulmonary Embolism Severity Index Score

PRETEST PROBABILITY FOR DVT

- **Before any diagnostic tests are ordered** to confirm or help rule out DVT **what is the patient's pretest probability** that they have the disease?

- Several pretest probability (**PTP**) **scoring systems** are available
  - Clinical "gestalt" should not be underestimated
  - Wells score for DVT
    - **Wells & modified Wells criteria for DVT** most studied & therefore **most used**
      - Wells assigns patients to three risk categories (**low; moderate; high**)
      - Modified Wells assigns patients to two categories (**unlikely; likely**)

Pretest probability of deep vein thrombosis (Wells score)

Clinical feature	Score
Active cancer (treatment ongoing or within the previous six months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for more than three days or major surgery, within four weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm when compared to the asymptomatic leg (measured below tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (nonvaricose)	1
Alternative diagnosis as likely or more likely than that of deep venous thrombosis	-2
Score	
High probability	3 or greater
Moderate probability	1 or 2
Low probability	0 or less
Modification:	
This clinical model has been modified to take one other clinical feature into account: a previously documented deep vein thrombosis (DVT) is given the score of 1. Using this modified scoring system, DVT is either likely or unlikely, as follows:	
DVT likely	2 or greater
DVT unlikely	1 or less

Chance of DVT:
LOW PROB = ~3%
MOD PROB = ~17%
HIGH PROB = ~50-75%

PERSONAL DIFFICULTIES WITH WELLS SCORE

- Three of points are related to swelling with some amount of **overlap**
  - **Entire leg swollen** (1 point)
  - **Calf swelling** 3 cm greater than other leg (1 point)
  - **Pitting edema** greater in the symptomatic leg (1 point)
- **Alternative diagnosis more likely** than DVT
  - Is this **subjective**?
    - Baker's cyst, cellulitis, muscle damage, superficial venous thrombosis, post phlebitic syndrome, inguinal lymphadenopathy, external venous compression

ADDING ON DIAGNOSTIC TESTS…

- **After** calculating the PTP a serum D-dimer should be obtained for patients in the ***low*** (~3%) or ***moderate probability*** (~17%) for DVT
- **Serum D- Dimer**
  - Degradation product of cross-linked fibrin
  - Detectable at levels **greater than 500 ng/mL** in **virtually all** patients with VTE (using ELISA testing)
  - **Sensitive test** but **lacks specificity** for DVT and is therefore, only **useful when negative** (**and *not a high* clinical suspicion**)
    - Commonly elevated in **hospitalized** patients, particularly the **elderly**, those with **malignancy**, **recent surgery**, **renal insufficiency,** etc.
    - Also elevated in women in the **2nd/3rd trimester of pregnancy**

Disorders associated with increased plasma levels of fibrin D-dimer

Arterial thromboembolic disease
Myocardial infarction
Stroke
Acute limb ischemia
Atrial fibrillation
Intracardiac thrombus
Venous thromboembolic disease
Deep vein thrombosis
Pulmonary embolism
Disseminated intravascular coagulation
Preeclampsia and eclampsia
Abnormal fibrinolysis; use of thrombolytic agents
Cardiovascular disease, congestive failure
Severe infection/sepsis/inflammation
Surgery/trauma (eg, tissue ischemia, necrosis)
Systemic inflammatory response syndrome
Vasoocclusive episode of sickle cell disease
Severe liver disease (decreased clearance)
Malignancy
Renal disease
Nephrotic syndrome (eg, renal vein thrombosis)
Acute renal failure
Chronic renal failure and underlying cardiovascular disease
Normal pregnancy
Venous malformations

NOT SPECIFIC

D-dimer should not be performed if it is expected to be positive due to another condition (e.g., surgery)

These patients can proceed directly to nest step in diagnostic work-up (ultrasonography)

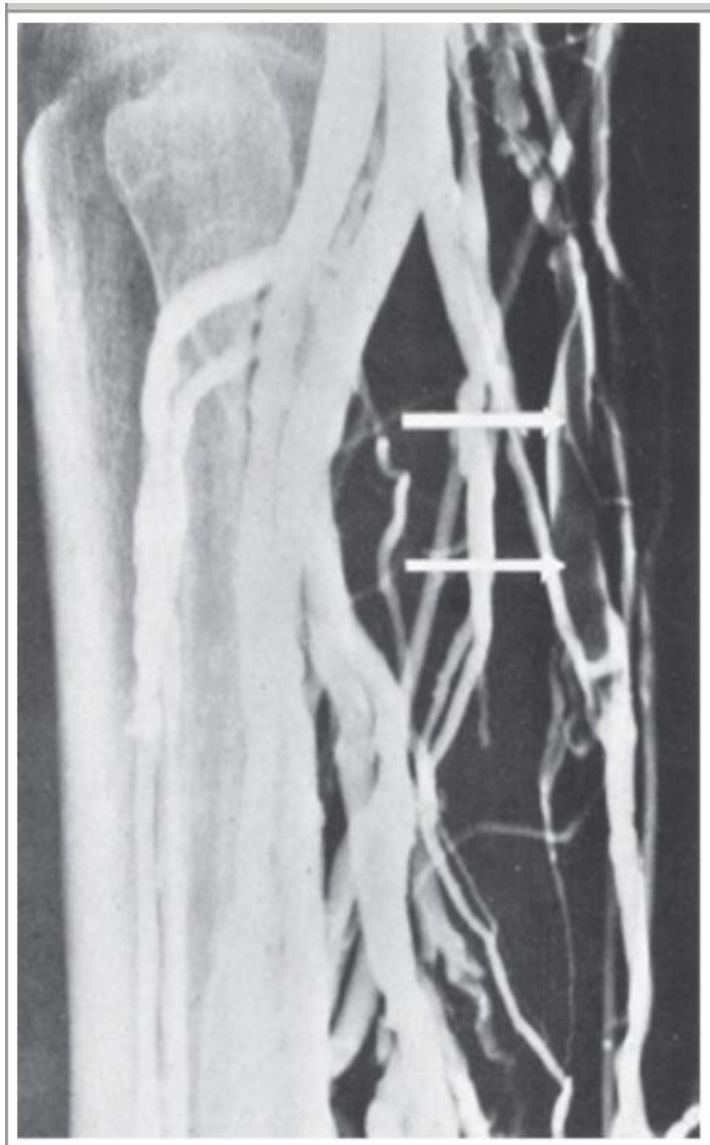
D-DIMER: THE BOTTOM LINE

- If a patient has a **low or moderate pretest probability for DVT** according to Wells score **AND** a **negative D-dimer**, **no further workup is need**
  - If D-dimer is positive, further work up is indicated
- In a patient with a **high pretest probability for DVT** it is inappropriate to use D-dimer → **further work up is indicated**
- Other diagnostics???
- Contrast venography
- Contrast-enhanced computed tomographic venography (**CTV**) and magnetic resonance venography (**MRV**)
- **Compression ultrasound**

RARELY USED DX STUDIES

- Contrast venography: long considered the "gold standard" but is **not recommended** as an initial screening due to patient discomfort (**INVASIVE**) and difficulty in obtaining an adequate study

- Non-invasive contrast-enhanced computed tomographic venography (**CTV**) and magnetic resonance venography (**MRV**) are rarely used diagnostically

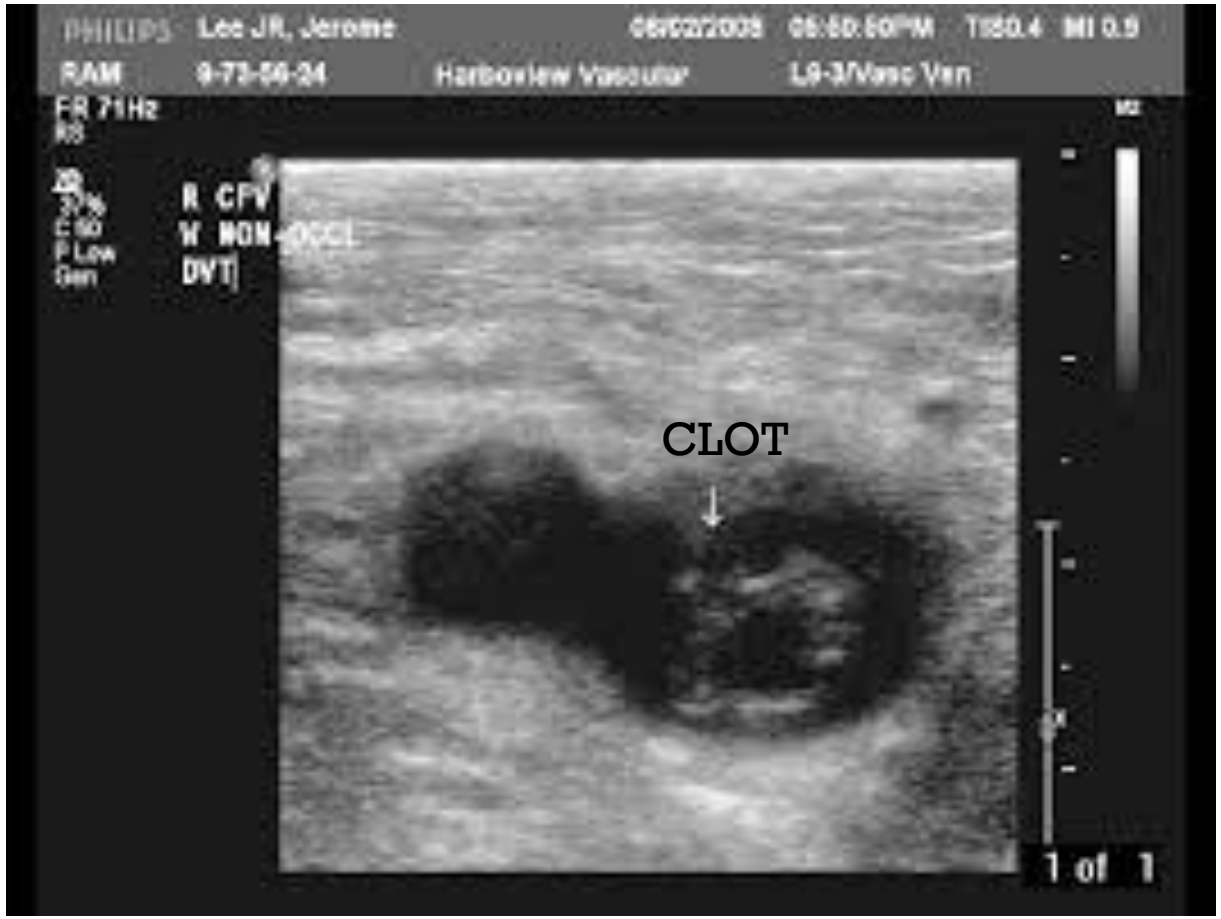


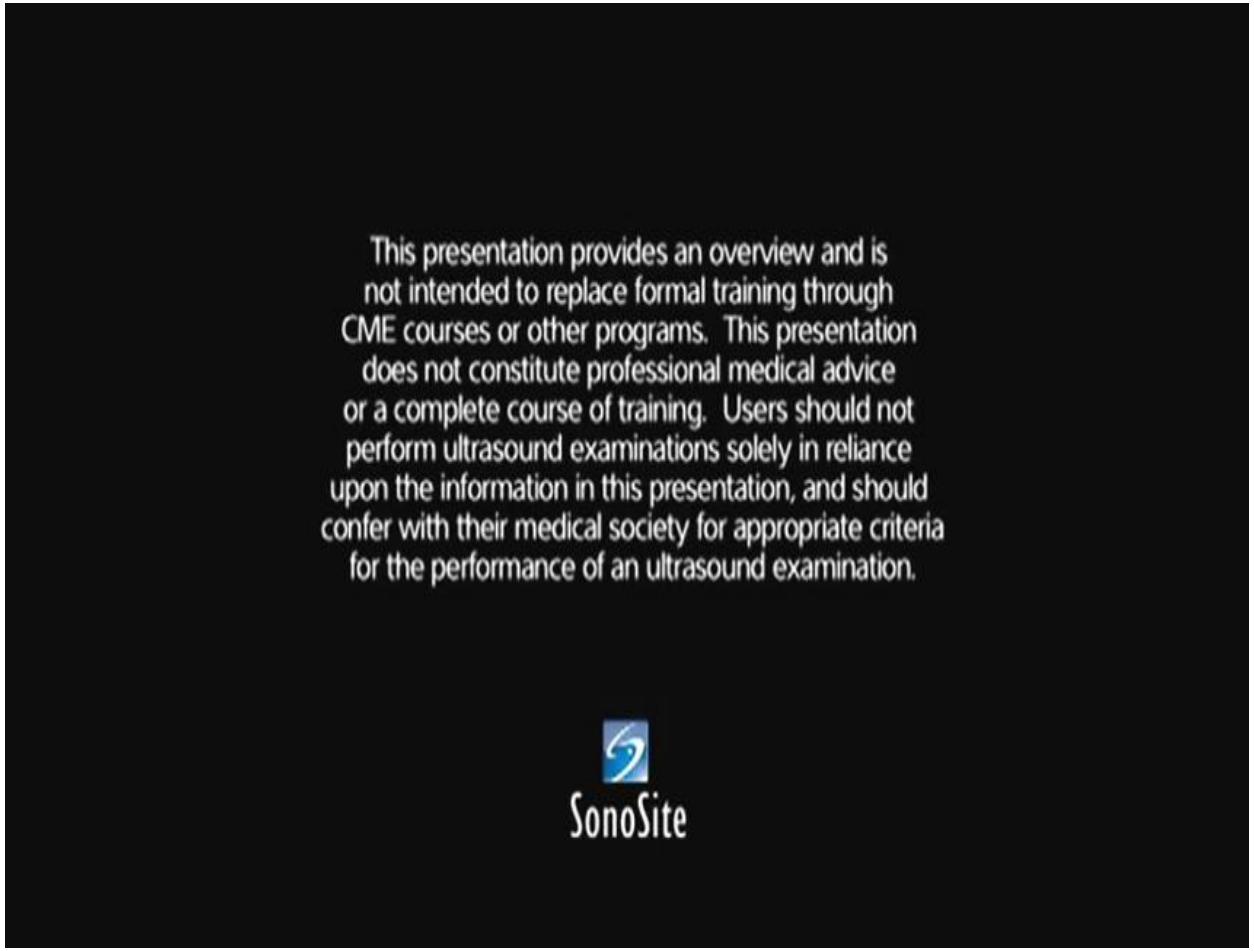
Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

Venogram showing a filling defect in the popliteal vein (*arrows*).

COMPRESSION ULTRASOUND

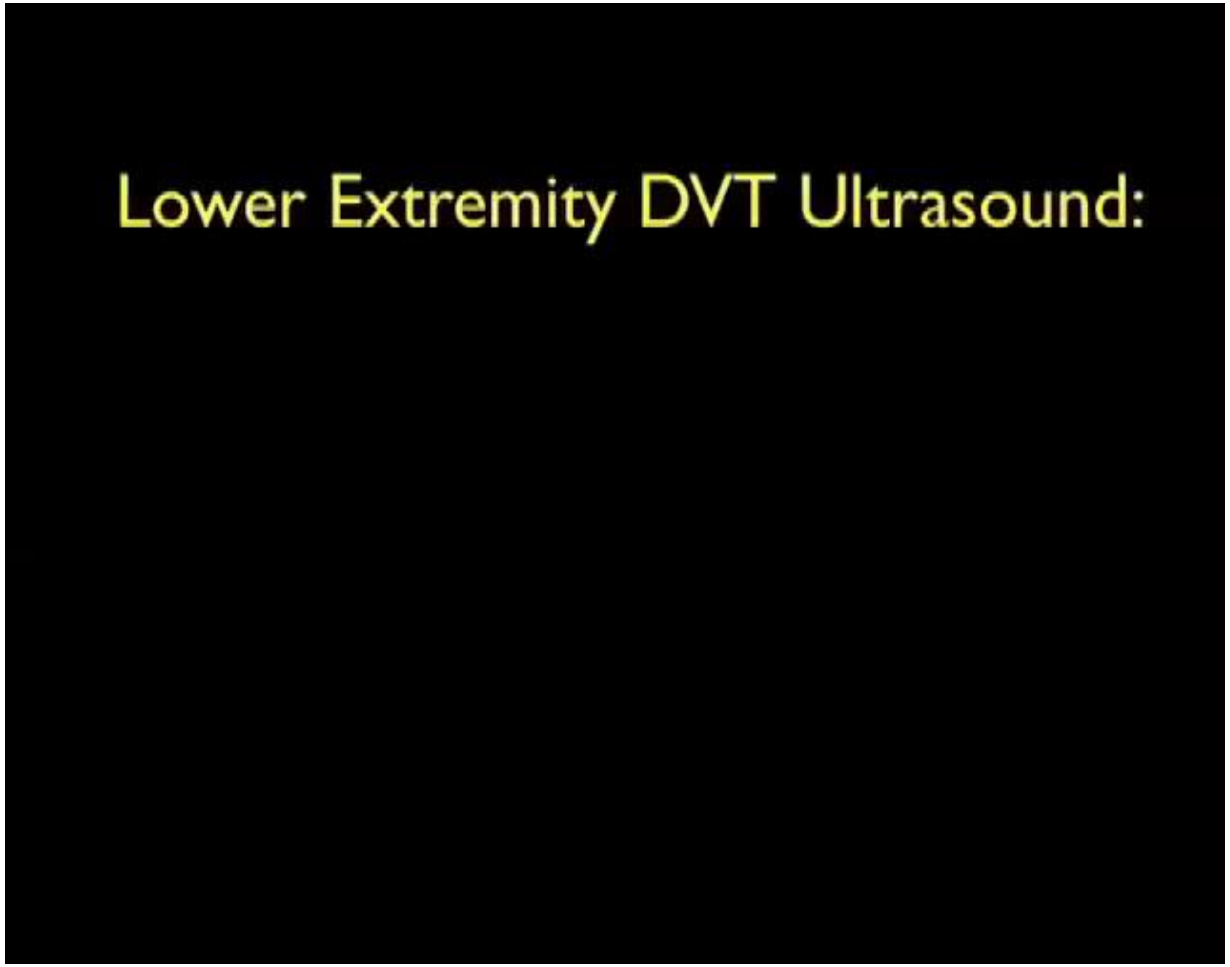
- **Test of choice!!!**
- **Loss of vein compressibility**
- **Doppler** technique **assesses blood flow** to a given region
- **Noninvasive**, relatively **available, inexpensive** and **easy to perform/read**
- May need serial exams definitively rule out DVT





Ultrasound technique for assessment of lower extremity vasculature

Using Doppler flow and compression to dx DVT



GOAL OF DIAGNOSTIC TESTING

- To **"rule-in" (>85% post-test probability of DVT)** or **"rule out" DVT (<2% post-test probability of VTE in the next 3 months)**

- Justifies instituting or withholding anticoagulant therapy

TREATMENT OF DVT THROUGH ANTICOAGULATION

- **Indications**
  - **Absolutely for proximal DVTs** (popliteal, femoral, or iliac veins)
    - Secondary to the risk of **PE → death**
  - Appropriate for ***most*** **distal DVTs** (below knee) – especially if symptomatic
    - If not started on anticoagulation, then followed with serial compression ultrasounds to assess for clot propagation
- **Purpose**
  - **Prevent further clot propagation**
  - **Prevent PE**
  - **↓ Risk of recurrent VTE**
  - **↓ Complications**
    - Post-thrombotic syndrome
    - Chronic venous insufficiency

Notice it does not say to "dissolve" the DVT or cause it to disappear

SO, YOU'VE DECIDED TO TREAT….

- How do we treat?
- The decision to anticoagulate must **weigh the benefits** of anticoagulation **against the risk of bleeding** for an individual

Anticoagulant medications and treatment for patients with high risk of bleeding or contraindication to anticoagulation will be discussed along with the treatment of PE

TREATMENT OF DVT

- **Early ambulation** (instead of bed rest) is recommended for patients fully anticoagulated, hemodynamically stable, and whose symptoms (e.g., pain/swelling) are under control
  - Non-aggressive exercise

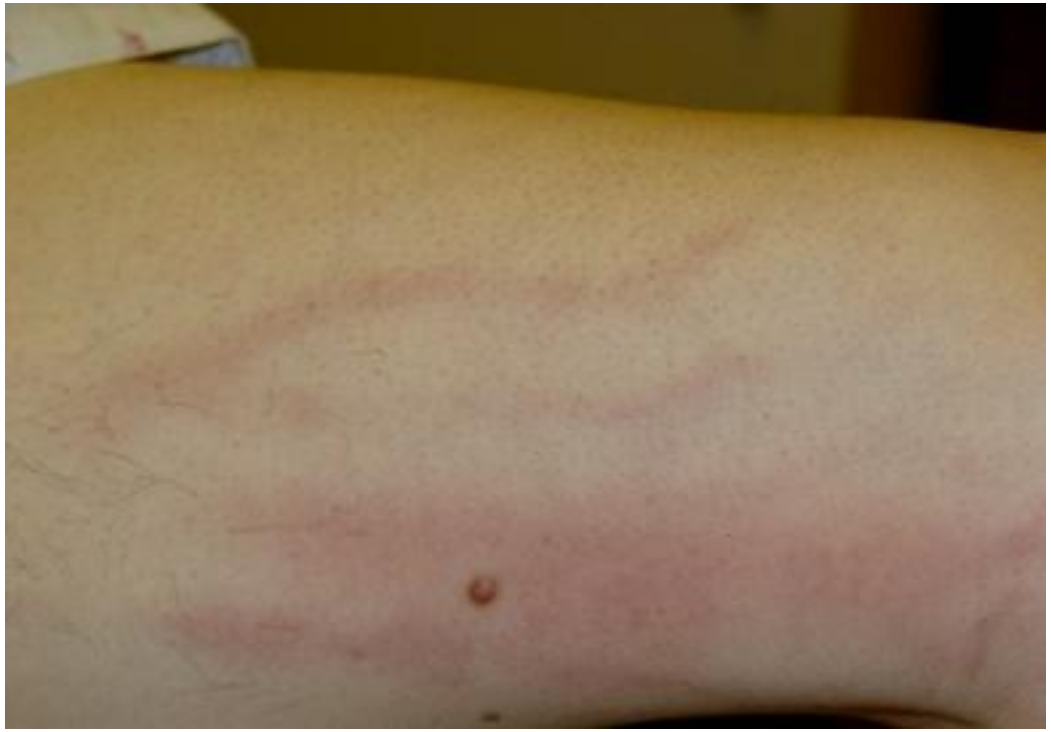
- **Elastic graduated compression stockings** for **prevention of post thrombotic syndrome** have been used in the past **BUT have not shown clear consistent benefit when studied**
  - They are uncomfortable, inconvenient, and costly

- Post thrombotic syndrome is a clinical diagnosis caused by **chronic venous insufficiency**
  - Symptoms may include extremity pain, vein dilation, extremity **edema**, skin pigmentation, and venous ulcers

A WORD ABOUT…UPPER EXTREMITY DVT (AXILLARY, SUBCLAVIAN VEINS)

- Only represent <4% of all DVTs
- Can either be:
  - **Spontaneous** (not common)
  - **Secondary** (much more common)
    - **Catheter** placement (esp. central line/pacemaker)
    - Prothrombotic states
- **PE occurs in about 4-10% of patients**
- Tx includes **anticoagulation**, thrombolysis ("clot busting") and/or surgical decompression of thoracic outlet

SUPERFICIAL THROMBOPHLEBITIS



Not a DVT

Usually caused by a peripherally inserted IV

33

PULMONARY EMBOLISM

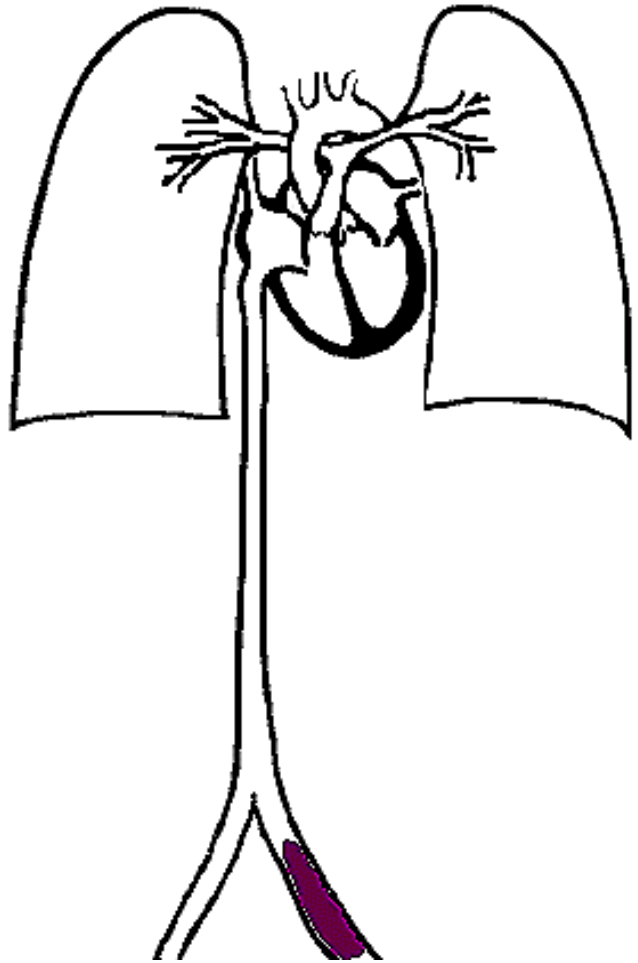
PULMONARY EMBOLISM: DEFINITION/CAUSE

- **Obstruction of the pulmonary artery** or **one of its branches** by material (e.g., **thrombus, tumor, air, or fat**) that **originated elsewhere** in the body and **embolized to pulmonary vasculature**
- **DVT** is most common cause
  - 50-60% of proximal DVT (iliac, femoral, popliteal) will embolize
  - **Isolated calf DVT embolize much less frequently**

PEs may also originate in the right heart, inferior vena cava or the pelvic veins, and in the renal and upper extremity veins

PE – PATHOPHYSIOLOGY

- The **IVC** drains blood from the **lower half** of the body, and the **SVC** drains blood from the **upper half** of the body into the **right atrium**
- Blood travels through the right atrium to the **right ventricle** and then from the **pulmonary artery** to the **lungs** for oxygenation
- Depending on how large the thrombus, it will travel through the lungs until it becomes wedged in the smaller arteries of the lungs, causing a **PE**
- Pathogenesis of PE is similar to DVT



CLASSIFICATION OF PE

- Classified one of **four** ways according to:
  - 1. Presence or absence of **hemodynamic stability**
    - Hemodynamically **stable or unstable**
  - 2. **Temporal pattern** of presentation
    - **Acute, subacute, or chronic**
  - 3. **Anatomic location**
    - **Saddle, lobar, segmental, subsegmental**
  - 4. Presence or absence of **symptoms**
    - **Symptomatic or asymptomatic**

CLASSIFICATION OF PE: HEMODYNAMIC INSTABILITY

- Sometimes called **massive PE**
  - Doesn't have to be massive if the patient has underlying cardiovascular disease
- Defined as a **systolic blood pressure <90 mmHg** or a drop in systolic blood pressure of ≥40 mmHg from baseline for >15 minutes
- These patients are more likely to **DIE** from obstructive shock in the first **two hours** of presentation
  - More aggressive treatment may be beneficial

PE: EPIDEMIOLOGY

- Slightly more common in **males** than females
- Overall incidence of PE is approximately **112 cases per 100,000**
- **Incidence rises with age**
- Deaths from PE account for approximately **100,000 deaths per year in the US**

PE: CLINICAL SIGNS AND SYMPTOMS

Wide variety…..from asymptomatic to DEATH

Symptoms

- **Dyspnea**
- **Pleuritic chest pain**
- Symptoms of DVT
  - Calf or thigh pain or swelling
- Cough

Signs

- Tachypnea
- Calf or thigh swelling, erythema, edema, tenderness, palpable cords
- Tachycardia

PE: INITIAL EVALUATION AND DIAGNOSIS

- **BE SUSPICIOUS!!!!** (clinical gestalt again)
- **ABCs** (BP, HR, RR, mental status)
- If hemodynamically **unstable**:
  - Definitive imaging is unsafe; bedside **echocardiography** may be used to obtain a presumptive diagnosis of PE (thrombus, increase in RV size and decreased RV function)

- If hemodynamically **stable**:
  - Combine **clinical and pretest probability assessment** (**Wells criteria for PE**), **D-dimer**, and definitive **diagnostic imaging** [CT pulmonary angiogram (**CTPA**) or possibly ventilation/perfusion scanning (V/Q scan)]

Personal difficulty again

Wells criteria and modified Wells criteria: clinical assessment for pulmonary embolism

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
Probability	**Score**
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

FYI…several pretest scoring system exist. Wells criteria is arguably the most popular

LOW CLINICAL PROBABILITY OF PE (PTP <15%/WELLS CRITERIA <2)

- PE rule out criteria (**PERC**) should be applied
- Patients who fulfill all eight criteria (**PERC negative**) **do not need additional testing**
- Patients who **do not fulfill PERC criteria** or in whom PERC cannot be applied (e.g., critically-ill patients, pregnant), further testing with **D-dimer measurement** is indicated
  - **No imaging** is required when the **D-dimer level is normal** (<500 ng/mL)
  - **Imaging** is indicated in those with a **positive D-dimer**

"PERC RULE"

- **PE rule-out criteria** ("PERC rule") is an **alternative to further testing** in patients with a **low-probability assessment for PE**

- **8 CRITERIA**
- Age <50 years
- Heart rate <100 beats/minute
- O2 saturation ≥95%
- No hemoptysis
- No estrogen use
- No prior DVT or PE
- No unilateral leg swelling
- No surgery/trauma requiring hospitalization within the prior four weeks

PERC RULE AND NEXT STEPS

- In patients with a **low** probability of PE who **fulfill ALL eight criteria**, the likelihood of PE is low, and **no further testing is required**
  - **All other patients** should be considered for further testing with **D-dimer or imaging**
- **PERC will miss <1% of low-test probability PEs**
  - ~20% reduction of unnecessary testing with PERC is used appropriately

- Patients that do not fulfill PERC criteria, proceed with D-dimer
  - **D-dimer** level is **normal → no imaging**
  - **Imaging is indicated** in those with a **positive D-dimer**

INTERMEDIATE OR HIGH CLINICAL PROBABILITY OF PE

- **Intermediate** probability of PE (Wells criteria between 2 – 6):
  - **D-dimer testing is necessary** to determine whether diagnostic imaging is indicated
    - D-dimer **positive** → proceed to **diagnostic imaging**
    - D-dimer **negative** → **no** further diagnostic **work-up** is necessary
      - Some providers use Wells 4-6 as the cut off

- **High** clinical probability of PE (Wells criteria >6):
  - **D-dimer not indicated and diagnostic imaging** is obtained

PE: DIAGNOSTIC IMAGING

- **Pulmonary angiography**
  - **Historical** "gold standard" for diagnosis
    - Highly specific and sensitive
    - **NOT used frequently due to new generation CTA scanning**

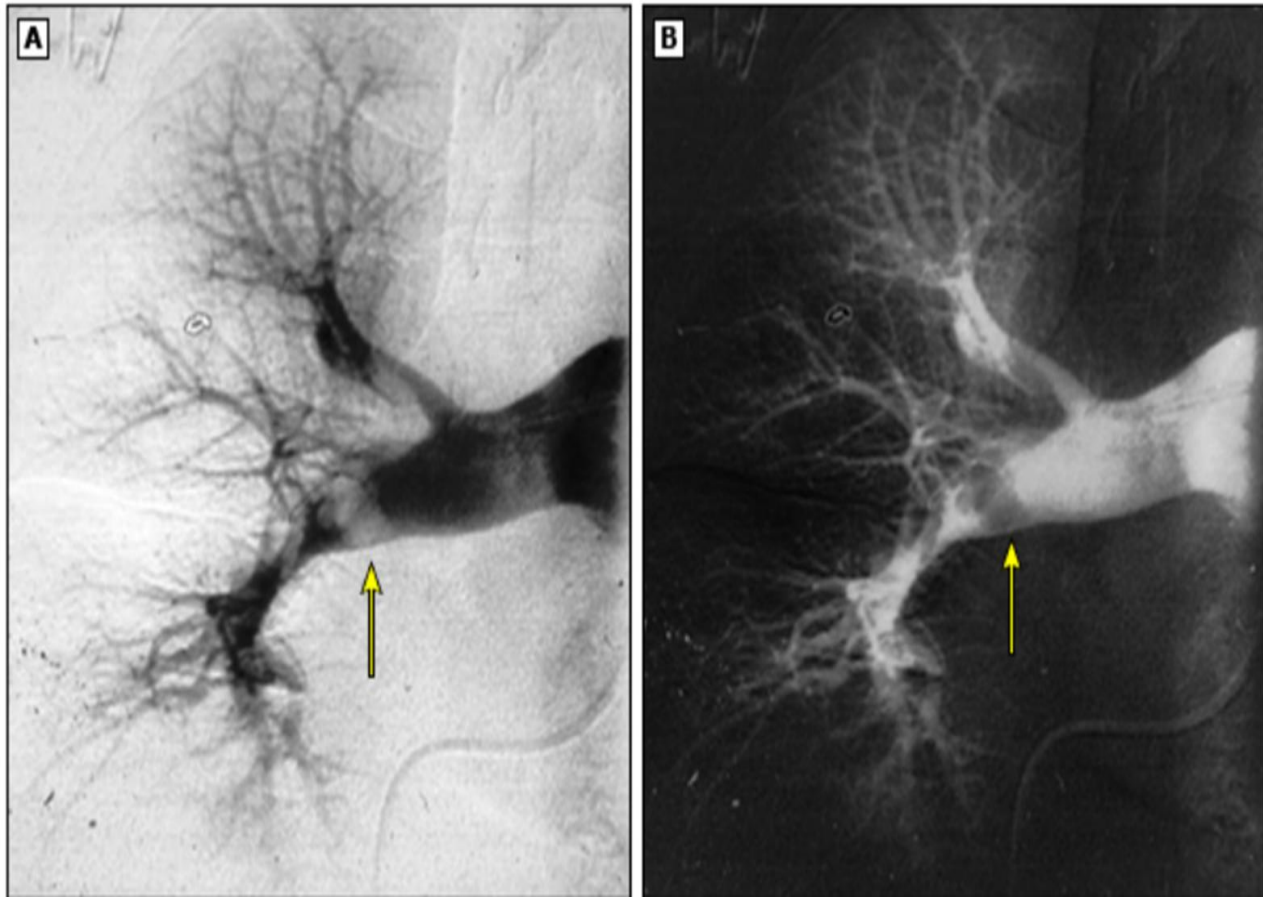
  - Disadvantages

    -**Invasive** procedure

    -High IV contrast load

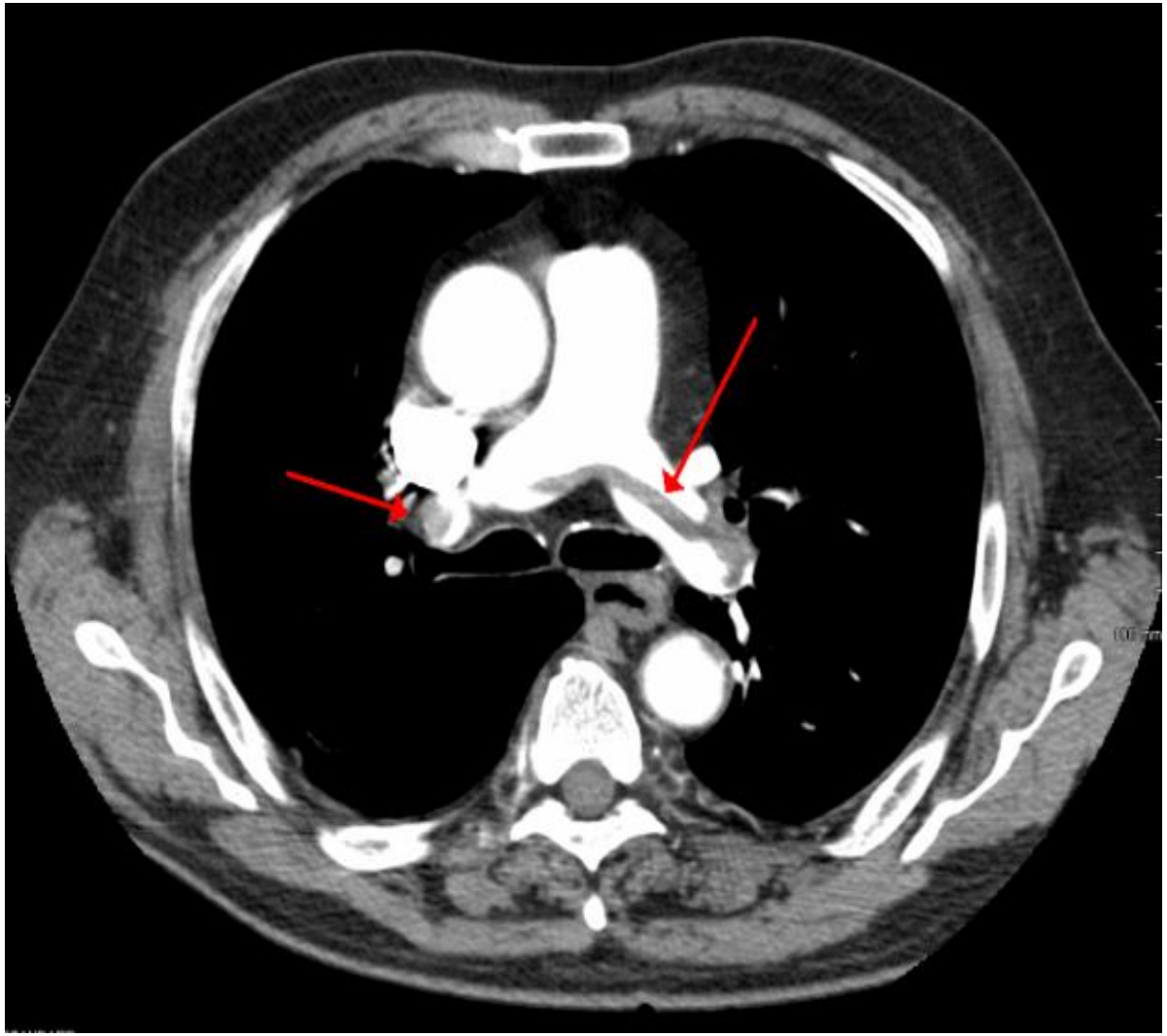
    -Technically demanding

    -Costly



PE: DIAGNOSTIC STUDIES: CTPA

- CT-Pulmonary Angiography (CTPA)
  - **Test of choice**
  - **Sensitive & specific**
    - >90% for low/intermediate prob
  - Accurate for the detection of **large, main, lobar, and segmental PE**
    - Less accurate for the detection of smaller, peripheral subsegmental PE
      - Tend to be clinically irrelevant
  - **Noninvasive**
  - IV contrast allergy, severe renal dysfunction **exclude use**



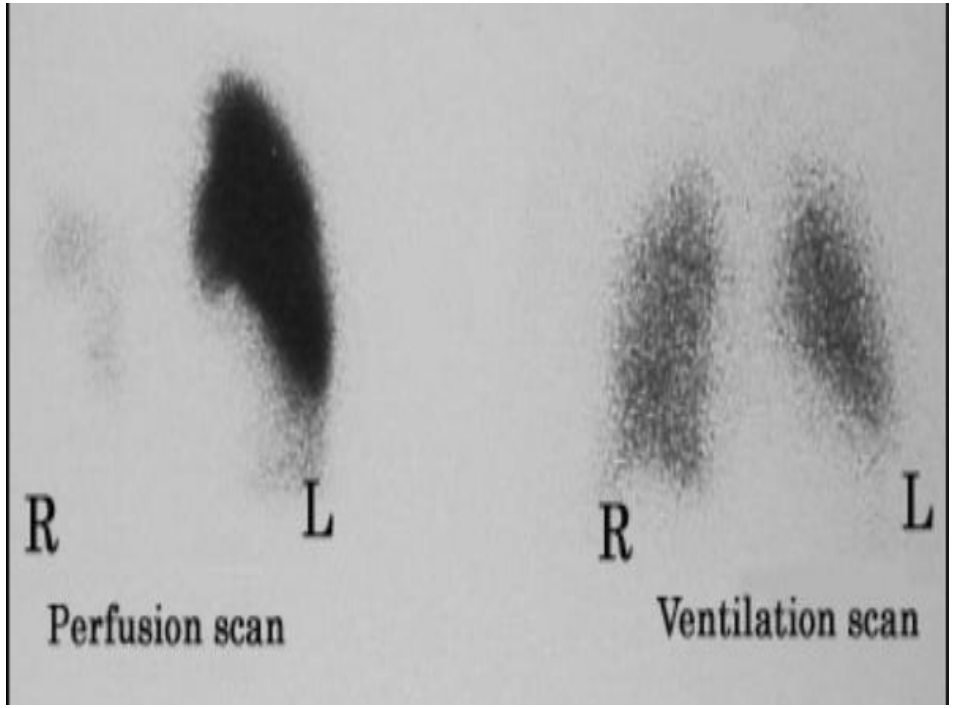
http://centegramedsource.com/suspected-pulmonary-embolism/

WHAT TO DO IF YOU CAN'T OBTAIN A CTPA…

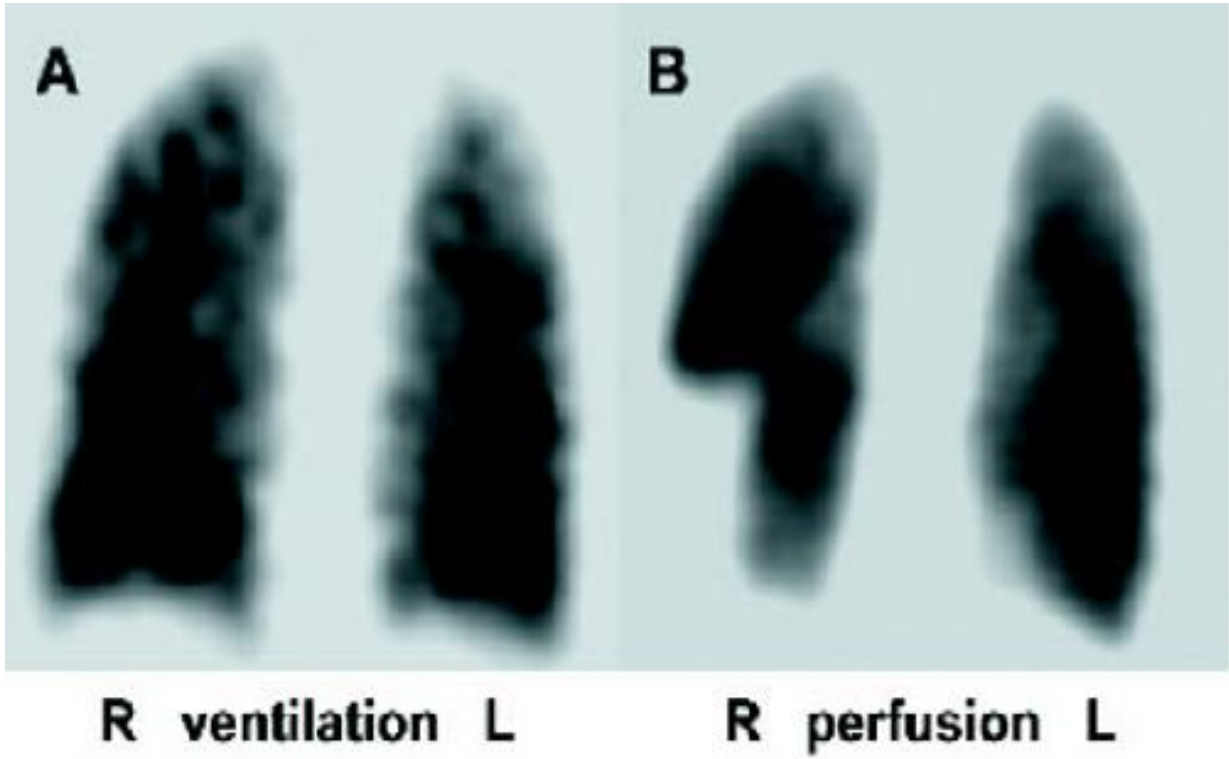
- For patients with suspected PE in whom CTPA is contraindicated, unavailable, or inconclusive, **ventilation perfusion (V/Q) scanning** is the alternative imaging exam
- **Sensitive** test for the diagnosis of PE, but is **poorly specific** due to the **high number of false-positive test results**
- Interpreted as:
  - Normal
  - Low-probability PE **(<4% chance of PE)**
  - Intermediate-probability PE ← **Diagnostic Dilemma**
  - High-probability PE **(~96% chance of PE)**

PE: DIAGNOSTIC STUDIES: V/Q SCAN

- **Ventilation-Perfusion Lung Scanning (V/Q scan) - Gadolinium**



V/Q MISMATCH



Best utilized in those who have a normal chest radiograph

Otherwise, false positives are likely

FYI until you have ECG

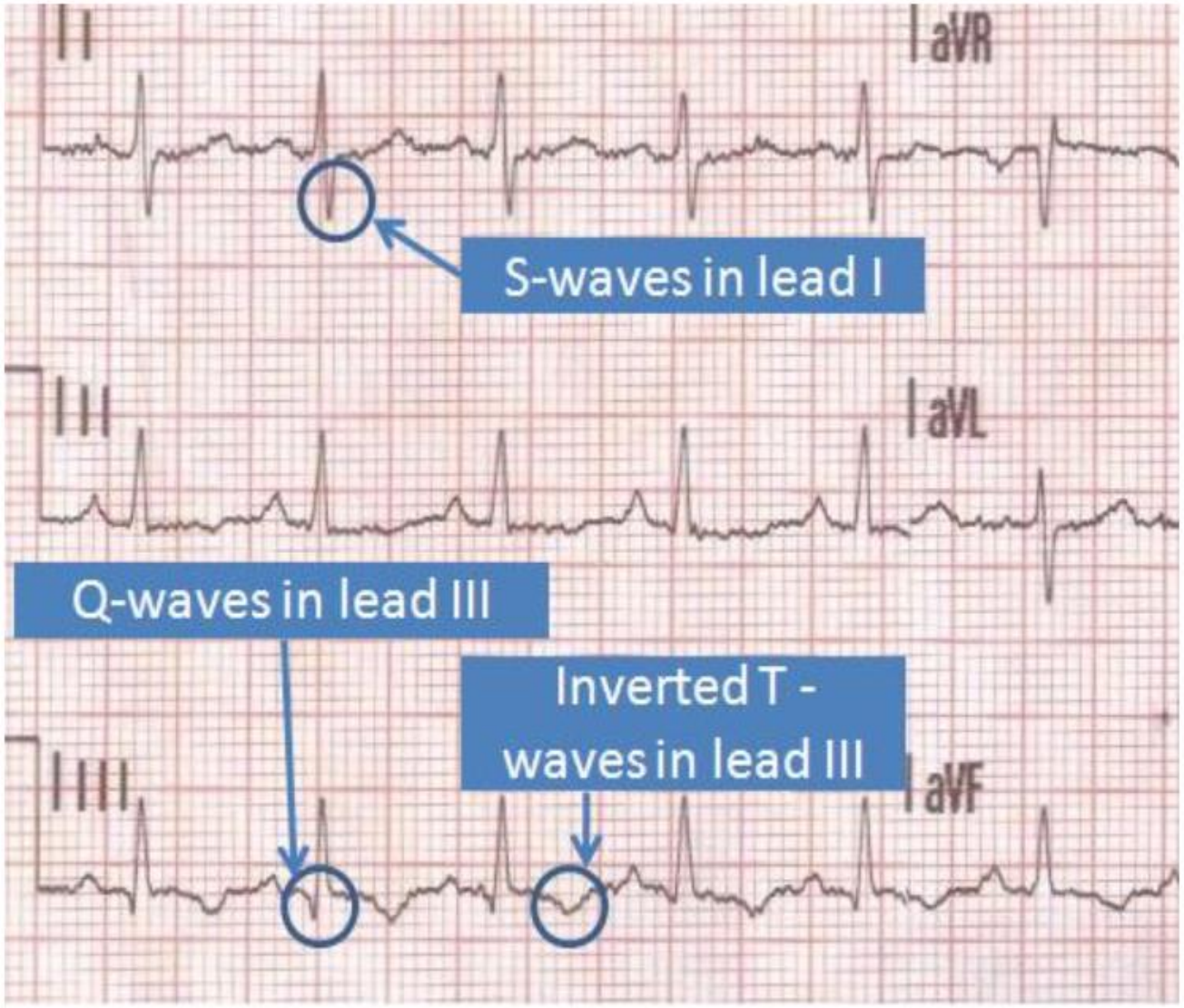
PE: ADJUNCTIVE STUDIES

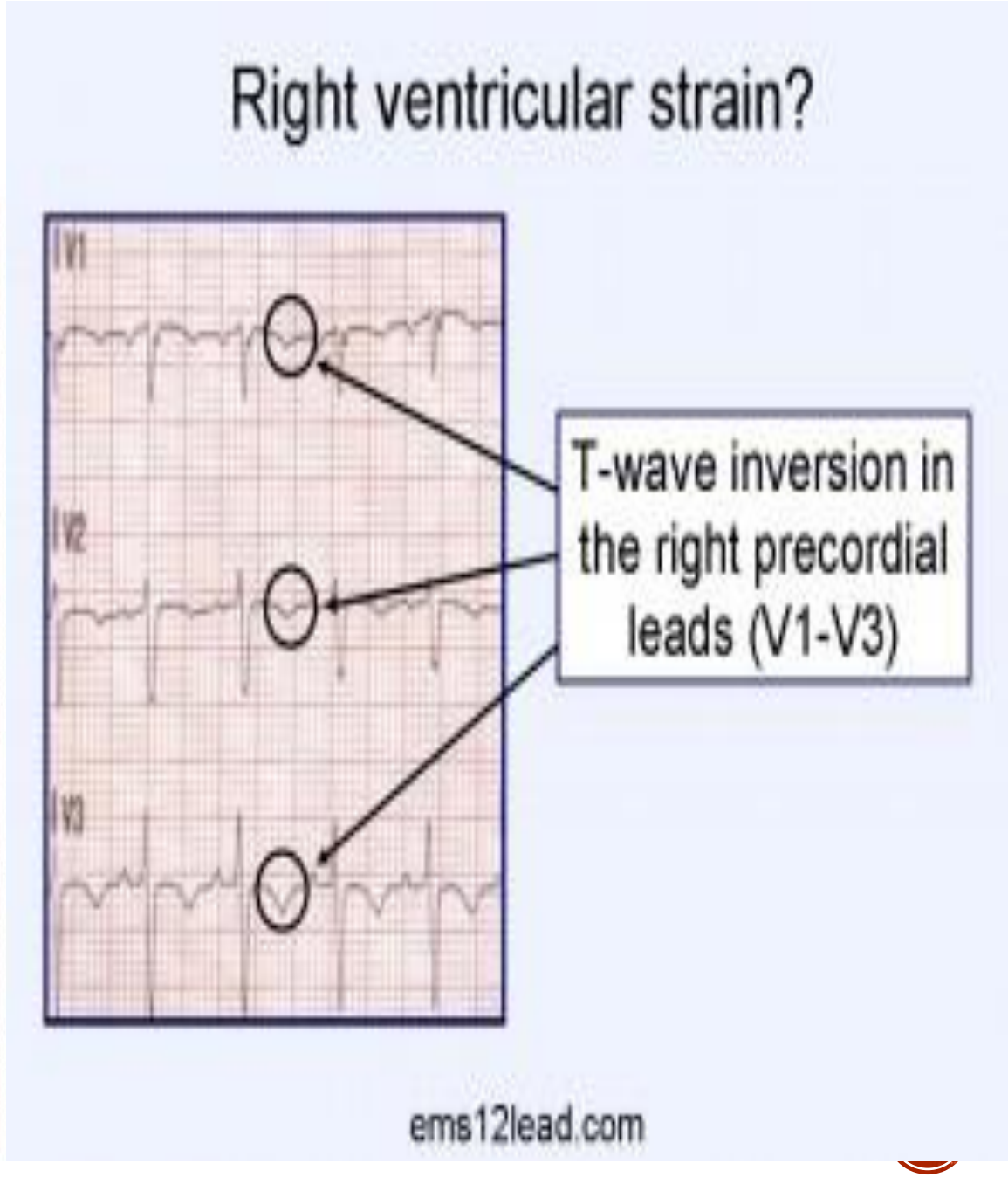
- **ECG**
  - **Abnormalities are common** in patients with PE, **BUT** typically they are **nonspecific** and of limited diagnostic value
    - Most common findings are **sinus tachycardia** and **nonspecific ST-segment and T-wave changes**
  - **"Classic findings on ECG"**
    - **S1Q3T3** pattern, **right ventricular strain**, **right axis deviation**, new incomplete right bundle branch block are seen in LESS that 10% of patients

It is commonly seen on board exams though. ☺

FYI until you have ECG

S1Q3T3



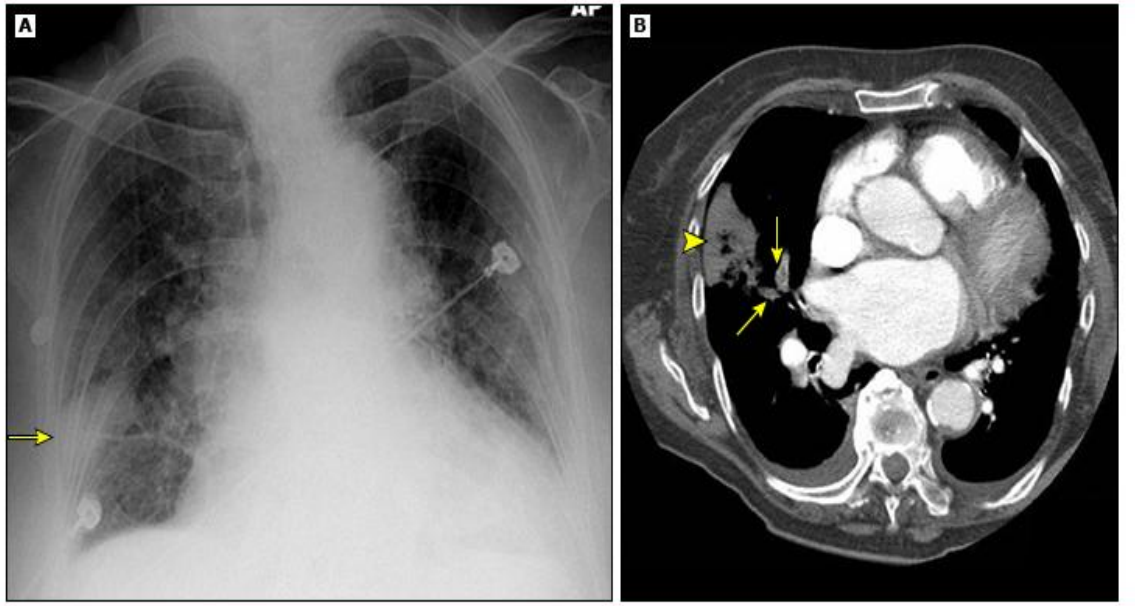


PE: ADJUNCTIVE STUDIES

- CXR is **NOT** sensitive **NOR** specific
  - **Hampton's hump** = opacity (infarct)
  - **Westermark sign** = oligemia

- Nonspecific findings are common (effusion, atelectasis)
- Can help determine eligibility for a V/Q scan

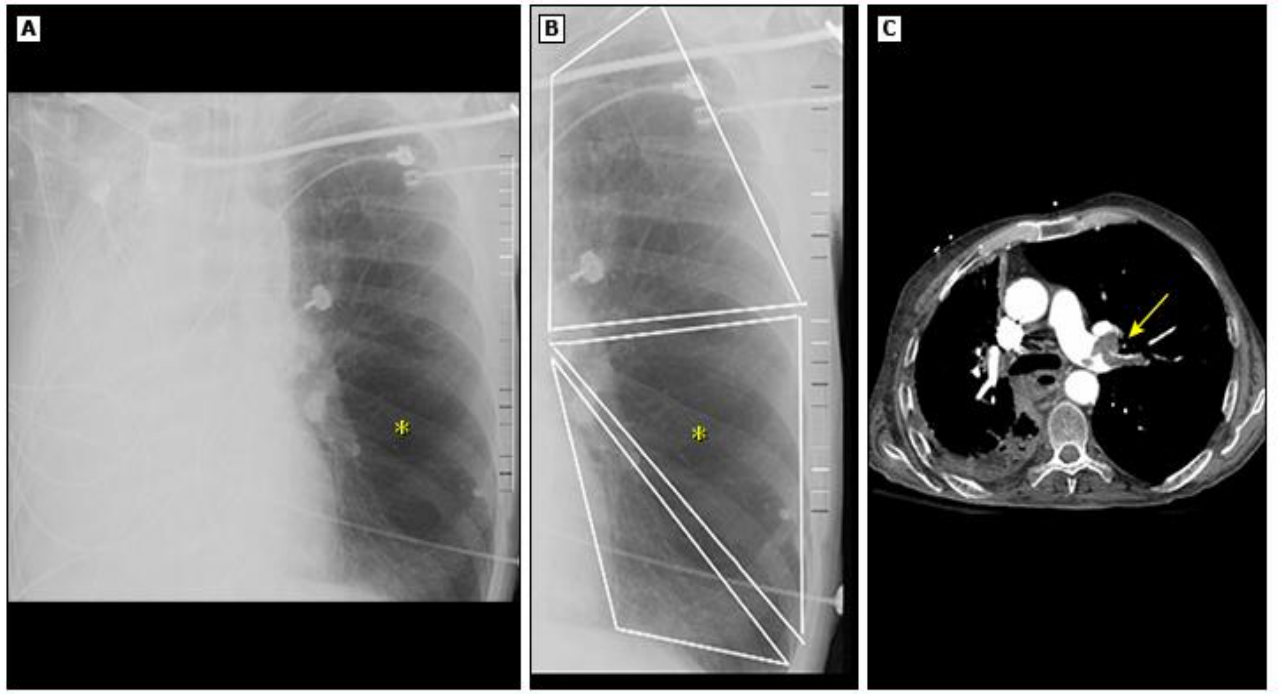
Hampton's hump on radiograph and CT scan



An anterior-posterior chest radiograph of a patient with suspected pulmonary embolus. Image A shows a wedge-shaped defect in the lateral segment of the middle lobe (arrow). Image B is a CT scan through the mid chest and shows the corresponding wedge-shaped defect (arrowhead) and thrombus in the pulmonary arteries subtending the middle lobe (arrows).

CT: computed tomography.

Westermark sign of PE on radiography and CT



A magnified A-P view of the left lung (A) shows a region of oligemia in the left lower chest (asterisk) in a patient with occlusive pulmonary embolism. Image B is a further magnification showing normal vasculature in the upper and lower lung regions but oligemia in the middle section (asterisk). The CT scan (C) shows a large saddle embolus of the left main pulmonary artery (arrow).

TREATMENT FOR PE

- **Supportive care**
  - **Supplemental O2** to target oxygen saturation of 90%
  - Intubation and **mechanical ventilation if necessary**
  - **Judicious use of IV fluids** to maintain BP
  - **Vasopressors** if IV fluids are not enough
- **ANTICOAGULATION!!!!**
- And some other stuff ☺

MAINSTAY OF THERAPY = ANTICOAGULATION

- **Initial** anticoagulation is administered immediately and up to the first **10 days** to provide **protection from recurrent thrombosis or embolization** in this period of highest risk

- **Long term (but finite)** anticoagulation for a **minimum of three months** and **extended for 6 to 12 months** in some cases
  - Depends on presence or absence of provoking events, risk factors for recurrence and bleeding risk, and the individual patient's preference

- A **small population** of patients will require **indefinite anticoagulation**

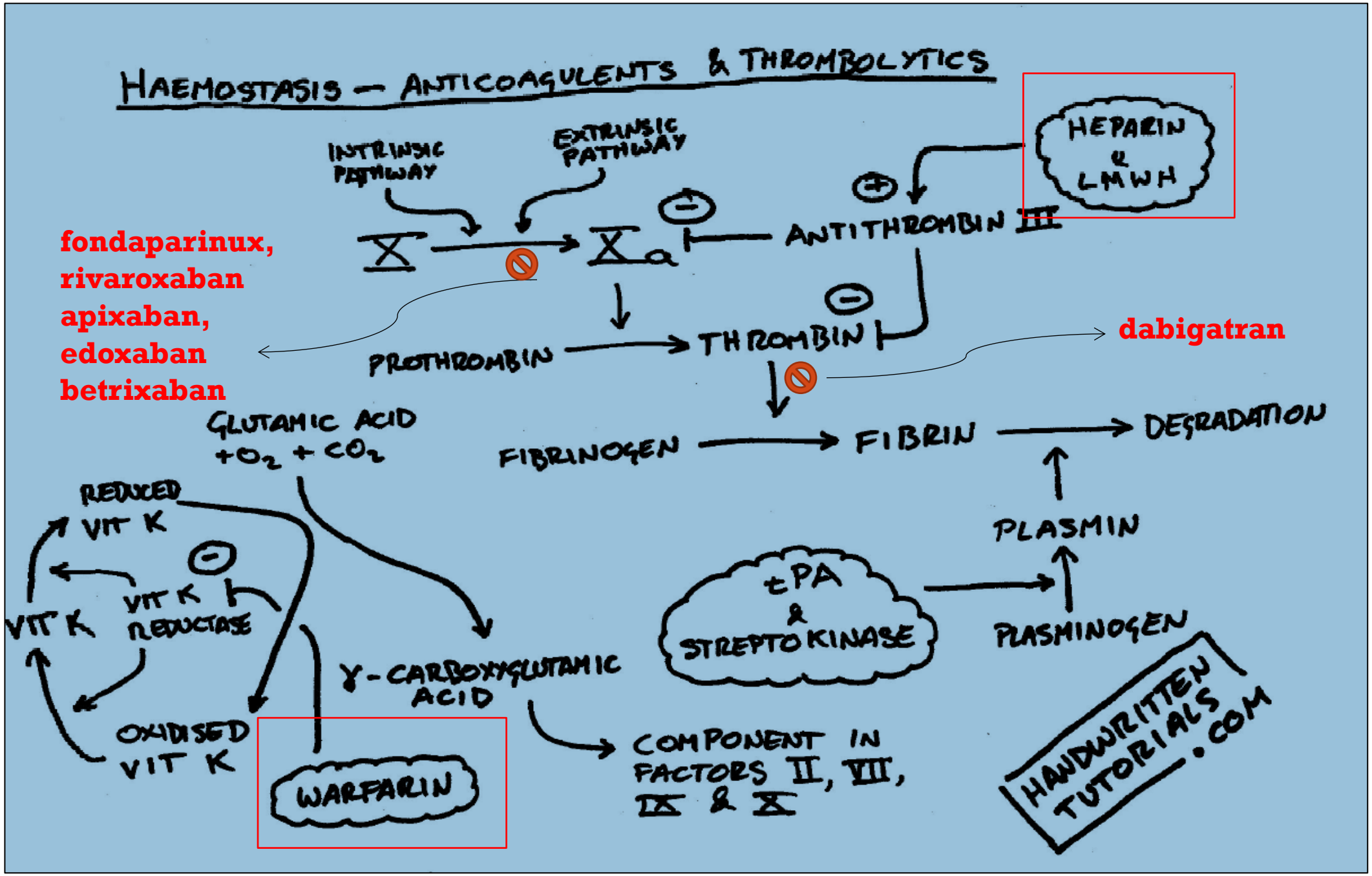
VTE TREATMENT STRATEGIES

- **Anticoagulation medications**
  - For patients with a **low risk of bleeding** and a **high clinical suspicion for PE**, consider **empiric anticoagulation** rather than waiting until definitive diagnostic tests are completed
- Thrombolytics
- IVC filter
- Thrombectomy/Embolectomy
- Prophylactic measures

VTE ANTICOAGULANTS

- **IV** Unfractionated Heparin **(UFH)**
- **SQ** Low-Molecular-Weight-Heparin (**LMWH**) – Lovenox
- **Oral Warfarin** (Coumadin)
- **Factor Xa Inhibitors**
  - **SQ** formulation - fondaparinux (Arixtra)
  - **Oral** formulations –rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Savaysa, Lixiana), betrixaban
- **Oral direct thrombin inhibitors** – dabigatran (Pradaxa)

Known as direct oral anticoagulants = **DOACs**


HAEMOSTASIS – ANTICOAGULENTS & THROMBOLYTICS
INTRINSIC PATHWAY
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X
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ANTITHROMBIN III
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fondaparinux,
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edoxaban
betrixaban
PROTHROMBIN
THROMBIN
dabigatran
GLUTAMIC ACID
+O2 + CO2
FIBRINOGEN
FIBRIN
DEGRADATION
REDUCED VIT K
VIT K
VIT K REDUCTASE
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VTE ANTICOAGULANTS – SHORT TERM

- For **most patients direct oral anticoagulants** (eg, apixaban and rivaroxaban) are recommended, owing to their efficacy, safety, and convenience
- **Pregnant** patients or those with **cancer** can be treated with **LMWH**
- Patients who **warrant parenteral anticoagulation**, **LMWH** is generally recommended over UFH in most patients owing to the unpredictable pharmacokinetics of UFH and increased risk of bleeding
- **UFH** is recommended in patients with **serious renal impairment** (creatinine clearance of ≤30 mL/min) or high bleeding risk

Managing Pulmonary Embolism
Westafer, Lauren M. et al. Annals of Emergency Medicine, Volume 82, Issue 3, 394 - 402

VTE LONG TERM ANTICOAGULATION

- When **transitioning** from **initial to long-term** (maintenance) treatment, **therapeutic anticoagulation** should be maintained
  - **Interruptions should be minimized during the first three months of anticoagulation due to the high risk of recurrent thrombosis**
- For many patients, the choice of initial anticoagulant will be the same as the drug chosen for long term maintenance

- ***Traditionally*** **long-term therapy** is achieved with the use of **warfarin**
  - Start at 5mg/day
    - Loading dose is not recommended (does not offer more rapid protection and may lead to increased bleeding risk)
  - The **action of warfarin is slow in onset so the patient needs "bridging" therapy**

WARFARIN BRIDGING & SUPRATHERAPEUTIC INR

- Parenteral therapy with UFH or LMWH should **overlap** with warfarin for at LEAST 5 days and until the **INR is therapeutic** for a minimum of 24 hours or 2 consecutive days
- Warfarin anticoagulation requires **monitoring with serum INR testing**
  - Titrate dose to appropriate INR (**usually between 2 and 3**)
  - Monitor INR frequently
    - Daily, then weekly, then once stabilized every 2-4 weeks
- **Supratherapeutic INR**
  - Optimal approach depends on bleeding, degree of INR elevation, and underlying thrombotic risk
  - Basic principals include **holding warfarin** and giving:
    - **Vitamin K**=antidote (po or IV),
    - **Prothrombin complex concentrate** (or fresh frozen plasma if no PCC)

VTE LONG TERM ANTICOAGULATION

- Options for patients who wish to **avoid the burden of INR monitoring** include the **oral factor Xa inhibitors** and **oral direct thrombin inhibitors**
  - Most sources prefer DOACs to warfarin
  - LMW heparin and fondaparinux are not as desirable for long-term use because they are not oral

- Choice of drug therapy is dependent on **MANY** factors including **cost**, **patient choice**, **specific patient factors** (underlying medical history) and **potential need for reversal of anticoagulation**
  - Consider the risks if a patient has major bleeding and you can't "shut off" the anticoagulant effect in their body
    - Trauma, elderly/alcoholics with propensity for falling, etc.

BLOOD TO THIN? BLEEDING OUT? ANTICOAGULATION REVERSAL

- **UFH** = **protamine**
- **LMW heparin** = **protamine** (typically incomplete reversal)
- **Warfarin** = **vitamin K, PCC, FFP**
- **Factor Xa inhibitors** = **andexanet alfa**
- **Direct thrombin inhibitor,** dabigatran = **idarucizumab**
- Can consider **(prothrombin complex concentrates for all)**, antifibrinolytic agents (transexamic acid), hemodialysis, activated charcoal

For all → discontinue drug, transfuse blood, if necessary, address hemorrhage anatomically (surgery, endoscopy, local measures)

DURATION OF ANTICOAGULANT THERAPY

Provoked – identifiable risk factors
Unprovoked – happened for no good reason

- First episode – **Minimum of 3 months**
- Recurrent clot risk, risk of bleeding, and patient preference dictate need for extended therapy
- If **provoked** by a resolved **transient risk factor – 3 months**
- **Unprovoked** clot or **continued transient risk factor**: consider **extending therapy** unless high risk of bleeding (usually 6 months)
- Patients most likely to benefit from **indefinite anticoagulation** are those with an **intermediate to high risk of recurrent DVT/PE**
  - Consider **indefinite anticoagulation** in patients with **underlying thrombophilia or active malignancy**

WORK UP FOR UNDERLYING THROMBOPHILIA

- **Testing for inherited thrombotic disorders and malignancy can lead to the discovery of risk factors, but does not improve mortality**
  - Testing following first episode of VTE is controversial (especially if VTE was provoked)

- **First episode of VTE and at least one 1° degree relative with documented VTE before age 45 yrs.** should be tested for:
  - All **5 inherited thrombotic disorders** (antithrombin deficiency, protein S and C deficiencies, factor V Leiden and prothrombin gene mutations)

    -- And --

  - If the **patient** is **under 45 years,** also test for **antiphospholipid syndrome**

WORK UP FOR UNDERLYING THROMBOPHILIA

- **Protein C, S or antithrombin deficiencies**
  - Consider in thrombosis < 45 y/o with family history of VTE
  - **Lab work-up:** assays for deficiencies
- **Factor V Leiden or prothrombin gene mutation**
  - Consider with thrombosis on **OCPs**, cerebral vein thrombosis, or DVT/PE in white population
  - **Lab work-up:** PCR for Factor V Leiden or prothrombin C gene mutation
- **Antiphospholipid antibody syndrome**
  - Consider with: **Unexplained VTE**, CVA/TIA < 50 y/o, recurrent VTE, unusual site, arterial and venous thrombosis, thrombocytopenia, **recurrent early pregnancy loss**
  - **Lab work-up:** Anti-cardiolipin antibody, Anti-beta-2 glycoprotein antibody, Lupus anticoagulant

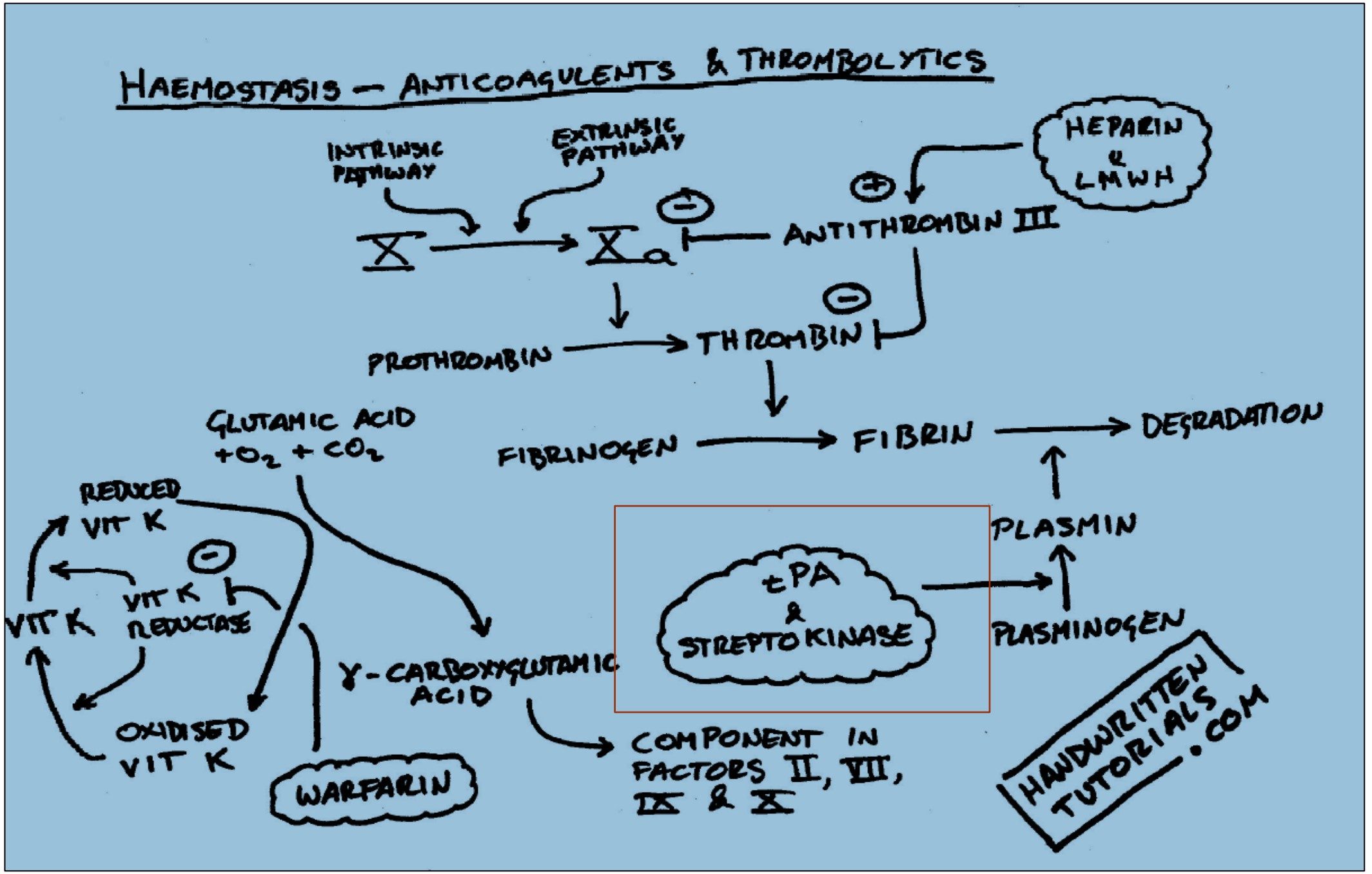
ADJUNCTIVE THERAPY: THROMBOLYTICS

- **Activates plasminogen to form plasmin, resulting in the accelerated lysis of thrombi ("clot buster")**
  - Also increases major bleeding and has not been convincingly shown to improve mortality or reduce the frequency of recurrent thromboembolism
- Given in conjunction with anticoagulation
- Used for **unstable** patients with PE
  - **Massive PE and sustained hypotension with cardiogenic shock**

- If **low risk of bleeding,** give through a **peripheral IV**
- If **moderate risk of bleeding,** give through a **catheter directed at the clot**
- **If high risk, do not give**

Examples:

Streptokinase, Urokinase, Recombinant tissue plasminogen activator (rt-PA, alteplase)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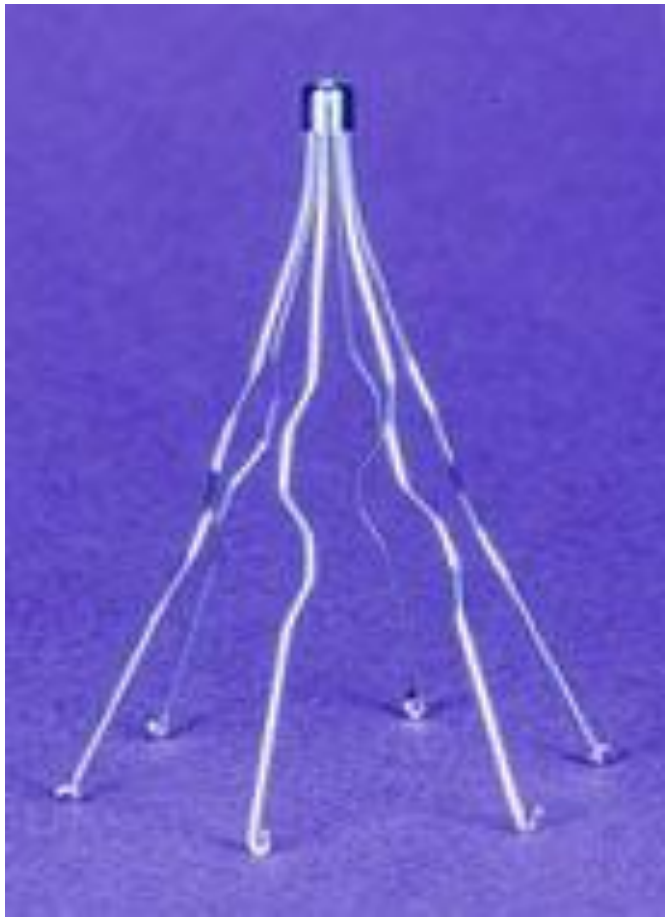
ALTERNATIVE OR ADJUNCT TO ANTICOAGULATION: INFERIOR VENA CAVA FILTER

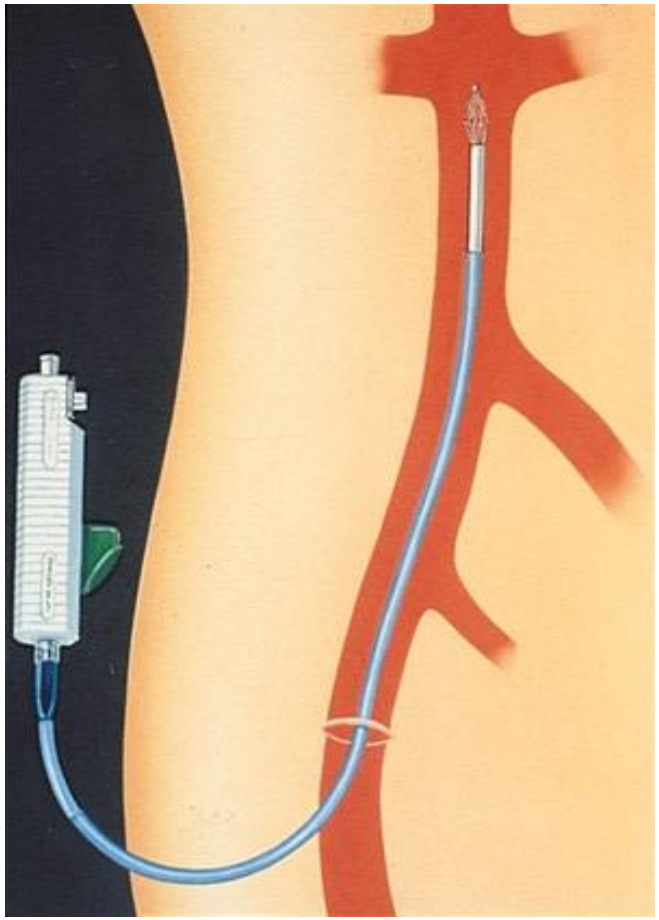
- In patients for which:
  - **Anticoagulation is contraindicated**
  - **Risk of bleeding is estimated to outweigh the risk of recurrent thromboembolism**
  - **Recurrent PE** despite adequate anticoagulation
  - Complication of anticoagulation (**severe bleeding**)
  - **Hemodynamic or respiratory compromise** that is severe enough that another PE may be life-threatening

- Insertion of an **IVC filter** rather than no therapy is indicated in these cases

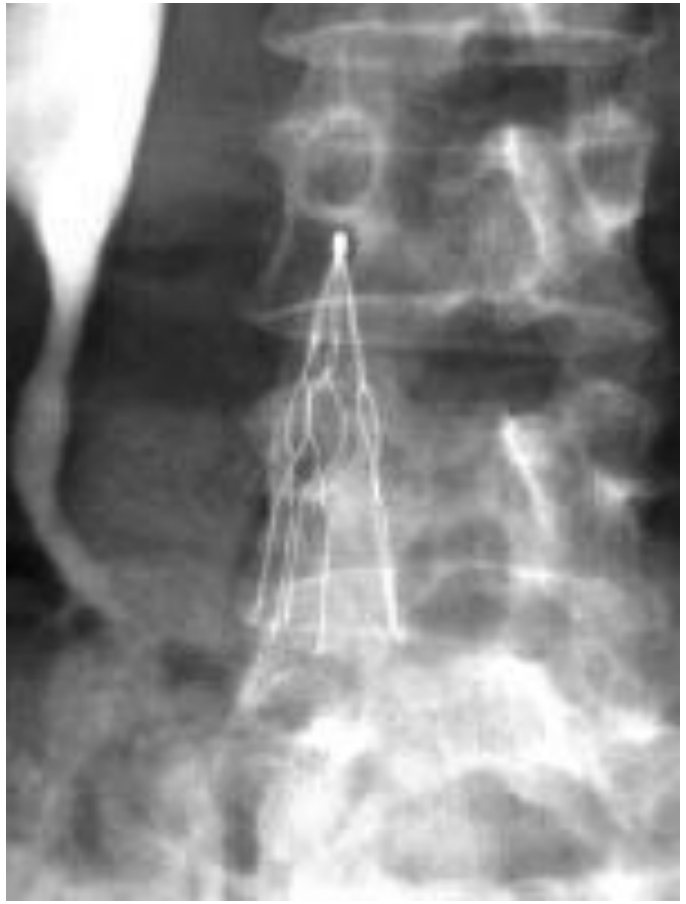
WHAT IS AN IVC FILTER, YOU ASK???

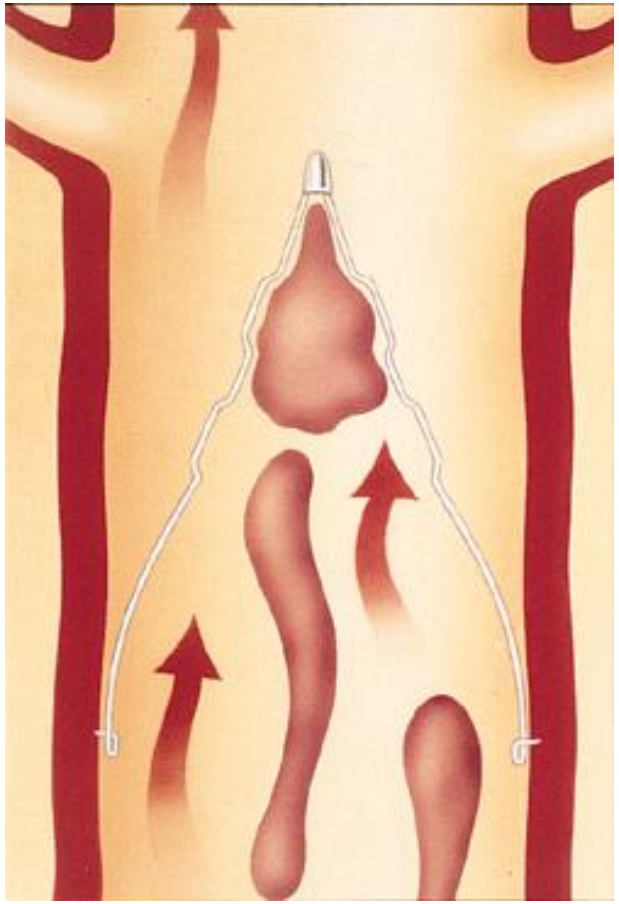
- **A "filter" is placed in the inferior vena cava**
- **Prevents DVT from propagating to lungs**
- Multiple types and none are proven to be better than another
  - Can be permanent or retrievable





IVC FILTERS





REMOVE the ICV filter when no longer needed!!!

Why wouldn't every patient with a DVT get one of these amazing devices inserted?

Placement is invasive and complications are a concern

There is no strong evidence that anticoagulation PLUS an IVF filter is better that anticoagulation alone

The filter works quite well in the short term, but that as time passes clots start to build up around and on top of the filter potentially embolizing to the heart/lungs. The filter can also migrate.

ADJUNCTIVE THERAPY: THROMBECTOMY/EMBOLECTOMY

A **mechanical device** designed to **remove clots** from the veins quickly to aid restoration of normal venous flow, reduce symptoms, and prevent post-thrombotic syndrome

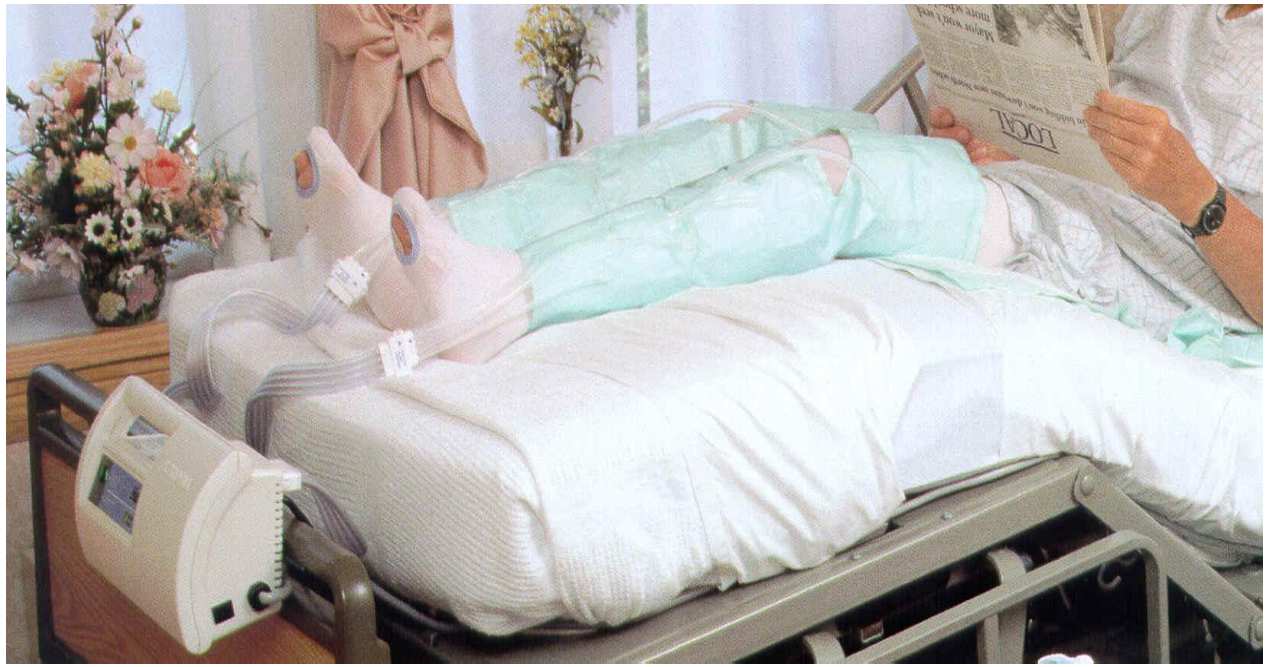
Indicated in patients with **hemodynamically unstable PE in whom thrombolytic therapy is contraindicated** or as a therapeutic option **in those who fail thrombolysis or did not received thrombolysis because they were high risk for bleeding**

Surgical embolectomy is an option if the catheter directed method fails

VTE: PROPHYLACTIC MEASURES

Early ambulation is a helpful VTE deterrent as well

Intermittent pneumatic compression (**IPCs**), thromboembolic deterrent (**TED**) hose, or graduated compression stocking (**GCS**) can be used alone or in combination with drugs (usually LMWH) for DVT prophylaxis in hospitalized patients



IPCs

Mechanical methods for prophylaxis

Sometimes called SCDs (sequential compression device)

INPATIENT OR OUTPATIENT TREATMENT

- Traditionally, **most every patient with a DVT and ALL patients with PE** were **admitted** to the hospital to **begin anticoagulant therapy** and for **clinical monitoring**
  - Disposition is based on provider, patient, facility and even geographic location

- To consider **discharge**…..At **minimum** patients **must**:
  - Be hemodynamically stable!
  - Have their pain controlled
  - Can obtain anticoagulants
  - Be motivated and capable of administering injections (if prescribing a SQ anticoagulant)
  - Be compliant and reliable

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