# Venous Thromboembolism and Pulmonary Embolism

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# Disclosures

- None

# Objectives

- Recognize patients at risk for and the signs and symptoms of VTE/PE
- Determine the right diagnostic test for the right patient
- Identify patients at risk for high morbidity/mortality
- Select the optimal treatment and duration for all patients

# Antithrombotic Therapy for VTE Disease

## CHEST Guideline and Expert Panel Report

*Clive Kearon, MD, PhD; Elie A. Akl, MD, MPH, PhD; Joseph Ornelas, PhD; Allen Blaivas, DO, FCCP; David Jimenez, MD, PhD, FCCP; Henri Bounameaux, MD; Menno Huisman, MD, PhD; Christopher S. King, MD, FCCP; Timothy A. Morris, MD, FCCP; Namita Sood, MD, FCCP; Scott M. Stevens, MD; Janine R. E. Vintch, MD, FCCP; Philip Wells, MD; Scott C. Woller, MD; and COL Lisa Moores, MD, FCCP*

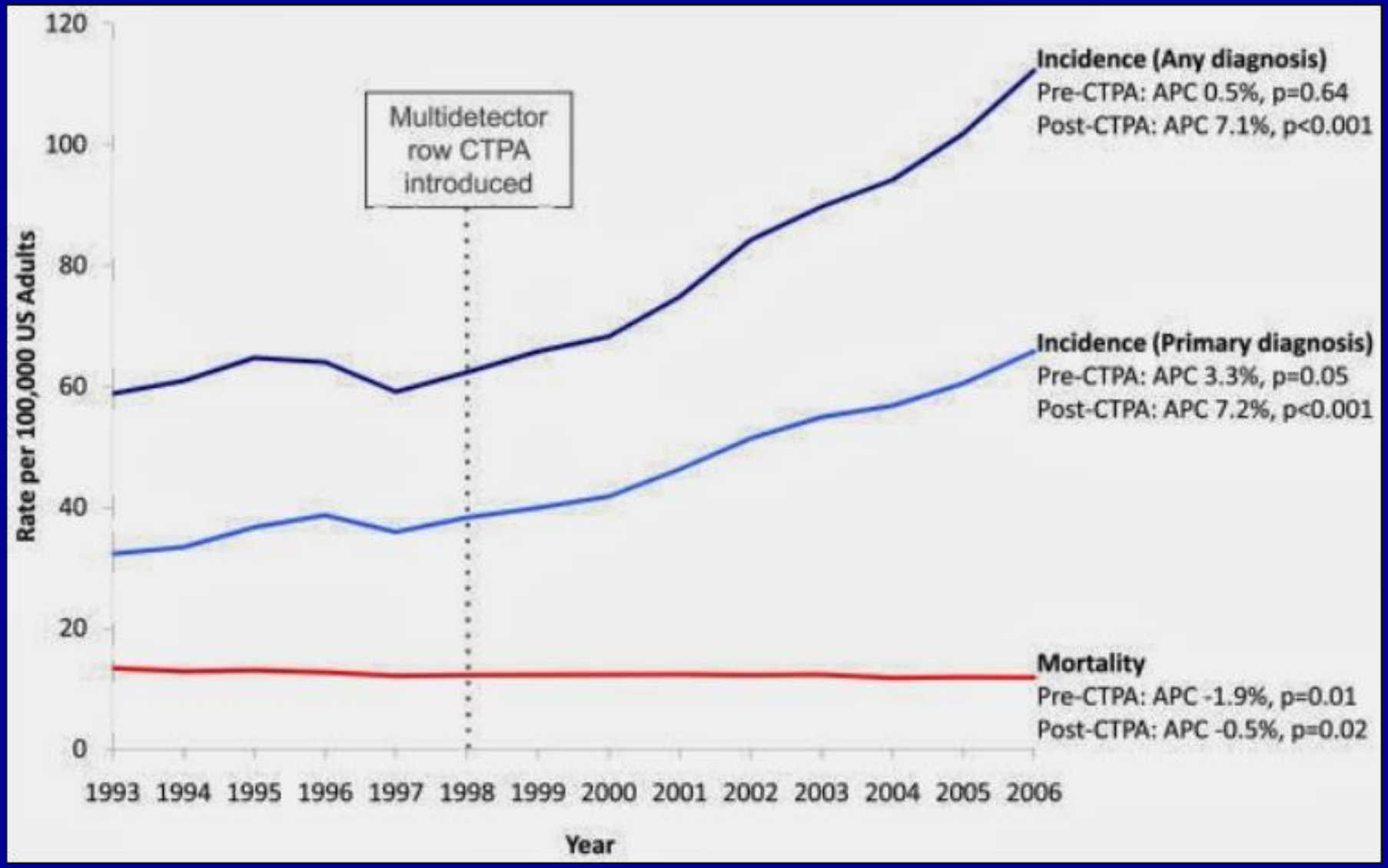
PODCAST

**BACKGROUND:** We update recommendations on 12 topics that were in the 9th edition of these guidelines, and address 3 new topics.

**METHODS:** We generate strong (Grade 1) and weak (Grade 2) recommendations based on high- (Grade A), moderate- (Grade B), and low- (Grade C) quality evidence.

# PE Epidemiology

- Incidence climbing w/ advent of D-dimer and CTA
  - 62/100k 1993-1998, 112/100k after
  - Outcomes have not improved
- Increases with age, Men more than women
- 100k deaths/year in US
  - Most were hospital-acquired


120
100
80
60
40
20
0
Rate per 100,000 US Adults
Multidetector row CTPA introduced
Incidence (Any diagnosis)
Pre-CTPA: APC 0.5%, p=0.64
Post-CTPA: APC 7.1%, p<0.001
Incidence (Primary diagnosis)
Pre-CTPA: APC 3.3%, p=0.05
Post-CTPA: APC 7.2%, p<0.001
Mortality
Pre-CTPA: APC -1.9%, p=0.01
Post-CTPA: APC -0.5%, p=0.02
1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006
Year

# Pathophysiology

- Virchow's triad
- Generally arise from large LE veins
- 10% can cause infarction
- Local inflammation and direct obstruction causes VQ mismatch and hypoxemia
- Hemodynamic compromise when significant obstruction occurs

# History and Physical

- Sometimes difficult to diagnose
- Nonspecific Symptoms
  - Shortness of breath, chest pain, cough
  - LE swelling, pain, erythema
  - Infrequently hemoptysis, hemodynamic compromise
  - Asymptomatic
- Tachypnea, tachycardia, accentuated P2, crackles, DVT sxs, rarely fever

# Risk Factors

- Immobility, Surgery, Hospitalization, Infection, Cancer
- Meds: Estrogen, Testosterone, Antidepressants, Steroids
- Antiphospholipid antibody syndrome
- Renal Disease
- Inherited thrombophilias
- Smoking
- Pregnancy
- Obesity

# Board Review

- A 61yo man w/o significant past medical history in the ED c/o worsening mild left calf pain for 10d. ROS otherwise negative, not on medications.

- On exam, Temp 37.2 °C, BP 132/82, HR 75, RR 16 SpO2 98% on RA. BMI is 32. Mild to moderately deep palpation of the calf muscles provokes diffuse discomfort. The left leg is not discolored, non edematous, but it feels slightly fuller than the right and is 1 cm larger.

Which of the following is the most appropriate management?

A. Testing is for sissies, start 3m Pradaxa, Eliquis, and Xarelto

B. D-dimer

C. Duplex

D. Venogram. Venograms for everyone.

# 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 |

*Adapted from:*


1. *Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. Lancet 1997; 350:1795*
2. *Wells PS, Anderson,DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med 2003; 349:1227.*

## *Table 1.* Pulmonary Embolism Rule-Out Criteria for Predicting Probability of Pulmonary Embolism in Patients With Low Pretest Probability*

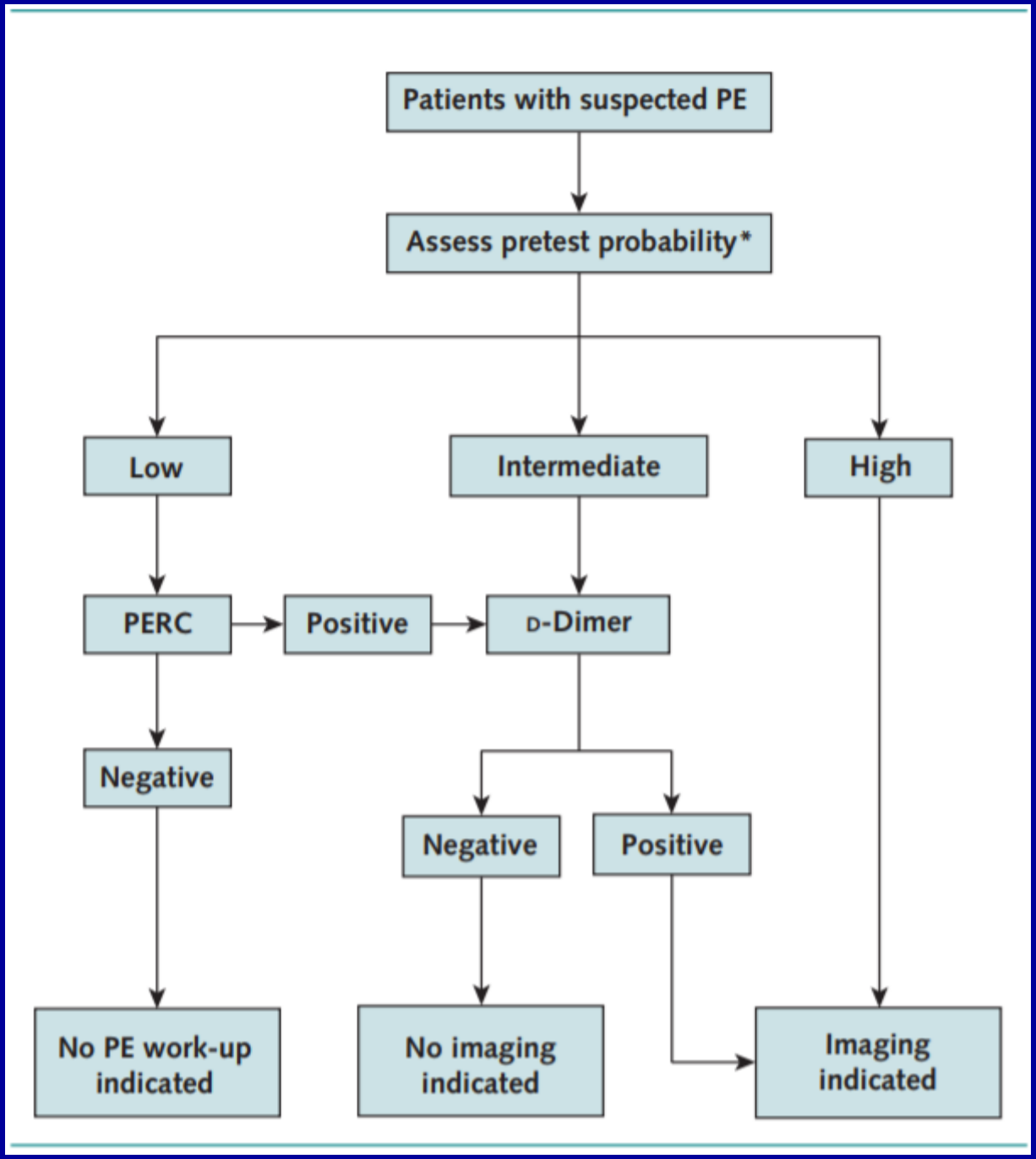
| Clinical Characteristic | Meets Criterion | Does Not Meet Criterion |
|---|---|---|
| Age <50 y | 0 | 1 |
| Initial heart rate <100 beats/min | 0 | 1 |
| Initial oxygen saturation >94% on room air | 0 | 1 |
| No unilateral leg swelling | 0 | 1 |
| No hemoptysis | 0 | 1 |
| No surgery or trauma within 4 wk | 0 | 1 |
| No history of venous thromboembolism | 0 | 1 |
| No estrogen use | 0 | 1 |
| | Pretest probability with score of 0 is <1% | |

Kline JA, et al. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. J Thromb Haemost 2008; 6:772.

# Choose Wisely

- Low risk patients meeting all 8 PERC criteria
  - Low risk = 0 points or less on Wells
  - Not a PE
  - Do not check D-dimer
  - Do not image

- Age-adjusted D-dimer adequate on low-risk PERC +, and intermediate-risk patients
  - Intermediate risk = 1-2 on Wells


Patients with suspected PE
Assess pretest probability*
Low
Intermediate
High
PERC
Positive
D-Dimer
Negative
Negative
Positive
No PE work-up indicated
No imaging indicated
Imaging indicated

# Acute DVT or PE!

**1. In patients with proximal DVT or pulmonary embolism (PE), we recommend long-term (3 months) anticoagulant therapy over no such therapy** (Grade 1B).

***2. In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy** (all Grade 2B).

***3. In patients with DVT of the leg or PE and cancer ("cancer-associated thrombosis"), as long-term (first 3 months) anticoagulant therapy, we suggest LMWH over VKA therapy** (Grade 2B), **dabigatran** (Grade 2C), **rivaroxaban** (Grade 2C), **apixaban** (Grade 2C), **or edoxaban** (Grade 2C).

Kearon C, et al. Antithrombotic therapy for VTE Disease CHEST guideline and expert panel report. CHEST 2016; 149(2):315-352

- Catheter-directed thrombolysis can, and should, be considered
- Compression stockings to prevent PTS are no longer recommended

# Distal DVT

- Serial US is recommended for isolated acute distal DVT for two weeks
  - Popliteal is proximal

- Anticoagulate those at risk for extension
  - Positive D-dimer, involves multiple veins or is 5cm in length or 7mm in diameter, unprovoked, malignancy, recurrent, inpatient, “close to proximal”

# Subsegmental PE

- Clinical surveillance is suggested if:
  - No proximal DVT
    - Weekly US for two weeks recommended
  - Low risk for recurrence
  - High risk patients:
    - Hospitalized, immobile, malignancy, unprovoked
  - High risk for bleeding

- Recommendation seems to depend on the confidence in the dx
  - Quality of the study, sxs, multiple defects, proximal extension

# More Board Review

- 61yo man follows up after an unprovoked proximal DVT 3 months ago. He has been managed appropriately on apixiban since the event. He has mild left leg discomfort after a long day of standing, but it is not limiting. He has no prior personal or family history of VTE. Social history is unremarkable. HAS-BLED is 0.
- Other than minimal Left leg edema and post-thrombotic pigmentation, his physical is unremarkable.

Which of the following is the most appropriate management?

A. Continue anticoagulation indefinitely
B. DC anticoagulation in another 3 months
C. DC AC
D. DC warfarin, start thrombophilia workup

# Unprovoked DVT or PE

**9. In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a (i) low or moderate bleeding risk (see text), we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy** (Grade 2B), **and (ii) high bleeding risk (see text), we recommend 3 months of anticoagulant therapy over extended therapy (no scheduled stop date)** (Grade 1B).

Kearon C, et al. Antithrombotic therapy for VTE Disease CHEST guideline and expert panel report. CHEST 2016; 149(2):315-352

# Recurrence

**Rate of venous thromboembolism (VTE) recurrence**

| VTE type | First year | Annual rate after first year |
|---|---|---|
| First episode of unprovoked VTE | 10 percent | 5 percent |
| Second episode of unprovoked VTE | 15 percent | 7.5 percent |
| First VTE provoked by surgery | 1 percent | 0.5 percent |
| First VTE provoked by non-surgical factor | 5 percent | 2.5 percent |

**Rate of bleeding stratified by risk in patients with venous thromboembolism (VTE) on anticoagulation**

| Bleeding risk | First 3 months | Annual rate after first 3 months |
|---|---|---|
| Low risk (no risk factors present) | 1.6 percent | 0.8 percent |
| Intermediate risk (one risk factor present) | 3.2 percent | 1.3 percent |
| High risk (two or more risk factors present) | 12.8 percent | ≥6.5 percent |

Kearon C et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141:e419S.

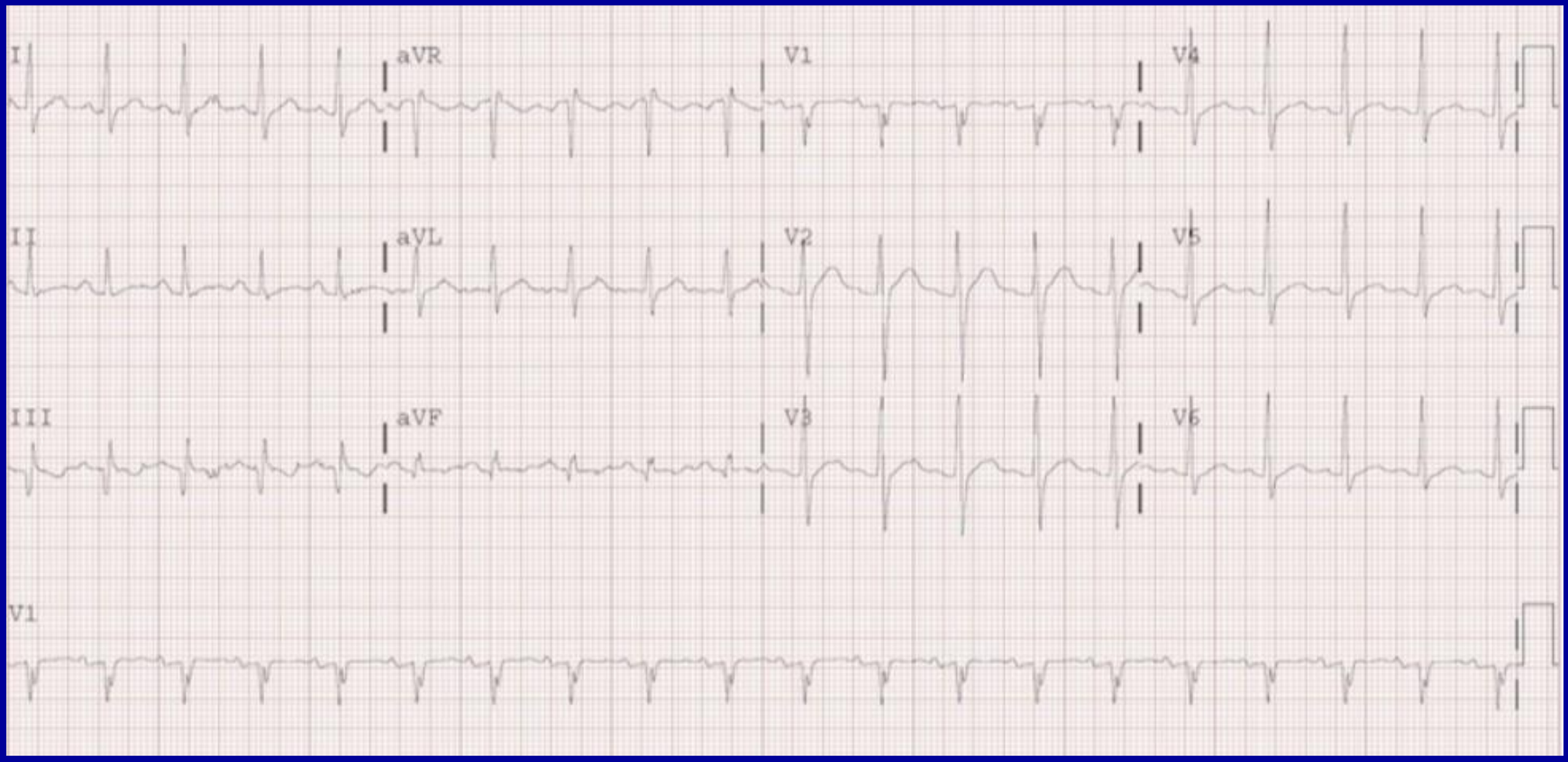
# Extended Therapy

- Recurrence in unprovoked is quite high
  - Increased risk in men, those w/ + D-dimer
- Strongly consider indefinite anticoagulation in patients at low-intermediate risk for bleeding
- Consider Aspirin in those who decline therapeutic anticoagulation (30% v 90% RRR)

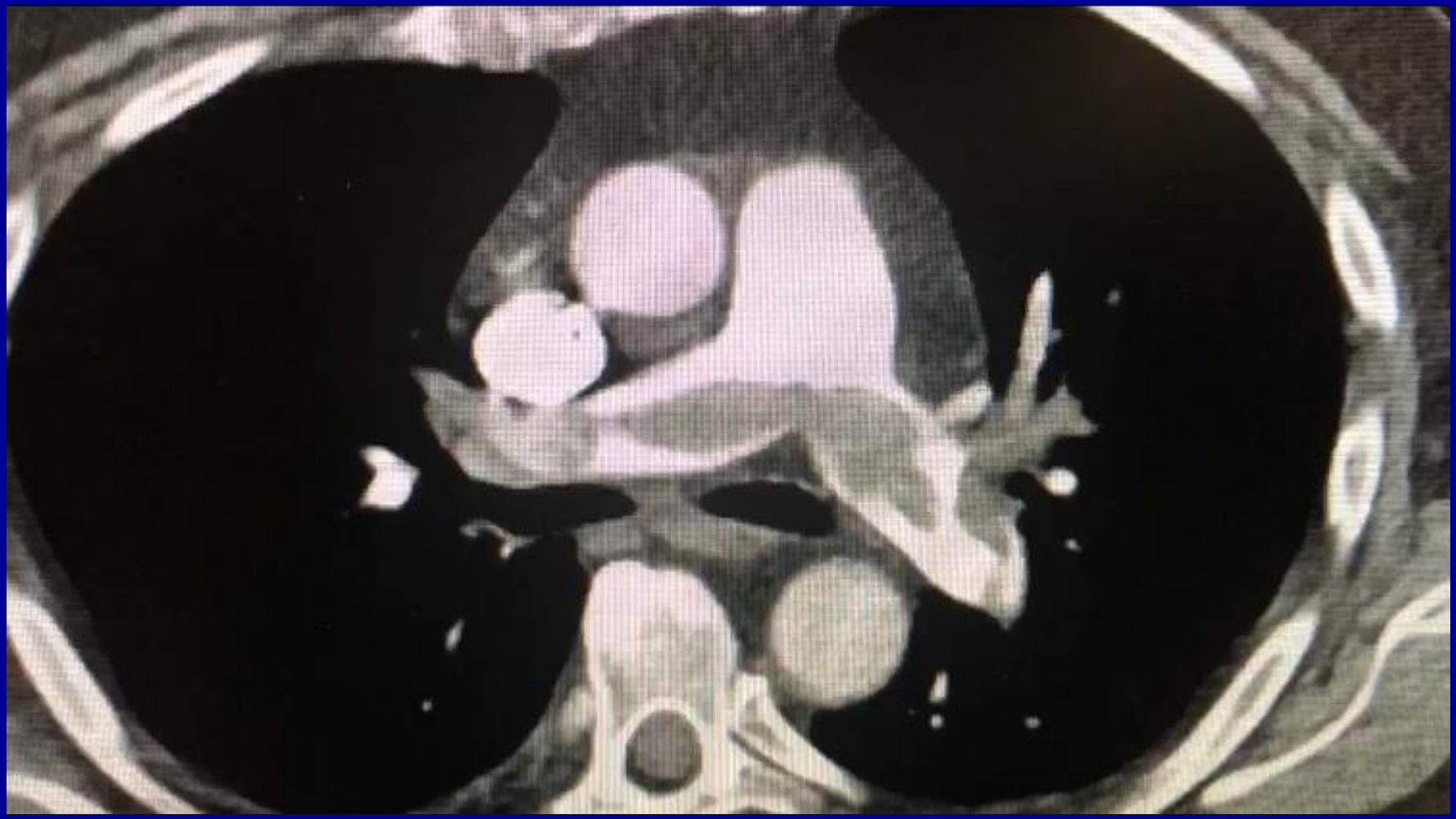
# Even MORE Board Review

- 76yo man receiving palliative radiotherapy w/ a remote history of ischemic CVA presents to the ER c/o acute shortness of breath and pleuritic chest pain
- Tm 37.6, HR 115, BP 105/65, RR 24, SpO2 95% on 4L NC, Wt 90kg
- Breath sounds are clear, there is a RV heave, a soft S3, and right leg swelling.
- Troponin and BNP are mildly elevated.
- Normal renal function

# EKG



# CTA



# What now?

- A. 100mg IV tPA, then heparin gtt
- B. 100mg IV tPA, then 90mg enoxaparin q12h
- C. IVC insertion
- D. Enoxaparin 90mg q12h

# Low Risk

- Hemodynamically stable
- No signs of RV dysfunction
- Size is irrelevant
- Should be managed as an outpatient

# Outpatient Treatment of Low Risk Patients

**Table 1. Original and Simplified Pulmonary Embolism Severity Index (PESI)**

| Variable | Score: Original PESI[a] | Score: Simplified PESI[b] |
|---|---|---|
| Age >80 y | Age in years | 1 |
| Male sex | +10 | |
| History of cancer | +30 | 1 |
| History of heart failure | +10 | 1[c] |
| History of chronic lung disease | +10 | |
| Pulse ≥110 beats/min | +20 | 1 |
| Systolic blood pressure <100 mm Hg | +30 | 1 |
| Respiratory rate ≥30 breaths/min | +20 | |
| Temperature <36°C | +20 | |
| Altered mental status | +60 | |
| Arterial oxyhemoglobin saturation level <90% | +20 | 1 |

| | |
|---|---|
| **Class I:≤65 points**<br>very low 30-day mortality risk (0–1.6%) | **0 points**= 30-day mortality risk 1.0% (95% CI 0.0%–2.1%) |
| **Class II: 66–85 points**<br>low mortality risk (1.7–3.5%) | |
| **Class III: 86–105 points**<br>moderate mortality risk (3.2–7.1%) | **≥1 point(s)**= 30-day mortality risk 10.9% (95% CI 8.5%–13.2%) |
| **Class IV: 106–125 points**<br>high mortality risk (4.0–11.4%) | |
| **Class V: >125 points**<br>very high mortality risk (10.0–24.5%) | |

- Those w/ scores less than 86 (old PESI) or 1 (simplified) had 3% 30d mortality

# Intermediate Risk

- Again, size doesn't matter
- Hemodynamically stable
- Signs of RV dysfunction
  - Echo
  - Troponin, BNP
  - EKG
- Extent of PE
- AC +/- adjunctive therapies
  - Systemic, "half-dose", and catheter-directed thrombolysis

# High Risk (Unstable) Massive PE

- Hemodynamically unstable
  - Systolic BP < 90 OR a <40 below baseline for 15 minutes
  - Requires vasopressor/inotropic support
- Not explained by other causes
- Often, but not always causes by large PEs
- High risk of death for 72h
- Treat w/ thrombolytics--individualized

# Reasons NOT to Give tPA

| Absolute Contraindications | Relative Contraindications |
|---|---|
| Intracranial anatomical pathology (mass, arteriovenous malformation) | Uncontrolled hypertension (systolic BP >180 mm Hg; diastolic BP >110 mm Hg) |
| Ischemic stroke within previous 3 months | Age >75 years |
| History of hemorrhagic stroke (ever) | GI or genitourinary hemorrhage in the previous 30 days |
| Brain or spinal surgery in the previous 3 months | Actively on anticoagulation or coagulopathic |
| Active bleeding | Major surgery within the previous 3 weeks |
| Known bleeding diathesis | Ischemic stroke >3 months ago |
| | Traumatic CPR within previous 3 weeks |
| | Pregnancy |
| | Diabetic retinopathy |
| | Pericarditis or pericardial fluid |

# DOAC Dosing Strategies

| | Initial Phase | Long-Term | Extended | Not recommended |
|---|---|---|---|---|
| Rivaroxaban | 15 mg BID | 20 mg QD | 20 mg QD | CrCl<30<br>Hepatic impairment<br>Combined P-gp and CYP3A4 inhibitors or inducers |
| Dabigatran | 150 mg BID* | 150 mg BID | 150 mg BID | CrCl <30<br>P-gp inhibitors or inducers and CrCl <50 |
| Apixaban | 10 MG BID for 7 days | 5 mg BID | 2.5 mg BID | CrCl <15<br>Severe hepatic impairment<br>CYP3A4 and P-gp |
| Edoxaban | 60 mg QD* | 60 mg QD | 60 mg QD | CrCl <15<br>Hepatic impairment<br>Concomitant rifampin |

* Overalpped with parenteral anticoagulation for 5-10 days

# Warfarin Dosing Strategy

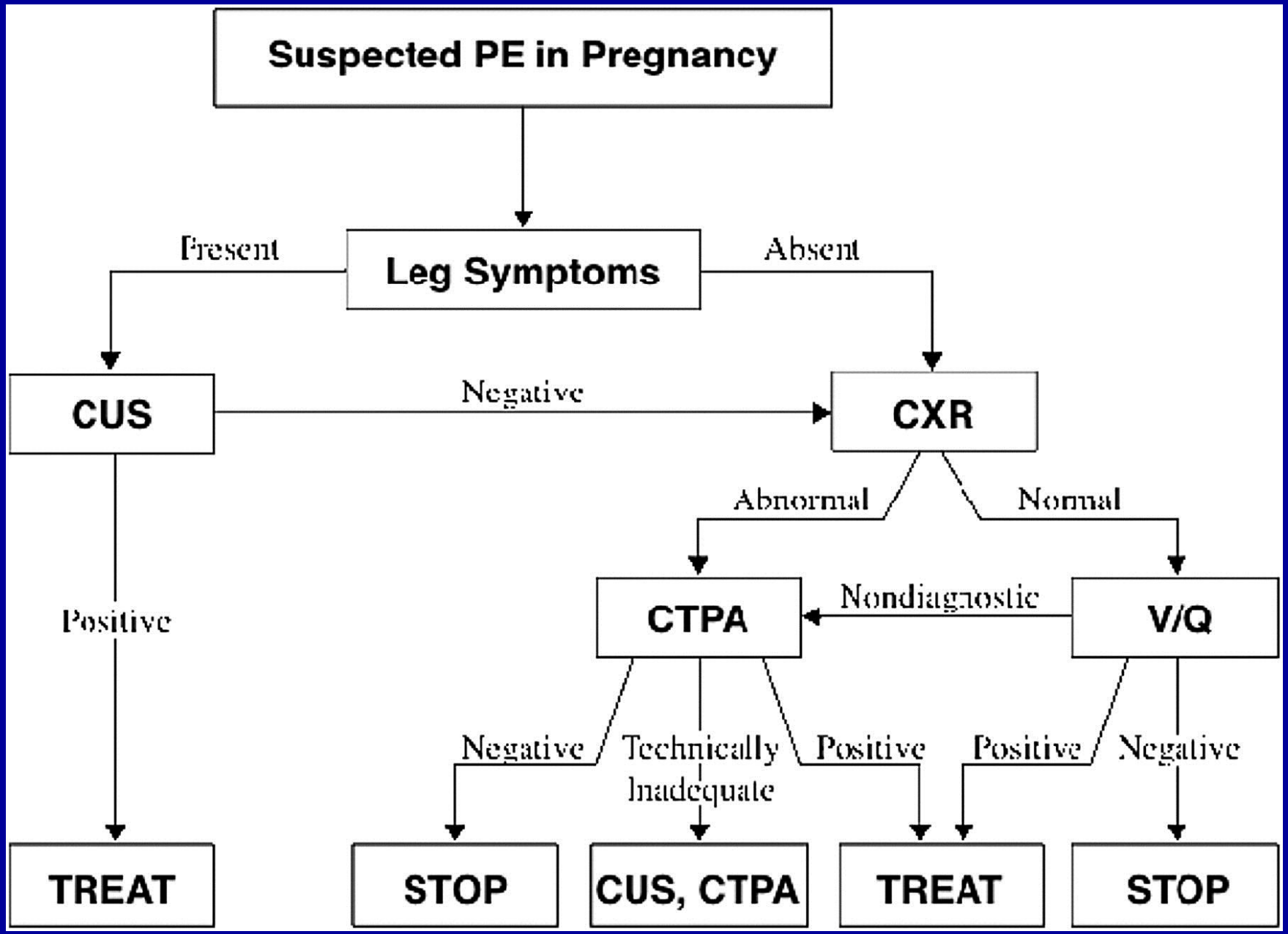
- Warfarin + LMWH/heparin for at least five days and the INR is above the minimum goal for at least 2 consecutive days

# Reversal Agents

- Warfarin: PCC, FFP + Vit K
- Xa Inhibitors: ~~Andexanet alpha~~ (Andexxa), PCC
- Dabigatran: ~~idarucizumab~~ (Praxbind), PCC, hemodialysis
- Adjuncts: Tranexamic acid, aminocaproic acid, activated charcoal if dosed recently

# Diagnosing PE in Pregnancy

- Presentation more difficult due to nonspecific sxs
- Concern regarding radiation exposure
  - Relatively low risk
  - 20-30% maternal mortality in untreated PE
  - VQ Scan not necessarily less radiation
- Studies actually suggest CTPA is either equivalent, perhaps INFERIOR in pregnancy
- Practical considerations—don't delay




Leung AN. An official American Thoracic Society/Society of Thoracic Radiology clinical practice guideline: evaluation of suspected pulmonary embolism in pregnancy. Am J Respir Crit Care Med. 2011 Nov 15;184(10):1200-8.

# Treating PE in Pregnancy

- LMWH is preferred Rx for at least three months but should persist for the duration of pregnancy
- AC should continue at least 6 weeks postpartum
- Warfarin ok after delivery
- Thrombolytics ok in life-threatening bleed, thrombectomy for rescue

# Follow-Up

- Determine if OK to stop AC
  - Assess risk for recurrence, bleeding
  - Consider thrombophilia testing here
    - Very rarely will this effect decision for anticoagulation
- 3-6 month TTE for those w/ high or intermediate-risk PE

# Group IV PH--CTEPH

- 1-5% of acute PEs
- Especially w/ dyspnea on exertion
- VQ Scan to confirm chronicity
- RHC to dx (Exercise?)
- Treat with Thromboembolectomy
  - Balloon angioplasty at centers with appropriate clinical trials
  - Riociguat for others

# IVC filters

- ONLY recommended when traditional AC is contraindicated or ineffective

- Can be considered if further insult would likely be fatal
  - Should be temporary in this setting

# UE DVT

- Primary = Paget-Schroetter Syndrome
  - Anticoagulation, CDT, and Surgical decompression all options
- Secondary = Iatrogenic
  - Very common, nearly 20% of CVC
  - Anticoagulate just like LE DVT
- Lower risk of PE
- Risk of Post-Thrombotic Syndrome considerable
  - Consider CDT despite 9% risk of major bleed

# Summary

- DVT/PE can be difficult to recognize, but scoring systems can help when they are suspected
- Prediction models and D-dimer can help prevent unnecessary imaging in low and moderate probability patients
- Guidelines are guidelines, treat each patient based on their risks and preferences

# References


- Kearon C, et al. Antithrombotic therapy for VTE Disease CHEST guideline and expert panel report. CHEST 2016; 149(2):315-352
- Raja AS, et al. Evaluation of patients with suspected acute pulmonary embolism: Best advice from teh clinical guidelines committee of the American college of physicians. Ann Intern Med. 2015;163:701-711.
- Kline JA, et al. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. J Thromb Haemost 2008; 6:772.
- Zhou XY, et al. The prognostic value of pulmonary embolism severity index in acute pulmonary embolism: a meta-analysis. Respir Res. 2012 Dec 4;13:111.
- Leung AN. An official American Thoracic Society/Society of Thoracic Radiology clinical practice guideline: evaluation of suspected pulmonary embolism in pregnancy. Am J Respir Crit Care Med. 2011 Nov 15;184(10):1200-8.
- Saint-Pierre M, Hockmann K, Arsigny CD. Follow-up of hospitalized patients with acute pulmonary embolism and documented pulmonary hypertension: A retrospective review. CHEST 2016; 150(4):1156A

Questions?