Pulmonary Embolus & Deep Vein Thrombosis: The New Frontier

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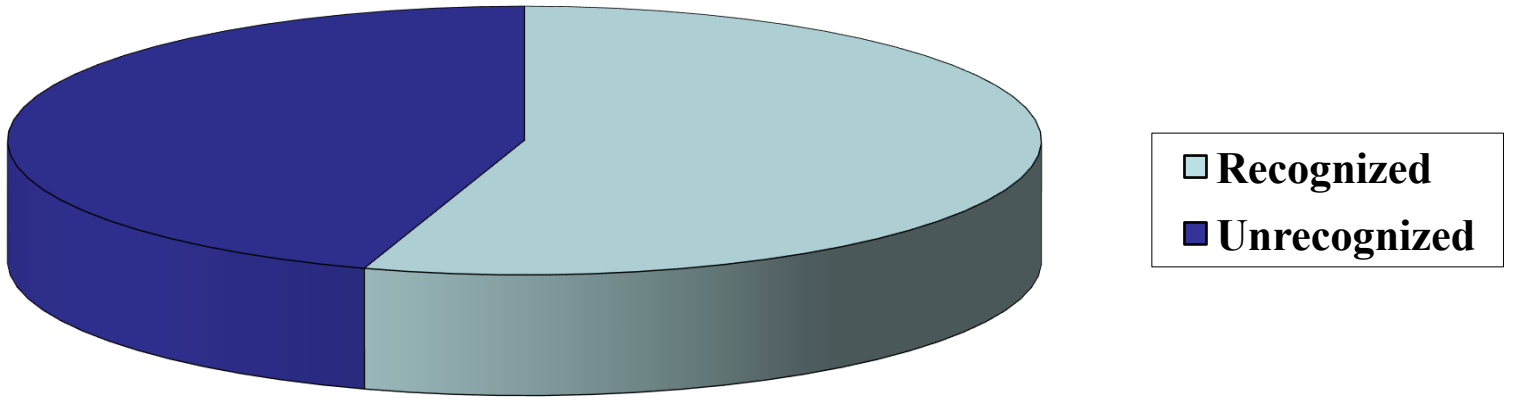
AMERICAN ACADEMY OF FAMILY PHYSICIANS

STRONG MEDICINE FOR AMERICA

Prevalence of VTE



Total > 500,000 cases/yr of DVT

5-10% of all hospital deaths/year from PE

VIRCHOW's TRIAD

- Circulatory STASIS:

  immobility, CHF, advanced age, obesity and venous obstruction

- Endothelial Injury (TRAUMA):

  surgery (e.g., orthopedic), postpartum, infections & valve damage

- HYPERCOAGULABLE state:

  Factor V Leiden, oral contraceptives, cancer, deficiencies of protein C&S or ATIII , homocysteine, impaired fibrinolysis

VTE Prophylaxis

Thromboprophylaxis in Surgical Patients: ACCP Risk Classification

- Low Risk (<10%)
  - Minor surgery
  - Medical pt's who are mobile
- Moderate Risk (10-40%)
  - Most surgery
  - Medical pt's who are bed rest/sick
- High Risk (40-80%)
  - Hip/knee arthroplasty
  - History of VTE
  - **Hip or total joint procedures**
  - Spinal cord injury; major trauma

Thromboprophylaxis in Surgical Patients

- Low risk: No prophylaxis
- Moderate risk: LDUH (5,000 U bid) or LMWH
- High risk: LMWH or Warfarin or Fondaparinux or Novel anticoagulants **+** IPC

Thromboprophylaxis in Knee/Hip Orthopedic Surgical Patients

- Low molecular weight heparin (LMWH)
- Warfarin, rx 2 days prior to surgery or immediately post surgery (INR 2.0-3.0)
- Fondaparinux 2.5 mg daily
- Novel anticoagulant – Dabigatran 220 mg daily, Rivaroxaban 10 mg daily, Apixaban 2.5 mg BID, Edoxaban 30 mg daily {post surgery}
- Length of tx – Hip (28–35 days) & Knee (10-12 days)
- Intermittent pneumatic compression is only an **adjuvant therapy**
- Low dose unfractionated heparin is ***inadequate***.

Prevention during travel

- ~~ASA~~
- Vitamin E
- LMWH
- Below knee compression stocking

- Recommended: Moving frequently, loose clothing and hydration

Deep Vein Thrombosis (DVT)

DVT: Signs and symptoms

- Unilateral Swelling
- Pain
- Erythema or warmth
- Palpable cords
- Homan sign

DVT - Deep Vein Thrombosis

- **PROXIMAL**

  *Any vein from the popliteal v. and up

  *Larger clot

  *High propensity to embolize (40-60%)

  *REMEMBER: Superficial femoral v is a deep v. - do tx.

- **DISTAL**

  *Below popliteal v.

  *Smaller clot

  *Less symptomatic and less likely to cz PE

  *Can propagate up to the proximal v.

Pretest probability of DVT

Active cancer	1
Paralysis, paresis or immobilization	1
Recently bedridden for > 3 days or major surgery within 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swollen by **> 3 cm** when compared to asymptomatic leg	1
Pitting edema	1
Collateral superficial veins	1
Alternative diagnosis greater than DVT	- 2

Low – Zero or less → 3% probability
Moderate -- 1-2 → 17%
High -- 3 or more → 75%

Case Study

- B.V. is a 35 y/o Caucasian gentleman who comes to the ER with left leg pain and swelling for 3 days and recent chest pain. Denies any insect bite, fall or trauma. Denies any shortness of breath, long travel, or previous surgical procedure.
- PMH: None. Denies any history of DM or cancer.
- FH: Denies any history of DVT or PE.
- PE: Afebrile, B/P 110/70, P = 100, R= 30. Normal exam except asymmetric thigh/leg size, mild tenderness on palpation, & unilateral pitting edema. No palpable chords, negative Homan's sign and nonerythematous.

What is the pretest clinical probability score for DVT?

A. 1
B. 2
C. 3
D. 4
E. 6

Role of D-dimer in DVT

- Prospective cohort study in Canada. 556 patients with suspected first DVT divided into two groups :

  negative D-dimer vs positive D-dimer
- Endpoint: Negative D-dimer assay with low or moderate pretest probability eliminates further testing
- Results
  - 1/283 (0.3%) vs 34/168 (16.8%) * on low/mod pretest prob
  - 0/20 (0.0%) vs 21/51 (41.2%) on high pretest probability
- Conclusion: Negative D-dimer with a low or moderate pretest probability safely eliminates the need for ultrasound

Summary

- High probability
  - Duplex U/S
    - Positive – TREAT
    - Negative - consider venography
      - » Positive – TREAT
      - » Negative – DVT r/o
- Intermediate probability
  - D-dimer
    - Positive - do U/S
      - Positive – Treat & consider venography or repeat U/S in 1 wk
      - Negative – DVT r/o
    - Negative – DVT r/o
- Low probability
  - D-dimer
    - Positive - do U/S
      - Positive – Treat & consider venography or repeat U/S in 1 wk
      - Negative – DVT r/o
    - Negative – DVT r/o

Complications

- pulmonary embolus
- postthrombotic syndrome
- phlegmasia alba dolens
- phlegmasia cerulean dolens

Pulmonary Embolus

Pulmonary Embolus: Signs & Symptoms

- Tachypnea (70% of patients)
- Chest pain (70%)
- Cough (40%)
- Tachycardia (33%)
- Shortness of breath (25%)
- Signs of DVT (10%)
- Syncope (5%)

Chest 1995; 107(suppl):25S-32S.

Pretest Probability of PE

• Clinical signs and symptoms of DVT	• 3 points
• An alternative diagnosis is less likely than PE	• 3 points
• Heart rate > 100	• 1.5 points
• Immobilization or surgery in previous 4 weeks	• 1.5 points
• Previous DVT/PE	• 1.5 points
• Hemoptysis	• 1 point
• Malignancy	• 1 point

Low – Less than 2 points → 3% probability
Moderate -- 2 – 6 points → 28%
High -- > 6 points → 78%

Wells PS, et al. Thromb Haemost 2000;83:416-20.

Case Study

- RS, a 65 y/o WF comes in with acute shortness of breath for the last 2-3 days. Denies any cough, hemoptysis, fever, or vomiting. Has h/o of hypercholesterelemia & DM type 2 for 10 years, otherwise negative PMH. FH was noncontributory. Vitals, BP 125/85, P=120, R=24. Physical was normal except an asymmetric leg swelling R>L and tenderness.

  Meds: Glucophage, Zestril, Estrogen, & Lipitor

What is the pretest clinical probability of PE?

A. 1.5
B. 3.0
C. 4.5
D. 6.0
E. 7.5

Basic tests

- CXR - normal in 50%
  - Hampton's hump (wedge shape consolidation)
  - Others: elevated diaphragm, pleural effusion, infiltrate, atelectasis.
- EKG
  - S1Q3T3 (pathognomonic) rarely seen.
  - Others: sinus tach, T wave inv on V1 to V4, acute RBBB, new onset a-fib, RV strain.
- ABG
  - Usually decreased PaO2 and PaCO2, and increased pH
  - Increase A-a gradient (150 - PaCO2/0.8 - PaO2)

VQ Scan

VQ Scan probability

Index of suspicion	High	Inter-mediate	Low	Normal
High	28/29 96%	27/41 66%	6/15 37%	0/5 0%
Low	5/9 56%	11/68 16%	4/90 4%	1/61 2%

The PIOPED Investigators. JAMA 1990;263:2753-2759.

Spiral CT

- **"The Good"**
  - Highly sensitive for central vessels
  - Can differentiate between acute vs chronic clot
  - Quick test (done in 30 sec and single breath)
  - May give clues to alternative diagnosis (67%)
- **"The Bad"**
  - Cost
  - Uses contrast: contraindicated in RI &/or history of contrast allergy
- **"The Ugly"**
  - Lower sensitivity for subsegmental vessels
  - Shunt, eg., patent foramen ovale

Remy-Jardin M, et al. Radiology 1992; 185:381-387.
Remy-Jardin M, et al. J Thoracic Imaging 1997; 12:103-117.

D-dimer: "An old timer"

- Several types of assays
  - Latex agglutination (LA)
  - Enzyme-linked immunosorbent assays (ELISA)
- *Advantages*
  - High negative predictive value - especially the ELISA test 91-100%
- *Disadvantages*
  - High false positive rate, ranges from 9 - 15%
  - Low specificity - especially in elderly over 80 y/o

Pulmonary Angiogram: "Mr. Right"

- High sensitivity - 98%
- High specificity - 97%
- *Advantages*
  - May perform adjunctive procedures, eg., local catheter-directed thrombolysis, suction thrombectomy, IVC filter placement
  - Can differentiate acute vs chronic PE
- *Disadvantages*
  - Invasive (risk: death - 0.5%, morbidity - 1%)
  - Contrast allergy patients and RI

The PIOPED Investigators. JAMA 1990; 263:2753-2759.
Stein PD, et al. Circulation 1992; 85:462-468.

Mortality Risk - Simplified PESI

- 995 outpatients with objectively confirmed acute symptomatic PE, validation cohort of 7,106 patients with acute symptomatic PE
- 7 factors
  - aged > 80 years old
  - history of cancer
  - history of chronic lung disease or heart failure
  - pulse ≥ 110 beats per minute
  - systolic blood pressure (SBP) < 100 mm Hg
  - arterial oxyhemoglobin saturation level < 90%
- 30-day mortality risk stratified by simplified PESI score
  - score = 0 for low-risk
  - score ≥ 1 for high-risk
- 30-day mortality in validation cohort
  - 1.1% of 2,569 patients classified as low risk (98.9% NPV)
  - 8.9% of 4,537 patients classified as high risk

Anticoagulation

UF-Heparin

- MW = 35-50,000 Kd
- Poor bioavailability due to binding to proteins
- Targets Xa, ATIII, & thrombin
- Needs regular lab monitoring - Q 6 hrs
- Rapid plasma clearance
- Needs platelet, H/H monitoring

LMWH

- MW = 5-10,000 Kd
- Good bioavailability., little binding to proteins
- Targets Xa & ATIII only
- No lab monitoring needed, except in obese (>110 kg) or renal disease
- Slow plasma clearance
- Needs platelet, H/H monitoring

Pentasaccharides

- Mode of mechanism: Inhibits factor Xa only
- Indicated for VTE prophylaxis and treatment
- VTE treatment (dose varies with weight)
  - < 50 kg --- 5.0 mg SC
  - > 50 to 100 kg --- 7.5 mg SC
  - >100 kg --- 10.0 mg SC
- Monitor platelets frequently
- Caution in pts with RI (CrCl < 30 mL /min)
- Caution in underweight pts (< 45 kg)

EPHESUS and PENTATHLON study, 2000

RECOVER

- 2,564 patients (mean age 55 years) with acute symptomatic VTE and normal renal function randomized to dabigatran 150 mg orally twice daily plus warfarin-like placebo vs. warfarin plus dabigatran-like placebo for 6 months
  - all patients initially given parenteral anticoagulation therapy for median 9 days
  - primary outcome was time to first occurrence of composite of symptomatic VTE or VTE-related death
  - comparing dabigatran vs. warfarin
    - symptomatic VTE or VTE-related death at 6 months in 2.3% vs. 2.2% (noninferiority met)
    - any death in 1.6% vs. 1.7% (not significant)
    - major bleeding episodes in 1.6% vs. 1.9% (not significant)
    - any bleeding episodes in 16.1% vs. 21.9% ($p < 0.05$, NNT 18)
  - no significant differences in acute coronary syndromes or abnormal liver function tests
  - Reference - RE-COVER trial N Engl J Med 2009 Dec 10;361(24):2342

EINSTEIN

- 3,449 patients with acute symptomatic DVT randomized to rivaroxaban (15 mg po BID for 3 wks then 20 mg daily) vs standard therapy (enoxaparin SubQ + warfarin)
- Results:
  - Early treatment discontinuation 11.3% v 14.2% (p=0.01)
  - Symptomatic recurrent VTE 2.1% v 3% (HR 0.68, CI 0.44-1.04
  - Major bleeding 0.8% v 1.2% (NS)

EINSTEIN Investigators, Bauersachs R, Berkowitz SD, et al. N Engl J Med 2010 Dec 23;363(26):2499.

AMPLIFY

- 5,395 adults (mean age 57 years) with acute symptomatic proximal deep vein thrombosis or pulmonary embolism were randomized conventional therapy vs apixaban 10 mg BID first 5 days then 5 mg BID for 6 months. Followed up for 7 months
- primary outcome was composite of recurrent symptomatic venous thromboembolism (VTE) and VTE-related death
- comparing apixaban vs. conventional therapy
  - primary outcome in 2.3% vs. 2.7% (95% CI for difference -1.3% to +0.4%, noninferiority met)
  - major bleeding in 0.6% vs. 1.8% ($p < 0.001$, NNT 84)
  - clinically relevant non-major bleeding in 3.8% vs. 8% ($p < 0.05$, NNT 24)
  - all-cause death in 1.5% vs. 1.9% (not significant)
  - any serious adverse event in 15.6% vs. 15.2% (no p value reported)
- Reference - AMPLIFY trial N Engl J Med 2013 Aug 29;369(9):799

Hokusai-VTE

- 4921 pts with DVT & 3319 patients with PE were randomized to conventional therapy vs LMWH/UFH + edoxaban 60 mg daily. Followed up for 12 months.
- Primary outcome was composite of VTE and VTE related death
- Comparing edoxaban vs conventional therapy
  - Primary outcome in 3.2% v 3.5 (95% CI 0.70-1.13, noninferiority met)
  - Major bleeding 8.5 v 10.3 (CI 0.71-0.94, superiority)
  - Any bleeding 21.7 v 25.6 (CI 0.75-0.90, superiority)

	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Indications	Nonvalvular a. fib. DVT & PE treatment DVT prophylaxis	Nonvalvular a. fib. DVT & PE treatment DVT prophylaxis	Nonvalvular a. fib. DVT & PE treatment DVT prophylaxis	Nonvalvular a. fib. DVT & PE treatment DVT prophylaxis
Mechanism of action	Thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Clearance	Renal	Renal & Hepatic	Renal & Hepatic	Renal & Hepatic
Usual dosage for VTE treatment/a fib	150 mg BID	5 mg BID	20 mg QD	60 mg QD
Usual dosage for VTE prophylaxis	110 mg 1-4 hrs after surgery then 220 mg daily	2.5 mg BID	10 mg QD	30 mg QD
Antidote	Idarucizumab	?PCC	?PCC	? PCC
Pregnancy	C	B	C	C
Drug interactions (key: **bold – increase**, nl – decrease)	**Azoles, amiadarone**, rifampin, anticonvulsants	**Azoles, diltiazem**, **macrolide, protease inh** rifampin, anticonvulsants	**Azoles, quinidine, HIV protease inh, macrolide** rifampin, anticonvulsants	**Verapamil, macrolide, Quinidine**, **azoles** rifampin, anticonvulsants
Dose adjustments	CrCl 15-30 mL/min – 75 mg BID CrCl < 15 -- **avoid**	If + on 2 out of 3: 1. Age > 80 yrs old 2. Body weight <60 kg 3. Creat > 1.5 mg/dL Reduce dose to 2.5 mg BID	CrCl 15-50 – 15 mg daily CrCl < 15 - **avoid** * Food is mandatory	Do not use if CrCl is **> 95** CrCl 15- 50 – 30 mg daily CrCl < 15 - **avoid**

Guidelines for Initiating Warfarin

- **Start low**
  - initiate at 2-5 mg daily esp. , in elderly, high bleeding risk, heart failure, liver disease, impaired nutrition
  - determine INR frequently after administration of initial dose
  - educate patient. DuPont Pharma or Barr Labs has info booklets available. 1-800-COUMADIN or 1-800-WARFARIN.
- **Stabilize**
  - titrate to appropriate INR of 2.0-3.0
  - once stabilized, determine INR 2-3 times weekly for 1-2 weeks, then less often depending on stability of INR
- **Monitor and adjust**
  - determine INR regularly (every 1-4 weeks) and adjust if necessary

Optional Warfarin Initiation

Day	INR	Warfarin Dose
1	< 1.5	10
2	< 1.8	10
	1.8 - 2.0	5
	2.1 - 3.0	2.5
	> 3.0	0
3	< 1.6	15
	1.6 - 2.0	10
	2.1 - 3.0	5
	3.1 - 3.5	2.5
	> 3.5	0
4	< 1.6	15
	1.6 - 2.0	10
	2.1 - 2.5	7.5
	2.6 - 3.0	5
	3.1 - 3.5	2.5
	>3.5	0

Warfarin reversal treatment: non-bleeding

INR	Vit K dose	Route
<5	none	Hold dose
5-10	none	Hold dose
>10	2.5 mg	PO

* Check INR in 6-12 hrs and repeat if necessary.

! In severe/life threatening bleeding use Vit K 5-10 mg slow IV infusion and four –factor PCC or FFP

Warfarin Drug Interactions

POTENTIATE

- **Antibiotics/Antifungal**
  - sulfamethoxazole, ciprofloxacin, tetracycline, metronidazole, all -azoles, isoniazid, macrolides
- **Cardiovas. agents**
  - amiodarone, disopyramide, propafenone
- **Others**
  - cimetidine, ASA, NSAID's, allopurinol, omeprazole, herbals; vitamin E, garlic, gingko biloba, garlic, ginseng

REDUCE

- **Antibiotics/Antifungal**
  - rifampin, nafcillin, dicloxacillin
- **Anticonvulsants**
  - phenytoin, barbiturates
- **Others**
  - sucralfate, cholestyramine, colestipol, chlorodiazepoxide, trazodone

VTE treatment – Chest Guideline 2016

No cancer

1. NOACs over VKA
2. VKA over LMWH

With cancer

- LMWH over VKA or NOACs

CLOT Study

- 676 pts with cancer who had a VTE were randomized to receive dalteparin 200 IU/kg SC on first month then 150 IU/kg SC on the next five months vs conventional therapy of concurrent dalteparin & VKA for five to seven days then VKA for six months. 50% are female
- Primary outcome was recurrent symptomatic VTE
- Comparing of dalteparin vs conventional treament
  - Primary outcome in 27/336 vs 53/336, p = 0.002
  - Major bleeding 6% v 4, p = 0.27
  - Death 39 % v 41, p = 0.53

2012 ACCP Recommendations
Duration of therapy of VTE

- 3 months - reversible risk factors* & 1st event
  - distal DVT
- 3 months or **more** - unprovoked VTE & 1st event
  d*epending on the risk-benefit ratio*
- 3-6 months -cancer, until resolved
- Indefinite -second episode of unprovoked

*Transient immobilization, trauma, surgical operation, or pharmacologic estrogen use.

Risk - Benefit

- >75 y/o
- Previous GI bleed
- Previous noncardioembolic stroke
- Chronic renal or hepatic disease
- Concomitant antiplatelet therapy
- Other serious illness
- Poor anticoagulant control

- Positive d-dimer
- Proximal DVT
- Antiphospholipid antibody
- Previous episode of VTE
- Hereditary thrombophilia
- Male
- Residual thrombosis in proximal veins
- Non-Asian ethnicity

D-dimer for anticoagulation duration?

- 608 patients, prospective, three armed study with first episode of symptomatic, idiopathic proximal DVT &/or PE who has been treated at least for 3 months with warfarin.
- One arm – normal D-dimer, the other – abnormal D-dimer
  - placebo vs warfarin
- Objective: Composite recurrent VTE and major bleeding during 1.4 years of follow-up
- Results:
  - Normal: 24/385 (6.2%)
  - Abnormal and placebo: 18/120 (15.0%)
  - Abnormal and treated: 3/103 (2.9%)
  - p value = 0.02 (2/3 comparison)
  - Major bleeding: 1 on the treated group, 0 on the others.
- Conclusion: Consider longer therapy with warfarin if D-dimer is abnormal.

Which anticoagulant?

• Cancer	• LMWH
• Poor compliance	• VKA
• Pregnancy	• LMWH
• Reversal agent needed	• VKA, UFH, Dabigatran
• Liver disease	• LMWH
• Renal disease & CrCl < 30 mL/min	• VKA

Other management options

- Inferior Venal Caval Filter
  - contraindication or complication from anticoagulant therapy
  - recurrent thromboembolism despite adequate anticoagulation
  - chronic recurrent embolism with pulmonary hypertension
  - concurrent performance of surgical pulmonary embolectomy
- Thrombolytic Therapy
- Surgical Pulmonary Embolectomy
- Catheter Transvenous Extraction

Patient Education and Follow up

- Take prescribed medications as directed
- Watch how much vitamin K intake (warfarin)
- Be on the look for excessive bleeding/bruising
- Wear compression stockings
- Avoid sitting still
- Make lifestyle changes
- Get regular exercises
- Check in with your doctor regularly

Top Three Pearls

3. D-dimer has a very high negative predictive value (NPV) *BUT* low PPV

2. Superficial femoral vein is a deep vein – DO TREAT

1. Don’t LOAD, be Happy, otherwise use NOAC

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QUESTIONS?