PULMONARY EMBOLISM: WHAT THE NECHA HCP NEEDS TO KNOW

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DISCLOSURES

Research Support:

BMS; BTG; Daiichi; NHLBI; Thrombosis Research Institute

Consultant:

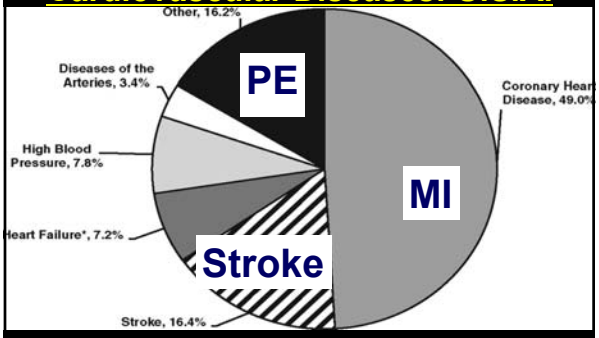
Ariad; Bayer; Boehringer-Ingelheim; BMS; Daiichi; Janssen; Merck; Pfizer; Portola

TOPICS

- Epidemiology and Risk Factors
- Pathophysiology and Thrombophilia
- Contraception
- Diagnosis and Risk Stratification
- Anticoagulation, including NOACs
- Peer pressure, psychological toll, advocacy, Support Groups
- Lifestyle Issues: Heart-healthy or self-destructive, or both

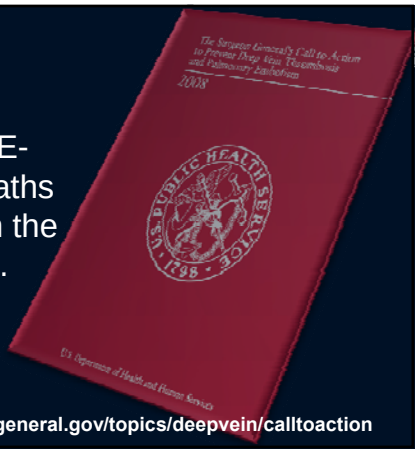
EPIDEMIOLOGY AND RISK FACTORS

Percent Deaths due to various Cardiovascular Diseases: U.S.A.



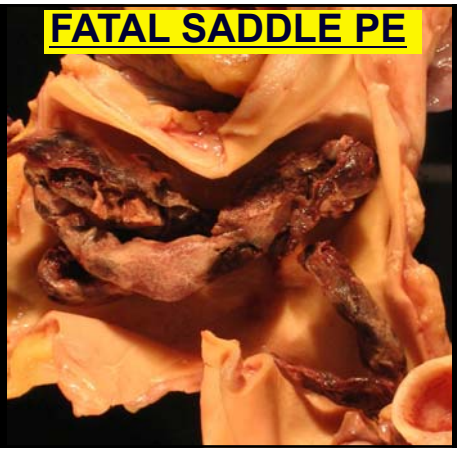
(Circulation 2013; 127: e6-e245)

100,000-180,000 PE-related deaths annually in the U.S. alone.



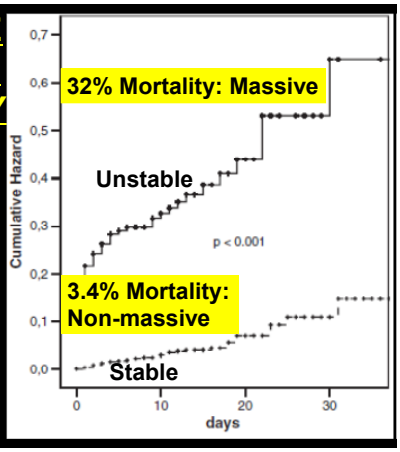
www.surgeongeneral.gov/topics/deepvein/calltoaction

FATAL SADDLE PE



ITALIAN PE REGISTRY: MORTALITY RATE N=1,787 (6.7% in-hospital mortality)

(Thrombosis Research 2012; 130: 847-852)



THE "NEW" EPIDEMIOLOGY

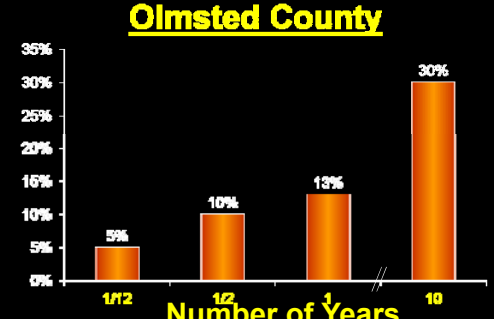
- PE/ DVT is mostly a chronic inflammatory illness, not a "one-shot" event "cured" with 3-6 months of anticoagulation.
- Implication: Extended duration anticoagulation is often needed.

LONG-TERM VTE MORTALITY

- Danish cohort: 128,223 VTE vs. 640,760 general population patients
- 30-year follow-up
- VTE patients: inc'd death rate X 30 y
- Most common cause of death: PE

(Sogaard KK. Circulation 2014; epub June 26)

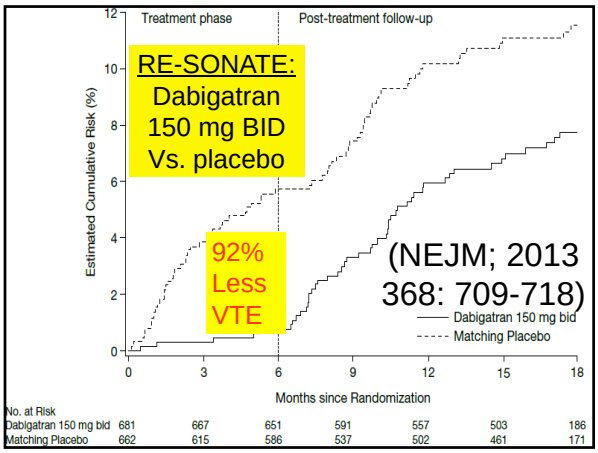
RATES OF RECURRENT VTE



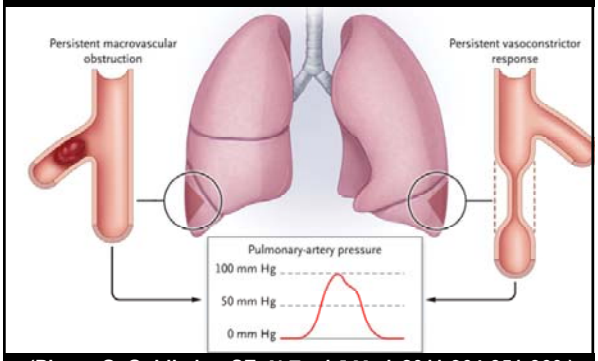
(Arch Intern Med 2000; 160:761-768)

MANAGING VTE AS A CHRONIC ILLNESS

- One approach is indefinite duration (lifelong) anticoagulation.
- As soon as extended duration anticoagulation is discontinued, the rate of new PE/ DVT soars.
- This phenomenon is well illustrated in an "extension study" of dabigatran.

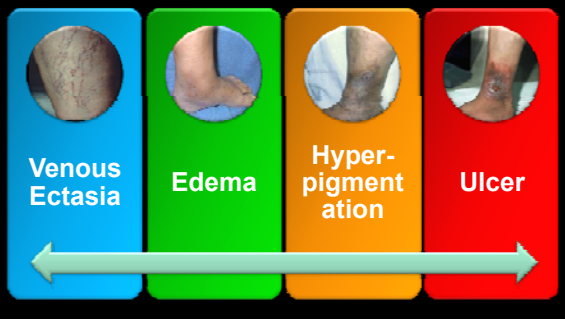


CTEPH PATHOPHYSIOLOGY



(Piazza G, Goldhaber SZ. *N Engl J Med.* 2011;364:351-360.)

POST-THROMBOTIC SYNDROME SPECTRUM



CARDIOVASCULAR RISK FACTORS AND VTE (N=63,552 meta-analysis)

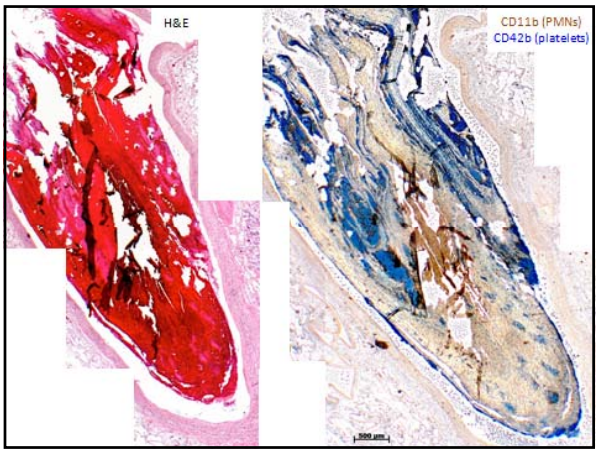
RF	RR
Obesity	2.3
Hypertension	1.5
Diabetes	1.4
Cigarettes	1.2
High Cholesterol	1.2

(Ageno W. Circulation 2008; 117: 93-102)

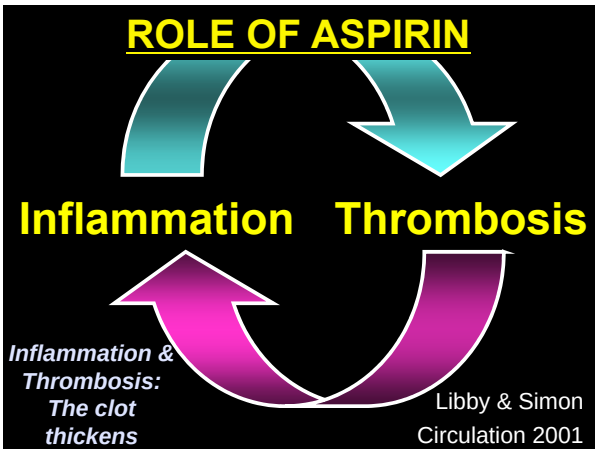
PATHOPHYSIOLGY AND THROMBOPHILIA

INFLAMMATION AND THROMBOSIS

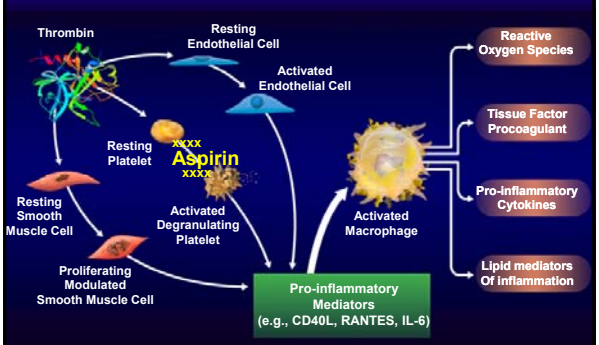
- Inflammation, platelet hyperactivity, hypercoagulability, and endothelial dysfunction contribute to thrombosis.
- Thrombin is an inflammatory agonist.
- The platelet is a cluster bomb with preformed inflammatory markers.
- Can anti-inflammatory therapy prevent new onset PE/ DVT?



ROLE OF ASPIRIN

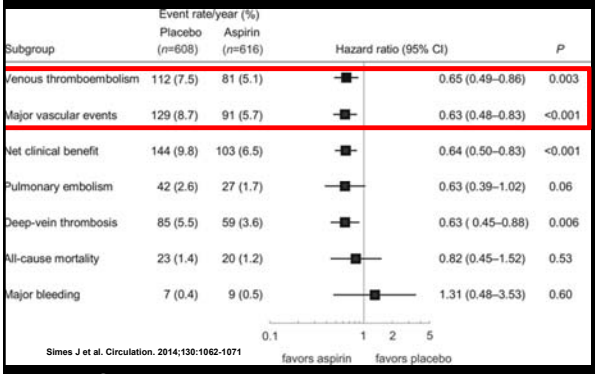


Inflammation and Thrombosis



Croce K, Libby P. Intertwining of thrombosis and inflammation in atherosclerosis. Curr Opin Hematol. 2007;14:55-61

LOW-DOSE ASPIRIN: 35% LESS VTE

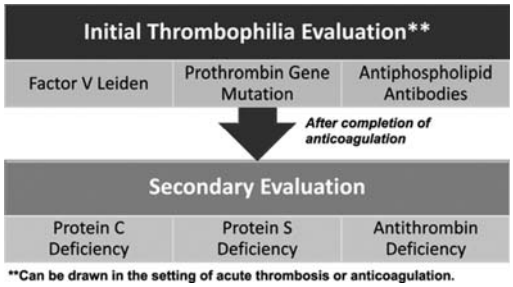


(Circulation 2014; 130: 1062-1071)

HYPERCOAGULABILITY WORKUP

- Antiphospholipid Antibody Syndrome:
  - Lupus Anticoagulant
  - Anticardiolipin Antibodies
  - Beta-2-Glycoprotein
  - Antiprothrombin
- Genetic Testing:
  - Factor V Leiden, Prothrombin Gene Mutation
- More specialized testing:
  - Antithrombin III, Protein C, Protein S

A STEPWISE APPROACH TO THROMBOPHILIA TESTING



**Can be drawn in the setting of acute thrombosis or anticoagulation.

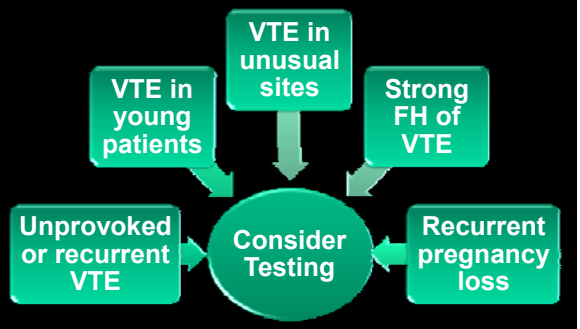
(Piazza G. Circulation 2014;130: 283-287)

THROMBOPHILIA TESTING TIPS

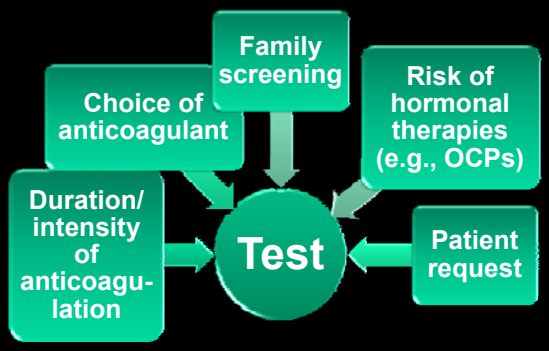
- Consider when, why, and how to test
- Focus on the high-yield testing first.
- Defer protein C, protein S, and antithrombin (to avoid false positives due to anticoagulation).
- Remind patients that a negative thrombophilia evaluation does not exclude thrombophilia.

(Piazza G. Circulation 2014;130: 283-287)

STEP 1: When to Test?



STEP 2: Why to Test?



HIGH-RISK THROMBOPHILIAS

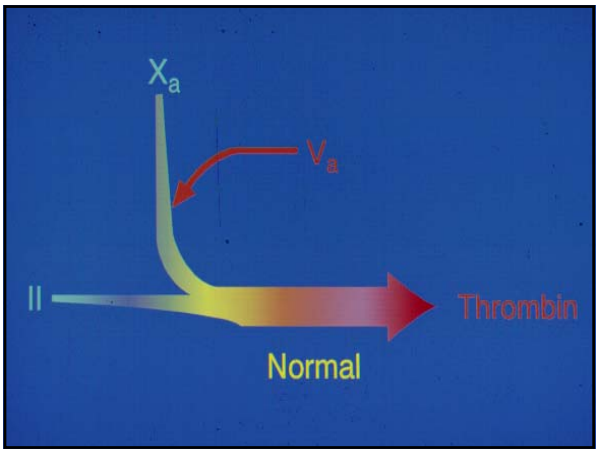
- Deficiencies of antithrombin, protein C, or protein S
- Homozygosity for factor V Leiden or prothrombin gene mutation 20210
- Compound heterozygosity for factor V Leiden and prothrombin gene mutation
- Elevated antiphospholipid antibodies

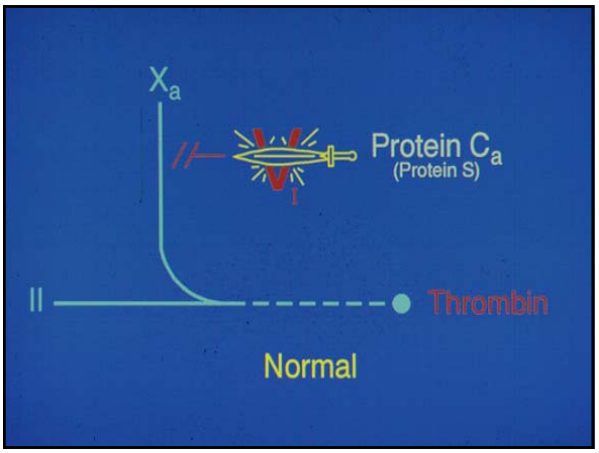
FACTOR V LEIDEN MUTATION

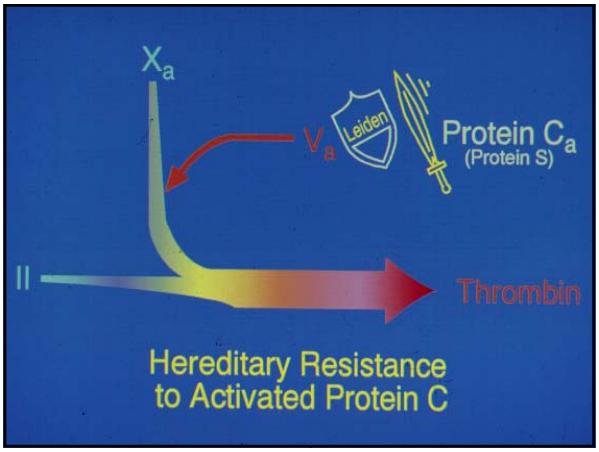
- Single point mutation in the Factor V gene (FV 506Q)
- Guanine to adenine substitution at nucleotide 1,691, resulting in glutamine rather than arginine at amino acid residue 506
- Factor V Leiden is resistant to cleavage by activated protein C

FACTOR V LEIDEN

1) Increases risk of 1st DVT/PE
2) Increases risk of 1st trimester pregnancy loss
3) Increases VTE risk, especially during OC use/pregnancy/HRT
4) Increases risk of pregnancy complications

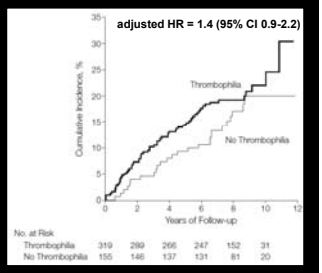






RECURRENT VTE RISK: LEIDEN THROMBOPHILIA STUDY

- N = 474 patients with 1st VTE (average follow-up of 7 years).
- Extensive thrombophilia testing performed:
  - Factor V Leiden
  - Protein C, S, and antithrombin
  - Homocysteine
  - Factors VIII, IX, and XI



Cumulative Incidence of Recurrent VTE

(Christiansen SC, et al. JAMA 2005;293:2352)

PROTHROMBIN GENE MUTATION

- Guanine-to-adenine substitution at nucleotide 20210.
- Heterozygous carriers have 30% higher plasma prothrombin levels than normals.
- Heterozygotes have a 4-fold increase in the risk of VTE.

(Emmerich J. Thromb Haemost 2001; 86: 809)

ESTROGEN-CONTAINING ORAL CONTRACEPTIVES

- **1st Generation:** > 50 mcg estrogen (no longer used; VTE risk too high)
- **2nd Generation:** < 50 mcg estrogen (triple VTE risk versus no OCPs)
- **3rd Generation:** has progestogens, desogestrel or gestodene, that decrease acne/ hirsutism; triple VTE risk versus 2nd generation OCPs

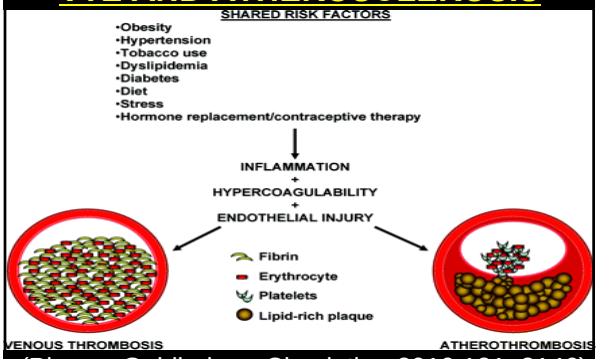
CONTRACEPTION AND THROMBOPHILIA

- Estrogen-based OCPs in patients with thrombophilia are associated with a 20-to-40-fold increased risk of VTE.
- The increased risk of VTE appears to be highest around the time of OCP initiation and within the first 6 months.

EFFECTIVE ALTERNATIVES TO ESTROGEN-OCPS

- **Progesterone-Only OCPs**
- **(Mirena®) IUD**

COMMON PATHOPHYSIOLOGY: VTE AND ATHEROSCLEROSIS



(Piazza, Goldhaber. Circulation 2010;121: 2146)

DIAGNOSIS AND RISK STRATIFICATION

SXS/ SIGNS OF DVT

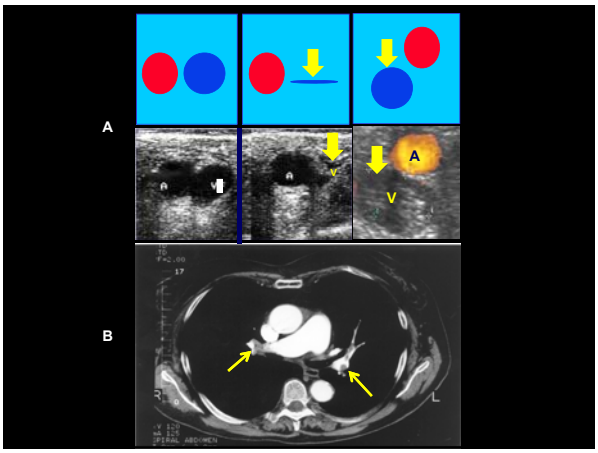
- Lower calf cramping that persists or worsens over several days
- Discomfort not alleviated by leg elevation, leg wrapping, massage
- Leg edema, erythema, tenderness, palpable cord
- Examine upper arms, supraclavicular fossae (asymmetry)

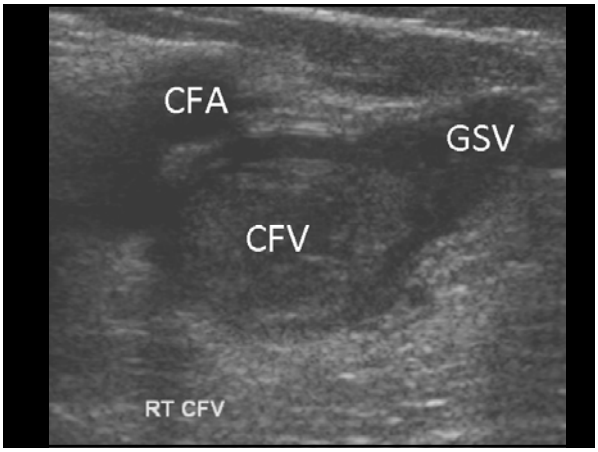
DVT: WELLS CRITERIA (HIGH > 2)

Variable (Lancet 1997; 350: 1795)	**Points**
Paralysis or ortho leg casting	1
Bedridden or major surgery	1
Localized deep vein tenderness	1
Swelling of entire leg	1
Unilateral calf swelling	1
Pitting edema in symptomatic leg	1
Collateral superficial veins	1
Cancer	1
Alternative diagnosis more likely	-2

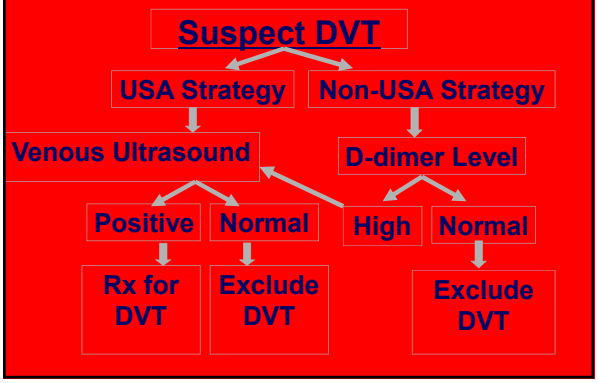
EUROPEAN DIAGNOSTIC APPROACH TO DVT WORKUP

- Clinical probability assessment
- If low-moderate, obtain D-dimer
- If D-dimer is normal, stop workup
- If high clinical probability, go directly to venous ultrasound; skip D-dimer
- This approach is proven; saves time and resources





DVT DIAGNOSTIC STRATEGY



IF INITIAL U/S IS NORMAL, WHEN IS A F/U WARRANTED?

- High clinical suspicion
- Symptoms do not abate or worsen
- D-dimer is elevated, in a patient without other reasons (such as cancer, infection, surgery) to explain high D-dimer
- If the conditions above are present, obtain a single F/U U/S in one week

HOW OFTEN AND FOR HOW LONG DOES U/S REMAIN ABNORMAL AFTER DVT?

F/U	ABNORMAL
6 Months	61%
12 Months	42%
24 Months	31%
36 Months	26%

(Prandoni P. Ann Intern Med 2002; 137: 955-960)

PE SXS/ SIGNS (PIOPED II): NONSPECIFIC

- Dyspnea (79%)
- Tachypnea (57%)
- Pleuritic pain (47%)
- Leg edema, erythema, tenderness, palpable cord (47%)
- Cough/ hemoptysis (43%)

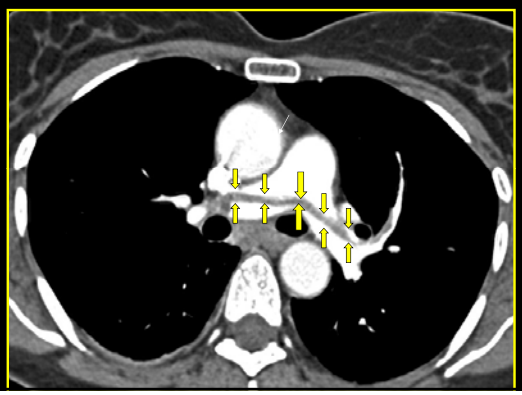
(Stein PD. Am J Med 2007; 120: 871-879)

PE: WELLS CRITERIA (LIKELY > 4)

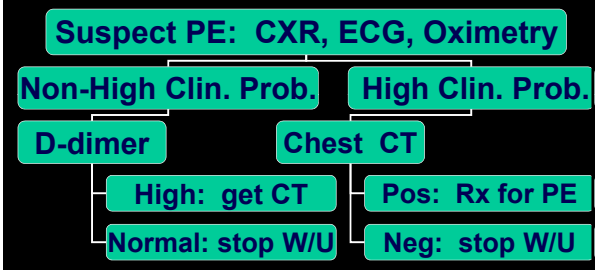
Variable	Points
Signs, symptoms of DVT	3.0
Alternative diagnosis unlikely	3.0
Heart Rate > 100/ minute	1.5
Immobilization; surgery	1.5
Prior PE or DVT	1.5
Hemoptysis	1.0
Cancer	1.0

(JAMA 2006; 295: 172-179)

SADDLE EMBOLUS



PE DIAGNOSIS



HOW OFTEN AND FOR HOW LONG DOES CT REMAIN ABNORMAL AFTER PE?

F/U	ABNORMAL
6 Weeks	68%
3 Months	65%
6 Months	57%
11 Months	52%

(Nijkeuter M. CHEST 2006; 129: 192-197)

IN A PATIENT WITH PE, WHEN IS A F/U CHEST CT WARRANTED?

- Symptoms worsen
- Concomitant illness suspected (cancer; pneumonia vs. heart failure)
- Persistent pulmonary hypertension
- Persistent exercise intolerance

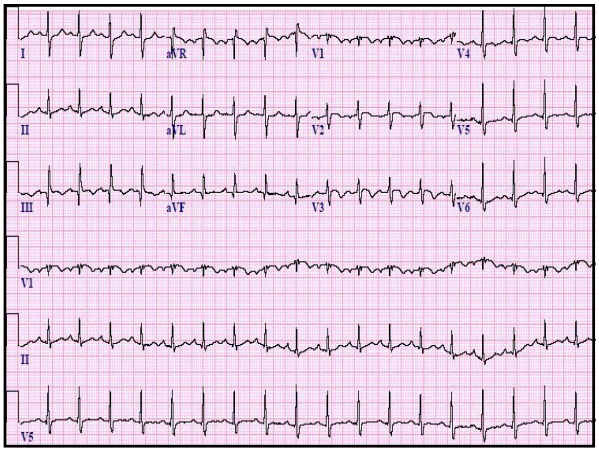
DEFINITIONS OF PE: AHA PE Guidelines 2011

- **Massive PE (5-10%):** sustained hypotension, pulselessness, or persistent bradycardia
- **Submassive PE (20-25%):** RV dysfunction or myocardial necrosis, without hypotension
- **Low Risk PE (70%):** no markers of adverse prognosis

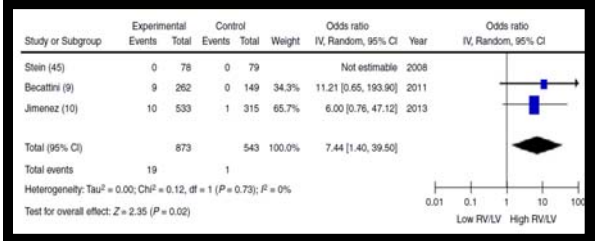
(Circulation 2011; 123: 1788-1830)

RISKS FOR POOR PROGNOSIS

1. Elevated biomarkers (troponin)
   (CHEST 2013; 144: 1539-1545)
2. RV enlargement/ hypokinesis:
   A) **ECG**
   B) **RV/ LV ratio > 0.9**
   CT—(JACC Cardiovasc Imaging 2011; 4: 841-849)
   ECHO—(Circ 2010;122: 1124-1129)

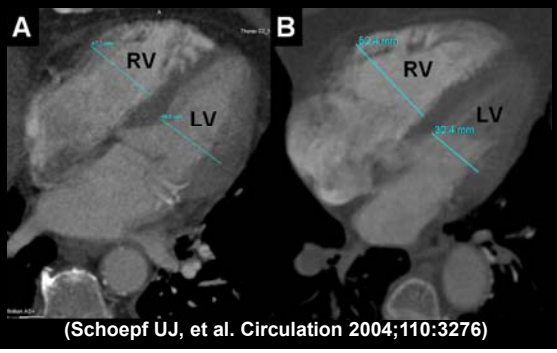


HIGH RV/LV RATIO ON CT INCREASES PE-RELATED MORTALITY

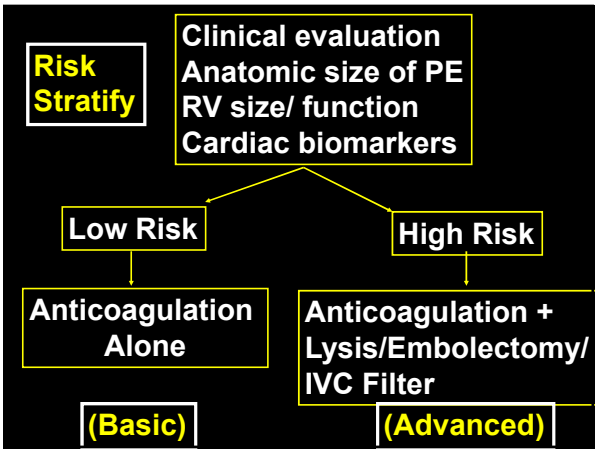


(Trujillo-Santos J. J Thromb Haemost 2013;11: 1823)

RV Enlargement on CT Predicts Increased 30-Day Mortality



(Schoepf UJ, et al. Circulation 2004;110:3276)



ANTICOAGULATION INCLUDING NOACS

PARENTERAL ANTICOAGULATION

1. **Unfractionated heparin**: target PTT between 60 to 80 seconds
2. **Low molecular weight heparins**: enoxaparin, dalteparin, tinzaparin
3. **Fondaparinux**
4. **Direct thrombin inhibitors (HIT)**: argatroban, bivalirudin

WHICH PARENTERAL ANTICOAGULANT SHOULD BE SELECTED?

1. **Unfractionated heparin**: use if patient might require thrombolysis, embolectomy, or IVC filter
2. **Low molecular weight heparins or fondaparinux**: use for patients only requiring anticoagulation
3. **Direct thrombin inhibitors (HIT)**: use for confirmed or suspected HIT

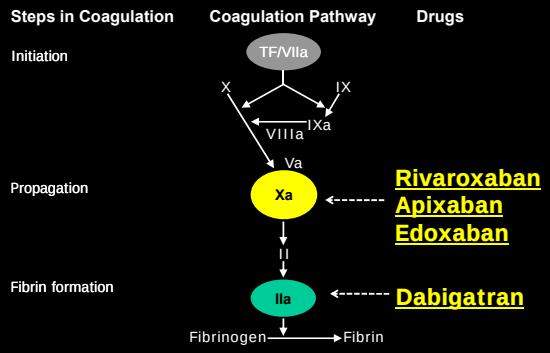
WARFARIN WILL SURVIVE:

1) Excellent efficacy
2) Low Cost ($4/month; $10/ 3 mos)
3) Long Track Record (1954)
4) Centralized Anticoagulation Clinics that maintain TTRs > 60%
5) Point-of-care self-testing
6) INR Testing q 12 weeks if stable

WARFARIN versus NOVEL ORAL ANTICOAGULANTS

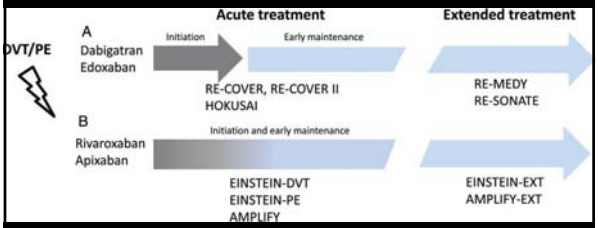
Feature	Warfarin	New Agents
Onset	Slow	**Rapid**
Dosing	Variable	**Fixed**
Food effect	Yes	**No**
Drug interactions	Many	**Few**
Routine lab monitoring	Yes	**No**
Half-life	Long	**Short**
Reversal agent	Yes	**Maybe**

SITES OF ACTION



(Hankey GJ and Eikelboom JW. *Circulation* 2011;123:1436-1450)

NOAC VTE TRIALS: ACUTE AND EXTENDED



(Fontana P, Goldhaber SZ, Bounameaux H. European Heart Journal 2014; epub)

ACUTE VTE TREATMENT TRIALS

Trial	Initial heparin/ fondaparinux	Duration (months)	Regimen
Rivaroxaban			
EINSTEIN DVT	No	3, 6, or 12	Daily
EINSTEIN PE	No	3, 6, or 12	Daily
Dabigatran			
RE-COVER	Yes	6	BID
RE-COVER II	Yes	6	BID
Apixaban			
AMPLIFY	No	6	BID
Edoxaban			
Hokusai-VTE	Yes	3–12	Daily

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ACUTE VTE TREATMENT: NOAC EFFICACY

- All 4 NOACs are noninferior to LMWH/ warfarin for efficacy, regardless of weight, PE vs. DVT, CKD, and cancer.
- Edoxaban: prespecified submassive PE subgroup showed superiority.

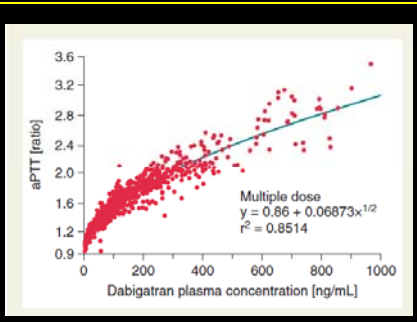
(van Es N, et al. Blood 2014; 124: 1968-1975)

ACUTE VTE TREATMENT: NOAC SAFETY

- **Meta-analysis (N=27,0235):**
  39% lower major bleeding,
  64% lower fatal bleeding,
  63% less ICH than LMWH/ warfarin

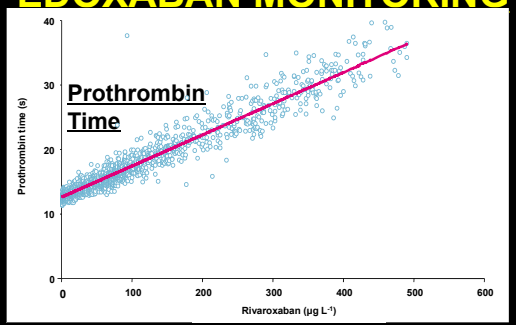
(van Es N, et al. Blood 2014; 124: 1968-1975)

aPTT/ DABIGATRAN LEVEL



(Van Ryn J. Thromb Haemost 2010; 103: 1116-27)

RIVAROXABAN/ APIXABAN/ EDOXABAN MONITORING



(Hillarp A, et al. J Thromb Haemost 2011)

MANAGING NOAC BLEEDING

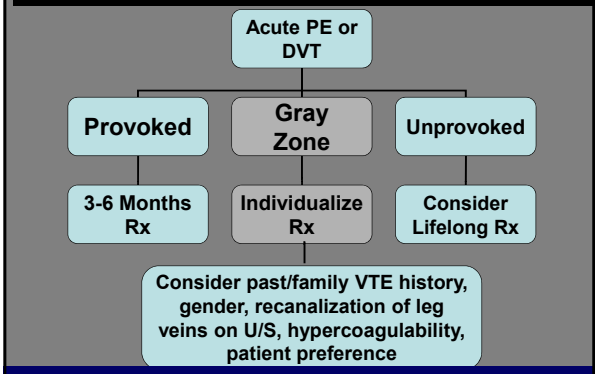
1) Tincture of Time
2) Prothrombin Complex Concentrate (PCC) (4-factor): Activated (FEIBA®)
3) PCC Inactivated (Kcentra®)
4) Dabigatran Ab (Idrarucizumab)
5) Xa Decoy (r-Antidote; Andexanet)

PREDICTORS OF RECURRENCE

1. Immobilization
2. Cancer
3. Overweight, obesity
4. Male gender
5. Family history and thrombophilia
6. Symptomatic PE
7. Elevated D-dimer after d/c anticoagulant
8. Failure to recanalize leg veins

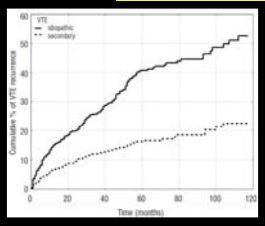
(Goldhaber SZ, Piazza G. Circulation 2011; 123: 664)

OPTIMAL DURATION STRATEGY



(Goldhaber, Piazza. Circ 2011; 123: 664-667)

PREVENTION OF RECURRENT VTE



Study	Intervention	Recurrent VTE**
PREVENT	Warfarin, INR 1.5-2 vs. placebo	↓64%
ELATE	Warfarin, INR 2-3 vs. INR 1.5-2	↓63%
EINSTEIN-DVT	Rivaroxaban vs. placebo	↓82%
AMPLIFY-EXT	Apixaban vs. placebo	↓81%
RE-SONATE	Dabigatran vs. placebo	↓93%
RE-MEDY	Dabigatran vs. warfarin, INR 2-3	Non-inferior

(Prandoni P, et al. Haematologica 2007;92:199
Goldhaber SZ, Piazza G. Circulation 2011; 123 :664)

ANTICOAGULATION MANAGEMENT

1) Bracelet specifying anticoagulant that is prescribed
2) Alcohol: no more than 1 drink per 24 hours; no binging; peer pressure issues
3) Skiing, basketball restrictions
4) Adhering to medication

PSYCHOLOGAL ISSUES, EMOTIONAL SUPPORT, ADVOCACY

ASKED QUESTIONS

1) Why did it take the doctors so long to diagnose my DVT/ PE?
2) Why didn't anyone ever tell me that birth control pills can cause DVT/ PE?
3) How long do I have to stay on a blood thinner?
3) Is my family at risk?

UNASKED QUESTIONS

1) How do I explain this to my friends, including my boyfriend?
2) I look and feel healthy, so is there really a serious medical problem?
3) Can I enjoy partying if I behave differently than my friends (no alcohol)?

LIFESTYLE

1) Exercise at least 30 mins/day, at least 6 days/week (AHA).
2) Eat heart-healthy, maintain ideal body weight. Limit carbohydrates. Stay well hydrated.
3) No restrictions on travel

BE PROACTIVE

1) Join a PE/ DVT Support Group.
2) Become an advocate for access to NOACS and other advanced technologies related to DVT/ PE treatment.
3) Join (or at least browse the webpage of) NATF (www.NATFonline.org)

CASE DISCUSSION

CONTRACEPTION

1) 19 y.o. sophomore asks for birth control pills but has FVL, diagnosed after her 1st cousin suffered DVT.
2) No DVT/ PE in parents, sibs.
3) Would your advice change if Mom or Sister had suffered DVT?

ANTICOAGULATION

1) 20 y.o. varsity football player develops PE out of the blue during Christmas break.
2) Returns to college on warfarin.
3) Would you switch him to a NOAC?
4) How long would you anticoagulate him?

CONCLUSIONS

1. PE is the #3 CV killer. VTE predisposes to a 30-year increased risk of CV death, especially from recurrent VTE.
2. VTE is mostly a chronic, inflammatory illness, not a “one shot deal”.
3. NOACs expand greatly our anticoagulation options.
4. Psychological and emotional support are the most challenging tasks for the healthcare provider.