PHILADELPHIA
INTERNATIONAL MEDICINE

Venous Thromboembolic Disease

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Pulmonary Embolus =

a complication of deep vein thrombosis

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a complication of deep vein thrombosis

- Majority of pts with proximal DVT have PE
- Risk factors are the same
- PE has a worse prognosis

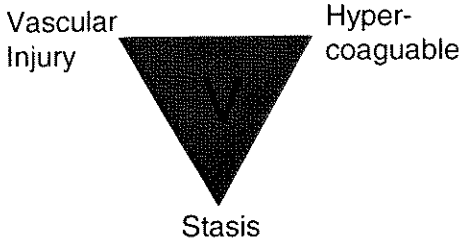
Outline

- Pathophysiology
- Risk Factors
- Assessment/ Diagnosis
- Treatment

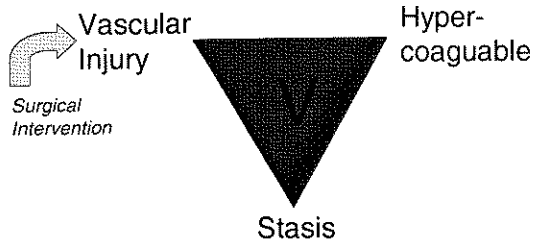
Venous Thromboembolism

- Common
  - 5,000,000 / year DVT
  - 500,000 with PE
  - 50,000 fatal
- Lethal
- Underdiagnosed (30% of fatal cases)
- In hospital mortality: DVT 5%; PE 23%

Pathogenesis- Venous Thrombosis Virchow's Triad



Pathogenesis-
Example: Hip Arthroplasty



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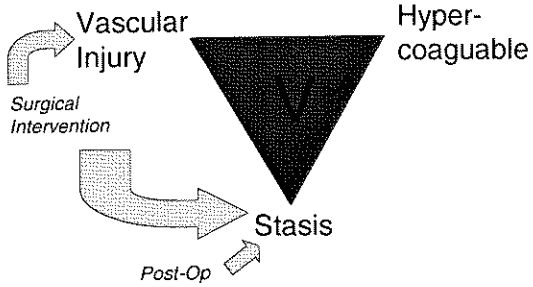

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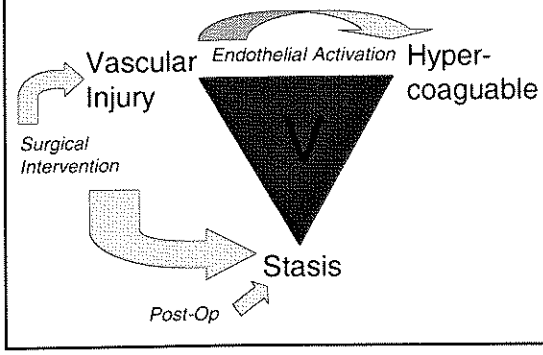

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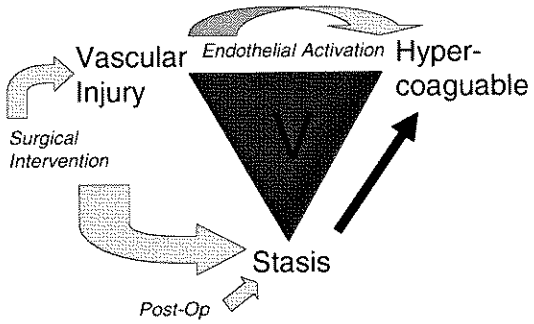
Example: Hip Arthroplasty



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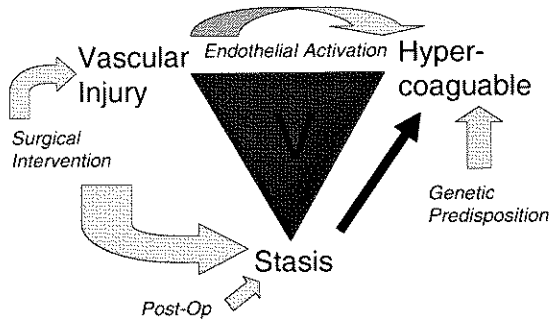
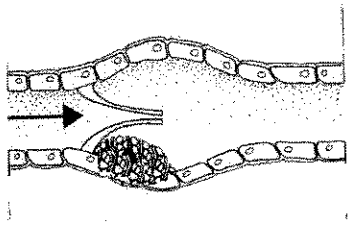
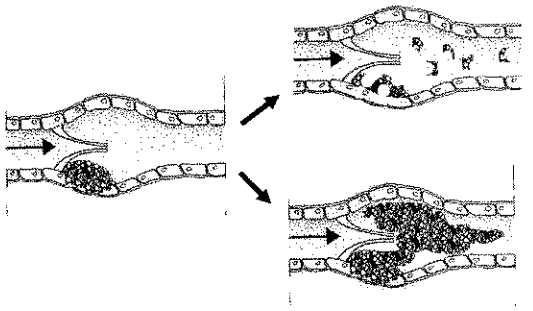


Pathophysiology: Thrombus



- valves, sites of injury
- aggregating platelets further activate endothelium / induce pro-thrombotic mediators



Pathophysiology – Thrombus (2)

- Dynamic process- either lysis of clot
- Or rapid organization (hours):
  - Good: anchors clot
  - Bad: vessel obstruction / valvular defects
- Any time (peak 72 h) – embolus breaks off
- Anticoagulation – halts thrombosis/ allows un-apposed fibrinolysis

Pathophysiology: Embolus

- Autopsy and clinical studies: 95% of PE causing sxs arise from LE deep veins
- Rarely: PE from UE, indwelling catheters, calf veins
- Calf thrombus: rarely cause clinically significant PE- ? Better wall attachment, ? Less likely symptomatic

Pathophysiology- PE

- Acute effects:
  - High V/Q (mismatch) → dead space
  - Pneumoconstriction (rare)
  - Bronchospasm and vasoconstriction – serotonin, bradykinin, prostaglandins
  - Impaired surfactant production – atalectasis and edema
  - Infarction is rare (<10%)- dual blood supply

Risk Factors

- Recently hospitalized
- Major Surgery
  - -ortho w/o prophylax: 40-70% (fatal 6-13%)
  - -neurosurg, pelvic
- Trauma- 50% w/o prophylaxis
- Prior VTE- 13% -1yr; 25% -5 yrs
- Malignancy (precedes dx < 15%)
- Immobilization

Thrombophilia

Hereditary:

- Antithrombin III
- protein C and S deficiencies
- Factor V Leiden
- Prothrombin mutations

? Hereditary

- Elevated factor VIII or Xi
- Hyperhomocysteinemia

Acquired

- Antiphospholipid Ab
- HIT
- Malignancy

Risks

- Increasing Age
- Pregnancy / post-partum
- Estrogen Rx
- Medical Conditions:
  - Stroke (50%)
  - COPD exac (20-30% autopsy; 2x mortality-1yr)
  - severe pneumonia, CHF, IBD
- Obesity
- Smoking

Prophylaxis

- Most hospitalized pts have ≥ risk
- Risks are generally cumulative
- w/o prophylaxis: objective DVT in 10 – 40%
- 10% hospital deaths attributable
- 70 – 80 % fatal PE are in non-surgical pts

ACCP Chest 2004: 124: 357S
126: 338S

Prophylaxis

- Prophylaxis works:
  - Pooled data 6 trials LDUH or LMWH: 70% reduction in risk
  - Example: 1,102 pts RCT: placebo 15%, enoxaparin 40 mg daily 5%

NEJM 1999; 341:793

- Under-utilized: survey 1,595 pts / 21 centers – 44% in USA w/ prophylaxis

Blood 2003; 102:1151

- Mechanical Methods (GCS, IPC):
  - better than nothing (few data) → recommended for high risk of bleeding
- Low dose UFH works:
  - Older/smaller studies with BID
  - TID likely is better – but more bleeding
  - BID still recommended
- Various surgical populations: LMWH superior
- Medical pts: LMWH equivalent to TID UFH
  - ? Lower bleeding; less HIT
  - Either UFH or LMWH recommended

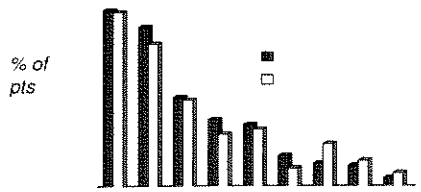
ACCP Chest 2004: 124: 357S
126: 338S

Presentation -PE

- DVT – PE a continuum, BUT
- < 30% with PE have *symptoms* of DVT
- ~25% with DVT have "silent" PE

Presenting Symptoms

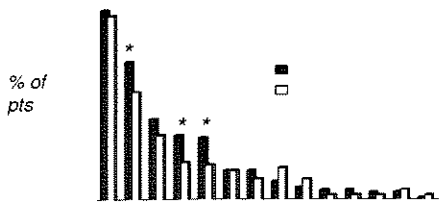
PIOPED – No prior heart / lung disease



No significant differences

Presenting Signs

PIOPED – No prior heart / lung disease

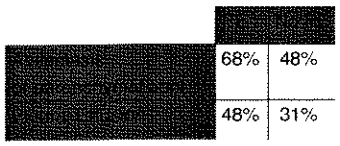


* $P < 0.05$

CXR Findings

PIOPED

- 12% with PE are normal



Statistically significant – not clinically

ABGs

- Are NOT useful to diagnose or R/O PE
- Should be performed as required for acute management of patient (e.g. ? CO2, trend, intubation)

Goal of Diagnosis: prevent recurrent DVT / embolus

- Your job is to find evidence of clot:
  - VTE is just that:
    - Venous → leg studies
    - Embolic → lung studies

Approach to Diagnosis

- Clinical Evaluation – Suspicion
- Diagnostic Testing
  - V/Q Scan
  - LE studies
  - Angiogram
  - Helical CT scan
  - D-dimer

Clinical Evaluation Pre-Test Probability

- Significant range in physician skills reported
- Remains appropriate / clinically useful
- PIOPED: 887 pts

High	68
Intermediate	30
Low	9

Pre-test probability

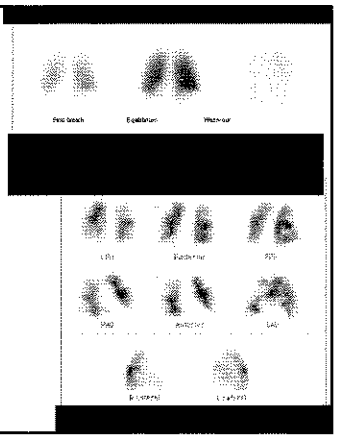
Signs / sxs of DVT	3.0 points
PE as / more likely than alternative dx	3.0 points
HR > 100	1.5 points
Immobilization / surgery in prior 4 weeks	1.5 points
Previous DVT / PE	1.5 points
Hemoptysis	1.0 points
Malignancy (or Rx, in last 6 mo)	1.0 points

Low prob <2.0 ***Intermed prob: 2.0–6.0*** ***High prob: >6.0***

Wells et al. Annals Int Med 129:997; 1998

V / Q Scanning

- Non-invasive
- Experience / validation
- Endangered species



PIOPED

	High	Intermed	Low
High	95	86	56
Intermediate	66	28	15
Low	40	15	4
Normal / near nl	0	6	2

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Normal / near nl			

LE Studies – Continue to hunt

- Remember – find evidence of clot!
- Finding LE clot:
  - -diagnostic
  - -initiates anticoagulation
  - -IVC filter
- Often the first test performed

LE studies

Ultrasound

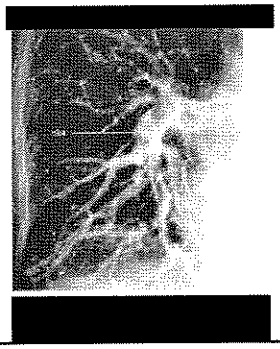
- Readily available, non-invasive / painless
- Now the standard, first-line imaging
- Accurate in *symptomatic* patients: 97% PPV, 98% NPV for proximal DVT
- Limited in *asymptomatic* pts: sensitivity 60% for proximal DVT

LE Studies

- Caveat:
  - *Does not* rule out PE
  - 1 test might not r/o extension of distal DVT
  - Serial studies over 10 – 14 days to r/o proximal extension of distal
  - (cumbersome, ? Compliance)

Pulmonary Angiogram

- Remains the "gold standard" (?)
- Intraluminal filling defect / abrupt cut-off



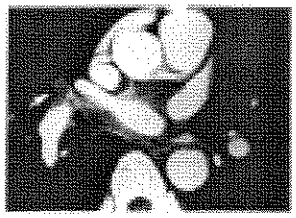
Pulmonary Angiogram

- Mortality 0.1- 0.5%; morbidity 0.4 - 1%
- Invasive, contrast (allergy, renal insufficiency), poor cardiopulmonary reserve, pulm htn
- Can prioritize areas for injection
- Negative angiography and no anticoagulation: 3 mo incidence PE 0.2%, one year 1.6 – 2.2%

Ann Int Med 1983;98:891; Chest1995;107:1375

Helical CT

- Contrast bolus timed with rapidly rotating scanner- captures flow; low acquisition time
- Filling defects



Helical CT

Problems:

- Sensitivity 53 – 100% (large/central vs peripheral)
- Expertise of center / reader
- Cooperative patient / holding breath
- False positives:
  - Confusion with hilar LAD
  - Partial opacification of pulm veins
  - Perivascular edema (CHF)
- Contrast required
  - Renal insufficiency
  - Allergy
  - Comparable to angio

Helical CT

Advantages

- Availability
- Safe
- Rapid
- Greater specificity than V/Q
- Other diagnoses:
  - -33% of cases (single study)
  - -use in patients with abnormal CXR
  - -combined with LE venogram

Helical CT for screening

- Prospective trial 510 pts w/ ? PE
- CT scan (and LE US if negative)
- No rx w/o dx – 3 mo f/u (inactive)
  - 24% w/ PE on CT
  - 25% alternative dx
  - 1.6% could not interpret
  - Of 248 with normal CT:
    - 2 positive LE US (day 1)
    - 3 developed VTE (sensitivity 99%)
  - 3 / 376 without anticoagulation (0.8%) with VTE at 3 months
    - comparable to V/Q (0.6% and pulm angiogram (0.2%)

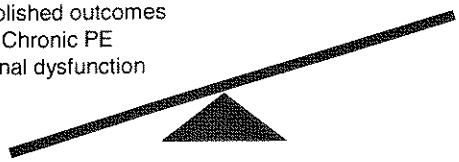
Ann Int Med 138:307; 2003

V/Q SCAN
Established outcomes

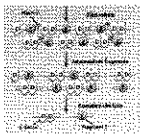
CT ANGIO
High Specificity
Availability
Utility w/ abnl CXR
Other diagnoses

CT ANGIO
High Specificity
Availability
Utility w/ abnl CXR
Other diagnoses

V/Q SCAN
Established outcomes
Chronic PE
Renal dysfunction



D-Dimer



- Degradation product of cross-linked fibrin
- Low specificity
  - Non-thrombotic disorders (hemorrhage, sepsis, malignancy, recent surgery, trauma)
  - Common among hospitalized patients
- Not for diagnosis / ruling in PE
- High sensitivity and negative predictive value
- Potential for ruling *out* VTE

D-Dimer: DVT

- Prospective 1096 pts / 5 centers; ? DVT
- Pre-test assessment, D-Dimer , ultrasound
- 3 mo f/u

- Assessment: Any of 2 = "likely" DVT
  - Active cancer
  - Immobility of limb
  - Bedridden 3 days or surgery with anesthesia w/l 12 wks
  - Local tenderness
  - Whole limb swollen
  - ≥ 3cm asymmetry limbs
  - Edema at symptomatic leg
  - Superficial veins
  - Prior DVT
  - (Alternative likely diagnosis = -2)

NEJM 2003; 349:1227-35

D-Dimer: DVT

- 601 pts "unlikely" to have DVT
  - –317 Negative D-Dimer
  - –2 with VTE on f/u = NPV 99.1%
- BUT : NPV for "likely" DVT & neg DD = 89 %

Must be truly "unlikely" clinical suspicion

D-Dimer: PE

- Prospective 930 pts / 4 centers: ? PE
- Low suspicion & DD neg → stop
- 527 pts with low suspicion: 437 D-Dimer negative, 1 PE (3 months):
  - Low pre-test prob & D-Dimer normal = 99.5 % NPV

(2 additional PE not following protocol; low prevalence PE)

Annals Int Med 2001; 135: 98-107

Must be truly low clinical suspicion

D-Dimer: Caveats

- ? If levels decline with anticoagulation
  - 25 % in 24 hours of heparin

Blood Coagul Fibrinolysis 2002; 13:241-246

- Not studied for inpatients

Treatment

Initiated promptly:

-Diagnosis established
-Before diagnosis:
  -high clinical suspicion
  -intermediate suspicion w/ poor cardiopulmonary reserve

Goals:

Arrest the thrombotic process

Prevent the next embolus

Unfractionated Heparin

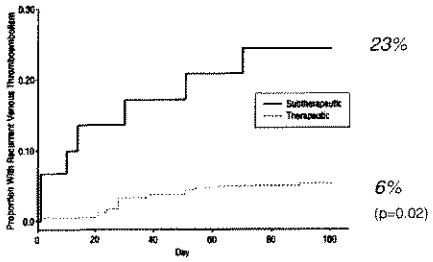
- Well studied and effective
- Action: Antithrombin III binds more effectively to / inhibits prothrombotic factors (thrombin, Xa, IXa)
- Single trial with untreated group:
  - Higher mortality (25%) w/o treatment
  - Autopsy verified PE as cause of death

Barritt and Jordan, Lancet, 1960

Heparin

- Given as continuous infusion – lower risk of bleeding than by intermittent dosing
- Important to achieve therapeutic APTT promptly

Failure to Achieve therapeutic APTT in first day: Increased risk of recurrence



- 750 patients
- Equivalent intensity of therapy after 24 hours

Hull et al., Arch Int Med 157:2562-68, 1997

Heparin- Unfractionated

- Weight- Based Dosing
- Initial: 80 IU/kg
- Maintenance infusion 18 IU/kg/h
- Check APTT in 6 hrs
- Goal: 1.5 – 2.3x normal

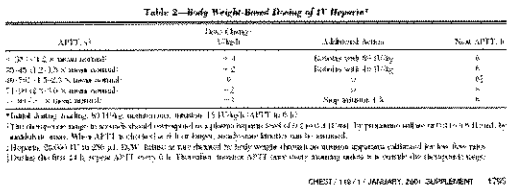


Table 2—*Body Weight-Based Dosing of IV Heparin**

APTT, x†	Dose Change in Units/h	Additional Action	Next APTT, h
< 1.2 x mean normal	+ 4	Bolus with 40 IU/kg	6
1.2–1.5 x mean normal	+ 2	Bolus with 20 IU/kg	6
1.5–2.3 x mean normal	0	—	6‡
2.3–3.0 x mean normal	− 2	—	6
> 3.0 x mean normal	− 3	Stop infusion 1 h	6

*Initial dosing: loading, 80 IU/kg; maintenance, infusion 18 IU/kg/h (APTT in 6 h).
†Therapeutic range: to screen, should correspond to a plasma heparin level of 0.2 to 0.4 IU/mL by protamine sulfate titration or 0.3 to 0.7 IU/mL by antifactor Xa assay. When APTT is elevated at 6 h or longer, subsequent titrations can be increased.
‡Reports, 25,000 IU to 250 µL D5W. Bolus is not checked by body weight (heparin accumulates) calibrated for low flow rates.
§During the first 24 h, repeat APTT every 6 h. Thereafter, monitor APTT once daily, assuming value is in middle (therapeutic) range.

Heparin- Unfractionated

- Frequent underdosing
- Weak association between supratherapy and increased bleeding; strong association between subtherapy and recurrent VTE

LMWH

Advantages over UFH:

- Uniform formulation & bioavailability
- once or twice daily dosing
- no monitoring / less phlebotomy (except obese, <40kg, CrCl <30 cc/h)
- no IV
- early ambulation
- home therapy

LMWH for DVT / PE: As Safe and Effective at UFH

Numerous LMWHs tried / similar results
Randomized trials in VTE:
- reviparin vs. UFH: 1021 pts (25% with PE)
- tinzaparin vs. UFH: 612 pts
- equivalent intensity of coumadin therapy – 3 mo
- excluded: contraindications to heparin, poor prognosis, pregnant

3 months: No difference in recurrent VTE, major bleeding, death

NEJM 1997;337:657
NEJM 1997;337:663

LMWH for Outpatient Therapy

- Proximal DVT- Stable Patients
- Home/early home LMWH vs. UFH
- 3 months anticoagulation and f/u
  - Enoxaparin (1 mg/kg q12) – 500 pts

	5.3%	2%	1.1
	6.7%	1.2%	6.5

120 / 247 Entirely as outpt

NEJM 1996;334:677
NEJM 1996;334:682

Outpatient Therapy of DVT

Requires:
- Stable condition w/ normal VS
- Low bleeding risk
- No severe renal insufficiency
- Practical system for admin LMWH / coumadin
- Practical system for surveillance for recurrent VTE and bleeding

ACCP- CHEST 2001;119:176S

LMWH - Inpatient

Caveats:

- Cannot readily reverse
- No data in unstable patients / ICU for treatment (some data for prophylaxis)
- Dosage adjustments in renal failure
- Cost

Continued Therapy - Warfarin

- Short courses anticoagulation are inadequate
- Longer term rx is required
- Initiate warfarin on day 1:
  - 5 mg q D x 3
- Combined heparin / warfarin 4 – 5 days & then stop with INR > 2.0
- Maintain goal INR 2.0 – 3.0
  - Increased bleeding risk INR > 3.0; no sig added benefit
  - Exception: high risk – antiphosholipid syndrome
  - Lower INR (1.5-1.9) less effective

NEJM 348; 631; 2003

Duration of Therapy

- Tailored according to risk
- First Events:
  - 3 – 6 mo: reversible (OCP, trauma, surgery, immobilization)
  - >6 mo: idiopathic
  - 12 mo – lifetime: cancer (unresolved), thrombophilia
- Recurrent Events: 12 mo to lifetime

ACCP Consensus, Chest 2001:119:176S-193S

Longer Rx is better (?)

- Randomized trial: following mean 6.5 mo standard Rx → 508 pts low intensity (INR 1.5 – 2.0) vs none
- Recurrent VTE lower with Rx (2.6 vs. 7.2 events / 100 person years; HR 0.6; $p < 0.001$)

NEJM 2003; 348: 1425

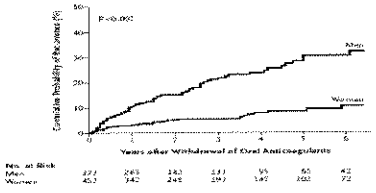
- Prolonged therapy *delays* period of increased risk after stopping
- Major bleeding ~ 1 episode/ 100 person-yr
- QOL ?- VTE risk vs. inconvenience / bleeding

? Predicting need

- 610 pts with "spontaneous" VTE
- Measured D-dimer after completing warfarin Rx
- Recurrent VTE at 2 years:
  - DDimer < 250 ng/mL = 3.7%
  - DDimer > 250 ng/mL = 11.5%
  - RR 0.4 (0.2 – 0.8) p=0.001
  - Do difference duration / intensity of initial anticoagulation (7.8 vs 8.3 mo)

JAMA 2003; 290: 1071-1074

? Predicting need – Men at greater risk?



Men were older
No data on estrogen / OCP use after first event
Passive follow-up (? Women less likely report/ evaluated)

NEJM 2004; 350:2558-63

A better oral anticoagulant ? Oral direct thrombin inhibitors

- ximelagatran:
- low protein binding→ fixed dose / no monitoring
  - 1^0 prevention knee surgery: superior to coumadin
  - Decreased distal DVT only

    NEJM 2003; 349:1703
  - 2^0 prevention after 6 mo coumadin:
    2.8 % vs. 12.6% placebo at 18 months
  - LFT abnl 6%
  - Long-term safety (thrombin interactions in cell proliferation / inflammation / angiogenesis)

    NEJM 2003; 349:1713

IVC filters

- "Indications":
  - Active bleeding / risk
  - Contraindication to long-term anticoagulation
  - Remaining clot / poor cardiopulmonary reserve
- Does not replace anticoagulation

IVC filters

- RCT: 400 pts prox DVT / high risk for PE
  - IVC filter or not; anticoagulated for 3 mo
  - IVC filter – lower PE at 12 days; higher recurrence DVT at 2 years
  - No difference in mortality

    NEJM:1998;228:409-15
- 8 yr follow-up:
  - no diff VTE events
  - IVC filter- more DVTs (36 vs 28%). Fewer PE (6 vs. 15%); no diff post-thrombotic syndrome

    Circulation 2005; 112:416-22

IVC filters

- Do not know the indication(s)
- Do not know if better / worse than anticoagulation alone in selected pts
- Removable filters: data from long-term
  - no filter group; 42% of PE's occurred in 1st year
    filter group: 22% of PE's in 1st year
  - ? Benefit to removable filters for initial period

? Thrombolytics

- "Indicated" (FDA) for "massive PE"
  - What constitutes "massive" ?
  - No demonstration of improved survival
- ? For hemodynamically stable patients?

? Thrombolytics

- Multicenter, RCT:
  - 256 hemodynamically stable pts
  - Evidence of RV dysfunction or PA htn
  - tPA + heparin vs placebo + heparin
- 1⁰ Endpoint: Death or "rx escalation" (30 days or by d/c)
- Results:
  - No difference in survival
  - Rx escalation in 24.6% placebo vs. 10.2 tPA (p=0.004)
  - No significant bleeding among tPA group
- BUT: very low mortality (3 %); "soft" end-point; not really blinded!!

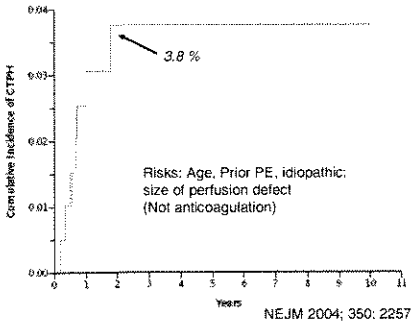
NEJM 2002; 347:1143-1150

Long term outcome

- Chronic Thromboembolic Pulmonary Htn
  - 223 pts with acute, first PE
  - Standard Rx / anticoagulation - > 6 months

NEJM 2004; 350: 2257

CTEPH



NEJM 2004; 350: 2257

Summary

- PE is a complication of DVT
- Common, under-diagnosed and lethal
- Approach:
  - Pretest clinical probability
  - Testing at legs and lungs
- Prompt anticoagulation
- ? IVC filter
- PROPHYLAXIS!