PULMONARY EMBOLISM, DVT, ANTICOAGULATION
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LEARNING OBJECTIVES
• VTE leads to CTEPH and PTS
• Rapid/Accurate Risk Stratification
• Selection of Parenteral Anticoagulant
• Warfarin Pharmacogenetics: TTR>70%
• Rivaroxaban monotherapy
• Fibrinolysis; Filters; Embolectomy
• Optimal Duration of Anticoagulation
• Aspirin: Prevention of Recurrent VTE

ICOPER CUMULATIVE MORTALITY
17.5%
Days From Diagnosis
(Lancet 1999; 353: 1386-1389)

CTEPH PATHOPHYSIOLOGY
(Piazza G, Goldhaber SZ. NEJM 2011; 364: 351)

DISCLOSURES
Research Support:
Eisai; EKOS; Johnson & Johnson, Sanofi-Aventis

Consultant:
Baxter; Boehringer-Ingelheim; BMS; Daiichi; Eisai; Merck; Pfizer; Portola; Sanofi-Aventis

69 y.o. WOMAN:
UNPROVOKED BILATERAL PE

Right lung with PE
Left lung with PE
POST THROMBOTIC SYNDROME

- Edema
- Hyperpigmentation
- Venous ulcer
- Skin induration
- Venous ectasia

CHEST ACCP GUIDELINES
2012: PREVENTING PTS

We suggest use of compression stockings (Grade 2B) for 2 years.

CHEST 2012; 141(2)(Suppl):e419S–e494S

ATTRACT TRIAL (N=692): (ILIO)FEMORAL DVT

STUDY ENROLLMENT
PRE-RANDOMIZATION PROCEDURES
RANDOMIZATION (1:1 Ratio)
CONTROL ARM
PCDT ARM
LONG-TERM TREATMENT
FOLLOW-UP

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

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

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

COMMON PATHOPHYSIOLOGY: VTE AND ATHEROSCLEROSIS

DEFINITIONS OF PE:
AHA PE Guidelines 2011

- Massive PE: sustained hypotension, pulselessness, or persistent bradycardia
- Submassive PE: RV dysfunction or myocardial necrosis, without hypotension
- Low Risk PE: no markers of adverse prognosis

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

(Piazza, Goldhaber. Circulation 2010;121: 2146)
**RISKS FOR POOR PROGNOSIS**

1. Elevated biomarkers (troponin)  
   (European Heart J 2010; 31: 1836)
2. RV volume and pressure overload: enlargement/ hypokinesis:  
   CT—(JACC Cardiovasc Imaging 2011; 4: 841-849)  
   ECHO—(Circulation 2010;122: 1124)
3. “Weekend Effect”

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**RV/LV VOLUME RATIO**

\[ \text{RVV/ LVV} = 1.6 \]

(HR 30-day death=6.5 for ratio > 1.2)

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**RV DYSFUNCTION/ TN ELEVATION COMBO in PE: PROGNOSIS**  
(n=1,273)

Stein et al.  Am J Cardiol 2010; 106: 558-563

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**SUBMASSIVE PE: INCREASED RV AND DIASTOLIC PRESSURE**


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**Impact of RV Dysfunction on PE**

Cumulative Mortality

Days from Diagnosis

RV Hypokinesis = 20.9%

Normal RV Function = 14.8%

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**WEEKEND IMPACT: MORTALITY RATE**

(Nanchal R, et al. CHEST 2012; epubl March 29)
**Clinical evaluation**
- Anatomic size of PE
- RV size/ function
- Cardiac biomarkers

**Risk Stratify**
- Low Risk
  - Anticoagulation Alone (Basic)
- High Risk
  - Anticoagulation + Lysis/Embolectomy (Advanced)

**Low Risk**
- Anticoagulation + Lysis/Embolectomy

**High Risk**
- Anticoagulation Alone

**PARENTERAL ANTICOAGULATION AS A “BRIDGE” TO WARFARIN**
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, lepirudin, 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 due to:**
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) Rapid turnaround genetic testing (CoumaGen-II. Circ 2012; March 19)
6) Point-of-care self-testing
7) INR Testing q 12 weeks if stable (CHEST 2012; 141: (Suppl) e153S)

**WARFARIN PHARMACOGENOMICS**
1. Cytochrome P450 2C9 genotyping identifies mutations associated with impaired warfarin metabolism.
2. Vitamin K receptor polymorphism testing can identify whether patients require low, intermediate, or high doses of warfarin.

(Schwartz Ul. NEJM 2008; 358: 999)

**COUMAGEN-II: PG DOSING ACHIEVES A TTR OF 71%**

(Circulation 2012; epub March 19)
TWO NIH-SPONSORED TRIALS ARE UNDER WAY

- Clinical Nomograms versus Rapid Turnaround Pharmacogenetic Nomograms for warfarin dosing
- “COAG” (N=1,238); “GIFT” (N=1,600)
- Stay tuned for results in 2014.

COMPARISON OF NEW ANTICOAGULANTS WITH WARFARIN

<table>
<thead>
<tr>
<th>Features</th>
<th>Warfarin</th>
<th>New Agents</th>
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<tbody>
<tr>
<td>Onset</td>
<td>Slow</td>
<td>Rapid</td>
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<tr>
<td>Dosing</td>
<td>Variable</td>
<td>Fixed</td>
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<tr>
<td>Food effect</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Many</td>
<td>Few</td>
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<tr>
<td>INR Monitoring</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Half-life</td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td>Antidote</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

SITES OF ACTION

Steps in Coagulation Coagulation Pathway Drugs

Initiation

Fibrin formation

(Fibrinogen) → Fibrin

(Rivaroxaban) → Apixaban → Edoxaban → Betrixaban → Dabigatran

(Rivaroxaban) → TF/VIa → Xa → IXa → VIIIa → X

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

RIVORAXABAN VS. ENOX/WARFARIN FOR DVT/PE TREATMENT

“EINSTEIN”

(NEJM 2010; 363: 2499-2510) [NEJM 2012; 366: 1287-1297]

EINSTEIN DVT/PE PROGRAM

**EINSTEIN-DVT** (Confirmed DVT without PE)

- Rivaroxaban 15 mg BID for 3 weeks; then 20 mg once daily

**EINSTEIN-PE** (Confirmed PE without DVT)

- Enoxaparin BID > 5 Days + VKA to target INR = 2.5 (range 2-3)

Primary Outcome:

Symptomatic recurrent VTE

(R(EINSTEIN-DVT. NEJM 2010; 363: 2499)

Immediate initiation with rivaroxaban; No parenteral anticoagulant given.

“clinical equipoise”; 1 of 4: provoked DVT.

(N=2,449)

(Einstein PE. NEJM 2012; 366: 1287-1297)

(N=1,196)
CHEST ACCP GUIDELINES 2012: DVT/PE (9TH EDITION)

For acute DVT or PE, we recommend initial parenteral anticoagulation (Grade 1B) or anticoagulation with rivaroxaban.

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PE PATHOPHYSIOLOGY

RV Pressure Overload → RV Wall Tension
RV Dysfunction → RV Ischemia or Infarction
LV Preload → Coronary Perfusion
LV Cardiac Output → Systemic Pressure

(Vascular Medicine 2010; 15: 419-428)

ADVANCED VTE THERAPIES

• PE thrombolysis with TPA (Piazza G, Goldhaber SZ. Vasc Med 2010; 15: 419-428)
• Catheter-based reperfusion for PE (Kucher N. Circulation 2011; 124: 2139-2144)
• IVC filter (Stein PD. Am J Med 2011; 124: 655-661)
• Surgical embolectomy (Stein PD. Am J Med 2012; 125: 471)

“PROMISE” OF THROMBOLYSIS

• Reverse right heart failure (reduce mortality)
• Reduce RV pressure overload
• Prevent release of serotonin
• Dissolve leg/ pelvic thrombus in situ (reduce recurrent PE)
• Improve capillary blood flow (reduce CTEPH)
THROMBOLYSIS IN PE: RAPID ANGIOGRAPHIC IMPROVEMENT

THROMBOLYSIS IN PE: RAPID RV AND ECHOCARDIOGRAPHIC IMPROVEMENT

USE OF LYTIC THERAPY IN UNSTABLE PE

LYTIC THERAPY AND MORTALITY: UNSTABLE PE

FIBRINOLYSIS FOR PE: AHA PE Guidelines 2011

- **Massive PE**: with acceptable risk of bleeding complications
- **Submassive PE**: severe RV dysfunction, or major myocardial necrosis, or worsening respiratory insufficiency, with low risk of bleeding

(Circulation 2011; 123: 1788-1830)
CATHETER TECHNIQUES
“Pharmacomechanical”
- Mechanical fragmentation
- Clot pulverization (rotational)
- Hydrodynamic (AngioJet®)
- Lysis plus ultrasound (EKOS®)
- Pulse spray low-dose lytic agent
- PA balloon dilatation/stenting
(Kuo WT et al. JVIR 2009; 20: 1431-1440)

ULTRASOUND THROMBOLYSIS
The premise: Use of low-power ultrasound energy loosens fibrin strands, speeds thrombolysis, and facilitates reduction in fibrinolytic drug dose.

EKOS® DRUG DELIVERY CATHETER

SURGICAL EMBOLECTOMY AT BWH: SURGEON’S CELL PHONE
N=47
Survival = 94 %
(J Thorac Cardiovasc Surg 2005;129:1018)
**EMBOLECTOMY FOR PE:**
AHA PE Guidelines 2011

- **Massive PE:** catheter embolectomy and fragmentation or surgical embolectomy, if contraindications to fibrinolysis—is “reasonable”
- **Submassive PE:** severe RV dysfunction, or major myocardial necrosis, or worsening respiratory insufficiency—may "be considered"

(Circulation 2011; 123: 1788-1830)

**BARD RECOVERY INFERIOR VENA CAVAL FILTER**

**INCREASING USE OF VC FILTERS**

(Stein PD. Am J Med 2011; 124: 655-661)

**IVC FILTERS FOR PE:**
AHA PE Guidelines 2011

- Contraindications to anticoagulation
- Recurrent PE despite adequate anticoagulation
- Very poor cardiopulmonary reserve, “including those with massive PE”

(Circulation 2011; 123: 1788-1830)

**IVC FILTERS AND IN-HOSPITAL MORTALITY**

(Stein PD. Am J Med 2012; epub)

**IVC FILTERS FOR PE:**
AHA PE Guidelines 2011

- Contraindications to anticoagulation
- Recurrent PE despite adequate anticoagulation
- Very poor cardiopulmonary reserve, “including those with massive PE”

(Circulation 2011; 123: 1788-1830)

**High VTE Recurrence Rate**

(Prandoni. Haematologica 2007; 92: 199-205)

(N=1,626 DVT patients)
RISKS FOR RECURRENCE
• “Unprovoked”—e.g., long-haul travel
• Strong FH; PMH of VTE
• Lupus anticoagulant, protein C or S deficiency (Eur Heart J 2008; 29: 2276)
• Cancer
• Male (McRae S. Lancet 2006; 368: 371)
• Presentation with PE Symptoms (Eichinger. Arch Intern Med 2004;164: 92)

DOES HYPERCOAGULABILITY PREDICT RECURRENT VTE?
• Probably: lupus anticoagulant, protein C or S deficiency
• No Evidence: heterozygous Leiden or prothrombin gene mutation (European Heart Journal 2008; 29: 2276-2315)

OPTIMAL DURATION STRATEGY

Acute PE or DVT

Provoked

3-6 Months Rx

Considering past/family VTE history, gender, recanalization of leg veins on U/S, hypercoagulability, patient preference

Unprovoked

Gray Zone

Individualize Rx

Consider Lifelong Rx

(Gray Zone Unprovoked)

CHEST ACCP GUIDELINES 2012: DURATION OF RX
If provoked by surgery or a nonsurgical transient risk factor, anticoagulation for 3 months (Grade 1B). If unprovoked with low to moderate bleeding risk, we suggest extended anticoagulant therapy rather than 3 months (Grade 2B).

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CLOT TRIAL for cancer pts: Reduction in Recurrent VTE

Risk reduction = 52%
p-value = 0.0017

Lee et al. NEJM 2003; 349: 146

CHEST ACCP GUIDELINES 2012: DVT AND CANCER
We recommend extended anticoagulant therapy rather than 3 months of therapy (Grade 1B). We suggest LMWH over VKA therapy (Grade 2B).

CHEST 2012; 141(2)(Suppl):e419S–e494S
Venous thrombi: fibrin, platelets, red cells, leukocytes.
(Becker RC. NEJM 2012; 366: 2028)

**RISK OF RECURRENT VTE: ASPIRIN VS. PLACEBO**

Placebo: 43/197=11.2%/yr; Aspirin: 28/205=6.6%/yr


**TAKE HOME MESSAGES**
1. CTEPH and PTS are late effects of VTE.
2. Risk stratify to guide use of thrombolysis or (catheter) embolectomy.
3. Select a parenteral anticoagulant, and “bridge” to warfarin.
4. Alternatively, use rivaroxaban as oral monotherapy without a parenteral agent.
5. Thrombolysis and IVC filters appear to reduce mortality in unstable patients.

**TAKE HOME MESSAGES**
6. Role of thrombolysis in submassive PE remains uncertain.
7. The 10-year VTE recurrence rate is high after anticoagulation is discontinued: about 20% for “secondary” and 50% for “primary” VTE.
8. Venous thrombi contain activated platelets and proinflammatory mediators.
9. Aspirin appears to halve the rate of idiopathic VTE following 6-12 months of initial standard anticoagulation.

**Which most completely describes pathophysiology leading to VTE?**

a) Inflammation, hypercoagulability, endothelial injury
b) Red blood cell “sludging”
c) Factor V Leiden genetic mutation
d) Prothrombin gene mutation
e) Plasminogen activator inhibitor combined with acquired resistance to LMWH

**Which most completely describes pathophysiology leading to VTE?**

a) Inflammation, hypercoagulability, endothelial injury
Which most accurately describes rivaroxaban (versus LMWH/warfarin) for PE treatment?

a) Superior efficacy; noninferior safety  
b) Superior efficacy; superior safety  
c) Noninferior efficacy; noninferior safety  
d) Noninferior efficacy; superior safety  
e) Best used with a LMWH “bridge”

Which most accurately describes rivaroxaban (versus LMWH/warfarin) for PE treatment?

d) Noninferior efficacy; superior safety

Supplementary References
5. Stein PD. Outcome in stable patients with acute pulmonary embolism who had right ventricular enlargement and/or elevated levels of troponin I. Am J Cardiol 2010;106:558-563.