

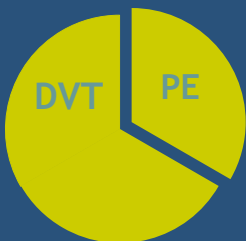
## Current Concepts in the Diagnosis and Management of Venous Thromboembolism

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WMSHP Spring Seminar  
May 17<sup>th</sup>, 2011

## Objectives

1. Discuss antithrombotic treatment options for venous thromboembolism.
2. Describe the role of thrombolytic therapy for pulmonary embolism.

## Venous Thromboembolism (VTE)



Osinbowale O, et al. Postgraduate Medicine 2010; 122:54-65.

## Venous Thromboembolism (VTE)

- Third most common cause of cardiovascular mortality
- Estimated annual incidence in the U.S.
  - 1,350,000

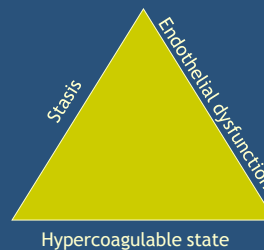
Osinbowale O, et al. Postgraduate Medicine 2010; 122:54-65.

## VTE Incidence

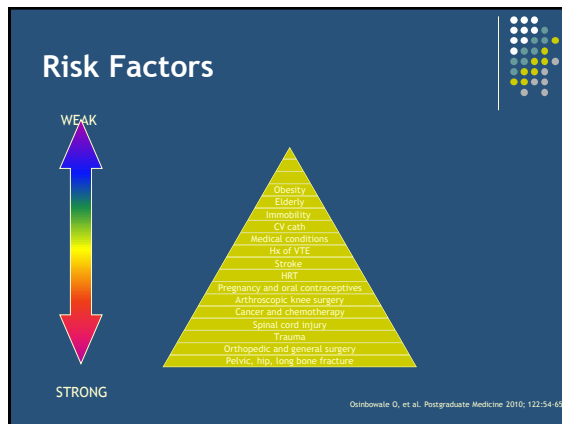
- Medical patients: 10-20%
- Spinal cord injury, trauma, critically ill: 80%
- Idiopathic: 25-50%

Osinbowale O, et al. Postgraduate Medicine 2010; 122:54-65.

## Virchow's Triad

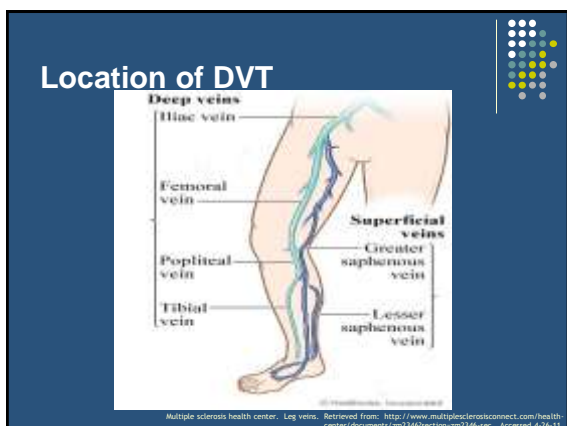


Osinbowale O, et al. Postgraduate Medicine 2010; 122:54-65.



- ### Hereditary Risk Factors
- Activated protein C (Factor V Leiden)
  - Prothrombin
  - Antithrombin deficiency
  - Protein C and Protein S deficiencies
  - Homocystinuria
  - Hyperhomocysteinemia
  - Antiphospholipid antibody
  - Increased levels of factors:
    - VIII
    - IX
    - XI
- Osinbawale O, et al. Postgraduate Medicine 2010; 122:54-65.  
Anderson FA Jr, et al. Circulation 2003;107 (23 suppl 1):1-9-1-16.

- ### Clinical Presentation
- DVT
    - Pain
    - Erythema
    - Warmth
    - Swelling of affected limb
  - PE
    - Dyspnea
    - Pleuritic pain
    - Cough
    - Tachypnea
    - Crepitation
    - Tachycardia
    - PEA
    - Hemoptysis
- 
- Hendel RC, et al. Circulation 2003;107:e224.



- ### Diagnosis of VTE
- Lab tests
    - D-dimer
  - Imaging
    - Compression ultrasonography
    - Doppler ultrasound
    - Ventilation-perfusion scan
    - Computed tomography
    - Pulmonary angiography
- Osinbawale O, et al. Postgraduate Medicine 2010; 122:54-65.

## D-dimer

- Fibrin degradation product
- Levels > 500 ng/mL generally indicate VTE
  - Find out hospital laboratory specific cut-off
- Nonspecific
  - Can be elevated in other conditions including:
    - Infection
    - Malignancy
    - Recent surgery
- Level alone cannot establish diagnosis

Ombrowale O, et al. Postgraduate Medicine 2010; 122:54-65.

## Compression Ultrasonography

- Noninvasive test of choice
- To perform external compression is applied by pushing down on the skin with the ultrasound probe
  - The vein should compress
  - If clot(s) present the vein will not compress
- Can be applied to deep veins of the upper and lower extremities

Marrin, Paul. The ICU book, 3<sup>rd</sup> edition. Philadelphia, PA.

## Compression Ultrasonography



J Clin Med Assoc. 2010 Nov;73(11):563-7. Non-compressibility ratio of sonography in deep venous thrombosis. Retrieved from: <http://emj.oxfordjournals.org/doi/full/10.1093/emj/cdq227>, accessed 4-26-11.

## Doppler Ultrasound

- Another noninvasive technique for detecting venous thrombosis
- Pressure to skin is applied with transducer
- Doppler shift determines the velocity of blood flow
- Velocity recorded two ways:
  - Audibly: faster flow, higher frequency of signal
  - Color changes: faster flow, shift from blue to red

Marrin, Paul. The ICU book, 3<sup>rd</sup> edition. Philadelphia, PA.

## Doppler Ultrasound



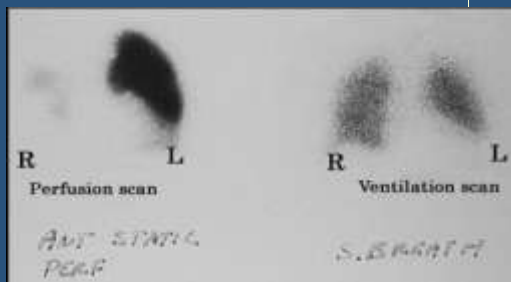
Massachusetts general hospital. New trial explores two sides of deep venous thrombosis treatment. 14 Feb 2011. Retrieved from: <http://www.massgeneral.org/about/newsarticle.aspx?id=2273>, accessed 5-6-11.

## Ventilation-Perfusion Scan

- VQ scan
  - Consists of two scans:
    - Ventilation: where air flows in the lungs
    - Perfusion: where blood flows in the lungs
- Utilizes a radioactive substance
  - Inhale gas during ventilation portion
  - Injected during perfusion study
- Avoid with underlying lung disease
  - Baseline CXR
- Results
  - Normal
  - Low-probability
  - High-probability
  - Intermediate-probability

National heart and lung institute. Lung ventilation/perfusion scan. Retrieved from: [http://www.nhlbi.nih.gov/health/dci/Diseases/lvq/lvq\\_all.html](http://www.nhlbi.nih.gov/health/dci/Diseases/lvq/lvq_all.html), Accessed on 4-27-11.

## Ventilation-Perfusion Scan



Nuclear Medicine V/Q Scan. Retrieved from [http://www.meddean.luc.edu/lumen/meded/Radio/curriculum/Medicine/NM\\_vq.htm](http://www.meddean.luc.edu/lumen/meded/Radio/curriculum/Medicine/NM_vq.htm) Accessed on 4-27-11.

## Computed Tomography

- Spiral (helical) CT
  - Detector rotates around patient to produce a 2-D view of lungs
- Conventional CT
  - 2-D slices of the lungs are created when the detector moves in increments along thorax



Deep venous thrombosis Academy. Pulmonary embolism. Retrieved from [http://www.academy.de/linkektion/cva/01\\_cva/07\\_deep\\_venous\\_thrombosis/stre/index02.html](http://www.academy.de/linkektion/cva/01_cva/07_deep_venous_thrombosis/stre/index02.html) Accessed on 4/27/11. Hertzog, Paul. The ICU book, 3rd edition. Philadelphia, PA.

## Pulmonary Angiography

- Catheter inserted in groin is threaded through heart into pulmonary arteries
- Dye is injected
- X-rays are taken as dye travels through arteries



National Heart and Lung Institute. Pulmonary Embolism. Retrieved from [http://www.nhlbi.nih.gov/health/od/diseases/pe/pe\\_diagnosis.html](http://www.nhlbi.nih.gov/health/od/diseases/pe/pe_diagnosis.html) Accessed 4-27-11.

Messing the outcome: an unusual presentation of pulmonary embolism. BMJ Case Reports Published 1 January 2009; published online 1 June 2009. Retrieved from: <http://casereports.bmj.com/content/2009/bcr.01.2009.1505.full>. Accessed 4-27-11.

## ECHO-2D Transthoracic

- Evaluate right ventricle
- Used as an alternative to CT angio in setting of renal insufficiency when contrast is best avoided
- May also consider lower extremity doppler if unable to do CT angio

## Treatment Goals of VTE

- Prevent fatal PE
- Reduce morbidity
- Prevent recurrent VTE
  - Chronic illness
  - ~33% of patients will develop recurrent VTE in 10 years
- Prevent complications
  - Post-thrombotic syndrome
  - HIT
  - Bleeding
  - Infection

Ignacio, J et al. Drugs 2010; 70 Suppl. 2:3-10.

## Treatment of VTE

- DVT
    - ACCP
      - LMWH
      - UFH
      - Fondaparinux
  - Initiate VKA on first day of therapy
  - Treat for minimum of 5 days and until INR  $\geq 2$  for 24 hours
- PE
    - ACCP
      - LMWH
      - UFH
      - Fondaparinux
  - Initiate VKA on first day of therapy
  - Treat for minimum of 5 days and until INR  $\geq 2$  for 24 hours

Kearon C, et al. CHEST 2008; 133:454S-545S. Ignacio, J et al. Drugs 2010; 70 Suppl. 2:3-10.

## Duration of Anticoagulant Therapy

- DVT/PE with reversible risk factor: 3 months
- 1<sup>st</sup> episode unprovoked DVT/PE: 3 months minimum and reassess risk-benefit of long term
- 2<sup>nd</sup> episode unprovoked DVT/PE: long term

Kearon C, et al. CHEST 2008; 133:4545-5455.

## Unfractionated Heparin

- Discovered in early 1900s
- Anticoagulant, potentiates antithrombin activity
  - Enhance inactivation of thrombin and factor Xa
- Isolated from porcine small intestine mucosa
- Glycosaminoglycan
- Large MW, highly sulfated, strong negative charge
- Onset: immediate
- Half-life: 1-2 hours

Pendleton, R et al. Clin Chest Med 2010; 31:691-706.  
Morris, TA et al. Clin Chest Med 2010; 31:707-718.

## Unfractionated Heparin

- Nonspecific binding to heparin-binding proteins
- Variable bioavailability
- Elimination not dependent on renal/hepatic function
- Monitoring based on aPTT
- IV infusion or SubQ administration acceptable
- Continuous IV infusion is preferred in setting of acute VTE

Pendleton, R et al. Clin Chest Med 2010; 31:691-706.  
Morris, TA et al. Clin Chest Med 2010; 31:707-718.

## Unfractionated Heparin

- IV bolus (80 units/kg) followed by continuous infusion start at 18 units/kg/hr (or 1300 units/hr)
- Titrate to achieve and maintain aPTT
- Monitored SubQ UFH, fixed-dose UFH, or IV UFH are treatment options for VTE
- Reversal agent: protamine IV
  - Heparin:antithrombin complex broken
  - 1-1.5 mg protamine/ 100 units heparin

Kearon C, et al. CHEST 2008; 133:4545-5455.

## Low Molecular Weight Heparin

- Enoxaparin, dalteparin, and tinzaparin
- Chemical or enzymatic depolymerization of UFH
- Enhance factor Xa inactivation
- Smaller MW, less negative charge
- Less nonspecific protein binding
- More predictable response
  - Onset ~2-3 hours
- Longer half-life (hrs)
  - Enoxaparin: 4.5-7; dalteparin: 2-5; tinzaparin: 3-4

Pendleton, R et al. Clin Chest Med 2010; 31:691-706.  
Morris, TA et al. Clin Chest Med 2010; 31:707-718.

## Low Molecular Weight Heparin

- Preferred initial therapy
  - Ease of administration
  - Effective
  - Safety profile
- Do not recommend routine anti-factor Xa level monitoring
- Elimination dependent on renal function
  - UFH over LMWH in setting of severe renal impairment
- Reversal agent (unlabeled use): protamine IV
  - 1 mg protamine/mg of enoxaparin
  - 1 mg protamine/100 anti-Xa int. units of dalteparin/tinzaparin

Kearon C, et al. CHEST 2008; 133:4545-5455.  
Pendleton, R et al. Clin Chest Med 2010; 31:691-706.

## LMWH Dosing Considerations

LMWH	enoxaparin (Lovenox®)	dalteparin (Fragmin®)	tinzaparin (Innohep®)
Treatment of DVT with or without PE	1 mg/kg SubQ q 12 hrs or 1.5 mg/kg SubQ daily	DVT: 200 IU/kg SubQ daily or 100 IU/kg SubQ BID (do not exceed 18,000 IU/day)	175 anti-Xa int. units/kg SubQ daily
Dosage adjustment for renal impairment	$Cl_{cr} < 30$ mL/min: 1 mg/kg daily	Reduced clearance, use caution	Reduced clearance, use caution

## LMWH Dosing and Obesity

- Obesity
  - Underrepresented in trials
  - Limited published data
  - No increased bleeding when using TBW for obese vs. nonobese
  - Anti-Xa monitoring should be considered for weight >190kg

Pendleton, R et al. Clin Chest Med 2010; 31:691-706.

## LMWH and Renal Insufficiency

- Reports of fatal bleeding and worse outcomes
- Diminished renal clearance with drug accumulation
- Weight based UFH is preferred over LMWH in setting of severe renal impairment
- Dosage adjustment with renal impairment
- Not approved for use in dialysis patients

Pendleton, R et al. Clin Chest Med 2010; 31:691-706.

## LMWH and Pregnancy

- Preferred anticoagulant
- Dosage adjustments with increasing weight
- Recommended monitoring of anti-Xa levels

Pendleton, R et al. Clin Chest Med 2010; 31:691-706.

## Fondaparinux (Arixtra®)

- Synthetic pentasaccharide
  - Smaller, less negatively charged
- Antithrombin mediated inhibition of factor Xa
  - Neutralization of factor Xa inhibits thrombin formation and thrombus development
- Excretion: urine (unchanged drug)
- Subcutaneous administration
- Reaches steady state concentrations in 3 hrs
- Reversal
  - Supportive care
    - No specific antidote—protamine not an option
    - Hemodialysis may remove ~20%

Morris, TA et al. Clin Chest Med 2010; 31:707-718.

## Fondaparinux (Arixtra®)

- Indications:
  - DVT prophylaxis (hip fracture surgery, hip replacement surgery, knee replacement, or abdominal surgery)
    - Adults  $\geq$  50kg: 2.5 mg SubQ daily
  - Treatment of PE or DVT
    - Adults < 50 kg: 5 mg SubQ daily
    - 50-100 kg: 7.5 mg SubQ daily
    - >100 kg: 10 mg SubQ daily
  - Dosage adjustment in renal impairment
    - $Cl_{cr}$  30-50 mL/min: use caution
    - $Cl_{cr}$  <30 mL/min: contraindicated

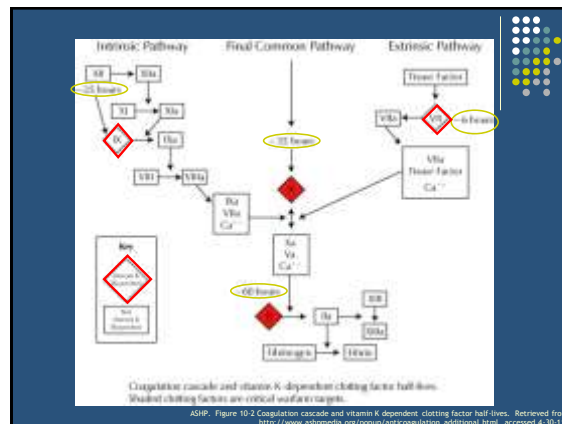
Morris, TA et al. Clin Chest Med 2010; 31:707-718.

## Vitamin K Antagonist



- Inhibit vitamin-K-epoxide reductase
  - Reduction in vitamin K available
  - Incomplete synthesis of factors II, VII, IX, X

ASHP. Figure 10-1 Vitamin K Cycle. Retrieved from [http://www.ashpmedia.org/pops/anticoagulation\\_additional.html](http://www.ashpmedia.org/pops/anticoagulation_additional.html), accessed 4/30/11.



ASHP. Figure 10-2 Coagulation cascade and vitamin K-dependent clotting factor half-lives. Retrieved from [http://www.ashpmedia.org/pops/anticoagulation\\_additional.html](http://www.ashpmedia.org/pops/anticoagulation_additional.html), accessed 4/30/11.

## Warfarin Dosing

- Personalized dosing can minimize prolonged duration of parenteral anticoagulants, adverse effects, and shorter length of stay
- Studies have compared 5 mg to 10 mg for initial doses
  - 5 mg effective and achieved therapeutic INR in 5 days with less overanticoagulation

Crowther MA, et al. Arch Intern Med 1999;159(1):46-48.  
Harrison L, et al. Ann Intern Med 1997;126(2):133-136.

Keaton C, et al. CHEST 2008; 133:4545-4545.

## INR Goal

- Target INR 2.5 (2.0-3.0)
- For patients with unprovoked DVT that have completed 3 months of therapy rather than stop recommend low-intensity INR (1.5-1.9)
- Do not recommend high-intensity (3.1-4.0)

## Warfarin and Genetic Testing

- Genetic polymorphisms explain variability
- Additional studies are needed to explore role
- Current dosing recommendations
  - non-gene based

Pendleton, R et al. Clin Chest Med 2010; 31:691-706.

## Massive Pulmonary Embolism

- Presentation:
  - Dyspnea at rest, anxiety, syncope, lightheadedness
- Criteria:
  - SBP < 90 mmHg or drop of  $\geq 40$  mmHg x 15 min
  - Cardiogenic shock
    - Hypoxia
    - Tissue hypoperfusion
    - Decreased level of consciousness
    - Oliguria
    - Cool, clammy extremities

Kucher N, et al. Circulation 2005; 112:e28-e32.

## Management of Massive PE

- UFH
  - Initiate high dose UFH as soon as suspected
- Fibrinolytics
  - Discontinue UFH when ready to administer
  - Obtain aPTT after infusion & resume UFH if <80
- Surgical embolectomy
- Catheter thrombectomy
  - If contraindication to thrombolytic
  - Removes thrombi from pulmonary arteries

Kucher N, et al. Circulation 2005; 112:e28-e32.

## FDA Approved Fibrinolytic Therapy for PE

- Mechansim: bind to plasminogen/plasmin complex activating plasminogen to form free plasmin, fibrin-bound plasmin initiates clot lysis.
- Alteplase (rt-PA) -fibrin specific
- Urokinase-nonselective
- Steptokinase-nonselective
- Reteplase and Tenecteplase are NOT

Todd JL, et al. CHEST 2009; 135:1321-1329.

## Contraindications to Fibrinolytics

- Absolute
  - History of ICH
  - Active internal bleeding
  - Head trauma
  - CVA w/in 2 months
  - Intracranial/intraspinal surgery w/in 3 months
  - Bleeding diathesis
  - Intracranial neoplasm, arteriovenous malformation, aneurysm
- Relative
  - Recent internal bleeding
  - Recent trauma (CPR)
  - Recent surgery/biopsy
  - Venipuncture at noncompressible site
  - Pregnancy
  - Age>75 yr
  - Pregnancy
  - Uncontrolled htn
  - Diabetic retinopathy

Todd JL, et al. CHEST 2009; 135:1321-1329.

## Alteplase

- Dose: 100 mg IV over 2 hours
  - 15 mg bolus followed by 85 mg over 2 hours
  - <67 kg: 15 mg bolus, 0.75 mg/kg over 30 mins (max=50), then 0.5 mg/kg (max=35) over 60 mins
  - >67 kg: 15 mg bolus, 50 mg over 30 mins, then 35 mg over 60 mins

Rivera-Bou WL et al. June 7, 2010). Thrombolytic therapy in emergency medicine. Retrieved 5.4.11 from <http://emedicine.medicap.com/article/811734-overview>.

## Rt-PA 50 mg/2h vs 100 mg/2h

- Compare efficacy & safety of regimens
- Prospective, randomized, multi-center
- N=118
  - Rt-PA 50 mg/2h (n=65)
  - Rt-PA 100 mg/2h (n=53)
- Efficacy measured by improved:
  - Right ventricle dysfunction on ECHO, lung perfusion defects on V/Q scans, pulmonary artery obstruction on CT
- Death, bleeding, and recurrent pulmonary thromboembolism were reported

Wang C, et al. CHEST 2010; 137:254-262.

## Results

- Both groups showed improvement in:
  - right ventricular function
  - lung perfusion
  - pulmonary artery obstruction

Wang C, et al. CHEST 2010; 137:254-262.

## Results

Adverse events	rt-PA 100mg	rt-PA 50mg	P- value
Death	3 (6)	1 (2)	.472
Death due to PTE	2 (4)	1 (2)	
Death due to bleeding	1 (2)	0 (0)	
Bleeding complications	17 (32)	11 (17)	.54
Recurrent PTE	2 (4)	1 (2)	.858

Wang C, et al. CHEST 2010; 137:254-262.

## Bleeding Complications

Body weight (kg)	rt-PA 100mg	rt-PA 50mg
<65	4/27 (14.8)	7/17 (41.2)
65-74	4/15 (26.7)	6/15 (40.0)
≥75	3/22 (13.6)	4/21 (19.0)

Wang C, et al. CHEST 2010; 137:254-262.

## Inferior Vena Cava (IVC) Filters

- Not routinely recommended in addition to anticoagulation
- If unable to anticoagulate due to risk of bleeding, consider IVC filter
- If bleeding resolves should receive appropriate duration of anticoagulation despite IVC filter in place

Kearon C, et al. CHEST 2008; 133:4545-5455.

## Superior Vena Cava (SVC) Filters

- Consider in patients with upper extremity DVT that meet the following criteria:
  - Unable to anticoagulate
  - Demonstrated progression or documented PE

Kearon C, et al. CHEST 2008; 133:4545-5455.

## New Options for VTE

- Dabigatran (Pradaxa®)
  - Oral direct thrombin inhibitor
  - Dabigatran etexilate (prodrug) → dabigatran
  - Indication: nonvalvular afib for prevention of stroke and embolism; postoperative thromboprophylaxis (Canada)
  - No monitoring necessary
  - Excretion: renal
  - Peak plasma levels: 2 hours
  - Half-life: ~8 hours (1 dose); ~14-17 hours (>1)

Morris, TA et al. Clin Chest Med 2010; 31:707-718.  
Palareti G, et al. Expert Opin 2010;15:107-117.

## Dabigatran vs Warfarin for VTE

- Randomized, double-blind
- VTE with initial parenteral therapy
  - Dabigatran 150 mg PO BID
  - Warfarin dose adjusted to INR of 2-3
- Primary outcome: recurrent VTE & related death
- Other end points:
  - Bleeding, ACS, LFTs, adverse events

The RE-COVER Study Group. NEJM 2009; 361:2342-2352.

## Results

- Recurrent VTE and related death
  - Dabigatran n=30 (2.4%)
  - Warfarin n=27 (2.1%)
  - HR 1.10;95% CI (0.65-1.84)
- Major bleeding
  - Dabigatran n=20 (1.6%)
  - Warfarin n=24 (1.9%)
  - HR 0.82;95% CI (0.45-1.48)
- Any bleeding
  - Dabigatran n=205 (16.1%)
  - Warfarin n=277 (21.9%)
- No difference in deaths, ACS, and abnormal LFTs
- Adverse events prompting discontinuation of the drug
  - Dabigatran 9%
  - Warfarin 6.8%
  - P=0.05

The RE-COVER Study Group. NEJM 2009; 361:2342-2352.

## New Options for VTE

- Rivaroxaban
  - Oral direct Xa inhibitor
  - Indication: postoperative thromboprophylaxis (Canada)
  - Excretion: hepatic (2/3) and renal (1/3)
  - Peak plasma levels: 3 hours
  - Half-life: 9 hours (young); 11-13 hours (elderly)

Morris, T.J. et al. Clin Chest Med 2010; 31:707-718.  
Palaretti G, et al. Expert Opin 2010;15:107-117.

## Rivaroxaban vs enoxaparin + VKA

- The Acute DVT Study
  - Randomized, open label
  - Oral rivaroxaban (15 mg BID x 3 weeks, then 20 mg daily) with subQ enoxaparin 1mg/kg BID + VKA
  - 3449 patients randomized
    - 1731 assigned to rivaroxaban→1718 received
    - 1718 assigned to enoxaparin + VKA →1711 included
  - Primary outcome
    - Recurrent VTE

The EINSTEIN Investigators. NEJM 2010; 363:2499-2510.

## Results

	Rivaroxaban	Enoxaparin + VKA	Hazard Ratio (95% CI)	P value
Recurrent VTE	36 (2.1)	51 (3.0)	0.68 (0.44-1.04)	<0.001
1 <sup>st</sup> major or clinically relevant nonmajor bleeding	139 (8.1)	138 (8.1)	0.97 (0.76-1.22)	0.77

The EINSTEIN Investigators. NEJM 2010; 363:2499-2510.

## Conclusion

- VTE is a common chronic condition
- Highly preventable cause of hospital death
- Thromboprophylaxis is often under utilized in hospital setting
- Effective antithrombotic agents available
- Ongoing clinical trials for newer therapy

## Questions