Venous Thromboembolism

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Disclosures- Michael Streiff, MD

• Consulting
  – Daiichi Sankyo
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• Clinical Trial Adjudication Committee- DalteCan study
  – Eisai
Objectives

• Review the pathophysiology of venous thromboembolism
• Review the prevention of VTE
• Review the acute and chronic therapy of VTE
What causes VTE?

- Stasis
- Vessel Wall
- Hypercoaguability

Rudolf Virchow (1821-1902)
VTE Risk Factors

Age and surgery are potent VTE risk factors

Epidemiology of VTE in pregnancy

- Incidence of VTE – 0.76 to 1.72 per 1000 pregnancies
- Incidence of fatal PE – 1.1-1.5 per 100,000 deliveries
- VTE increases with age
  - < 20 – 1.47 per 1000 deliveries
  - 20-29 years – 1.63
  - 30-39 years – 1.93
  - 40+ years – 2.75
- VTE varies with ethnicity
  - African American – 2.64 per 1000 deliveries
  - Caucasian – 1.75
  - Hispanic – 1.25
  - Asian – 1.07

Travel and VTE

• Prospective cohort study of 8775 employees (1/1/98-1/1/06)
• Web questionnaire with objective event documentation
• Flights= 315,762
• VTE- DVT=36, PE=17
• Travel is a modest time-dependent risk factor for VTE

Kuipers S et al. PLOS Med 2007
Mechanisms of Thromboembolism in Cancer

- Patient
  - Age
  - Ethnicity
  - Thrombophilia
- Cancer
  - Type
  - Stage
  - Pro-coagulants
  - Host interactions
- Treatment
  - Surgery
  - Chemotherapy
  - Growth factors

The risk of VTE varies with tumor type

VTE risk increases with number of risk factors

N=1464

Venous Thromboembolism: the culmination of multiple risk factors

Thrombosis Threshold

1 2 3
VTE prophylaxis works


- Sx DVT: 63% reduction, NNT 345
- Sx PE: 67% reduction, NNT 345
- Fatal PE: 62% reduction, NNT 400
- Major Bleeding: 32% increase

N=19,958
2010 NCCN DVT Prophylaxis Guideline

Adult Cancer Inpatient

No

Contraindication to Anticoagulation Treatment

Yes

Pharmacologic Prophylaxis
- UFH
- LMWH
- Pentasaccharide

Mechanical Prophylaxis
- Sequential Compression Devices
- Compression Stockings
INPATIENT/OUTPATIENT PROPHYLACTIC ANTICOAGULATION TREATMENT

- LMWH: (category 1 for inpatient)
  - Dalteparin 5,000 units subcutaneous daily
  - Enoxaparin 40 mg subcutaneous daily
  - Tinzaparin 4,500 units (fixed dose) subcutaneous daily or 75 units/kg subcutaneous daily
- Fondaparinux (category 1 for inpatient)
  - Fondaparinux 2.5 mg subcutaneous daily
- Unfractionated heparin: 5,000 units subcutaneous 3 times daily (category 1 for inpatient)
- Aspirin 81-325 mg daily
- Warfarin (adjusted to INR 2-3)
Contraindications to DVT prophylaxis

• Active or high risk of bleeding
• Therapeutic anticoagulation
• Thrombocytopenia (Platelets < 50,000/μL)
• Elevated INR (INR > 1.5) or aPTT ratio > 1.3 (excluding lupus inhibitor)
• UFH or LMWH- HIT
• SCDs or GCS- known acute DVT, arterial insufficiency, open wound
VTE Prophylaxis – Duration of Therapy

- Internal Medicine- duration of hospital stay (or at least 6-10 days?)
- Oncology- duration of hospital stay
  - Myeloma and high risk ambulatory pts- outpatient prophylaxis
  - Cancer surgery- up to 30 days
- General surgery- duration of hospital stay (or at least 10-14 days)
- Total Knee Arthoplasty- at least 14 days (consider up to 35 days)
- Total Hip Arthroplasty- at least 35 days
- Trauma- duration of rehabilitation
## Catheter Prophylaxis

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Outcome assessment</th>
<th>DVT (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bern et al. 1990</td>
<td>Warfarin 1 mg</td>
<td>Venogram</td>
<td>9.5</td>
<td>&lt;0.001</td>
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<tr>
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<td>No treatment</td>
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<td>37.5</td>
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<td>Monreal et al. 1996</td>
<td>Dalteparin 2500</td>
<td>Venogram</td>
<td>6</td>
<td>0.002</td>
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<tr>
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<td>No treatment</td>
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<td>62</td>
<td></td>
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<tr>
<td>Reichardt et al. 2002</td>
<td>Dalteparin 5000</td>
<td>Clinical</td>
<td>3.7</td>
<td>0.9</td>
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<tr>
<td></td>
<td>No treatment</td>
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<td>3.4</td>
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<tr>
<td>Couban et al. 2003</td>
<td>Warfarin 1 mg</td>
<td>Clinical</td>
<td>4.6</td>
<td>0.81</td>
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<td></td>
<td>Placebo</td>
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<tr>
<td>Verso et al. 2004</td>
<td>Enoxaparin 40 mg</td>
<td>Venogram</td>
<td>14.1</td>
<td>0.35</td>
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<tr>
<td></td>
<td>Placebo</td>
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<td>18</td>
<td></td>
</tr>
</tbody>
</table>
Adjusted dose warfarin prevents CVC thrombosis: WARP study

- A multicenter (N=68) open label study of warfarin CVC prophylaxis (N=1590)
- Study Arms-
  - No warfarin (404) vs. warfarin 1 mg (408)
  - Warfarin 1 mg (471) vs. warfarin (INR1.5-2.0) (473)
- Conclusion- Dose-adjusted warfarin is required to prevent CVC DVT

Initial VTE Treatment

• Pharmacologic
  – Unfractionated heparin
    • Bolus 70 U/kg IV
    • Infusion 16 U/kg/h adjusted to aPTT 50-80 seconds
  – LMWH
    • Dalteparin 200 IU/kg sc qday
    • Enoxaparin 1 mg/kg sc q12h
    • Tinzaparin 175 IU/kg sc qday
  – Fondaparinux 5-10 mg sc qday

• Mechanical
  – Vena caval filter (optional or permanent)
Unfractionated heparin: dosing

• Use weight based dosing
  – Venous thromboembolism- Bolus 70 units/kg, infusion 15 units/kg/hr (target aPTT 50-80 seconds)
  – Acute coronary syndrome- Bolus 60 units/kg, infusion 12 units/kg/hr (target aPTT 50-65 seconds 1.5-2.0)
  – Post-procedure- No bolus, infusion 8 units/kg/hr (target aPTT 50-65 seconds)
• Monitor aPTT at least qDay
• Monitor CBC at least qoDay
• Start warfarin once heparin therapeutic
• Continue UFH for at least 5-7 days until INR > 2
Low Molecular Weight Heparin- Properties

- Chemically/enzymatically fractionated forms of heparin
  - MW- 3-9 kD (4.5 kD)
- Available preparations-
  - Dalteparin (Fragmin™)
  - Enoxaparin (Lovenox™)
  - Tinzaparin (Innohep™)
- SC administration
- Cell/protein binding-lower
  - More predictable dose response
- Half-life- 3.5-5.5 hours
- Elimination- renal
- Monitoring- not routinely needed- anti-Xa assay

UFH

LMWH

AT  IIa

AT  gla domain
LMWH dosing

- **Enoxaparin (Lovenox™)**
  - 1 mg/kg SC q12h or 1.5 mg/kg SC qDay (latter discouraged in obese or cancer pts.)
  - Renal insufficiency
    - 1mg/kg SC qDay (CrCl < 30 ml/min)
    - Use heparin
  - Obesity
    - No dose reduction, consider Xa levels
- **Dalteparin (Fragmin™)**
  - 200 units/kg SC qDay or 100 units/kg SC q12h
- **Tinzaparin (Innohep™)**
  - 175 units/kg SC qDay
Fondaparinux (Arixtra®)

- Synthetic pentasaccharide
- Half-life- 17-21 hours
- Clearance- renal
- Daily Dose
  - < 50 kg = 5 mg
  - 50-100 kg = 7.5 mg
  - >100 kg = 10 mg
- Monitoring- not necessary, anti-Xa activity
- As effective as UFH or LMWH
- No HIT or osteoporosis
Acute VTE Therapy with Warfarin

• Warfarin
  – No loading doses
  – Watch for drug interactions
  – Starting dose = 2.5-5 mg
  – Concomitant therapy with parenteral agent for at least 5-7 days

• Indications for lower warfarin dose
  – Post-operative pts.
  – Concomitant interacting meds
  – Poor oral intake
  – Age > 75
  – Liver disease
  – Baseline INR ≥ 1.3

Ansell J. AHA Meeting 2004
## Warfarin-Drug interactions

<table>
<thead>
<tr>
<th>Increase INR</th>
<th>Decrease INR</th>
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<tbody>
<tr>
<td>TMP/SMX (Bactrim)</td>
<td>Rifampin, rifabutin</td>
</tr>
<tr>
<td>Metronidazole (Flagyl)</td>
<td>Barbiturates</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Carbamazepine</td>
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<tr>
<td>Fluconazole</td>
<td>Phenytoin</td>
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<tr>
<td>Voriconazole</td>
<td>Sucralfate</td>
</tr>
<tr>
<td>Broad-spectrum antibiotics</td>
<td>Ritonavir</td>
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<tr>
<td>Ciprofloxacin</td>
<td>Vitamin K</td>
</tr>
<tr>
<td>Quinidine</td>
<td></td>
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<tr>
<td>Thyroid hormones</td>
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</tr>
</tbody>
</table>
The Typical VTE Cohort

N=15,520

Recurrence rate 5.5 per 100 pt.-yrs.

Recurrence rate 1 per 100 pt.-yrs.

Recurrence rate 6 per 100 pt.-yrs.

Location of VTE influences Outcome

- The risk of fatal PE is less after DVT than PE
- Thrombus burden influences fatal PE risk
- Proximal DVT is associated with a higher recurrence rate (Pop DVT=5.1%, Fem DVT= 5.3%, Iliac DVT= 11.8%)
- Recurrent events mirror initial events (DVT=DVT in 79%; PE=PE in 81%)
- Conclusion- Location/event type influence outcomes

VTE Setting influences recurrence risk

- Systematic review of prospective cohort studies and RCTs
- 15 Studies
- 5159 Subjects
- Follow up- 3-96 months
- Conclusion- Setting of thrombosis strongly influences recurrence rate

Iorio A et al. Arch Intern Med 2010
Influence of duration of therapy on outcome

N=4,240

Outcome of idiopathic VTE

- Prospective cohort study (Prandoni P et al.)
- Patients=1626
- Follow up=10 years
- Conclusion- Only 50% of idiopathic VTE recur over 10 years

Not all idiopathic VTE are the same

D dimer and recurrent VTE

- D dimer - product of fibrinolysis
- PROLONG study (Palareti G et al. NEJM 2006)
  - F/U 1.4 years
  - 7 studies, 1888 patients
  - Recurrent VTE- Abnl vs. nl DD (8.9% vs. 3.5% per year)
How do we identify the low risk patient with idiopathic VTE?

• Prospective cohort study of 665 patients with idiopathic VTE
  – Enrolled at 12 centers, 4 countries prior to DC of warfarin after 5-7 months of therapy
  – Information of 76 laboratory and clinical variables associated with VTE were collected
  – Multivariate analysis used to develop clinical prediction rule for recurrent VTE

• Results
  – F/U population 600/665 (90%)
  – Mean F/U -18 months (1-47 mos.)
  – Annual risk of recurrent VTE 9.3% per year (7.7%-11.3%)
    • Men 13.7% (10.8%-17%)
    • Women 5.5% (3.7%-7.8%)

Clinical prediction rule for recurrent VTE in women

<table>
<thead>
<tr>
<th>Model</th>
<th>Variable</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>Low-risk group</th>
<th>High-risk group</th>
<th>% of patients identified by model as being at low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hyperpigmentation, edema and redness</td>
<td>0.89</td>
<td>0.37</td>
<td>0.97</td>
<td>1.6%</td>
<td>7.9%</td>
<td>34.7%</td>
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<td>Body mass index $\geq$ 30 kg/m$^2$</td>
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<tr>
<td></td>
<td>Age $\geq$ 65 yr</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>2</td>
<td>Hyperpigmentation, edema and redness</td>
<td>0.88</td>
<td>0.38</td>
<td>0.97</td>
<td>2.3%</td>
<td>10.4%</td>
<td>35.5%</td>
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<tr>
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<td>d-Dimer $\geq$ 250 $\mu$g/L</td>
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<td></td>
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<tr>
<td>3</td>
<td>Hyperpigmentation, edema and redness</td>
<td>0.88</td>
<td>0.57</td>
<td>0.98</td>
<td>1.6%</td>
<td>14.1%</td>
<td>52.2%</td>
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<tr>
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<td>d-Dimer $\geq$ 250 $\mu$g/L</td>
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<td></td>
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<tr>
<td>4</td>
<td>Hyperpigmentation, edema and redness</td>
<td>0.76</td>
<td>0.65</td>
<td>0.96</td>
<td>2.3%</td>
<td>14.8%</td>
<td>38.7%</td>
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<tr>
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<td>d-Dimer $\geq$ 250 $\mu$g/L</td>
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<td></td>
<td>Previous secondary VTE</td>
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<tr>
<td>5</td>
<td>Hyperpigmentation, edema and redness</td>
<td>0.88</td>
<td>0.56</td>
<td>0.98</td>
<td>1.7%</td>
<td>13.8%</td>
<td>51.4%</td>
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<td>d-Dimer $\geq$ 250 $\mu$g/L</td>
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<td></td>
<td>Age $\geq$ 65 yr</td>
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</tbody>
</table>

Note: NPV = negative predictive value, VTE = venous thromboembolism.
*Model 3 was selected as the final model for women because it had the smallest annual risk of recurrent venous thromboembolism in the low-risk group, the highest NPV, $>10\%$ risk of recurrence in the high-risk group, and the highest low-risk excluded proportion. This model was also considered the most parsimonious and easy to remember and apply in the clinical setting.

Risk stratification for recurrent VTE: The Vienna Risk Model

Case 1: 45 M with idiopathic PE, D Dimer 1.0 mg/L
Total Points= 229
RR at 12 mo. = 9%
RR at 60 mo. = 30%

Case 2 58 F distal DVT, D dimer 0.25 mg/L
Total points= 80
RR at 12 mo. = <2%
RR at 60 mo. = <10%
Duration of Therapy for VTE

- Surgical/major trauma associated VTE- 3-6 months
  - Extended prophylaxis for subsequent surgery
    - Ambulatory surgery 10-14 days
    - Inpatient surgery 1-3 months
- Estrogen-associated VTE- 3-6 months
  - Therapeutic AC for pregnancy
- Pregnancy-associated VTE- 3-6 months and beyond the post-partum period (6-12 weeks)
  - Therapeutic AC for all subsequent pregnancies
- Cancer- associated VTE- at least 3-6 months or until cancer in remission whichever is longer
- Medical-illness VTE- at least 3-6 months
- Idiopathic VTE- indefinite therapy
- VTE with major thrombophilic risk factor (FVL homozygote, FVL/FII mutation compound heterozygote, Antithrombin, protein C or protein S deficiency, Antiphospholipid syndrome) – indefinite therapy
- VTE with IVC filter in place- indefinite
Calf Vein DVT Treatment

- 3 months of warfarin better than 5 days of heparin alone (Lagerstedt et al.)
- 6 weeks of VKA = 12 weeks (Pinede et al.)
- Clinical outcomes with calf DVT (Galanaud JP et al.)
  - Recurrent VTE at 3 mo.
    - Distal (2.2%) vs. Proximal (2.5%)
  - Major Bleeding at 3 mo.
    - Distal (0.8%) vs. Proximal (1.3%)

CVC associated thrombosis

• Common in cancer patients
  – 4.3% of cancer patients with a CVC (0.3 per 1000 CVC days) (Lee AYY et al. JCO 2006)
  – In 1514 HSCT patients 73% of VTE CVC related (3.6%) (Gerber D et al. Blood 2008)

• Diagnosis
  – Duplex US or CT venography

• Management
  – Anticoagulation w/o CVC removal – No recurrent VTE, 3 major bleeds (4%) (Kovacs M et al. J Thromb Haemost 2007)
  – CVC Removal ± AC
  – Thrombolytic therapy
Venous Anatomy
Lower Extremity Venous Anatomy

- External iliac vein
- Common femoral vein
- Deep femoral vein
- Femoral vein
- Popliteal segment of femoral vein
- Anterior tibial veins
- Peroneal veins
- Posterior tibial veins
- Plantar metatarsal vein
May-Thurner syndrome

Narrowed left iliac vein
(by pressure from right iliac artery)
Upper extremity venous anatomy
### Management of high INR

<table>
<thead>
<tr>
<th>INR</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR 5-9</td>
<td>Hold warfarin 1-2 days, follow INR, consider vit K 1-2.5 mg</td>
</tr>
<tr>
<td>INR &gt; 9</td>
<td>Hold warfarin, follow INR, consider vit K 2.5-5 mg</td>
</tr>
<tr>
<td>Serious bleeding</td>
<td>Hold warfarin, follow INR, give IV vit K 5-10 mg over 1 hour, consider FFP or Profilnine 25 units/kg + 2 units FFP</td>
</tr>
<tr>
<td>Life threatening bleeding</td>
<td>Hold warfarin, follow INR closely, give IV vit K 10 mg over 1 hour, Administer Profilnine 50 units/kg + 2 units FFP</td>
</tr>
</tbody>
</table>

### Anticoagulation Reversal

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Reversal</th>
<th>Additional considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated Heparin (Half-life ~ 60 min)</td>
<td>Protamine 1 mg/100 units UFH Infuse slowly (&lt; 5mg/min)</td>
<td>Max dose = 50 mg Risk of anaphylaxis</td>
</tr>
<tr>
<td>LMWH (Half-life 3.5-7 hrs)</td>
<td>Within 8 hrs: Protamine 1mg/1mg Enoxaparin More than 8 hrs: Protamine 0.5mg/mg Enox</td>
<td>Max dose = 50 mg Risk of anaphylaxis</td>
</tr>
<tr>
<td>Fondaparinux (Half-life 17-21 hrs)</td>
<td>FVIIa 90 mcg/kg IV or FEIBA 50-100 u/kg</td>
<td>rhFVIIa has been associated with thromboembolic events</td>
</tr>
<tr>
<td>Direct Thrombin Inhibitors (Half-life 25-80 min.)</td>
<td>1. Hemodialysis 2. rhFVIIa 90 mcg/kg IV or FEIBA 50-100 u/kg</td>
<td>rhFVIIa has been associated with thromboembolic events</td>
</tr>
</tbody>
</table>
## Recurrent VTE on anticoagulation

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtherapeutic AC</td>
<td>On VKA- UFH/LMWH bridge to INR 2-3 Consider LMWH or Fondaparinux</td>
</tr>
<tr>
<td>Therapeutic AC</td>
<td>On VKA- consider LMWH or fondaparinux LMWH- empiric 25% dose escalation or fondaparinux</td>
</tr>
<tr>
<td>Anatomic Compression</td>
<td>Relieve compression, reinstitute AC</td>
</tr>
<tr>
<td>Trousseau’s syndrome</td>
<td>Switch to UFH/LMWH</td>
</tr>
<tr>
<td>Heparin-induced thrombocytopenia</td>
<td>DTI or fondaparinux (?)</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td>Higher INR target (3-4) or alternative anticoagulation (LMWH, fonda)</td>
</tr>
</tbody>
</table>
Post-phlebitic syndrome

- **Symptoms**
  - Heaviness
  - Pain
  - Cramps
  - Pruritis
  - Paresthesias

- **Signs**
  - Pretibial edema
  - Induration
  - Hyperpigmentation
  - New venous ectasia
  - Redness
  - Pain during calf compression
  - Ulceration

Villalta et al. Haemostasis 1994;24(Suppl 1):157a

Absence=0, Mild=1, Moderate=2, Severe=3
No PTS= 0-4 pts., Mild=5-9 pts., Moderate=10-14 pts., Severe≥15 pts. or ulcer
Incidence of post-thrombotic syndrome

Cumulative incidence (%)

- Post-thrombotic syndrome
- Severe PTS

PTS Risk Factors:
- Recurrent DVT
- Proximal DVT
- Obesity
- Poor Quality AC
- Older age

Kahn S Ann Intern Med 2008; Kahn S Blood 2009:
VTE treatment: Compression stockings reduce the incidence of PTS

- PTS occurs in 29% of DVT patients by 8 years
- Compression stockings (30-40 mm Hg) reduce the incidence of PTS
- Compression stockings should be prescribed for 2 years in all patients with DVT

DVT thrombolyis significantly reduces thrombus burden.

CDT and Post-thrombotic syndrome: The CaVenT Study

- Open RCT of AC vs. CDT
- Objective iliofemoral DVT within 21 days
- TPA 0.01 mg/kg/hr up to 96 hrs with UFH (aPTT 1.2-1.7) ± stent
- Outcome - patency at 6 mos. and PTS at 24 mos.

Enden T et al. Lancet 2011
Chronic Thromboembolic Pulmonary Hypertension

Risk Factors
- Previous PE (OR 19)
- Idiopathic PE (OR 5.7)
- Large Perfusion Defect (OR 2.2)
- Younger Age (OR 1.8)

N=223

Questions ?