Venous Thromboembolic Disease

Tom DeLoughery, MD MACP FAWM
Oregon Health and Sciences University

DISCLOSURE

Relevant Financial Relationship(s)
Speaker Bureau - None
Consultant/Research – none
What I am Talking About

• Non-anticoagulant therapy of VTE
• Duration of anticoagulation
• New anticoagulants

Treatment of DVT/PE

• Bed rest
• Inferior Vena Cava Filter
• Thrombolytic Therapy
• Home therapy
• Post-thrombotic syndrome
Is Bedrest Useful in DVT Patients?

- At eight trials (N= 5700) compared bedrest with activity
- No trial showed a difference in PE or thrombosis
- One study showed decreased pain and swelling with activity
- Management
  - Activity: as tolerated
  - Trial of elastic stockings knee-high 30-40 mmHg

Exercise: Key Therapy

- Less post-thrombotic syndrome in more active patients
- Less bleeding in anticoagulated patients
- Encourage activity!
Inferior Vena Cava Filters

• Overused and under studied!

Filters

• Only 2 RCT
• No influence on mortality in anticoagulated patients
  – Only one study showed reduction in PE
• ~1-2% fatal PE rate in IVC filters patients in ICU studies
• Raises risk of future DVT (~2x)
IVC Filter by State

Wyoming: 13/100,000
NJ: 67/100,000
Retrievable Filters: Panacea or Pandemic?

• Rapid acceptance of retrievable filters

• Caveats
  – 10-20% cannot be removed
  – > 50% aren’t removed
  – Limited clinical studies
  – Limited long term follow-up
Retrievable Filters

- Need system in place to retrieve
- Reports of retrieval many months out
- Can retrieve while anticoagulated
- Strut fractures from non-removed filters increasing issue

IVC Filters

- Still should be used with caution
- Indications
  - Large DVT and temporary contraindication to anticoagulation
  - NOT indicated for PE prophylaxis
- Patients must be warned that "retrievable" filter may be permanent
- Will RAISE the risk of DVT!
- Need to anticoagulate as soon as feasible
Reasons NOT to Put in a Filter

- **Pulmonary embolism:**
  - 1\textsuperscript{st} week of anticoagulation
  - Despite warfarin

- **Deep venous thrombosis:**
  - With free floating thrombus
  - Extension of DVT
  - Despite warfarin
  - In cancer patients

*Curr Opin Hem 2009 Sep;16(5):402-6*
Thrombolytic Therapy: DVT

• Selected patients with femoral or iliac DVT consider catheter directed thrombolytic therapy
  – Symptoms < 14 days
  – Good health status
  – Good candidate for thrombolytic therapy

• Venous lesions should be corrected by angioplasty or stents
Cochrane Review 2014

- Early patency RR: 4.91
- Later patency RR: 2.37
- Post thrombotic syndrome RR: 0.64
- Bleeding RR: 2.23

Goal is LONG term prevention of post-thrombotic syndrome

Catheter Directed Thrombolytic Therapy

- Large proximal venous thrombosis
- Good candidates for thrombolytic therapy
  - Age < 65
- Can “cool” off with heparin
Thrombolytic Therapy: PE

There is no clinical utility in thrombolytic therapy for the vast majority of patients with pulmonary embolism

PEITHO

- Large 1000 patient RCT of heparin vs thrombolytic for “high-risk” patients
  - + Troponin
  - + R heart strain
  - Normal BP
- N Engl J Med 2014; 370:1402-1411
## Results

<table>
<thead>
<tr>
<th></th>
<th>Lytics (506)</th>
<th>Placebo (499)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or “collapse”</td>
<td>13 (2.6%)</td>
<td>28 (5.6%)</td>
</tr>
<tr>
<td>Death</td>
<td>6 (1.2%)</td>
<td>9 (1.8%)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>32 (6.3%)</td>
<td>6 (1.5%)</td>
</tr>
<tr>
<td>ICH</td>
<td>12 (2.4%)</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>

**Table: PE-related early mortality risk**

<table>
<thead>
<tr>
<th>MORTALITY RISK</th>
<th>CLINICAL (Shock or hypotension)</th>
<th>RV Dysfunction</th>
<th>Myocardial Injury</th>
<th>Potential treatment implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGH (&gt; 15%)</td>
<td>+</td>
<td>(+)*</td>
<td>(+)*</td>
<td>Thrombolysis or Embolectomy</td>
</tr>
<tr>
<td>NON HIGH</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Hospital Admission</td>
</tr>
<tr>
<td>Low (&lt;1%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Early discharge or home treatment</td>
</tr>
</tbody>
</table>

**Diagram: Risk Markers for PE-related early mortality risk**
JTH Meta-Analysis

- Look at trials specifically for submassive PE
- No benefit for lysis
- 1.7% ICH vs 0.1%

- **A** All-cause death

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis</th>
<th>Heparin</th>
<th>Risk ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldhaber 1993</td>
<td>0</td>
<td>18</td>
<td>0.20 [0.01, 3.92]</td>
<td>1993</td>
</tr>
<tr>
<td>MSPHES 2002</td>
<td>4</td>
<td>115</td>
<td>1.54 [0.36, 6.83]</td>
<td>2002</td>
</tr>
<tr>
<td>TIPES 2010</td>
<td>0</td>
<td>28</td>
<td>0.36 [0.02, 4.40]</td>
<td>2010</td>
</tr>
<tr>
<td>Frick 2011</td>
<td>0</td>
<td>37</td>
<td>0.19 [0.01, 1.52]</td>
<td>2011</td>
</tr>
<tr>
<td>PEITHO 2014</td>
<td>12</td>
<td>606</td>
<td>0.73 [0.36, 1.56]</td>
<td>2014</td>
</tr>
<tr>
<td>TOPCOAT 2014</td>
<td>1</td>
<td>40</td>
<td>1.07 [0.07, 16.62]</td>
<td>2014</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>17</td>
<td>29</td>
<td>0.72 [0.39, 1.39]</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

- **G** Intracranial bleeding

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis</th>
<th>Heparin</th>
<th>Risk ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldhaber 1993</td>
<td>1</td>
<td>18</td>
<td>3.00 [0.13, 69.69]</td>
<td>1993</td>
</tr>
<tr>
<td>MSPHES 2002</td>
<td>0</td>
<td>115</td>
<td>Not estimable</td>
<td>2002</td>
</tr>
<tr>
<td>TIPES 2010</td>
<td>1</td>
<td>28</td>
<td>3.21 [0.14, 75.61]</td>
<td>2010</td>
</tr>
<tr>
<td>Frick 2011</td>
<td>0</td>
<td>37</td>
<td>Not estimable</td>
<td>2011</td>
</tr>
<tr>
<td>PEITHO 2014</td>
<td>10</td>
<td>606</td>
<td>0.86 [0.17, 76.76]</td>
<td>2014</td>
</tr>
<tr>
<td>TOPCOAT 2014</td>
<td>1</td>
<td>40</td>
<td>3.32 [0.15, 76.82]</td>
<td>2014</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>13</td>
<td>785</td>
<td>0.20 [0.01, 20.91]</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Thrombolytic Therapy: PE

• Large RCT shows no benefit in PE
• Use should be restricted to patient with refractory hypotension
  – Two studies show doubling risk of death with thrombolytic therapy when used in normotensive patients
• Screen carefully for bleeding risks
• Uncertain best way to give heparin
  – Containing during lytics
  – Holding and restart after lytics
  – Holding and restarting with aPTT < 2x control

Lytics for PE: Does it Even Make Sense?

• Two modes of death with PE
  – Sudden death
  – Die of underlying disease
• Next wave of therapy
  – Low dose thrombolitics
  – Catheter direct therapy
  – Hopefully RCT will precede clinical acceptance
Can PE be Treated as Outpatients?

• Increasing incidence of “mild” PE

• Key is systems in place for home therapy of thrombosis
  – Compliance with medication
  – Close follow-up

Pulmonary Embolism Severity Index (PESI)

• Points are assigned as follows:
  • 1 for each year of age
  • 10 for male sex
  • 20 for HR>110 beats/min
  • 10 for heart failure
  • 30 for malignancy
  • 10 for chronic lung disease
  • 30 for SBP<100
  • 20 for RR>30
  • 20 for temp <36 degrees C
  • 60 for AMS
  • 20 for PaO2<90%
**PESI score**

- Class I <65
- Class II 66-85<br>  \( \text{Low Risk} \)
- Class III 86-105
- Class IV 106-125
- Class V >125
- 30 day mortality increases with each class
- Class V has a 25 fold higher risk of post-discharge death than Class I

**Aujesky Trial**

- N = 344
- PESI < 85
- Out vs inpatient care of PE
- No difference in death, bleeding, or recurrent thrombosis
- Lancet. 2011 Jul 2;378(9785):41-8
Outpatient Therapy

- PESI < 85
  - No hypoxia, SBP < 100, recent bleeding, plts < 70,000, comorbidities or recurrent DVT
- Good social support
- Expected to be compliant

Post-Thrombotic Syndrome

- Common complication of DVT
- 20-50% of all patients
- 5-10% severe
- Can be very disabling
PTS: Risk Factors

- Common femoral or iliac vein thrombosis
- Previous DVT
- High BMI
- Older age
- Inadequate initial anticoagulation
**Prevention**

- Prevent thrombosis!
- Catheter direct lytic therapy
- Knee-high compression stockings – NOT! – but may help symptoms
  - 30-40mmHg
  - At least 6 months
- Keep the patient active

**Therapy of PTS**

- Compression stockings
  - Knee high
- Leg elevation
- Horse chestnut seed extract
  - BID for a 3 weeks trial
- Treat neuropathic pain
- Leg massage
Post-PE Syndrome?

- 50% of patients with PE report dyspnea 6 months later
- 20-70% state health status worse
- Seeming not related to clot residual or scarring
- Chest pain/discomfort very common
- Large study ongoing to better define

Duration of Therapy

Idiopathic versus provoked thrombosis is **the biggest** determinant of risk of recurrent thrombosis
Duration of Therapy

• Not all thrombosis are the same
• Can stratify patients by:
  – Site of thrombosis
  – Circumstances of thrombosis
    • Most important!
  – Presence of hypercoagulable states

Upper Extremity Thrombosis

• Mechanical defects
  – Catheter
    • PICC 3-5%
  – Local venous trauma
• Prophylaxis ineffective
• Low risk of serious sequela
Upper Extremity Thrombosis

- Therapy: PICC Catheter
  - Key is removing catheter
  - No new one for at least 10 days
  - Benefit of anticoagulation uncertain
  - Remember many are superficial thrombosis
Upper Extremity Thrombosis

- Therapy: Non-PICC Catheter
  - Line can be removed
    - Assess need for anticoagulation
  - Line cannot be removed
    - 3 months anticoagulation
    - High rates of serious bleeding
Upper Extremity Thrombosis

- “Spontaneous”
  - 3 months anticoagulation
  - Look for underlying vascular defects
  - Consider thrombolytic therapy
    - ~75% with underlying lesions

Superficial Thrombophlebitis

- Very common
- Strong inflammatory component
- Wide range of therapeutic options
STP: LMWH

STTEPS
• Symptomatic STP
• 8-12 day of therapy
  – Placebo: 30.6% (3.6%)
  – NSAIA: 14.9% (2.1%)
  – 40 mg LMWH: 8.3% (0.9%)
  – 1.5 mg/kg LMWH: 6.9% (1.0%)

Vesalio Study Group
• Greater saphenous vein STP
• One month of therapy
  – Prophylactic dose: 7.2%
  – Treatment dose: 7.2%

Superficial Thrombophlebitis
• Fondaparinux 2.5 mg/day x 45 days
  – Endpoint: F: 0.9% P: 5.9%
  – DVT/PE F: 0.2% P: 1.5%
  – No difference in bleeding
  – Need to treat 88 patients to prevent one DVT/PE

  – NEJM 363:1222-32, 2010
Superficial Thrombophlebitis

- Small and distal: NSAIA and heat
- Painful, large (> 5cm) or greater saphenous vein
  - At least 10 days of prophylactic dose LMWH or fondaparinux
Calf Vein Thrombosis

- Muscular vein thrombosis
  - 10 days of LMWH
- Other sites: high risk of progression
  - Up to 10% progression
  - PE rate 2-3%
- 6 weeks therapy for most patients

Calf Vein: Observation

- Consider doppler in one week and no treatment if:
  - Outpatient
  - No cancer
  - No history of thrombosis
  - < 5cm
Muscular vein Thrombosis
10 days LMWH Therapy

<table>
<thead>
<tr>
<th>Outcome at 3 months</th>
<th>Placebo</th>
<th>LMWH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression to calf DVT</td>
<td>25%</td>
<td>0%</td>
</tr>
<tr>
<td>Recurrent muscular vein DVT</td>
<td>16%</td>
<td>2%</td>
</tr>
<tr>
<td>Recanalization</td>
<td>50%</td>
<td>86%</td>
</tr>
</tbody>
</table>

Calf Vein Thrombosis Therapy

Fig 1—Kaplan-Meier plot showing the proportion of patients free from recurrence during the first year.


Calf Vein DVT

Duration of Therapy: Proximal DVT

- 3 months
  - Provoked DVT
    - Especially estrogen related
- No benefit with 6 months except more bleeding
- Obtain scan at end of therapy for new baseline
  - J Thromb Haemost. 2011 Dec;9(12):2406-10

Proximal DVT

Duration of Therapy

• What is an Idiopathic Thrombosis?
  – No trauma, surgery or hospital stay for 1-3 months
  – No estrogens
  – No long travel
  – No cancer or major risk factors
  – Varies from study to study

• Balancing the risk of recurrent VTE vs risk of warfarin
1st Idiopathic VTE

- High rates (20-30%) of recurrence off anticoagulation
- Multiple RCTs show benefit of long term anticoagulation
  - Marked increase in recurrence when stopping anticoagulation

Two Phases of VTE Therapy

- Active phase (3 months)
  - Prevents reactivation of initial thrombosis
- Secondary prevention (> 3 months)
  - Prevents new thrombosis
  - Need to identify patients who will benefit

**D-Dimers**

- D-dimers checked off therapy to predict risk
- Meta-analysis
  - 7 studies
  - Positive D-Dimer: 10%/yr
  - Negative D-Dimer: 2.9 - 4.0%/yr
- Unclear if repeat testing helps
- Most recent study showed high rates of recurrence with negative D-dimer 5%/yr

**Idiopathic VTE**

- No good prediction rules
  - Negative D-dimer - NOT predictive
  - Thrombus resolution – NOT predictive
- Still need better prediction rules!
- Safer anticoagulants is shifting balance toward longer treatment
Duration of Therapy

- Indefinite
  - >1 DVT (except upper ext)
  - Acquired hypercoagulable states
  - Idiopathic unusual site
  - Idiopathic severe pulmonary embolism
- 3 months
  - Provoked pulmonary embolism
What about Hypercoagulable States?

Hypercoagulable State

• Clear risk factor for 1st VTE
• No evidence with classic genetic states predict recurrence
• Multiple guidelines against checking in provoked thrombosis
Thrombophilia Work-Ups

• Don’t screen for genetic causes
  – For provoked thrombosis
  – Arterial thrombosis
  – Upper extremity thrombosis
• ~$1200

Novel Anticoagulants

• Robust randomized trial data for all new anticoagulants
• Now recommend by ACCP first line over warfarin
Rivaroxaban: Acute Venous Thrombosis

- N = 3,449 with DVT/ 4,832 with PE
- RCT
  - Rivaroxaban 15mg BID then 20mg after 3 weeks
  - Enoxaparin -> Warfarin


Results

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (4150)</th>
<th>LMWH/Warfarin (4131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>86 (2%)</td>
<td>96 (2.3%)</td>
</tr>
<tr>
<td>Any Bleeding</td>
<td>388 (9%)</td>
<td>412 (10%)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>40 (1.0%)</td>
<td>70 (1.7%)</td>
</tr>
<tr>
<td>ICH</td>
<td>5 (0.1%)</td>
<td>14 (0.3%)</td>
</tr>
</tbody>
</table>
Apixaban: Acute Venous Thrombosis

- N = 5395 with VTE
  - 33% with PE
- RCT
  - Apixaban 10mg BID then 5 mg BID after 7 days
  - Enoxaparin -> Warfarin

### Results

<table>
<thead>
<tr>
<th></th>
<th>Apixaban (2691)</th>
<th>LMWH/Warfarin (2704)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>59 (2.3%)</td>
<td>71 (2.7%)</td>
</tr>
<tr>
<td>Any Bleeding</td>
<td>115 (4.3%)</td>
<td>261 (9.7%)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>15 (0.6%)</td>
<td>49 (1.8%)</td>
</tr>
<tr>
<td>ICH</td>
<td>3 (0.1%)</td>
<td>6 (0.2%)</td>
</tr>
</tbody>
</table>
**Apixaban: Chronic Venous Thrombosis**

- **N = 2482 with VTE**
  - 34% with PE
  - 6-12 months of therapy
- **RCT**
  - Apixaban 5 mg BID
  - Apixaban 2.5 mg BID
  - Placebo

**Results**

<table>
<thead>
<tr>
<th></th>
<th>Apixaban 2.5mg BID (840)</th>
<th>Apixaban 5mg BID (813)</th>
<th>Placebo (829)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>32 (3.8%)</td>
<td>34 (4.2%)</td>
<td>96 (11.6%)</td>
</tr>
<tr>
<td>Any Bleeding</td>
<td>27 (3.2%)</td>
<td>35 (4.3%)</td>
<td>19 (2.3%)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>2 (0.2%)</td>
<td>1 (0.1%)</td>
<td>4 (0.5%)</td>
</tr>
</tbody>
</table>

Ongoing RCT of Rivaroxaban 20mg vs 10mg vs ASA
Venous Thrombosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Heparin First?</th>
<th>Thrombosis</th>
<th>Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>No*</td>
<td>Equal</td>
<td>Safer</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Yes</td>
<td>Equal</td>
<td>Equal</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Yes</td>
<td>Equal</td>
<td>Safer</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>No*</td>
<td>Equal</td>
<td>Safer</td>
</tr>
</tbody>
</table>

*Apixaban 10mg bid x 7 days then 5mg BID
*Rivaroxaban 15mg bid x 21 days then 20mg daily

DOAC in VTE

- Recurrent VTE: 0.90 (0.77-1.06)
- Major bleeding: 0.74 (0.59-0.85)
- ICH: 0.37 (0.21-0.68)
- Fatal bleeding: 0.36 (0.15-0.84)

Long Term Treatment of VTE

<table>
<thead>
<tr>
<th>Drug</th>
<th>VTE- D</th>
<th>VTE - P</th>
<th>RRR</th>
<th>Bleed-A</th>
<th>Bleed -P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>1.3%</td>
<td>27.4%</td>
<td>95</td>
<td>3.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>1.3%</td>
<td>7.1%</td>
<td>82</td>
<td>0.7%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>0.4%</td>
<td>5.6%</td>
<td>92</td>
<td>0.4%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Apixaban</td>
<td>1.7%</td>
<td>8.8%</td>
<td>80</td>
<td>0.5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Aspirin</td>
<td>14%</td>
<td>19%</td>
<td>32</td>
<td>2.9%</td>
<td>2.0%*</td>
</tr>
</tbody>
</table>

AVERROES showed bleeding equal with apixaban and aspirin (NEJM 2011. 364:806-817)
New Direct Oral Anticoagulants

- Easier to use and safer
- Both rivaroxaban and apixaban tested without heparin
  - Both use higher initial doses
- Irreversibility = Myth
  - Less need to reverse
  - No difference in bleeding outcomes in multiple studies

Who NOT to use New Anticoagulants

- Dialysis patients
  - Apixaban exception
- Mechanical Valves
- < 50 or > 150 kg
- Remember “loading dose”
Direct Oral Anticoagulants

• First line therapy for VTE
• Simplified management
• But
  – Patients still need close follow-up
  – Still need to manage anticoagulants
  – Expense an issue

What I Talked About

• Therapy of VTE
• Duration of anticoagulation
• New anticoagulants