Thrombosis

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DISCLOSURE

Relevant Financial Relationship(s)
Speaker Bureau - None
Consultant – Amgen, Alexion
What I am Talking About

• New Anticoagulants
  – Dabigatran
  – Rivaroxiban
  – Apixiban
  – Edoxaban

• D-Dimers for duration of therapy
Dabigatran

• Oral thrombin inhibitor
• Strong trial results
  – DVT prophylaxis
  – DVT Therapy
  – Afib stroke prophylaxis
Atrial Fibrillation

- RCT of 18,113
- Warfarin INR 2-3
- Dabigatran 110mg or 150 mg BID
- Mean F/u 2 years
<table>
<thead>
<tr>
<th></th>
<th>D 110mg</th>
<th>D 150mg</th>
<th>warfarin</th>
<th>D 110mg vs. Warfarin</th>
<th>D 150mg vs. Warfarin</th>
<th>p</th>
<th>RR 95% CI</th>
<th>p</th>
<th>RR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic Embolism</td>
<td>182</td>
<td>134</td>
<td>199</td>
<td>0.91</td>
<td>0.66</td>
<td>0.34</td>
<td>0.74-1.11</td>
<td>&lt;0.001</td>
<td>0.53-0.82</td>
</tr>
<tr>
<td>Stroke</td>
<td>171</td>
<td>122</td>
<td>185</td>
<td>0.92</td>
<td>0.64</td>
<td>0.41</td>
<td>0.74-1.13</td>
<td>&lt;0.001</td>
<td>0.51-0.81</td>
</tr>
<tr>
<td>Systemic Embolism</td>
<td>14</td>
<td>13</td>
<td>19</td>
<td>0.73</td>
<td>0.67</td>
<td>0.38</td>
<td>0.37-1.46</td>
<td>0.27</td>
<td>0.33-1.36</td>
</tr>
</tbody>
</table>
### Bleeding and Net Clinical Benefit

<table>
<thead>
<tr>
<th></th>
<th>D 110mg</th>
<th>D 150mg</th>
<th>warfarin</th>
<th>D 110mg vs. Warfarin</th>
<th>D 150mg vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Annual rate</td>
<td>Annual rate</td>
<td>Annual rate</td>
<td>RR 95% CI</td>
<td>p</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>2.7%</td>
<td>3.1%</td>
<td>3.4%</td>
<td>0.80</td>
<td>0.69-0.93</td>
</tr>
<tr>
<td>Life-Threatening major</td>
<td>1.2%</td>
<td>1.5%</td>
<td>1.8%</td>
<td>0.68</td>
<td>0.55-0.83</td>
</tr>
<tr>
<td>Minor Bleeding</td>
<td>13.2%</td>
<td>14.8%</td>
<td>16.4%</td>
<td>0.79</td>
<td>0.74-0.84</td>
</tr>
<tr>
<td>Net Clinical Benefit*</td>
<td>7.1%</td>
<td>6.9%</td>
<td>7.6%</td>
<td>0.92</td>
<td>0.84-1.02</td>
</tr>
</tbody>
</table>
DVT Therapy

• NEJM Volume 361:2342-2352, 2009
• All patients got heparin
• Randomized between warfarin and dabigatran 150 mg BID
• N = 1274
Recurrent DVT or Death
Bleeding

Dabigatran
Major bleeding
0.82
(0.45 to 1.48; P=0.38)

Dabigatran
Any bleeding
0.71
(0.59 to 0.85; P<0.001)

![Graph showing estimated cumulative risk of bleeding over months since first intake of study drug for Dabigatran and Warfarin for major and any bleeding events.]
Side Effects

• No difference in liver function tests
• Increase in dyspepsia
  – 3 vs 0.7%
Dabigatran

- Effective in DVT prevention
- Effective in DVT therapy
- Effective in stroke prevention in atrial fibrillation
- Same or lesser bleeding risk
Dabigatran

• 150 and 75 mg dose approved by FDA

• Dosing
  – CrCl > 30 mL/ml – 150mg BID
  – CrCl 15-30mL/ml 75 mg BID
  – CrCl < 15 not indicated

• No major drug-drug interactions
  – Rifampin
Dabigatran- Surgery

<table>
<thead>
<tr>
<th>Renal function (CL&lt;sub&gt;CR&lt;/sub&gt;, ml/min)</th>
<th>Half-life (hours)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Timing of discontinuation after last dose of dabigatran before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 80</td>
<td>13 (11–22)</td>
<td>24 hours</td>
</tr>
<tr>
<td>&gt; 50 to ≤ 80</td>
<td>15 (12–34)</td>
<td>24 hours</td>
</tr>
<tr>
<td>&gt; 30 to ≤ 50</td>
<td>18 (13–23)</td>
<td>at least 2 days (48 hours)</td>
</tr>
<tr>
<td>≤ 30&lt;sup&gt;c&lt;/sup&gt;</td>
<td>27 (22–35)</td>
<td>2–5 days</td>
</tr>
</tbody>
</table>

<sup>a</sup>Data from renal impairment study in healthy volunteers (11), geometric mean (range).<sup>b</sup>Types of surgery associated with a high risk of bleeding (or in major surgery where complete hemostasis may be required) include but is not limited to cardiac surgery, neurosurgery, abdominal surgery or those involving a major organ. Other procedures such as spinal anesthesia may also require complete hemostatic function. Other important determinants of bleeding risk include advancing age, co-morbidities (e.g. major cardiac, respiratory or liver disease) and concomitant use of antiplatelet therapy. <sup>c</sup>Dabigatran etexilate is contraindicated for use in these patients. CL<sub>CR</sub> = creatinine clearance.
Monitoring

- aPTT
  - 150 mg twice daily the median peak aPTT is approximately 2x control.
  - Twelve hours after the last dose the median aPTT is 1.5x control
- Unsure if can be use to adjust dose
- Assess compliance and drug effect
- INR insensitive
Multiple dose

\[ y = 0.86 + 0.06873x^{1/2} \]

\[ r^2 = 0.8514 \]
Dabigatran

• Reversal
  – Animal modes
    • aPCC
    • PCC
    • PCC + rVIIa
  – Dialyzable
Dabigatran

• Who am I using it in?
  – DVT prophylaxis
  – Unstable INR
  – Difficult to get testing
  – Chronic LMWH patients
    • Cancer??????

• Not!!
  – Valves
  – Pregnancy
Rivaroxaban

- Oral drug – Factor Xa blocker
  - Fixed dose
  - Limited drug-drug interactions
  - No monitoring
# Rivaroxiban: Main Outcomes

<table>
<thead>
<tr>
<th>Trial</th>
<th>Setting</th>
<th>Enoxaparin regimen</th>
<th>Rivaroxaban regimen</th>
<th>DVT/PE/death (%)</th>
<th>RRR (%)</th>
<th>Symptomatic VTE (%)</th>
<th>RRR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECORD1, n=4541</td>
<td>THA 40 mg, 35d</td>
<td>40 mg, 35 d</td>
<td>10 mg, 35 d</td>
<td>3.7 vs 1.1</td>
<td>70</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>RECORD2, n=2509</td>
<td>THA 40 mg, 10–14d</td>
<td>40 mg, 10–14d</td>
<td>10 mg, 31–39d</td>
<td>9.3 vs 2.0</td>
<td>79</td>
<td>1.2 vs 0.2</td>
<td>80</td>
</tr>
<tr>
<td>RECORD3, n=2531</td>
<td>TKA 40 mg, 10–14d</td>
<td>40 mg, 10–14d</td>
<td>10 mg 10–14 d</td>
<td>18.9 vs 9.6</td>
<td>49</td>
<td>2.0 vs 0.7</td>
<td>66</td>
</tr>
<tr>
<td>RECORD4, n=3148</td>
<td>TKA 30 mg bid, 10-14 d</td>
<td>30 mg bid, 10-14 d</td>
<td>10 mg, 10–14 d</td>
<td>10.1 vs 6.9</td>
<td>31</td>
<td>1.2 vs 0.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Equal or better than LMWH in orthopedic DVT Prevention**
Rivaroxaban

• Oral Xa Blocker
• Shown to be effective in DVT prevention
• Shown to be effective in stroke prevention in afib
• What about thrombosis?
Einstien

- No prespecified heparin
- ~8% cancer patients
- Only DVT
Einstein-DVT Study

Rivaroxaban
15 mg BID for 3 wks followed by
20 mg QD (n = 1731)

Patients with confirmed acute symptomatic DVT without symptomatic PE
(N = 3449)

Enoxaparin
1 mg/kg BID for at least 5 days + VKA
Warfarin or acenocoumarol target INR 2.5 (range: 2.0-3.0)
(n = 1718)

3, 6, or 12 mos

Einstein-Extension Study

Rivaroxaban
20 mg QD (n = 602)

Patients who completed 6-12 mos of anticoagulant treatment for either DVT or PE
(N = 1197)

Placebo
(n = 594)

6 or 12 mos

INR, international normalized ratio; PE, pulmonary embolism.
Rivaroxaban: DVT Therapy

- N = 3,449 with DVT
- RCT
  - Rivaroxaban 15mg BID then 20mg after 3 weeks
  - Enoxaparin -> Warfarin
## Results

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rivaroxaban (1,731)</th>
<th>LMWH/Warfarin (1,718)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First symptomatic recurrence</td>
<td>36 (2.1%)</td>
<td>51 (3.0%)</td>
</tr>
<tr>
<td>Recurrent DVT</td>
<td>14 (0.8)</td>
<td>28 (1.6)</td>
</tr>
<tr>
<td>New PE</td>
<td>20 (1.2%)</td>
<td>18 (1.0%)</td>
</tr>
<tr>
<td>Any Bleeding</td>
<td>139 (8.1%)</td>
<td>138 (8.1%)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>14 (0.8%)</td>
<td>20 (1.2%)</td>
</tr>
<tr>
<td>Minor Bleeding</td>
<td>129 (7.5%)</td>
<td>122 (7.1%)</td>
</tr>
</tbody>
</table>
A  Acute DVT Study

Cumulative Event Rate for Primary Efficacy Outcome (%)

- P<0.001 for noninferiority
- Enoxaparin-VKA (N=1718)
- Rivaroxaban (N=1731)

No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Days</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>1731</td>
<td>1668</td>
<td>1648</td>
<td>1621</td>
<td>1424</td>
<td>1412</td>
<td>1220</td>
<td>400</td>
<td>369</td>
<td>363</td>
<td>345</td>
</tr>
<tr>
<td>Enoxaparin-VKA</td>
<td>1718</td>
<td>1616</td>
<td>1581</td>
<td>1553</td>
<td>1368</td>
<td>1358</td>
<td>1186</td>
<td>380</td>
<td>362</td>
<td>337</td>
<td>325</td>
</tr>
</tbody>
</table>

B  Continued Treatment Study

Cumulative Event Rate for Primary Efficacy Outcome (%)

- P<0.001 for superiority
- Placebo (N=594)
- Rivaroxaban (N=602)

No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Days</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>602</td>
<td>590</td>
<td>583</td>
<td>573</td>
<td>552</td>
<td>503</td>
<td>482</td>
<td>171</td>
<td>138</td>
<td>132</td>
<td>114</td>
<td>92</td>
<td>81</td>
</tr>
<tr>
<td>Placebo</td>
<td>594</td>
<td>582</td>
<td>570</td>
<td>555</td>
<td>522</td>
<td>468</td>
<td>444</td>
<td>164</td>
<td>138</td>
<td>133</td>
<td>110</td>
<td>93</td>
<td>85</td>
</tr>
</tbody>
</table>
Safety

P = 0.77

No. at Risk

Rivaroxaban  |  1718  |  1585  |  1538  |  1382  |  1317  |  1297  |  715  |  355  |  338  |  304  |  278  |  265  |  140
Enoxaparin–VKA | 1711  |  1554  |  1503  |  1340  |  1263  |  1238  |  619  |  338  |  321  |  287  |  268  |  249  |  118

Days

Cumulative Event Rate for Principal Safety Outcome (%)
Extension Study

• N = 1,197
• Finished 6-12 months of therapy
• RCT to 20mg of rivaroxaban vs placebo
• No increase in major bleeding
Extension Study

<table>
<thead>
<tr>
<th>Type of recurrent VTE</th>
<th>0</th>
<th>1</th>
<th>0</th>
<th>0</th>
<th>2</th>
<th>13</th>
<th>5</th>
<th>31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal PE</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE cannot be ruled out</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal PE</td>
<td>2</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent DVT</td>
<td>5</td>
<td>31</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A  Acute DVT Study

Cumulative Event Rate for Primary Efficacy Outcome (%)

P<0.001 for noninferiority

Enoxaparin–VKA (N=1718)
Rivaroxaban (N=1731)

Days

No. at Risk

Rivaroxaban
1731 1668 1648 1621 1424 1412 1220 400 369 363 345 309 266
Enoxaparin–VKA
1718 1616 1581 1553 1368 1358 1186 380 362 337 325 297 264

B  Continued Treatment Study

Cumulative Event Rate for Primary Efficacy Outcome (%)

P<0.001 for superiority

Rivaroxaban (N=602)
Placebo (N=594)

Days

No. at Risk

Rivaroxaban
602 590 583 573 552 503 482 171 138 132 114 92 81
Placebo
594 582 570 555 522 468 444 164 138 133 110 93 85
# Extension Study

## Safety

<table>
<thead>
<tr>
<th>Safety population</th>
<th>598</th>
<th>590</th>
<th></th>
<th>5.19 (2.3–11.7)</th>
<th>&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>First major or clinically relevant nonmajor bleeding</td>
<td>36 (6.0)</td>
<td>7 (1.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding†</td>
<td>4 (0.7)‡</td>
<td>0</td>
<td>NA</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Contributing to death</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In a critical site</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associated with a fall in hemoglobin of ≥2 g per deciliter, transfusion of ≥2 units, or both</td>
<td>4</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically relevant nonmajor bleeding†</td>
<td>32 (5.4)‡</td>
<td>7 (1.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>9</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>8</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal</td>
<td>7</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>4</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterine</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Related to tooth extraction</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Rivaroxaban

- Effective in short and long term therapy of DVT
- Ongoing trials
  - Atrial Fib
    - 20mg/day
    - 15mg in patients with renal impairment
Conclusion

• Acute DVT
  – Rivaroxaban safe and effective
  – No need for heparin in DVT therapy

• Chronic
  – 75% of patients with idiopathic DVT
  – Effective
Rivaroxaban Afib
**Study Design**

**Atrial Fibrillation**

- **Rivaroxaban**
  - 20 mg daily
  - 15 mg for Cr Cl 30-49 ml/min

- **Warfarin**
  - Randomize Double Blind / Double Dummy (n ~ 14,000)
  - INR target - 2.5 (2.0-3.0 inclusive)

- Monthly Monitoring
- Adherence to standard of care guidelines

**Primary Endpoint:** Stroke or non-CNS Systemic Embolism

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* Enrolment of patients without prior Stroke, TIA or systemic embolism and only 2 factors capped at 10%
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban (n=7081)</th>
<th>Warfarin (n=7090)</th>
<th>Hazard ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point, noninferiority</td>
<td>1.71</td>
<td>2.16</td>
<td>0.79 (0.66–0.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Primary end point, on-treatment superiority</td>
<td>1.70</td>
<td>2.15</td>
<td>0.79 (0.65–0.95)</td>
<td>0.015</td>
</tr>
<tr>
<td>Primary end point, intention-to-treat superiority</td>
<td>2.12</td>
<td>2.42</td>
<td>0.88 (0.74–1.03)</td>
<td>0.117</td>
</tr>
<tr>
<td>Vascular death, stroke, embolism</td>
<td>3.11</td>
<td>3.63</td>
<td>0.86 (0.74–0.99)</td>
<td>0.034</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.26</td>
<td>0.44</td>
<td>0.59 (0.37–0.93)</td>
<td>0.024</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.34</td>
<td>1.42</td>
<td>0.94 (0.75–1.17)</td>
<td>0.581</td>
</tr>
<tr>
<td>Unknown stroke</td>
<td>0.06</td>
<td>0.10</td>
<td>0.65 (0.25–1.67)</td>
<td>0.366</td>
</tr>
</tbody>
</table>
Primary Efficacy Outcome

Stroke and non-CNS Embolism

Event Rates are per 100 patient-years

Based on Protocol Compliant on Treatment Population

No. at risk:

- Rivaroxaban: 6958, 6211, 5786, 5468, 4406, 3407, 2472, 1496, 634
- Warfarin: 7004, 6327, 5911, 5542, 4461, 3478, 2539, 1538, 655

HR (95% CI): 0.79 (0.66, 0.96)
P-value Non-Inferiority: <0.001

Days from Randomization vs Cumulative event rate (%)
## ROCKET-AF: Bleeding outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban (n=7081)</th>
<th>Warfarin (n=7090)</th>
<th>Hazard ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major and nonmajor bleeding</td>
<td>14.91</td>
<td>14.52</td>
<td>1.03 (0.96–1.11)</td>
<td>0.442</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3.60</td>
<td>3.45</td>
<td>1.04 (0.90–1.20)</td>
<td>0.576</td>
</tr>
<tr>
<td>•&gt;2 g/dL hemoglobin drop</td>
<td>2.77</td>
<td>2.26</td>
<td>1.22 (1.03–1.44)</td>
<td>0.019</td>
</tr>
<tr>
<td>•Transfusion</td>
<td>1.65</td>
<td>1.32</td>
<td>1.25 (1.01–1.55)</td>
<td>0.044</td>
</tr>
<tr>
<td>•Critical organ bleeding</td>
<td>0.82</td>
<td>1.18</td>
<td>0.69 (0.53–0.91)</td>
<td>0.007</td>
</tr>
<tr>
<td>•Bleeding causing death</td>
<td>0.24</td>
<td>0.48</td>
<td>0.50 (0.31–0.79)</td>
<td>0.003</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.49</td>
<td>0.74</td>
<td>0.67 (0.47–0.94)</td>
<td>0.019</td>
</tr>
</tbody>
</table>
Rivaroxaban

- Before FDA
- Good
  - Once daily
  - Robust Data
- Not so good
  - Renal clearance
  - Longer half-life
  - No PE data yet
Reversal of Rivaroxaban

- PCC effective in animals studies
- Human study
  - 12 volunteers on 20mb BID of rivaroxaban for 2.5 days
  - Randomized to 50 u/kg of PCC (4-factor)
  - Endogenous Thrombin Potential performed
PT
Before:
15.8±1.3
C: 16.2 ±0.8
PCC: 12.8 ±1.0

Figure 1. Effect of Rivaroxaban followed by Prothrombin Complex Concentrate (PCC) or placebo on Endogenous Thrombin Potential (Mean ± SD). P <0.001 (Repeated Measures ANOVA.)
Conclusions

• Four factor PCC may be an options for Rivaroxiban reversal
  – In theory rVIIa will also work but shorter $T_{1/2}$
Apixaban

• Oral
• Limited renal clearance
• Effective in DVT prevention
• Better than aspirin in afib
• Being studied in Afib and DVT therapy
# The Big Four

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class</td>
<td>Anti-thrombin</td>
<td>Anti-Xa</td>
<td>Anti-Xa</td>
<td>Anti-Xa</td>
</tr>
<tr>
<td>Half-life (hrs)</td>
<td>14-17</td>
<td>7-11</td>
<td>8-15</td>
<td>6-11</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>~6</td>
<td>80-100</td>
<td>34-88</td>
<td>~40</td>
</tr>
<tr>
<td>Dosing</td>
<td>BID</td>
<td>Daily</td>
<td>BID</td>
<td>Daily</td>
</tr>
<tr>
<td>Tmax (hrs)</td>
<td>1.5</td>
<td>2-4</td>
<td>1.5-3.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Renal (%)</td>
<td>~80</td>
<td>33</td>
<td>~22</td>
<td>~40</td>
</tr>
</tbody>
</table>
New Anticoagulants: Bottom Line

• Concerns
  – Renal clearance
  – Lack of reversibility
  – Rare but severe side effects
  – Tested for limited indications
  – Economics
  – Compliance
  – Choosing right agent for patient
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
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
  - Symptomatic STP x 5 cm
  - N = 3002
  - DBRCT
  - Endpoint – death, extension of STP, DVT/PE

NEJM 363:1222-32, 2010
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
50% of events at day 10

Hazard ratio at day 47, 0.14 (95% CI, 0.08–0.26); P<0.001

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Day 10±2</th>
<th>Day 30±2</th>
<th>Day 45±2</th>
<th>Day 75±2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1437</td>
<td>1399</td>
<td>1388</td>
<td>1330</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>1483</td>
<td>1477</td>
<td>1468</td>
<td>1410</td>
</tr>
</tbody>
</table>

Superficial Thrombophlebitis

- Small and distal: NSAIA and heat
- Painful, large or greater saphenous
  - At least 10 days of prophylactic dose LMWH or fondaparinux
Upper Extremity Thrombosis

- Mechanical defects
  - Catheter
    - PICC 3-27% symptomatic DVT
  - Compression
- Prophylaxis ineffective
- Low risk of serious sequela
Characterizing Resolution Of Catheter-associated Upper Extremity Deep Venous Thrombosis

Jones MA, Lee DY, Segall JA, Landry GJ, Liem TK, Mitchell EL, Moneta GL.

Results

• 101 thrombosis
• 40% PICC, 55% central venous, 5% ports
• Thrombus resolution in 46%
  – Only 25% if catheter not removed
• Anticoagulation with no effect on resolution
  – Stopped for bleeding complication in 26%
• New thrombosis form in 86% if new line placed within 10 days of diagnosis of old line thrombosis
Bottom Line

- Catheter thrombosis
  - Common
  - Need to pull line for resolution
    - Time not critical
  - No new line for 10 days
  - Uncertain effect of anticoagulation
    - Associated with high risk of bleeding
- Prospective data needed!
Upper Extremity Thrombosis

• “Spontaneous”
  • 3 months anticoagulation
  • Look for underlying vascular defects
  • Consider thrombolytic therapy
Calf Vein Thrombosis

- Muscular vein thrombosis
  - 10 days of LMWH
- Other sites: high risk of progression
  - 30% progression
  - Timing unpredictable
- 6 weeks therapy for most patients
# Muscular vein thrombosis

10 days LMWH Therapy

## Table 1. Comparison of patients characteristics and outcome

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Therapeutic Nadroparin (n = 52)</th>
<th>Compression therapy, no therapeutic Nadroparin (n = 32)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range) (years)</td>
<td>57.0 (16–84)</td>
<td>58.6 (21–85)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>30/22</td>
<td>19/13</td>
<td>n.s.</td>
</tr>
<tr>
<td>Soleal thrombosis</td>
<td>41 (75.92%)</td>
<td>29 (90.63%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Gastrocnemial thrombosis</td>
<td>13 (24.07%)</td>
<td>3 (9.37%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Malignancy</td>
<td>8 (15.38%)</td>
<td>10 (31.25%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Trauma or surgery</td>
<td>29 (55.75%)</td>
<td>16 (50%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Immobilization</td>
<td>10 (19.23%)</td>
<td>12 (37.5%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>6 (11.53%)</td>
<td>3 (9.37%)</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Outcome at 3 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression to calf DVT</td>
<td>0 (95% CI, 0–6.8%)</td>
<td>8 (25%; 95% CI, 11.5–43.4%)</td>
<td>&lt; 0.0002</td>
</tr>
<tr>
<td>Recurrent MVT</td>
<td>1 (1.92%)</td>
<td>5 (15.62%)</td>
<td>&lt; 0.028</td>
</tr>
<tr>
<td>Complete recanalization</td>
<td>45 (86.54%)</td>
<td>16 (50%)</td>
<td>&lt; 0.004</td>
</tr>
<tr>
<td>Symptomatic PE</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1 (1.92%)</td>
<td>1 (3.12%)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

VTE, venous thromboembolism; DVT, deep vein thrombosis; MVT, muscle vein thrombosis; PE, pulmonary embolism; n.s., not significant.

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

Duration of Therapy

• 3 months
  – Provoked DVT
    • Especially estrogen related
• Trials show 3 = 6 months and one that 1 month is not enough
Proximal DVT

Duration of Therapy

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

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

• High rates (20-30%) of recurrence off anticoagulation
• RCT show benefit of long term anticoagulation
Overall cumulative recurrence rate in 929 patients with a first unprovoked VTE estimated by Kaplan-Meier analysis, with 95% CIs (dotted lines)

### Comparing Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>INR</th>
<th>VTE</th>
<th>Major Bleeding</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PREVENT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>7.2</td>
<td>0.4</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>1.5-2.0</td>
<td>2.6</td>
<td>0.9</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td><strong>ELATE</strong></td>
<td>1.5-2.0</td>
<td>1.6</td>
<td>0.9</td>
<td>2.8</td>
</tr>
<tr>
<td>2-3</td>
<td>0.6</td>
<td>0.9</td>
<td>1.6</td>
<td></td>
</tr>
</tbody>
</table>

All with 2 years f/u
Can We Do Better?

- Does every patient with idiopathic DVT need indefinite anticoagulation?
D-Dimers

• Breakdown products of thrombosis
• Higher D-dimers $\rightarrow$ higher chance of recurrent thrombosis
• Do high levels of post-treatment D-dimers predict recurrence?
D-Dimers

- All D-dimers checked off therapy
- Meta-analysis
  - 7 studies (N = 1888)
  - Negative D-Dimer: 3.5%/yr
  - Positive D-Dimer: 8.9%/yr
Prolong I

- 619 patients after first idiopathic DVT had D-dimer measured after stopping anticoagulation
- Three groups:
  - Normal D-dimer (63%)- no anticoagulation
  - Abnormal D-dimer (37%)
    - Randomized to placebo vs anticoagulation

Off anticoagulation for 30 days \rightarrow D-Dimer

Positive \rightarrow R

Negative

Anticoagulation

No Anticoagulation
## Events at 1.4 Years

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Normal D-Dimer</th>
<th>Abnl DD no Anticoag</th>
<th>Abnl DD anticoag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>6.2%</td>
<td>15%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Events/100 pt-yrs</td>
<td>4.4</td>
<td>10.9</td>
<td>2.0</td>
</tr>
</tbody>
</table>
Prolong I

![Graph showing cumulative incidence of outcomes for different conditions with and without anticoagulation. The graph includes Kaplan-Meier survival curves for:
- Abnormal d-dimer level without anticoagulation
- Normal d-dimer level
- Abnormal d-dimer level with anticoagulation

Key points:
- HR = 2.49, P = 0.003
- HR = 5.36, P = 0.007
- HR = 2.17, P = 0.21]
Drilling Down

- Estrogen related DVT low recurrence risk (0.6/100 pt-yr)
  - Women < 65: 1.1/100 pt-yr
    - Excludes estrogen DVT
  - Men < 65: 5.1/100 pt-yr
  - Women > 65: 6.7/100 pt-yr
  - Men > 65: 8.2/100 pt-yr

J Throm Haem 8:1322, 2010
## Events at 2.55 Years

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Normal D-Dimer</th>
<th>Abnl DD no Anticoag</th>
<th>Abnl DD anticoag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>6.2-&gt;13.2%</td>
<td>15-&gt;23.1%</td>
<td>2.9-&gt;5.0%</td>
</tr>
<tr>
<td>Events/100 pt-yrs</td>
<td>4.4-&gt;5.0</td>
<td>10.9-&gt;9.6</td>
<td>2.0-&gt;2.0</td>
</tr>
</tbody>
</table>
Prolong II

- Very convoluted study
- N = 355
- D-dimers on therapy
  - If positive remain anticoagulation
- 30 day D-dimer
  - If positive remain anticoagulation
- Every 60 days D-dimer but no anticoagulation if positive
  - Day 90, 150, 210, 270, 330, 370
VKA = vitamin K antagonist treatment; DVT = deep vein thrombosis; PE = pulmonary embolism; rVTE = recurrent venous thromboembolism; SVT = superficial vein thrombosis; LAC = lupus anticoagulant
Prolong II

- D-dimers on therapy (5.3% abnl)
- 30 day D-dimer (26% abnl)
- Day 90 ->270
  - 10-15% new abnormal D-dimers at each time point
Prolong II

• Recurrence rates – day 90 D-Dimer
  – Abnl DD Day 90 – 22.6% (27/100 pt-yr)
  – NI DD Day 90 - 4.6% (2.7/100 pt-yr)
  – Abnl DD after Day 90 – 11% (11.1/pt-yr)
• Normal DD at day 30 & stays normal (66% of patients) – 2.9%/pt-yr
Group 1: Patients in whom D-d was normal at T90 and afterward (with D-d becoming abnormal only once)

Group 2: Patients in whom D-d became abnormal at T90 and afterward remained altered persistently or at least twice.

Group 3: Patients in whom D-d became abnormal after T90 and afterward remained abnormal persistently or at least twice
Prolong II

• Repeated D-dimer testing for 3 months after stopping anticoagulation may be of benefit
• RCT in progress
Issues

• Testing
• Practicality
• Good enough?
Testing

• All Prolong studies use Simplify point of care test kit
• Uncertain what this translates to in “our” D-dimers
Table 2. Results obtained with the different D-dimer assays in all patients. The table reports the results calculated using the cut-off levels indicated by the manufacturers to be used in diagnostic strategies for the exclusion of venous thromboembolism in symptomatic patients and the cut-off levels giving the results most comparable to those obtained with the qualitative Clearview Simplify D-dimer assay.

<table>
<thead>
<tr>
<th>D-dimer assay</th>
<th>Cut-off</th>
<th>N. (%) of patients with abnormal D-dimer</th>
<th>N. (%) of VTE recurrences in patients with abnormal D-dimer</th>
<th>N. (%) of VTE recurrences in patients with normal D-dimer</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearview Simplify D-dimer (n=321)</td>
<td>......</td>
<td>81 (25.2)</td>
<td>12 (14.8)</td>
<td>13 (5.4)</td>
<td>2.94 (1.34-6.45)</td>
</tr>
<tr>
<td>VIDAS D-dimer Exclusion (n=317)</td>
<td>500 ng/mL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>160 (50.5)</td>
<td>17 (10.6)</td>
<td>8 (5.1)</td>
<td>2.08 (0.93-4.69)</td>
</tr>
<tr>
<td></td>
<td>800 ng/mL&lt;sup&gt;b&lt;/sup&gt;</td>
<td>86 (27.1)</td>
<td>13 (15.1)</td>
<td>12 (5.2)</td>
<td>3.23 (1.47-7.08)</td>
</tr>
<tr>
<td>Innovance D-DIMER (n=252)</td>
<td>500 ng/mL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>109 (43.2)</td>
<td>14 (12.8)</td>
<td>7 (4.9)</td>
<td>2.62 (1.10-6.28)</td>
</tr>
<tr>
<td></td>
<td>800 ng/mL&lt;sup&gt;b&lt;/sup&gt;</td>
<td>57 (22.6)</td>
<td>10 (17.5)</td>
<td>11 (5.6)</td>
<td>3.41 (1.45-8.03)</td>
</tr>
<tr>
<td>HemosIL D-dimer HS (n=304)</td>
<td>230 ng/mL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>99 (32.6)</td>
<td>13 (13.1)</td>
<td>12 (5.9)</td>
<td>2.24 (1.06-4.73)</td>
</tr>
<tr>
<td></td>
<td>300 ng/mL&lt;sup&gt;b&lt;/sup&gt;</td>
<td>75 (24.7)</td>
<td>12 (16.0)</td>
<td>13 (5.7)</td>
<td>3.10 (1.41-6.80)</td>
</tr>
<tr>
<td>STA Liatest D-dimer (n=319)</td>
<td>500 ng/mL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>102 (32.0)</td>
<td>12 (11.8)</td>
<td>13 (6.0)</td>
<td>1.96 (0.93-4.15)</td>
</tr>
<tr>
<td></td>
<td>700 ng/mL&lt;sup&gt;b&lt;/sup&gt;</td>
<td>71 (22.2)</td>
<td>12 (16.9)</td>
<td>13 (5.2)</td>
<td>3.58 (1.63-7.85)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Results calculated using the cut-off level indicated by the manufacturers for VTE exclusion; <sup>b</sup>results calculated using the cut-off level giving the results most comparable to those obtained with the qualitative Clearview Simplify D-dimer assay. VTE: venous thromboembolism; HR: hazard ratio; CI: confidence interval.
Practicality

• Need to bring patient back for at least two repeat tests
  – Compliance
  – Willingness to restart
  – Break thru thrombosis
    • 0-30: 0.6%
    • 30-90: 3.3%
Good Enough?

- Risk of anticoagulation 2-3%/yr
- Negative D-dimers 2.9-3.5%/yr?
- Clinical history more predictive
  - Women < 65 low risk
HERDOO

• Canadian decision rule for idiopathic DVT
  – Predict group with < 3%/yr DVT risk
• Men: Continue
• Women:
  – HER (hyperpigmentation, edema or redness on exam
  – D-dimer (on therapy) > 250
  – Obesity (BMI > 30)
  – Older ( > 65)
  – ≥ 2 continue anticoagulation
HERDOO

• Recurrence rates
  – Men - 9.9%/yr
  – Women ≥ 2 - 8.3%/yr
  – Women 0-1 – 1.3%/yr
• Men with HER has 24%/yr recurrence risk
• RCT in progress
Idiopathic DVT

- Consider stopping anticoagulation after three months if
  - Negative D-dimer (??)
  - Not life-threatening PE or huge DVT
  - Female
  - Age < 65
  - Thrombus resolution – not predictive

- Still need better prediction rules!
Duration of Therapy

• Indefinite
  – >1 DVT (except upper ext)
  – Acquired hypercoagulable states
  – Idiopathic unusual site
  – Idiopathic severe pulmonary embolism

• 3 months
  – Provoked pulmonary embolism
3 months - $\infty$

Femoral

3 months - $\infty$

Common iliac

3 months - $\infty$

External iliac

14 days

Great saphenous

3 months - $\infty$

Popliteal

3 months - $\infty$

Peroneal

6 weeks

Posterior tibial

10-14 days

Soleus