What I am Talking About

1. New Antithrombotic Agents
   1. Ticagrelor
   2. Dabigatran
   3. Rivaroxaban
   4. Apixiban
2. Compare and contrast trials
3. Practical issues in use

Ticagrelor

• “Reversible” P2Y12 receptor inhibitor
  • Still takes 5 days to wear off!!!
  • Non-thienopyridine
  • Very effective in ACS
    – Reduce deaths
    – No increase in major bleeding

Time of Offset of Action

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022433s000lbl.pdf

The Trial

• N = 18,624
• Acute coronary syndrome
• Clopidogrel + ASA vs Ticagrelor + ASA

Major Efficacy End Points At 12 Months

<table>
<thead>
<tr>
<th>End point</th>
<th>Ticagrelor (%)</th>
<th>Clopidogrel (%)</th>
<th>Hazard ratio for ticagrelor</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point: death</td>
<td>9.8</td>
<td>11.7</td>
<td>0.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>from vascular causes, MI, or stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause, MI, or stroke</td>
<td>10.2</td>
<td>12.3</td>
<td>0.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from vascular causes, MI, stroke</td>
<td>14.6</td>
<td>16.7</td>
<td>0.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>recurrent ischemia, recurrent ischemia, TIA, or other arterial thrombotic event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No increase in major bleeding

Primary Safety Event: Major bleeding

<table>
<thead>
<tr>
<th>K-M estimated rate (% per 100 patients)</th>
<th>Ticagrelor 11.5</th>
<th>Clopidogrel 11.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days after randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>300</td>
<td>5.67</td>
<td>5.47</td>
</tr>
<tr>
<td>240</td>
<td>5.16</td>
<td>4.94</td>
</tr>
<tr>
<td>180</td>
<td>4.62</td>
<td>4.41</td>
</tr>
<tr>
<td>120</td>
<td>4.07</td>
<td>3.86</td>
</tr>
<tr>
<td>60</td>
<td>3.58</td>
<td>3.37</td>
</tr>
<tr>
<td>0</td>
<td>3.09</td>
<td>2.88</td>
</tr>
<tr>
<td>HR 0.99 (95% CI = 0.89–1.10), p=0.88</td>
<td></td>
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Effect of Asprin Dose

<table>
<thead>
<tr>
<th>Aspirin Dose</th>
<th>US</th>
<th>Non-US</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;300</td>
<td>1.62 (0.99-2.64)</td>
<td>1.23 (0.71-2.42)</td>
</tr>
<tr>
<td>100-300</td>
<td>-</td>
<td>1.00 (0.71-1.42)</td>
</tr>
<tr>
<td>&lt; 100</td>
<td>0.73 (0.4-1.33)</td>
<td>0.78 (0.49-0.87)</td>
</tr>
</tbody>
</table>

• Doses of aspirin > 100 seem to impair action of drug
• Majority of US patients received > 100mg aspirin

Good

• Ticagrelor very promising
  – Better than clopidogrel
  – No increase in risk of bleeding
  – No concerns about genetics or drug interactions with one curious exception….

However…. 

• Concerns
  – BID dosing
  – Slight increase in dyspnea
  – Takes days to wear off….

• Results varied by trial site
  – NO benefit in USA patients
Ticagrelor: Bottom Line
- 180mg load then 90mg bid
- More effective than clopidogrel in acute coronary syndromes
- Cannot use > 100 mg of aspirin
- Major issue
  – Compliance
  – Dyspnea
  – Reversal

New Anticoagulants
- Warfarin and Heparin around since 1940’s
- Will there ever be anything else?

Disadvantages of Heparin
- Not oral
- Variable dosing (UFH)
- Short half-life
- Heparin thrombocytopenia
- Injection site reactions

Disadvantages of Warfarin
- Drug interactions
- Food interactions
- Variable metabolism
- Frequent monitoring

Advantages of Old Anticoagulants
- Familiarity
- No unexpected side effects
- Demonstrated use in multiple clinical areas

New Anticoagulants
- Two Classes
  – Thrombin inhibitors
  – Anti-Xa inhibitors
### Direct Thrombin Inhibitors

- Thrombin is key step in thrombosis
  - Turns fibrinogen into clot
  - Activates platelets
  - Activates clotting factors

### DTI

- Parental
  - Argatroban
  - Lepirudin
  - Bivalirudin
- Oral
  - Ximelagatran
  - Dabigatran

### Factor Xa Inhibitors

- Xa creates thrombin
- Blocking prevents amplification of coagulation

### Factor Xa Inhibitors

- Rivaroxaban
- Apixaban
- Endobaxiban
- Betrixaban

### Dabigatran

- Oral Thrombin Inhibitor
- Bioavailability: 6.5%
- Onset of action: 2-3 hours
- Half-life: 12-14 hours
- Renal excretion: 80%
- Drug interactions: p-glycoprotein
  - Rifampin

### Dabigatran

- Completed studies
  - DVT prophylaxis
  - DVT Therapy
  - Afib stroke prophylaxis
- Ongoing
  - Long term DVT treatment
  - Cardiac Valves
### Atrial Fibrillation

- **RCT of 18,113**
- **Warfarin INR 2-3**
- **Dabigatran 110mg or 150 mg BID**
- **Mean F/u 2 years**
- **N Engl J Med. 2009 Sep 17;361(12):1139-51.**

### Atrial Fibrillation - 150

- **RCT**
  - Warfarin INR 2-3
  - Dabigatran 150 mg BID
- **More effective than warfarin**
  - RR 0.66 (0.53-0.80)
- **No increase in bleeding**
  - RR 0.93 (0.81-1.07)
  - Intracranial hemorrhage 0.40 (0.14-0.49)

### Atrial Fibrillation - 110

- **RCT**
  - Warfarin INR 2-3
  - Dabigatran 110 mg BID
- **Same as warfarin**
  - RR 0.91 (0.74-1.11)
- **Decrease in bleeding**
  - RR 0.80 (0.69-0.93)
  - Intracranial hemorrhage 0.32 (0.20-0.47)

### Effectiveness vs CHADS2

<table>
<thead>
<tr>
<th>CHADS2</th>
<th>Dabigatran 110</th>
<th>Dabigatran 150</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>1.00 (0.65-1.55)</td>
<td>0.62 (0.38-1.02)</td>
</tr>
<tr>
<td>2</td>
<td>1.04 (0.73-1.49)</td>
<td>0.61 (0.40-0.92)</td>
</tr>
<tr>
<td>3-6</td>
<td>0.79 (0.59-1.06)</td>
<td>0.70 (0.52-0.95)</td>
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</tbody>
</table>

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**Dabigatran: TKR**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>REMODEL N = 2076</th>
<th>REMOBILIZE N = 3034</th>
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<tbody>
<tr>
<td></td>
<td>E40</td>
<td>D220</td>
</tr>
<tr>
<td>Total 6-10 days</td>
<td>37.7%</td>
<td>36.4%*</td>
</tr>
<tr>
<td>Total 10-14 days</td>
<td>6-10 days</td>
<td>37.7%</td>
</tr>
<tr>
<td>Major VTE/D</td>
<td>3.5%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>1.6%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Minor Bleed</td>
<td>6.4%</td>
<td>6.1%</td>
</tr>
</tbody>
</table>

*P < 0.01


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**Dabigatran: THR**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>RENOVATE N = 2076</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E40</td>
</tr>
<tr>
<td>Total 28-25 days</td>
<td>6.7%</td>
</tr>
<tr>
<td>Total VTE/D</td>
<td>6.7%</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>1.6%</td>
</tr>
<tr>
<td>Minor Bleed</td>
<td>6.4%</td>
</tr>
</tbody>
</table>

**Lancet. 2007 370:949-56.**
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)

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 (CLcr, ml/min)</th>
<th>Half-life (hours)</th>
<th>Timing of discontinuation after last dose of dabigatran before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;180</td>
<td>13 (11-22)</td>
<td>24 hours</td>
</tr>
<tr>
<td>&gt;50 to &lt;180</td>
<td>15 (10-45)</td>
<td>4-8 days</td>
</tr>
<tr>
<td>&gt;30 to &lt;50</td>
<td>18 (13-22)</td>
<td>at least 2 days (48 hours)</td>
</tr>
<tr>
<td>&lt;30</td>
<td>27 (22-75)</td>
<td>5-5 days</td>
</tr>
</tbody>
</table>

*Data from renal impairment study in healthy volunteers (N), gender and mean (range). Type of surgery associated with a high risk of bleeding for its major surgery when complete hemostasis may be required. Includes 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 handling. Other important hemostatic risks include advancing age, co-morbidities (e.g., major cardiac, respiratory or liver disease) and concurrent use of antiplatelet therapies. *Dabigatran esifenoxil is contraindicated for use in these patients. CLcr = 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 used to adjust dose
- Assess compliance and drug effect
- INR insensitive

Rivaroxaban

- Oral Xa Inhibitor
- Bioavailability: 80-100%
- Onset of action: 2.5-4 hours
- Half-life: 5-9 hours
- Renal excretion: ~66%
- Drug interactions: CYP 3A4

Total Hip Replacement

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>RECORD 1 N = 4435</th>
<th>RECORD 2 N = 2457</th>
</tr>
</thead>
<tbody>
<tr>
<td>E 40mg</td>
<td>R 10mg</td>
<td>E 40mg</td>
</tr>
<tr>
<td>42 days</td>
<td>10-14d</td>
<td>42d</td>
</tr>
<tr>
<td>Total VTE</td>
<td>3.7%</td>
<td>1.1%*</td>
</tr>
<tr>
<td>Major VTE</td>
<td>2.0%</td>
<td>0.2%*</td>
</tr>
<tr>
<td>Symp VTE</td>
<td>0.5%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>0.1%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Minor Bleed</td>
<td>2.4%</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

*P < 0.01

R4: EFFORT 2008

Total Knee Replacement

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>RECORD 3 N = 2439</th>
<th>RECORD 4 N = 3034</th>
</tr>
</thead>
<tbody>
<tr>
<td>E 40mg</td>
<td>R 10mg</td>
<td>E 30mg</td>
</tr>
<tr>
<td>BID</td>
<td></td>
<td>R 10mg</td>
</tr>
<tr>
<td>10-14 days</td>
<td></td>
<td>10-14 days</td>
</tr>
<tr>
<td>Total VTE</td>
<td>18.9%</td>
<td>9.6%*</td>
</tr>
<tr>
<td>Major VTE</td>
<td>2.6%</td>
<td>1.0%*</td>
</tr>
<tr>
<td>Symp VTE</td>
<td>2.0%</td>
<td>0.7%*</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>0.5%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Minor Bleed</td>
<td>2.3%</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

*P < 0.01

R4: EFFORT 2008
Rivaroxaban

- Shown to be effective in DVT prevention
  - Better than LMWH for THR and TKR

Rivaroxaban: Acute DVT Therapy

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

Results

<table>
<thead>
<tr>
<th></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>

Safety

Extension Study

- N = 1,197
- Finished 6-12 months of therapy
- RCT: 20mg of rivaroxaban vs placebo
- No increase in major bleeding
Results

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (602)</th>
<th>Placebo (594)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any recurrence</td>
<td>8 (1.3%)</td>
<td>42 (7.1%)</td>
</tr>
<tr>
<td>Recurrent DVT</td>
<td>5 (%)</td>
<td>31 (5.2%)</td>
</tr>
<tr>
<td>New PE</td>
<td>3 (%)</td>
<td>14 (2.2%)</td>
</tr>
<tr>
<td>Any Bleeding</td>
<td>36 (6.0%)</td>
<td>7 (1.2%)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>4 (0.7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Minor Bleeding</td>
<td>32 (5.4%)</td>
<td>7 (1.2%)</td>
</tr>
</tbody>
</table>

Rivaroxaban

• Effective in short and long term therapy of DVT

Atrial Fibrillation

• RCT of 14,264
• Warfarin INR 2-3
• Rivaroxaban 20mg
  – 15mg CrCl 49-30
• Mean F/u 1.6 years


Atrial Fibrillation

• RCT
  – Warfarin INR 2-3
  – Rivaroxaban 20mg
• As effective than warfarin
  – RR 0.79 (0.66-0.96)
• No increase in bleeding
  – RR 1.04 (0.90-1.20)
  – Intracranial hemorrhage 0.67 (0.47-0.94)
**Rivaroxaban**

- Trials
  - Prophylaxis
  - Atrial Fibrillation
  - DVT therapy
- Ongoing
  - PE therapy
  - Acute coronary syndromes

**Rivaroxaban**

- Approved 10mg daily for DVT prophylaxis in TKR and THR
- Contraindicated if CrCl <30
- Drug interactions
  - Ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan

**Rivaroxaban**

- Potential with renal insufficiency
  - Erythromycin, azithromycin, diltiazem, verapamil, quinidine, ranolazine, dronedarone, amiodarone, and felodipin
- Need 20mg/day
  - Carbamazepine, phenytoin, rifampin, St. John’s wort

**Apixaban**

- Oral Xa Inhibitor
- Bioavailability: 66%
- Onset of action: 1-3 hours
- Half-life: 8-15 hours
- Renal excretion: 25%
- Drug interactions: CYP 3A4

**Apixaban: THR**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>ADVANCE 3 - 5407</th>
<th>ADVANCE 1 N = 3195</th>
<th>ADVANCE 2 N = 3057</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E40 BID</td>
<td>A 2.5 BID</td>
<td>E 30mg BID</td>
</tr>
<tr>
<td>Total VTE/D</td>
<td>8.8%</td>
<td>3.9%</td>
<td>9.0%</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>0.8%</td>
<td>0.7%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Minor Bleed</td>
<td>7.5%</td>
<td>6.9%</td>
<td>2.2%</td>
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</tbody>
</table>

**Apixaban: TKR**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>ADVANCE 3 - 5407</th>
<th>ADVANCE 1 N = 3195</th>
<th>ADVANCE 2 N = 3057</th>
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<tbody>
<tr>
<td></td>
<td>E40 BID</td>
<td>A 2.5 BID</td>
<td>E 30mg BID</td>
</tr>
<tr>
<td>Total VTE</td>
<td>8.8%*</td>
<td>9.0%</td>
<td>24%</td>
</tr>
<tr>
<td>Major VTE</td>
<td>1.6%</td>
<td>2.0%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Sympt VTE</td>
<td>0.8%</td>
<td>1.2%</td>
<td>0.46%</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>2.2%</td>
<td>1.1%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Minor Bleed</td>
<td>3.8%</td>
<td>2.9%</td>
<td>3.8%</td>
</tr>
</tbody>
</table>

*P < 0.01


Lancet 375:807 – 815, 2010
Atrial Fibrillation –
Vs ASA

• RCT of 5599
• Aspirin 81-324 mg/day
• Apixaban 5mg BID
  – 2.5mg if 2/3
  • Age > 80
  • Cr > 1.5
  • Weight < 60 kg
• Mean F/u 1.1 years
• N Engl J Med 2011 364:806-817

Atrial Fibrillation - ASA

• RCT
  – Aspirin 81-324mg
  – Apixiban 5mg bid
• More effective than aspirin
  – RR 0.45 (0.32-0.62)
• Same risk of bleeding
  – RR 1.13 (0.74-2.05)
  – Intracranial hemorrhage 0.85 (0.38-1.90)

Atrial Fibrillation -
Warfarin

• RCT of 18,201
• Warfarin INR 2-3
• Apixaban 5mg BID
  – 2.5mg if 2/3
  • Age > 80
  • Cr > 1.5
  • Weight < 60 kg
• Mean F/u 1.8 years
• N Engl J Med 2011; on line

Atrial Fibrillation -
Warfarin

• RCT
  – Warfarin INR 2-3
  – Apixiban 5mg bid
• More effective than warfarin
  – RR 0.79 (0.66-0.95)
• Decrease in bleeding
  – RR 0.69 (0.60-0.80)
  – Intracranial hemorrhage 0.42 (0.30-0.58)

Edoxaban

• Oral Xa Inhibitor
• Bioavailability: 45%
• Onset of action: 1-1.5 hours
• Half-life : 9-11 hours
• Renal excretion: 33%
• Drug interactions: CYP 3A4

Betrixaban

• Oral Xa Inhibitor
• Bioavailability: 47%
• Onset of action: ?
• Half-life : 19 hours
• Renal excretion: 0%
• Drug interactions: None
### The Big Five

<table>
<thead>
<tr>
<th>Class</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Betrixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life (hrs)</td>
<td>14-17</td>
<td>7-11</td>
<td>8-15</td>
<td>6-11</td>
<td>20</td>
</tr>
<tr>
<td>Bioavail</td>
<td>~6</td>
<td>80-100</td>
<td>34-88</td>
<td>~40</td>
<td>47%</td>
</tr>
<tr>
<td>Dosing</td>
<td>BID</td>
<td>Daily</td>
<td>BID</td>
<td>Daily</td>
<td></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>
<td></td>
</tr>
<tr>
<td>Renal (%)</td>
<td>~80</td>
<td>33</td>
<td>~22</td>
<td>~40</td>
<td>0%</td>
</tr>
</tbody>
</table>

### Total Hip Replacement

<table>
<thead>
<tr>
<th>Drug</th>
<th>Thrombosis</th>
<th>Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>Better</td>
<td>Equal</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Equal</td>
<td>Equal</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Better</td>
<td>Equal</td>
</tr>
</tbody>
</table>

### Total Knee Replacement

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### Prophylaxis

- All three agents effective
- 220mg dose of dabigatran not available in US
- Rivaroxaban approved
  - Oral and cheaper!
- Apixiban promising

### Atrial Fibrillation

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<td>Equal</td>
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</table>

### ICH – Atrial Fibrillation

<table>
<thead>
<tr>
<th></th>
<th>Stroke</th>
<th>Intracranial Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events/100 years</td>
<td>RR</td>
</tr>
<tr>
<td>Dabigatran 110</td>
<td>1.53</td>
<td>0.91 (0.74-1.11)</td>
</tr>
<tr>
<td>Dabigatran 150</td>
<td>1.11</td>
<td>0.66 (0.53-0.82)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>1.76</td>
<td>0.79 (0.66-0.96)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>1.19</td>
<td>0.79 (0.65-0.95)</td>
</tr>
</tbody>
</table>
Atrial Fibrillation
- Dabigatran
  - Robust trial data for all CHADS2
- Apixaban
  - Effective for all groups
  - Safer – “the sweet spot”
- Rivaroxaban

Deep Venous Thrombosis

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</table>

Deep Venous Thrombosis
- None approved
- Dabigatran with robust data
- Rivaroxaban
  - Need PE data

Who Am I Changing Over?
- Intolerant of warfarin
- Tired of warfarin
- Unstable INR
- Unable to get INR
- Offer to new patients
- When to change over stable patients?

Valves
- Will need good data
- Studies underway
- Bileaflet aortic valves
- Bridging
  - Cheaper and more convenient than LMWH

Cancer
- 4 trials show superiority of LMWH over warfarin
- No cancer data yet for new drugs
- LMWH still agents of choice
- Consider substituting for warfarin
  - Less diet/drug interactions
**Monitoring**

- Dabigatran
  - aPTT
  - Anti-IIa activity
    - PeaceHealth Labs
- Xa inhibitors
  - INR
  - Prothrombin time
  - Anti-Xa levels

**Reversal**

- Ximelagran trials
  - No clear difference in outcomes reversible vs irreversible agents
  - Hard to know what endpoints to follow

**Dabigatran**

- Reversal
  - Animal modes
    - Activated prothrombin complex concentrates
    - Prothrombin complex concentrates
  - Human
    - PCC not as effective
- Dialyzable
- Specific antibody in development

**Xa Blockers**

- rVIIa
  - Human studies
- Prothrombin Complex concentrates
  - Animal and human studies
PRT064445

- Recombinant fXa derivative
  - Catalytically inactive
  - Lacks the Gla-domain
- Reverses both direct and indirect Xa inhibitors
- In clinical trials

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