What I am Talking About

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

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

Atrial Fibrillation – 150mg

- RCT of 18,113
- Warfarin INR 2-3
- Dabigatran 110mg or 150 mg BID
- Mean F/u 2 years

- 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)
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>
</tr>
</tbody>
</table>

The MI Issue

- RE-LY – Circ 2012
- MI:
  - D: 0.81% / yr vs W: 0.64% / yr (p=0.12)
- MI, ACS, arrest, cardiac death
  - D: 3.33 % / yr vs 3.41% / yr (p=0.77)
- No difference with previous cardiac disease
- Most events off drug (>6 or 90 days)

The MI Issue

- Meta-analysis
  - All studies
  - Multiple cardiac events evaluated
  - RR -1.33
  - Mortality benefit with dabigatran
    - 0.89: (0.80-0.99) P = .04

MI Bottom Line

- RCTs with no difference
- Most events off drug
- Overall agent shows benefit

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

- Effective in DVT prevention
  - 220mg dose in EU/Canada
- Effective in DVT therapy
  - Short and long term
- Effective in stroke prevention in atrial fibrillation

Drug Interactions

- Contraindicated
  - Quinidine, ketoconazole
- Caution
  - Rifampin, St John’s wort
- Caution with renal disease
  - Verapamil, amiodarone

Side Effects

- No difference in liver function tests
- Increase in dyspepsia
  - May be improved by PPI
  - May be improved by food

Dabigatran

- 150 and 75 mg dose approved by FDA
  - Weirdly not 110mg
- Dosing
  - CrCl > 30 mL/ml - 150mg BID
  - Caution with < 50mL/ml in older patients
  - CrCl 15-30mL/ml 75 mg BID
  - CrCl < 15 not indicated
Dabigatran- Surgery

<table>
<thead>
<tr>
<th>GFR</th>
<th>T1/2</th>
<th>Standard Risk of Bleeding</th>
<th>High Risk of Bleeding</th>
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<tbody>
<tr>
<td>&gt; 80</td>
<td>~ 13</td>
<td>24</td>
<td>2-4 days</td>
</tr>
<tr>
<td>50-80</td>
<td>~ 15</td>
<td>24</td>
<td>2-4 days</td>
</tr>
<tr>
<td>30-50</td>
<td>~ 18</td>
<td>48</td>
<td>4 day</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>~ 27</td>
<td>2-5 days</td>
<td>5 days</td>
</tr>
</tbody>
</table>

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
- Assess compliance and drug effect
- Reference labs can do specific level
  - Peace Health Labs
- 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></td>
<td>E 40mg</td>
<td>R 10mg</td>
</tr>
<tr>
<td></td>
<td>42 days</td>
<td>10-14d</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>0.3%</td>
</tr>
<tr>
<td>Minor Bleed</td>
<td>2.4%</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

* P < 0.01
Total Knee Replacement

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>RECORD 3 N = 2439</th>
<th>RECORD 4 N = 3034</th>
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<tbody>
<tr>
<td></td>
<td>E 40mg</td>
<td>R 10mg</td>
</tr>
<tr>
<td></td>
<td>10-14 days</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


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: 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 (21%)</td>
<td>51 (30%)</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>
Rivaroxaban: Acute PE

- N = 4,832 with PE
- RCT
  - Rivaroxaban 15mg BID then 20mg after 3 weeks
  - Enoxaparin -> Warfarin
- PE burden
  - 12% with mild (< 25% of one lobe)
  - 58% intermediate
  - 25% extensive (25% of total vascular field)

Results

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (2419)</th>
<th>Placebo (2413)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any recurrence</td>
<td>50 (2.1%)</td>
<td>44 (1.8%)</td>
</tr>
<tr>
<td>Recurrent DVT</td>
<td>15 (0.7%)</td>
<td>17 (0.7%)</td>
</tr>
<tr>
<td>New PE</td>
<td>24 (1.0%)</td>
<td>22 (0.9%)</td>
</tr>
<tr>
<td>Any Bleeding</td>
<td>249 (10.0%)</td>
<td>274 (11.5%)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>26 (1.1%)</td>
<td>52 (2.2%)</td>
</tr>
<tr>
<td>ICH</td>
<td>2 (0.08%)</td>
<td>12 (0.5%)</td>
</tr>
</tbody>
</table>

Rivaroxaban

- Effective in:
  - Prophylaxis
  - Atrial Fibrillation
  - DVT/PE therapy

Rivaroxaban

- Approved 10mg daily for DVT prophylaxis in TKR and THR
- Approved 20mg daily for afib
  - 15mg if CrCl 15-49mL/m
  - Contraindicated < 15mL/m
Drug interactions

- Ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan
- Potential with renal insufficiency
  - Erythromycin, azithromycin, diltiazem, verapamil, quinidine, ranolazine, dronedarone, amiodarone, and felodipin
- Double dose?
  - 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
  - Multiple other pathways

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

Atrial Fibrillation - ASA

- RCT
  - Aspirin 81-324mg
  - Apixaban 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)
Is Aspirin Safer than Warfarin?

- Aspirin often given to atrial fibrillation (afib) patients because it is perceived to be “safer”
- But is it???

BAFTA

- N = 973 with afib
- All over 75 year of age (mean 81.5)
- RCT
  - Warfarin 2-3 vs aspirin 81mg/day
  - f/u 2.7 years


Hazard Ratios For Bleeding Compared To Aspirin

<table>
<thead>
<tr>
<th>Drug/combo</th>
<th>Adjusted hazard ratio</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>1.23</td>
<td>0.94–1.61</td>
</tr>
<tr>
<td>Aspirin/clopidogrel</td>
<td>1.47</td>
<td>1.28–1.69</td>
</tr>
<tr>
<td>Aspirin/VKA</td>
<td>1.84</td>
<td>1.51–2.23</td>
</tr>
<tr>
<td>VKA/clopidogrel</td>
<td>3.52</td>
<td>2.42–5.11</td>
</tr>
<tr>
<td>VKA/clopidogrel/aspirin</td>
<td>4.05</td>
<td>3.08–5.33</td>
</tr>
</tbody>
</table>


Aspirin vs Warfarin

- 52% reduction in ischemic stroke with warfarin
  - History of stroke ARR = 6%/yr
  - No history of stroke ARR = 1.2%/yr
  - Low risk of stroke ARR = 0.4%/yr

Aspirin and Stroke Severity

- Aspirin does not reduce risk of disabling stroke
  - 22-->13% (NS)
- Warfarin does reduce fatal stroke
  - 0.5-->0.2 events/yr
Denmark Study

- 132,372 patients with AF
- VKA consistent lowered stroke rate
- No effect of aspirin
- Benefit seen CHADS2 > 0

- Thromb Haem 106:737, 2011

Aspirin: Bottom Line

- Limited to no effectiveness
- Not effective in older patients
- Not effective in preventing disabling strokes
- Not the safer choice

Atrial Fibrillation: vs 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

Atrial Fibrillation - Warfarin

- RCT
  - Warfarin INR 2-3
  - Apixaban 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)

Apixaban: Renal Disease

- GRF < 50 mL/min
  - Stroke: 0.61 (0.39-0.94)
  - Mortality: 0.78 (0.63-0.96)
  - Bleeding: 0.48 (0.37-0.64)

Apixaban

- Effective in
  - Atrial fibrillation
  - Prophylaxis
- Ongoing
  - DVT therapy

The Big Five

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Betrixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class</td>
<td>Anti-IIa</td>
<td>Anti-Xa</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>5-9</td>
<td>6-11</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Bioavail</td>
<td>80-100</td>
<td>8-15</td>
<td>24-88</td>
<td>40 47%</td>
<td></td>
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<tr>
<td>Dosing</td>
<td>BID</td>
<td>Daily</td>
<td>Daily</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>

Comparing Trials

<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 Hip Replacement

- LMWH: $25-30/day
- Rivaroxaban: $6.75/day
- Dabigatran: $3.50/day**
## Total Knee Replacement

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

LMWH: $25-30/day  
Rivaroxaban: $6.75/day  
Dabigatan: $3.50/day**

## Prophylaxis

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

## Atrial Fibrillation

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

Warfarin: $4/month + monitoring ($20-50/visit)  
Rivaroxaban: $247/month  
Dabigatan: $235/month

## Atrial Fibrillation

<table>
<thead>
<tr>
<th>Drug</th>
<th>CHAD2</th>
<th>TTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>2.1</td>
<td>64%</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>2.1</td>
<td>66%</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>3.5</td>
<td>58%</td>
</tr>
</tbody>
</table>

## ICH – Atrial Fibrillation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Stroke RR</th>
<th>Intracranial Hemorrhage RR</th>
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<tbody>
<tr>
<td>Dabigatran 110</td>
<td>0.91 (0.74-1.11)</td>
<td>0.23 (0.20-0.47)</td>
</tr>
<tr>
<td>Dabigatran 150</td>
<td>0.66 (0.53-0.82)</td>
<td>0.30 (0.27-0.60)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>0.79 (0.66-0.96)</td>
<td>0.49 (0.47-0.94)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>0.79 (0.65-0.95)</td>
<td>0.33 (0.30-0.58)</td>
</tr>
</tbody>
</table>

Potential for 10-12,000 less ICH in USA

## Atrial Fibrillation

- Dabigatran  
  - Robust trial data for all CHADS2  
  - ACCP 9th preferred agent
- Apixaban  
  - More effective than warfarin  
  - Safer – “the sweet spot”
- Rivaroxaban  
  - Effective
Venous Thrombosis

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

- Warfarin: $4/month + monitoring ($20-50/visit)
- LMWH: $100-120/day
- Rivaroxaban: $247/month
- Dabigatran: $235/month

Venous Thrombosis

- None approved
- Dabigatran with robust data
  - Two trials and extended therapy
- Rivaroxaban
  - Cost effective?
- Apixaban
  - In trials

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
  - 150mg, 220mg, 300mg BID
- Bileaflet aortic valves?

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
Bridging
- Great potential
- Rivaroxaban
  - Short $T_{1/2}$
- Caveats
  - Valves
  - Renal impairment
  - Timing of stopping and starting

Pregnancy
- NO!
- LMWH remains anticoagulants of choice

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

Warfarin: “The Gold Standard”
- Prothrombin Complex Concentrates (PCC) standard
  - FFP not effective for rapid reversal
- 75% patients dead or disabled after intracranial hemorrhage

New Agents: Reversal
- Ximelagatran trials
  - No clear difference in outcomes reversible vs irreversible agents
- Hard to know what endpoints to study
Dabigatran

- Reversal
  - Animal modes
    - Activated prothrombin complex concentrates
    - Prothrombin complex concentrates
  - Human
    - PCC did not effect *in-vitro* tests
- Dialyzable
- Specific antibody in development

Xa Blockers

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

- “R-antidote”
- 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