Recent Advances in Anticoagulant Therapy:

Will New Oral Agents Render Warfarin a Thing of the Past?

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Clinical Specialist – Cardiology/Anticoagulation  
Director: Inpatient Anticoagulation – Thrombosis Management Service  
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Objectives

• Differentiate new anticoagulant agents with respect to their pharmacokinetics, pharmacodynamics, and recommended dosing strategies

• Outline current literature supporting the role of new anticoagulant agents in the prevention and treatment of thromboembolic disorders

• Given a patient who is receiving a new anticoagulant agent, assess whether current therapy is appropriate
Oral Anticoagulation - Warfarin

• Main oral agent for long term prevention and treatment of thromboembolic disease > 50 years

• Advances
  – INR
  – Anticoagulation Management Services

• Despite Advances
  – Challenges still exist in determining optimal and safest dose
    – *Individualized patient to patient*
  – Warfarin continues to rank among top 10 medications associated with adverse events
    • Bleeding
      – Cumulative increase over time
      – Rates vary depending on indication
      – *Rate is highest during initiation of therapy*
Warfarin Key Variables for Dosing

- **Metabolism**
  - CYP system
  - Drug interactions

- **Variable response**
  - Food
  - Age
  - Concomitant disease states
  - ETOH
  - Ethnicity

- **Half-life**
  - 36-48 hours
  - Peak effect single dose
  - Steady state 2 weeks

- **Initiation**
  - Loading vs predicted maintenance dose

- **Ethnicity and average daily dose**
  - 6.1 mg: African-Americans
  - 5.1 mg: Caucasians
  - 3.4 mg: Asians

Johnson JA. Circulation 2008;118:1383-1393
Warfarin for Atrial Fibrillation

Limitations Lead to Under-treatment

# Ideal Anticoagulant

<table>
<thead>
<tr>
<th>Disadvantage of Warfarin</th>
<th>Ideal Anticoagulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow onset of action</td>
<td>Fast onset of action, allowing for acute treatment of VTE and use post-procedures</td>
</tr>
<tr>
<td>Slow resolution of action</td>
<td>Fast resolution of action, allowing for use pre-procedures</td>
</tr>
<tr>
<td>Regular blood monitoring</td>
<td>No routine blood monitoring</td>
</tr>
<tr>
<td>Many drug interactions</td>
<td>No drug interactions</td>
</tr>
<tr>
<td>Interactions with diet</td>
<td>No interactions with diet</td>
</tr>
<tr>
<td>Wide range of therapeutic doses</td>
<td>Narrow-ranged, fixed doses</td>
</tr>
<tr>
<td>Unpredictable dose-response</td>
<td>Predictable dose-response</td>
</tr>
<tr>
<td>Teratogenicity</td>
<td>Safe in pregnancy</td>
</tr>
<tr>
<td>Slow reversibility via vitamin K</td>
<td>Immediate reversibility</td>
</tr>
</tbody>
</table>

*Need for Injectable agent*
New Oral Anticoagulants - Targets

MANY CHOICES
The coagulation cascade is complex, but anticoagulant drugs in late-stage development hit it at just two points, Factor Xa or thrombin.

- **Factor XIIa**
- **Factor Xa**
- **Factor IXa**
- **Factor VIIIa**
- **Tissue factor**
- **Factor Xa**
- **Factor Va**
- **Factor Va**
- **Thrombin**
- **Fibrin**

**Dabigatran etexilate**

**Apixaban**

**Rivaroxaban**

**Betrixaban**

Bereznicki et al. New antithrombotics for atrial fibrillation. Cardiovascular Therapeutics 2010 (28) 278–286
DABIGATRAN ETESILATE
(Pradaxa®, Boeringher-Ingelheim)

• PHARMACOLOGY:
  – Prodrug, converted to the active dabigatran moiety by hydrolysis via nonspecific esterases.
  – Dabigatran is a reversible and selective direct thrombin inhibitor.
  – Dabigatran inhibits human thrombin and thrombin-induced platelet aggregation.
  – Dabigatran inhibits both clot-bound and fluid-phase thrombin.

• FDA indication (Approved October 2010):
  – Dabigatran is a direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
RE-LY: Study Design

Atrial fibrillation
≥1 Risk Factor
Absence of contra-indications
951 centers in 44 countries

Open
N = 18,113

Blinded

Warfarin adjusted (INR 2.0-3.0)
N=6000

Dabigatran Etexilate
110 mg BID
N=6000

Dabigatran Etexilate
150 mg BID
N=6000

Patients were eligible if they had atrial fibrillation documented on electrocardiography performed at screening or within 6 months beforehand and at least one of the following characteristics:

1. Previous stroke or transient ischemic attack
2. A left ventricular ejection fraction of less than 40%
3. New York Heart Association class II or higher heart-failure symptoms within 6 months before screening
4. An age of at least 75 years or an age of 65 to 74 years plus diabetes mellitus, hypertension, or coronary artery disease.

## RE-LY: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dabigatran 110 mg</th>
<th>Dabigatran 150 mg</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>6015</td>
<td>6076</td>
<td>6022</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>71.4</td>
<td>71.5</td>
<td>71.6</td>
</tr>
<tr>
<td>Male (%)</td>
<td>64.3</td>
<td>63.2</td>
<td>63.3</td>
</tr>
<tr>
<td>CHADS2 score (mean)</td>
<td>2.1</td>
<td>2.2</td>
<td>2.1</td>
</tr>
<tr>
<td>0-1 (%)</td>
<td>32.6</td>
<td>32.2</td>
<td>30.9</td>
</tr>
<tr>
<td>2 (%)</td>
<td>34.7</td>
<td>35.2</td>
<td>37.0</td>
</tr>
<tr>
<td>3+ (%)</td>
<td>32.7</td>
<td>32.6</td>
<td>32.1</td>
</tr>
<tr>
<td>Prior stroke/TIA (%)</td>
<td>19.9</td>
<td>20.3</td>
<td>19.8</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>16.8</td>
<td>16.9</td>
<td>16.1</td>
</tr>
<tr>
<td>CHF (%)</td>
<td>32.2</td>
<td>31.8</td>
<td>31.9</td>
</tr>
<tr>
<td>Baseline ASA (%)</td>
<td>40.0</td>
<td>38.7</td>
<td>40.6</td>
</tr>
<tr>
<td>Warfarin Naïve (%)</td>
<td>49.9</td>
<td>49.8</td>
<td>51.4</td>
</tr>
</tbody>
</table>

RE-LY: Primary Outcome
Composite: Stroke or Systemic Embolism

- Warfarin time-in-range = 64%

RE-LY: Primary Outcome
Composite: Stroke or Systemic Embolism

NON-INFERIOR

Dabigatran 110 mg vs. Warfarin

SUPERIOR

Dabigatran 150 mg vs. Warfarin

Dabigatran 150 mg results driven by reduction in stroke

RE-LY: Primary Safety Outcome

<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><strong>Total</strong></td>
<td>Annual</td>
<td>Annual</td>
<td>Annual</td>
<td>RR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td></td>
<td>rate</td>
<td>rate</td>
<td>rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14.6%</td>
<td>16.4%</td>
<td>18.2%</td>
<td>0.78 (0.74-0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.91 (0.86-0.97)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Major</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.7%</td>
<td>3.1%</td>
<td>3.4%</td>
<td>0.80 (0.69-0.93)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.93 (0.81-1.07)</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Life-threatening</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>1.2%</td>
<td>1.5%</td>
<td>1.8%</td>
<td>0.68 (0.55-0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major</td>
<td></td>
<td></td>
<td></td>
<td>0.81 (0.66-0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>1.1%</td>
<td>1.5%</td>
<td>1.0%</td>
<td>1.10 (0.86-1.41)</td>
<td>0.43</td>
</tr>
<tr>
<td>Major</td>
<td></td>
<td></td>
<td></td>
<td>1.50 (1.19-1.89)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

## RE-LY: Adverse Events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>D 110 mg (%)</th>
<th>D 150 mg (%)</th>
<th>Warfarin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspepsia *</td>
<td>11.8</td>
<td>11.3</td>
<td>5.8</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>9.3</td>
<td>9.5</td>
<td>9.7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8.1</td>
<td>8.3</td>
<td>9.4</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>7.9</td>
<td>7.9</td>
<td>7.8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6.6</td>
<td>6.6</td>
<td>6.2</td>
</tr>
<tr>
<td>Cough</td>
<td>5.7</td>
<td>5.7</td>
<td>6.0</td>
</tr>
<tr>
<td>Chest pain</td>
<td>5.2</td>
<td>6.2</td>
<td>5.9</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4.5</td>
<td>5.5</td>
<td>5.7</td>
</tr>
<tr>
<td>Back pain</td>
<td>5.3</td>
<td>5.2</td>
<td>5.6</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5.6</td>
<td>5.4</td>
<td>5.6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.3</td>
<td>6.5</td>
<td>5.7</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5.5</td>
<td>5.9</td>
<td>5.8</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4.5</td>
<td>4.8</td>
<td>5.6</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>4.8</td>
<td>4.7</td>
<td>5.2</td>
</tr>
</tbody>
</table>

*Occurred more commonly with dabigatran (p<0.001)

### RE-LY:
**Effect of TTR on Primary Outcome**

**Stroke and Systemic Embolism**

<table>
<thead>
<tr>
<th>cTTR</th>
<th>D 110mg Rate*</th>
<th>D 150mg Rate*</th>
<th>Warfarin Rate*</th>
<th>RR (95% CI)</th>
<th>p-value</th>
<th>RR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;57.1%</td>
<td>1.91</td>
<td>1.10</td>
<td>1.92</td>
<td>1.00</td>
<td>(0.68-1.45)</td>
<td>0.57</td>
<td>(0.37-0.88)</td>
</tr>
<tr>
<td>57.1-65.5%</td>
<td>1.67</td>
<td>1.04</td>
<td>2.06</td>
<td>0.81</td>
<td>(0.56-1.17)</td>
<td>0.50</td>
<td>(0.33-0.77)</td>
</tr>
<tr>
<td>65.5-72.6%</td>
<td>1.34</td>
<td>1.04</td>
<td>1.51</td>
<td>0.89</td>
<td>(0.58-1.36)</td>
<td>0.69</td>
<td>(0.44-1.09)</td>
</tr>
<tr>
<td>&gt;72.6%</td>
<td>1.23</td>
<td>1.27</td>
<td>1.34</td>
<td>0.92</td>
<td>(0.59-1.45)</td>
<td>0.89</td>
<td>(0.61-1.48)</td>
</tr>
</tbody>
</table>

* Rate per 100 person-years

* cTTR = Centre’s mean time in therapeutic range
## RE-LY: Effect of TTR on Safety Outcome

### Major Bleeding

<table>
<thead>
<tr>
<th>cTTR</th>
<th>D 110mg Rate*</th>
<th>D 150mg Rate*</th>
<th>Warfarin Rate*</th>
<th>D 110mg vs. Warfarin RR (95% CI)</th>
<th>p-value</th>
<th>D 150mg vs. Warfarin RR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;57.1%</td>
<td>2.36</td>
<td>2.54</td>
<td>3.59</td>
<td>0.65 (0.48-0.89)</td>
<td></td>
<td>0.71 (0.52-0.96)</td>
<td></td>
</tr>
<tr>
<td>57.1-65.5%</td>
<td>3.38</td>
<td>3.33</td>
<td>4.13</td>
<td>0.82 (0.63-1.06)</td>
<td></td>
<td>0.81 (0.62-1.05)</td>
<td></td>
</tr>
<tr>
<td>65.5-72.6%</td>
<td>2.82</td>
<td>3.80</td>
<td>3.40</td>
<td>0.83 (0.62-1.11)</td>
<td></td>
<td>1.13 (0.87-1.48)</td>
<td></td>
</tr>
<tr>
<td>&gt;72.6%</td>
<td>2.81</td>
<td>3.60</td>
<td>3.11</td>
<td>0.90 (0.67-1.21)</td>
<td>0.50</td>
<td>1.16 (0.88-1.54)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Rate per 100 person-years

cTTR = Centre’s mean time in therapeutic range
Role of Dabigatran for Stroke Prevention in AF

• 2011 ACCF/AHA/HRS Guidelines
  – Dabigatran given a Class I (LOE B) recommendation
    • Dabigatran is useful as an alternative to warfarin for prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have the following:
      – Prosthetic heart valve or hemodynamically significant valve disease
      – CrCl <15 mL/min
      – Advanced liver disease

Wann LS et al. Heart Rhythm. 2011; 8:e1-e8
Role of Dabigatran for Stroke Prevention in AF

• 2011 ACCF/AHA/HRS guidelines also state the following:
  – Patients already taking warfarin with excellent INR control may have little to gain by switching to dabigatran because of dabigatran’s:
    • Twice-daily dosing
    • Greater risk of nonhemorrhagic side effects,
  – Selection of patients with AF and ≥1 additional risk factor for stroke who could benefit from treatment with dabigatran as opposed to warfarin should consider individual factors, including:
    • Ability to comply with twice-daily dosing
    • Availability of an anticoagulation management program to sustain routine monitoring of INR
    • Patient preferences
    • Cost
    • Other factors

RE-COVER: Dabigatran in Acute VTE Treatment

Acute, symptomatic, objectively verified proximal DVT of legs or PE and for whom 6 mos. of anticoagulant therapy was considered to be appropriate treatment

Initial parenteral anticoagulation

- Dabigatran 150 mg twice daily x 6 months
  - N=1274

- Dose- adjusted Warfarin for INR 2-3 x 6 months
  - N= 1265

- Double-blinded, double-dummy, randomized, non-inferiority trial
- Primary outcome: time to 1st occurrence of symptomatic VTE or death assoc. w/ VTE w/in 6 mos.
- Assessed at 7 days, then qmos. for 6 months

RE-COVER: Dabigatran in Acute VTE

Open label, randomized non-inferiority trial of AT + Dabigatran 150mg BID versus AT+VKA (INR 2-3) for 6 months (n=2,564)

Event Rates (%)

- VTE/Death: 2.1 (Warfarin) vs 2.4 (Dabigatran 150 bid), p<0.001 for non-inferiority
- Non-fatal PE: 0.6 (Warfarin) vs 1 (Dabigatran 150 bid)
- Mjr Bleed: 1.9 (Warfarin) vs 1.6 (Dabigatran 150 bid)
- All Bleed: 21.9 (Warfarin) vs 16.1 (Dabigatran 150 bid)

HR, 0.71; 95% CI, 0.59 to 0.85

Schulman S et al. NEJM 2009; 361:2342-5
## Dabigatran for Prevention of VTE after Major Orthopaedic Surgery: Results

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin</th>
<th>Dabigatran (150 mg)</th>
<th>Dabigatran (220 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DVT, PE and all-cause mortality (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-NOVATE</td>
<td>6.7</td>
<td>8.6</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>p&lt;0.0001</em></td>
<td><em>p&lt;0.0001</em></td>
</tr>
<tr>
<td>RE-MOBILIZE</td>
<td>25.3</td>
<td>33.7</td>
<td>31.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>p=0.0009</em>†</td>
<td><em>p=0.02</em>†</td>
</tr>
<tr>
<td>RE-MODEL</td>
<td>37.7</td>
<td>40.5</td>
<td>36.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>p=0.0005</em>†</td>
<td><em>p=0.0345</em>†</td>
</tr>
<tr>
<td><strong>Major bleeding (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-NOVATE</td>
<td>1.6</td>
<td>1.3</td>
<td>2.0</td>
</tr>
<tr>
<td>RE-MOBILIZE</td>
<td>1.4</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>RE-MODEL</td>
<td>1.3</td>
<td>1.3</td>
<td>1.5</td>
</tr>
</tbody>
</table>

*Non-inferior to enoxaparin; †inferior to enoxaparin
ROCKET AF: Study Design

Atrial Fibrillation

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

Randomize Double Blind / Double Dummy (n ~ 14,000)

Monthly Monitoring Adherence to standard of care guidelines

Warfarin
- INR target - 2.5 (2.0-3.0 inclusive)

Primary Endpoint: Stroke or non-CNS Systemic Embolism

Risk Factors
- CHF
- Hypertension
- Age ≥ 75
- Diabetes OR
- Stroke, TIA or Systemic embolus ≥2 required*

- Enrollment of patients without prior Stroke, TIA or systemic embolism and only 2 factors capped at 10%
- Remainder of patients with CHADS2 ≥ 3

AHA November 2010
## ROCKET-AF: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rivaroxaban 20 mg</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>7131</td>
<td>7133</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>73</td>
<td>73</td>
</tr>
<tr>
<td>Female (%)</td>
<td>39.7</td>
<td>39.7</td>
</tr>
<tr>
<td>CHADS2 score (mean)</td>
<td>3.48</td>
<td>3.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (%)</td>
<td>13</td>
<td>13.1</td>
</tr>
<tr>
<td>3 (%)</td>
<td>42.9</td>
<td>44.3</td>
</tr>
<tr>
<td>4 (%)</td>
<td>29.3</td>
<td>28.0</td>
</tr>
<tr>
<td>5 (%)</td>
<td>13.1</td>
<td>12.4</td>
</tr>
<tr>
<td>6 (%)</td>
<td>1.7</td>
<td>2.2</td>
</tr>
<tr>
<td>Prior stroke/TIA/Syst Embolism(%)</td>
<td>54.9</td>
<td>54.6</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>16.6</td>
<td>18.0</td>
</tr>
<tr>
<td>CHF (%)</td>
<td>62.6</td>
<td>62.3</td>
</tr>
<tr>
<td>Baseline ASA (%)</td>
<td>36.3</td>
<td>36.7</td>
</tr>
<tr>
<td>Baseline Warfarin (%)</td>
<td>62.3</td>
<td>62.5</td>
</tr>
</tbody>
</table>

Patel MR, et al. NEJM 2011
ROCKET AF: Primary Endpoint
Composite: Stroke or Systemic Embolism
On-Treatment Analysis

Event Rate
(%/pt-yr)

<table>
<thead>
<tr>
<th>Rivaroxaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.7</td>
<td>2.2</td>
</tr>
</tbody>
</table>

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

Patel MR, et al. NEJM 2011
ROCKET AF: Primary Endpoint Results
Composite: Stroke or Systemic Embolism

On Treatment Analysis

Intention to Treat Analysis

RR (95% CI)
0.79 (0.65 – 0.95)
0.88 (0.74 – 1.03)

ROCKET AF: Bleeding Rates

ICH = intracranial hemorrhage

EINSTEIN: Rivaroxaban in Acute VTE

Open label, randomized non-inferiority trial of Rivaroxaban* versus Enoxaparin + VKA (INR 2-3) for 6 months in 3,449 DVT/PE patients

*15mg BID x 3 weeks then 20mg QDay

NEJM 2010;363:2499-510
## Rivaroxaban in Orthopedic Surgery

<table>
<thead>
<tr>
<th></th>
<th>Hip Trials</th>
<th>Knee Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>RECORD 1</td>
<td>RECORD 2</td>
</tr>
<tr>
<td><strong>dosing</strong></td>
<td>10 mg qd</td>
<td>10 mg qd</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>RECORD 3</td>
<td>RECORD 4</td>
</tr>
<tr>
<td><strong>dosing</strong></td>
<td>RECORD 1</td>
<td>RECORD 2</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>RECORD 1</td>
<td>RECORD 2</td>
</tr>
<tr>
<td><strong>Riva:</strong> 35 days</td>
<td>RECORD 1</td>
<td>RECORD 2</td>
</tr>
<tr>
<td><strong>Enox:</strong> 35 days</td>
<td>RECORD 1</td>
<td>RECORD 2</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>RECORD 1</td>
<td>RECORD 2</td>
</tr>
<tr>
<td><strong>Riva:</strong> 35 days</td>
<td>RECORD 1</td>
<td>RECORD 2</td>
</tr>
<tr>
<td><strong>Enox:</strong> 14 days</td>
<td>RECORD 1</td>
<td>RECORD 2</td>
</tr>
<tr>
<td><strong>Target or ongoing enrollment</strong></td>
<td>RECORD 1</td>
<td>RECORD 2</td>
</tr>
<tr>
<td>4541</td>
<td>2509</td>
<td>2531</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>RECORD 1</td>
<td>RECORD 2</td>
</tr>
<tr>
<td>40 ± 4 days</td>
<td>36 ± 4 days</td>
<td></td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>RECORD 1</td>
<td>RECORD 2</td>
</tr>
<tr>
<td>Total VTE or death</td>
<td>Total VTE or death</td>
<td>Total VTE or death</td>
</tr>
</tbody>
</table>
Rivaroxaban efficacy in TKA’s RECORD 3 and 4 Results

8,101 medical patients were randomized to either oral rivaroxaban 10mg once daily for 35 days or subcutaneous enoxaparin 40mg once daily for 10 days followed by placebo.
FDA approves oral anticoagulant rivaroxaban for DVT prevention at surgery

July 1, 2011 | Steve Stiles (www.theheart.org)

• **INDICATIONS AND USAGE**
  – XARELTO is a factor Xa inhibitor indicated for the prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery. (1)

• **DOSAGE AND ADMINISTRATION**
  – The recommended dose of XARELTO is 10 mg taken orally once daily with or without food. The initial dose should be taken at least 6 to 10 hours after surgery once hemostasis has been established.
  – For patients undergoing hip replacement surgery, treatment duration of 35 days is recommended.
  – For patients undergoing knee replacement surgery, treatment duration of 12 days is recommended.
OK, so how do we make this work in the real world???
# Pharmacokinetics of New Antithrombotic Agents

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tmax</strong></td>
<td>1.25-3 hours</td>
<td>2-4 hours</td>
<td>1-3 hours</td>
</tr>
<tr>
<td><strong>T 1/2</strong></td>
<td>12-14 hours</td>
<td>5-9 hours</td>
<td>8-15 hours</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Conjugation</td>
<td>Oxidation (via CYP3A4 and CYP2J2) and hydrolysis</td>
<td>Oxidation (via CYP3A4) and conjugation</td>
</tr>
<tr>
<td></td>
<td>(no CYP involvement)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Renal Excretion of Unchanged Drug</strong></td>
<td>80%</td>
<td>36%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Dialyzability</strong></td>
<td>Yes</td>
<td>Not expected</td>
<td>Unlikely</td>
</tr>
<tr>
<td><strong>Reversibility</strong></td>
<td>No antidote</td>
<td>No antidote</td>
<td>No antidote</td>
</tr>
</tbody>
</table>
# Dosing Regimens for Stroke Prevention in AF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>CrCl &gt;30 mL/min: 150 mg po BID</td>
</tr>
<tr>
<td></td>
<td>CrCl 15-29 mL/min: 75 mg po BID</td>
</tr>
<tr>
<td></td>
<td>CrCl &lt;15 mL/min: Not recommended</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>CrCl ≥50 mL/min: 20 mg po daily</td>
</tr>
<tr>
<td></td>
<td>CrCl 30-49 mL/min: 15 mg po daily</td>
</tr>
<tr>
<td></td>
<td>CrCl &lt;30 mL/min: Excluded from ROCKET AF</td>
</tr>
<tr>
<td>Apixaban</td>
<td>5 mg po BID</td>
</tr>
<tr>
<td></td>
<td>Dose adjusted to 2.5 mg po BID based on age, wt, and SCr in ARISTOTLE (CrCl &lt;25 mL/min excluded)</td>
</tr>
</tbody>
</table>

1 Based on pharmacokinetic modeling. Not studied clinically
2 Not FDA approved
Dabigatran Dosing and Risk for Bleeding

• Major bleeding in overall population
  – 110 mg: 2.71%
  – 150 mg: 3.11%
  – Warfarin: 3.36%

• Major bleeding in patients > 75 years of age
  – 110 mg: 4.17%
  – 150 mg: 4.81%
  – Warfarin: 4.09%
## Drug Interactions: CYP 450 enzymes

<table>
<thead>
<tr>
<th>CYP Inducers ↓ AC effect</th>
<th>Apixaban (Eliquis®)</th>
<th>Rivaroxaban (Xarelto®)</th>
<th>Dabigatran (Pradaxa®)</th>
<th>Warfarin (Coumadin®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td>Rifampin, Phenytoin, Carbamazepine, St John’s Wort</td>
<td>None</td>
<td>Many</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CYP Inhibitors ↑ AC effect</th>
<th>Apixaban (Eliquis®)</th>
<th>Rivaroxaban (Xarelto®)</th>
<th>Dabigatran (Pradaxa®)</th>
<th>Warfarin (Coumadin®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azole antifungals*</td>
<td>Azole antifungals*</td>
<td>None</td>
<td>None</td>
<td>Many</td>
</tr>
<tr>
<td>Macrolide abx Ritonavir</td>
<td>Macrolide abx Ritonavir</td>
<td>None</td>
<td>None</td>
<td>Many</td>
</tr>
</tbody>
</table>
Drug Interactions: P-glycoprotein

Dabigatran and Rivaroxaban are P-gp substrates

P-gp inducers ↓ AC effect
- Rifampin

P-gp inhibitors ↑ AC effect
- Amiodarone
- Verapamil
- Dronedarone
Dabigatran: Drug Interactions

• Not a substrate of CYP P450

• P-glycoprotein substrate
  – P-gp inhibitors
    • Ketoconazole – AUC ↑ by 153%
    • Verapamil – Effect dependent on formulation and timing of administration of verapamil.
      – 1 hr before dabigatran →↑ AUC by 250%
      – Concurrent administration →↑ AUC by 170%
      – 2 hr after dabigatran → No change in AUC
    • Amiodarone – AUC ↑ by 58%; renal clearance ↑ 65% to compensate
    • Quinidine – AUC ↑ by 53%
  – P-gp inducers
    • Rifampin – AUC ↓ by 66% (AVOID combination with dabigatran)

• No interaction with PPIs, H₂ antagonists, or digoxin

Rivaroxaban: Drug Interactions

7.1 Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems

• In drug interaction studies evaluating the concomitant use with drugs that are combined P-gp and CYP3A4 inhibitors, increases in rivaroxaban exposure and pharmacodynamic effects (i.e., factor Xa inhibition and PT prolongation) were observed. Significant increases in rivaroxaban exposure may increase bleeding risk.

  – *Ketoconazole (combined P-gp and strong CYP3A4 inhibitor):* Steady-state rivaroxaban AUC and Cmax increased by 160% and 70%, respectively. Similar increases in pharmacodynamic effects were also observed.
  – *Ritonavir (combined P-gp and strong CYP3A4 inhibitor):* Single-dose rivaroxaban AUC and Cmax increased by 150% and 60%, respectively. Similar increases in pharmacodynamic effects were also observed.
  – *Clarithromycin (combined P-gp and strong CYP3A4 inhibitor):* Single-dose rivaroxaban AUC and Cmax increased by 50% and 40%, respectively. The smaller increases in exposure observed for clarithromycin compared to ketoconazole or ritonavir may be due to the relative difference in P-gp inhibition.
  – *Erythromycin (combined P-gp and moderate CYP3A4 inhibitor):* Both the single-dose rivaroxaban AUC and Cmax increased by 30%.

• Avoid concomitant administration of XARELTO with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan) which cause significant increases in rivaroxaban exposure that may increase bleeding risk.
Rivaroxaban: Drug Interactions

7.2 Drug-Disease Interactions with Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems

- Based on simulated pharmacokinetic data, patients with renal impairment receiving XARELTO with drugs that are combined P-gp and weak or moderate CYP3A4 inhibitors (e.g., erythromycin, azithromycin, diltiazem, verapamil, quinidine, ranolazine, dronedarone, amiodarone, and felodipine), may have significant increases in exposure compared with patients with normal renal function and no inhibitor use, since both pathways of rivaroxaban elimination are affected. Since these increases may increase bleeding risk, use XARELTO in this situation only if the potential benefit justifies the potential risk [see Use in Specific Populations (8.7)].
Patients Not Necessarily Represented in Clinical Trials

An 88-year-old woman with atrial fibrillation was rhythm controlled with sustained-release verapamil and amiodarone. Her antithrombotic therapy with warfarin had been stable for more than 2 years without a change in dosage. A recent hospital admission for anxiety-related shortness of breath, unrelated to her atrial fibrillation or antithrombotic therapy, prompted a review of her therapy.
Additional Considerations

- Missed Doses
- Managing transitions from other anticoagulant agents
- Peri-operative Management
- Treatment of Bleeding
- Monitoring
- Agent specific considerations
Monitoring – new oral agents

• “OK, so I don’t need to monitor”
• “But, can I monitor if the clinical situation dictates that I have some knowledge of the extent of anticoagulation?”
  – Overdose
  – Pregnancy
  – Extremes of body weight
  – Major bleeding
  – Urgent surgical procedure
  – Assessment of compliance
  – Thromboembolic event
  – Titration of therapy if therapeutic failure
  – Organ dysfunction
  – Drug Interactions
Monitoring - Issues

• Unlike warfarin, new oral agents exhibit circadian peak and trough activities

  – Need to know when in relation to dosing coagulation parameter was checked

  – Need to know when and how much last dose was
Dabigatran – Effect on Clotting Assays

Management of Bleeding on Dabigatran

- No antidote available
- In overdose setting
  - Activated charcoal has been demonstrated to work in vitro
- Local control measures should be employed
- Adequate diuresis should be maintained
- Administration of blood-products of FFP
- One study suggested dabigatran can be dialyzed
  - 62% removed at 2 hours
  - 68% removed at 4 hours
- Recombinant Factor VIIa has been shown to reverse effects of dabigatran ex vivo (rat model)

Thromb Haemost 2010; 103: 1116–1127
Dabigatran: Ensuring Appropriate Use
Capsule Stability

- Dabigatran exetilate requires an acid environment for absorption
- Capsules contain multiple drug pellets
- Each pellet has a tartaric acid core (coated with drug) that creates an acidic microenvironment to improve dissolution and absorption independent of gastric pH

DO NOT CRUSH, CHEW OR BREAK CAPSULES
Dabigatran: Ensuring Appropriate Use
Capsule Stability

• Once bottle is opened, contents must be used within 30 days
  – Cap on bottle contains dessicant to reduce moisture and avoid degradation

• Blister packs should be used in inpatient setting
Potential Advantages of New Oral Anticoagulants

- Oral administration

- Rapid onset of action
  - Eliminates 2 AC regimen

- Predictable effect with fixed or weight-based dosing
  - No monitoring

- Less food/drug interactions

- Short half-life
  - Ease of reversal/ no bridging

- More convenient
  - Potentially leading to greater use

- More cost effective
  - No routine monitoring
  - Fewer ADEs requiring ER visits and hospitalizations

- Possible superior efficacy

- Possible superior safety
### PK / PD Attributes
- **Short half-life**
- **Disadvantageous in nonadherent population**
- **AC effect declines quickly if compliance poor**
- **No antidote**
- **No evidence based reversal strategy**
- **Inability to titrate**
- **Dose adjustment for renal/hepatic impairment? Varying situations?**
- **Cost**
- **No generics available**

### Clinical Management Attributes
- No routine lab marker available to monitor drug activity
- Decreases early detection of issues/ education
- Determine ‘therapy failure’ vs. poor compliance
- No ability to tailor intensity of therapy (esp. with drug interactions)
- Inability to titrate when needed
- ‘One dose fits all’ may be limiting
- Dose adjustment for renal/hepatic impairment? Varying weights?
- No INR to guide therapy

### Societal Attributes
The Future for Warfarin?

• Warfarin will not disappear!

• Use will continue in many circumstances, including:
  – Mechanical heart valves and other un-studied indications
  – Patients who ‘fail’ therapy on a new AC
  – A monitored drug may be preferred for patients with:
    • Compliance issues
    • Drug interaction issues
    • Changing/ poor renal or hepatic function (dialysis?)
  – There may be initial resistance to new agents
    • Especially to convert over a stable warfarin patient

• More data
  – Head-to-head anti-Xa vs. DTI!