Update on Anticoagulants

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Disclosures

• None

Overview

• General discussion of anticoagulants
• New oral anticoagulants (NOACs) and their targets
• Oral direct thrombin inhibitor - Dabigatran
• Oral factor Xa Inhibitors – Rivaroxaban, Apixaban
• Reversal of anticoagulants

The ‘Ideal’ Oral Anticoagulant

• Good bioavailability
• No food or drug interactions
• Rapid onset of action
• Wide therapeutic window
• Predictable anticoagulant response
• Available antidote
• No unexpected toxicities
• Reasonable cost
• Mechanism to ensure compliance with therapy

Warfarin

• When warfarin therapy is started, its anticoagulant effects may not be apparent for several days.
• The duration of action of a single dose is 2–5 days.
• The therapeutic effect of warfarin exists within a narrow therapeutic window as dictated by the INR.
• Considerable inter- and intra-individual dose variability may be affected by a wide range of physiologic (liver and thyroid function), genetic, and environmental (eg, diet, other drugs) factors.
• Regular monitoring is required to avoid excessive or insufficient anticoagulation.

Warfarin’s Therapeutic Window in A-fib

• Ischaemic stroke
• Intracranial bleeding

International normalized ratio
Cumulative Incidence Rates of Bleeding in VTE Patients on Anticoagulation in the ‘Real World’

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patients With VTE (With or Without DVT)</th>
<th>Patients With VTE (Without DVT)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>9.6</td>
<td>9.5</td>
<td>.56</td>
</tr>
<tr>
<td>Retrosent VTE (DVT or PE)</td>
<td>3.3</td>
<td>4.6</td>
<td>.14</td>
</tr>
<tr>
<td>Malignant tumor</td>
<td>1.1</td>
<td>1.1</td>
<td>.36</td>
</tr>
<tr>
<td>Stroke</td>
<td>15.0</td>
<td>8.9</td>
<td>.01</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>17.6</td>
<td>10.0</td>
<td>.01</td>
</tr>
</tbody>
</table>

Limitations of Warfarin Therapy

<table>
<thead>
<tr>
<th>Limitations</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow onset of actions</td>
<td>Overlap with parenteral anticoagulant</td>
</tr>
<tr>
<td>Genetic variation in metabolism</td>
<td>Variable dose requirement</td>
</tr>
<tr>
<td>Multiple food &amp; drug interactions</td>
<td>Frequent INR monitoring</td>
</tr>
<tr>
<td>Narrow therapeutic index</td>
<td>Frequent INR monitoring</td>
</tr>
</tbody>
</table>

Most Common Currently Available Anticoagulants

<table>
<thead>
<tr>
<th>Sub-class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombin inhibitors</td>
<td>UFH, Bivalirudin, Lepirudin**, Argatroban, Dabigatran</td>
</tr>
<tr>
<td>Xa-inhibitor</td>
<td>UFH, LMWH, Fondaparinux, Rivaroxaban, Apixaban (Edoxaban)</td>
</tr>
<tr>
<td>Vit K antagonists</td>
<td>Warfarin</td>
</tr>
</tbody>
</table>

Generic and Brand Names

- Dabigatran – Pradaxa®
- Rivaroxaban – Xarelto®
- Apixaban – Eliquis®

Use of Newer Oral Anticoagulants

- Advantages:
  - Fixed oral dosing
  - No need to monitor anticoagulant effect with labs
  - Fewer drug interactions (but there still are some!)
  - No dietary restrictions

- Disadvantages:
  - Lack of validated tests of anticoagulant effect
  - No clinically proven antidotes
  - More difficult to assess patient compliance
  - Lack of data on long-term adverse events
  - Absence of head-to-head comparisons between novel oral anticoagulants
Targeting Specific Coagulation Factors

- Newer oral anticoagulants target specific points in the coagulation cascade:
  - Factor Xa inhibitors (e.g., rivaroxaban, apixaban) target factor Xa, preventing the conversion of prothrombin to thrombin.
  - Direct thrombin inhibitors (e.g., dabigatran, ximelagatran) target thrombin (factor IIa), blocking the conversion of fibrinogen to fibrin.
- The goal of novel oral anticoagulants is to offer more specific targeting and to afford more predictable responses than current anticoagulant therapies offer.

**Targets of New Oral Anticoagulants**

**Comparison of New Oral Agents**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td>Prodrug</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Dosing</td>
<td>Fixed, 2x daily</td>
<td>Fixed, once daily</td>
<td>Fixed, twice daily</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>6</td>
<td>80</td>
<td>50</td>
</tr>
<tr>
<td>Time to onset (hrs)</td>
<td>2</td>
<td>2-4</td>
<td>1-3</td>
</tr>
<tr>
<td>Coagulation monitoring</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Half-life (hr)</td>
<td>12-17</td>
<td>9-13</td>
<td>9-15</td>
</tr>
<tr>
<td>Renal clearance (%)</td>
<td>80</td>
<td>65</td>
<td>25</td>
</tr>
<tr>
<td>Interactions</td>
<td>P-gp inhibitors*</td>
<td>Combined P-gp and CYP3A4 inhibitors</td>
<td>Combined P-gp and CYP3A4 inhibitors*</td>
</tr>
<tr>
<td>US approved indications</td>
<td>A-Ib</td>
<td>VTE prevention and treatment, A-Ib</td>
<td>A-Ib</td>
</tr>
</tbody>
</table>

**Phase III Randomized Controlled Trials for VTE Prevention**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hip Arthroplasty</th>
<th>Knee Arthroplasty</th>
<th>Medical</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>RE-NOVATE II</td>
<td>RE-MODEL</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RE-NOVATE III</td>
<td>RE-MOBILIZE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>RECORD3</td>
<td>RECORD4</td>
<td>MAGELLAN</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RECORD2</td>
<td>RECORD4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>ADVANCE2</td>
<td>ADVANCE1</td>
<td>ADAPT</td>
<td></td>
</tr>
</tbody>
</table>

**Phase III Randomized Controlled Trials non-VTE prophylaxis**

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>VTE Treatment</th>
<th>ACS</th>
<th>AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idarabigatran</td>
<td>CASIOPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>RE-COVER I</td>
<td>RE-LY</td>
<td>RE-LY</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>EINSTEIN DVT</td>
<td>ATLAS</td>
<td>Japanese AF</td>
</tr>
<tr>
<td>Apixaban</td>
<td>APRAISE2</td>
<td>AVERROES</td>
<td></td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Hokusei-DVT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Eikelboom et al. Circulation 2010 (121(1))
**FDA Approvals**

- **Dabigatran**
  - CVA and systemic embolism prevention in non-valvular A-fib
- **Rivaroxaban**
  - CVA and systemic embolism prevention in non-valvular A-fib
  - VTE prevention in TKR and THR
  - Treatment of VTE/PE
- **Apixaban**
  - CVA and systemic embolism prevention in non-valvular A-fib

**Dabigatran etexilate**

- Oral prodrug, converted to Dabigatran
- Binds clot-bound and free thrombin with high affinity and specificity
- Bioavailability: 6.5%
- Renal excretion: 80%
- Half-life: 12–17 hours
- No interaction with food

**Dabigatran etexilate**

- No participation with CYP450
- Predictable anticoagulant effect – no need for monitoring
- No liver toxicity based on available clinical data
- Dyspepsia is a side effect
- PPIs and H2 blockers may affect absorption
- Potential medication interactions with P-gp affecting drugs – Amiodarone, Dronedarone, Quinidine, Verapamil, Ketoconazole, Rifampin, St Johns Wort

**Dabigatran**

- Other considerations
  - Hygroscopic
  - Capsules should not be removed from original container except for immediate use
  - Capsules only approved for 60 days after opening bottle
  - Capsule should not be placed in pill boxes
  - Cannot crush or open pills for use in feeding tubes

**Dabigatran: FDA Approval**

- **RE-LY (stroke prevention in patients with A-fib)**
  - 18,113 patients
  - Dabigatran 110 and 150 mg bid compared with warfarin
  - Treatment duration up to 3 years, median follow-up of 2 yrs
  - 110 mg associated with rates of stroke or systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage
  - Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke or systemic embolism but similar rates of major hemorrhage

**RE-LY: Major Bleeding & ICH**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran 110 mg</th>
<th>Warfarin</th>
<th>Dabigatran 110 mg vs warfarin</th>
<th>Dabigatran 150 mg vs warfarin</th>
<th>Dabigatran 150 mg vs 110 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate/year</td>
<td>Rate/year</td>
<td>RR (95% CI)</td>
<td>P</td>
<td>RR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3.0%</td>
<td>1.9%</td>
<td>0.80 (0.69-0.93)</td>
<td>.003</td>
<td>0.80 (0.69-0.93)</td>
</tr>
<tr>
<td>All ICH</td>
<td>0.2%</td>
<td>0.2%</td>
<td>0.31 (0.20-0.47)</td>
<td>&lt; .001</td>
<td>0.46 (0.34-0.64)</td>
</tr>
</tbody>
</table>

**RE-LY: Sites of Major Bleeding**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran 110mg vs Warfarin</th>
<th>Dabigatran 150mg vs Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Annual rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial</td>
<td>0.23%</td>
<td>0.30%</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>2.71%</td>
<td>3.11%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1.12%</td>
<td>1.51%</td>
</tr>
</tbody>
</table>

**Annual rate (95% CI)**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial</td>
<td>0.31 (0.20-0.47)</td>
<td>0.40 (0.27-0.60)</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>0.80 (0.69-0.93)</td>
<td>0.93 (0.83-1.07)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1.10 (0.86-1.41)</td>
<td>1.50 (1.19-1.89)</td>
</tr>
</tbody>
</table>

**RE-LY: GI Major Bleeding & MI**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran 110 mg vs Warfarin</th>
<th>Dabigatran 150 mg vs Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rate/Year</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial</td>
<td>1.1%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Major GI</td>
<td>0.72%</td>
<td>0.74%</td>
</tr>
</tbody>
</table>

**Rate/Year (95% CI)**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial</td>
<td>1.10 (0.86-1.41)</td>
<td>1.50 (1.19-1.89)</td>
</tr>
<tr>
<td>Major GI</td>
<td>0.72 (0.58-0.87)</td>
<td>1.36 (1.02-1.80)</td>
</tr>
</tbody>
</table>

**RE-LY: Drug Discontinuation**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dabigatran 110 mg (n = 6015)</th>
<th>Dabigatran 150 mg (n = 6076)</th>
<th>Warfarin (n = 6022)</th>
<th>P-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinued at 1 year, %</td>
<td>15%</td>
<td>16%</td>
<td>10%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Discontinued at 2 years, %</td>
<td>21%</td>
<td>21%</td>
<td>17%</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

* Rates of discontinuation at 1 and 2 years were higher with dabigatran than warfarin (P < .001). Rates are based on Kaplan-Meier estimates.

**Dabigatran: Dosing in US**

- **CrCl > 30 – 150mg bid**
- **CrCl 15-30 – 75mg bid**
- **CrCl < 15 – not recommended**

- **CrCl should be assessed yearly in patients > 75**

**Rivaroxaban**

- Predictable pharmacology
- High bioavailability
- Fixed dose
- No requirement for monitoring
- Inhibits free and thrombus associated Xa
- Contraindicated in severe renal insufficiency
- Drug interactions with meds that affect P-gp and CYP3A4 – Candesartan, Rifampin, Clarithromycin, St Johns Wort and HIV-protease inhibitors (ritonavir)

**Rivaroxaban**

- Specific, competitive, direct FXa inhibitor
- Inhibits free and clot-associated FXa activity, and prothrombinase activity
- Inhibits thrombin generation via inhibition of FXa activity
- Prolongs time to thrombin generation
- Inhibits peak thrombin generation
- Reduces the total amount of thrombin generated
- Does not require a cofactor
Rivaroxaban: FDA Approvals

- VTE prevention following TKR and THR
  - RECORD studies
- Stroke prevention in non-valvular A-fib
  - ROCKET-AF studies
- Treatment of DVT and PE
  - EINSTEIN-DVT and EINSTEIN-PE studies

**Phase III RECORD - VTE prevention**

- Oral rivaroxaban 10 mg qd compared with subcutaneous enoxaparin

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration of rivaroxaban therapy</th>
<th>Duration of enoxaparin therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECORD1</td>
<td>THR 5 weeks</td>
<td>5 weeks</td>
</tr>
<tr>
<td>RECORD2</td>
<td>THR 5 weeks</td>
<td>10–14 days, followed by placebo</td>
</tr>
<tr>
<td>RECORD3</td>
<td>TKR 10–14 days</td>
<td>10–14 days</td>
</tr>
<tr>
<td>RECORD4</td>
<td>TKR 10–14 days</td>
<td>10–14 days</td>
</tr>
</tbody>
</table>

**RECORD - Efficacy endpoints**

**Primary**
- Total venous thromboembolism (VTE): any deep vein thrombosis (DVT, judged by venography), non-fatal pulmonary embolism (PE), and all-cause mortality

**Secondary**
- Major VTE: proximal DVT, non-fatal PE, and VTE-related death
- DVT: any, proximal, distal
- Symptomatic VTE

**Phase III outcomes in Rivaroxaban VTE prophylaxis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Rivaroxaban</th>
<th>Enoxaparin</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECORD1</td>
<td>(10 mg qd)</td>
<td>(40mg qd or 30mg bid)</td>
<td></td>
</tr>
<tr>
<td>n p/d</td>
<td>n p/d</td>
<td>n p/d</td>
<td></td>
</tr>
<tr>
<td>Total VTE</td>
<td>1.1 (181/1,595)</td>
<td>3.7 (261/1,558)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major VTE</td>
<td>0.2 (41/1,666)</td>
<td>2.0 (231/1,678)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.3 (63/2,003)</td>
<td>0.1 (22/2,204)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

**RECORD - Safety endpoints**

**Main**
- Major bleeding starting after the first blinded dose and ≤2 days after last dose
  - Bleeding that was fatal, into a critical organ or required re-operation
  - Extra-surgical-site bleeding associated with a drop in hemoglobin ≥2 g/dL or requiring transfusion of ≥2 units blood

**Other**
- Any bleeding on treatment*
- Non-major bleeding*
- Hemorrhagic wound complications*
- Cardiovascular adverse events
- Liver enzyme levels

**Conclusions**

Rivaroxaban at a dose 10mg po qd shows efficacy and tolerable side effects for VTE prophylaxis
ROCKET AF: Study Design

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

- Enrollment of patients without prior Stroke, TIA or systemic embolism and only 2 factors capped at 10%
- Risk Factors, at least 2 of:
  - CHF
  - Hypertension
  - Age ≥ 75
  - Diabetes
  - Stroke, TIA or systemic embolus

**Atrial Fibrillation**

- Rivaroxaban 20 mg daily (15 mg for Cr Cl 30-49 ml/min)
- Warfarin INR target: 2.5 (2.0 - 3.0 inclusive)

**Randomized Double Blind / Double Dummy**

(N= 14,264)

**Monthly Monitoring**

Adherence to standard of care guidelines

Data presented by Mahaffey, KW. AHA Scientific Sessions, Chicago, IL, November 2010

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ROCKET AF: Primary Efficacy Outcome

**Stoke and non-CNS Embolism**

Event Rates are per 100 patient-years. Based on Protocol Compliant on Treatment Population

<table>
<thead>
<tr>
<th>Event Rate</th>
<th>HR (95% CI)</th>
<th>P-value Non-Inferiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>1.71</td>
<td>0.79 (0.66, 0.96)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>2.16</td>
<td></td>
</tr>
</tbody>
</table>

---

ROCKET AF: Primary Safety Outcomes

**Bleeding:**

<table>
<thead>
<tr>
<th>Event Rate or N (Rate)</th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major and non-major Clinically Relevant</td>
<td>14.91</td>
<td>14.52</td>
<td>1.03</td>
<td>.442</td>
</tr>
<tr>
<td>Major</td>
<td>3.60</td>
<td>3.45</td>
<td>1.04</td>
<td>.576</td>
</tr>
<tr>
<td>Non-major Clinically Relevant</td>
<td>11.80</td>
<td>11.37</td>
<td>1.04</td>
<td>.345</td>
</tr>
</tbody>
</table>

Event Rates are per 100 patient-years Based on Safety on Treatment Population

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ROCKET AF: conclusions

- Rivaroxaban demonstrated non-inferiority to Warfarin for primary efficacy and safety outcomes: HR=0.79 (0.66-0.96), p<0.001; HR=1.03, (0.96-1.11), p=0.442, respectively
Rivaroxaban: EINSTEIN Studies – Phase III Trials

Open label, assessor blind, non-inferiority studies comparing standard VKA anticoagulation to Rivaroxaban for treatment of acute VTE and prevention of recurrent VTE

- **EINSTEIN-DVT** – patients with objectively confirmed proximal DVT
- **EINSTEIN-PE** – patients with objectively confirmed pulmonary embolus
  - Primary efficacy endpoint – Prevention of recurrent symptomatic VTE
  - Primary safety endpoint – Combination of major and non-major clinically relevant bleeding

### EINSTEIN PE: study design

Randomized, open-label, event-driven, non-inferiority study

- 88 primary efficacy outcomes needed
- Non-inferiority margin: 2.0
- Predefined treatment period of 3, 6, or 12 months

**15 mg bid Rivaroxaban**

**Day 1**

**Day 21**

Enoxaparin bid for at least 5 days, plus VKA INR 2.5 (range 2.0–3.0)

### EINSTEIN PE: primary efficacy

<table>
<thead>
<tr>
<th>Time to symptomatic recurrence of VTE</th>
<th>Rivaroxaban (N=2412)</th>
<th>Enoxaparin/VKA (N=2405)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent DVT</td>
<td>(8.7)</td>
<td>(10.2)</td>
<td>0.75 (0.63–0.90)</td>
<td>0.015</td>
</tr>
<tr>
<td>Recurrent DVT + PE</td>
<td>(0.2)</td>
<td>(0.3)</td>
<td>0.70 (0.44–1.11)</td>
<td>0.19</td>
</tr>
<tr>
<td>Fatal PE/unexplained death where PE cannot be ruled out</td>
<td>(0.4)</td>
<td>(0.5)</td>
<td>0.75 (0.44–1.28)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

**Rivaroxaban superior**

p=0.0057 for superiority (one-sided)

**Rivaroxaban non-inferior**

p=0.0025 for non-inferiority (one-sided)

*Potential relative risk increase 264.4%; absolute risk difference 0.24% (-0.5 to 1.02)

### EINSTEIN PE: principal safety outcome – major or non-major clinically relevant bleeding

<table>
<thead>
<tr>
<th>Time to event (days)</th>
<th>Rivaroxaban (N=2412)</th>
<th>Enoxaparin/VKA (N=2405)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of primary efficacy outcome and major bleeding</td>
<td>2.9%</td>
<td>8.1%</td>
<td>0.67 (0.54–0.86)</td>
<td>0.0026</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>2.2%</td>
<td>2.9%</td>
<td>0.67 (0.54–0.86)</td>
<td>0.0026</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>0.7%</td>
<td>0.8%</td>
<td>0.79 (0.58–1.09)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

**Rivaroxaban non-inferior**

p=0.57 for non-inferiority (two-sided)

**Rivaroxaban inferior**

p<0.0001 for non-inferiority (one-sided)
Rivaroxaban: Dosing in US

- **A-fib**
  - 20mg daily with evening meal if CrCl > 50
  - 15mg daily with evening meal if CrCl 15-50
- **DVT/PE**
  - 15mg bid with meals x 21 days followed by 20mg daily with meal
  - For patients with CrCl > 30
- **Joint replacement surgery**
  - 10mg daily, 12 days for TKR, 35 days for THR
  - For patients with CrCl > 30

Apixaban

- Predictable pharmacology
- High bioavailability
- Fixed dose
- No requirement for monitoring
- Inhibits free and thrombus associated Xa
- Contraindicated in severe renal insufficiency
- Drug interactions with meds that affect P-gp and CYP3A4 – Ketoconazole, Rifampin, Clarithromycin, St Johns Wort and HIV-protease inhibitors (ritonavir)

Apixaban: FDA Approval

- Stoke and thromboembolic prevention in non-valvular AF
- ARISTOTLE and AVERROES Studies

Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation: ARISTOTLE

- **AF + ≥ 1 additional risk factor:**
  - N = 18,236
  - Age ≥ 75 years
  - P for stroke, TIA, SE
  - CHF or LVEF ≤ 40%
  - BMI
  - Hypertension

- **Apixaban 5 mg PO BID + Placebo**
  - Warfarin+ (target INR 2-3) + Placebo

Primary outcome: Stroke/SE
**ARISTOTLE: Primary Outcome**

Stoke (ischemic or hemorrhagic) or systemic embolism

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td>9120</td>
<td>8726</td>
</tr>
<tr>
<td>6 months</td>
<td>9081</td>
<td>8620</td>
</tr>
<tr>
<td>12 months</td>
<td>8440</td>
<td>8301</td>
</tr>
<tr>
<td>18 months</td>
<td>6051</td>
<td>5972</td>
</tr>
<tr>
<td>24 months</td>
<td>3464</td>
<td>3405</td>
</tr>
<tr>
<td>30 months</td>
<td>1754</td>
<td>1768</td>
</tr>
</tbody>
</table>

21% RRR

P (non-inferiority)<0.001

Granger CB, et al. NEJM 2011;365:981-92

**ARISTOTLE: Efficacy Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban (No/1828)</th>
<th>Warfarin (75/806)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism*</td>
<td>1.27</td>
<td>1.60</td>
<td>0.73 (0.6, 0.9)</td>
<td>0.031</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.78</td>
<td>1.50</td>
<td>0.79 (0.6, 0.99)</td>
<td>0.132</td>
</tr>
<tr>
<td>Ischemic or uncertain</td>
<td>0.97</td>
<td>1.05</td>
<td>0.92 (0.74, 1.15)</td>
<td>0.42</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>0.24</td>
<td>0.47</td>
<td>0.51 (0.35, 0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systemic embolism (SE)</td>
<td>0.99</td>
<td>1.10</td>
<td>0.87 (0.44, 1.76)</td>
<td>0.73</td>
</tr>
<tr>
<td>All-cause death*</td>
<td>3.12</td>
<td>3.94</td>
<td>0.89 (0.6, 0.99)</td>
<td>0.047</td>
</tr>
<tr>
<td>Stroke, SE, or all-cause death</td>
<td>4.48</td>
<td>5.56</td>
<td>0.89 (0.6, 0.98)</td>
<td>0.019</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.53</td>
<td>0.61</td>
<td>0.88 (0.6, 1.17)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Granger CB, et al. NEJM 2011;365:981-92

**ARISTOTLE: Major bleeding**

<table>
<thead>
<tr>
<th>Event Rate (%/yr)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Apixaban (N=9088)</td>
<td>Warfarin (N=9052)</td>
</tr>
<tr>
<td>2.13</td>
<td>3.09</td>
</tr>
<tr>
<td>0.33</td>
<td>0.60</td>
</tr>
<tr>
<td>0.76</td>
<td>0.86</td>
</tr>
<tr>
<td>0.92</td>
<td>1.13</td>
</tr>
<tr>
<td>0.86</td>
<td>1.40</td>
</tr>
<tr>
<td>0.57</td>
<td>0.70</td>
</tr>
</tbody>
</table>

APixaban: 320 patients, 2.13% per year
Warfarin: 402 patients, 3.09% per year

**ARISTOTLE: Bleeding outcomes**

<table>
<thead>
<tr>
<th>Event Rate (%/yr)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Apixaban (N=9088)</td>
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<td>0.86</td>
<td>1.40</td>
</tr>
<tr>
<td>0.57</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Primary safety outcome: ISTH major bleeding:
2.13 3.09 0.69 (0.60, 0.80) <0.001

Intracranial:
0.33 0.60 0.62 (0.30, 0.58) <0.001

Gastrointestinal:
0.76 0.86 0.89 (0.70, 1.13) 0.37

Major or clinically relevant non-major bleeding:
0.92 1.13 0.68 (0.61, 0.75) <0.001

GUSTO severe bleeding:
0.86 1.40 0.86 (0.35, 0.60) <0.001

TIMI major bleeding:
0.96 1.40 0.57 (0.46, 0.70) <0.001

Any bleeding:
18.1 20.6 0.71 (0.68, 0.75) <0.001

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**ARISTOTLE: Conclusions**

• In patients with non-valvular a-fib, Apixaban showed:
  • Non-inferiority to VKA for efficacy: HR=0.79 (0.66-0.95)
  • Superiority for major bleeding: HR=0.69 (0.60-0.80) p<0.001
  • Superiority for reduction in all cause mortality: HR=0.89 (0.89-0.98) p=0.046

**Assessment of New Oral Anticoagulants**

• In general, they demonstrate equivalent or superior efficacy and major bleeding safety compared to recent standards of care.
Comparison of New Oral Anticoagulants

• **There are no head to head trials comparing these agents. Trends that may suggest any comparative superiority are only hypothesis generating and need confirmation in head to head trials.**

Comparable Efficacy of NOACs in A-Fib

Comparable Major Bleeding with NOACs in A-Fib

Time Warfarin in Therapeutic Range (TTR)

- **RE-LY (DABIGATRAN)**
  - 64% in Warfarin-experienced, 61% in Warfarin-naive

- **ROCKET AF (RIVAROXABAN)**
  - Mean 55%, Median 58%

- **ARISTOTLE (APIXABAN)**
  - Mean 62%, Median 66%

Testing of Hemostatic Function

- **DABIGATRAN**
  - aPTT, thrombin clotting time (TCT) and ecarin clotting time are prolonged
  - TCT has a linear correlation with concentration but prolongs quickly
  - If TCT is not prolonged, Dabigatran level likely is low

- **RIVAROXABAN**
  - Prothrombin time (PT) and anti-Xa affected
  - Prothrombin time (PT) shows a linear dose response and is prolonged to a similar extent as the degree of inhibition of Xa (assay dependent)

Testing of Hemostatic Function

- **APIXABAN**
  - Prothrombin time (PT) and anti-Xa affected

  - Predictive ability of coag assays has not been clinically proven and target drug levels have not been determined. trough levels may not be detected.

  - Anti-Xa activities can be measured against standard curves for each Xa inhibitor but currently unsure what levels are consistent with clinical efficacy or safety
### Anticoagulation Interruption Before Surgery

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Half-life (hrs)</th>
<th>Low bleeding risk</th>
<th>Moderate or high bleeding risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 80</td>
<td>13 (11-22)</td>
<td>24 hrs</td>
<td>2 days</td>
</tr>
<tr>
<td>&gt; 50 ≤ 80</td>
<td>15 (12-24)</td>
<td>24 hrs</td>
<td>2 days</td>
</tr>
<tr>
<td>&gt; 30 ≤ 50</td>
<td>18 (13-23)</td>
<td>2 days</td>
<td>4 days</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>27 (22-30)</td>
<td>4 days</td>
<td>6 days</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>≥ 30</td>
<td>Unknown</td>
<td>2 days</td>
</tr>
<tr>
<td></td>
<td>&lt; 30</td>
<td>24 hrs</td>
<td>2 days</td>
</tr>
<tr>
<td>Apixaban</td>
<td>≥ 30</td>
<td>-</td>
<td>2 days</td>
</tr>
</tbody>
</table>

### Reversal of NOACs

- **Dabigatran**
  - Gastric lavage or activated charcoal to reduce absorption
  - Prothrombin complex concentrate (PCC) with efficacy in some animal models, but no effect in reversing coagulation assay abnormalities in human volunteers
  - Recombinant activated factor VII (rFVIIa) did not reverse coagulation assay abnormalities in human volunteers taking Melagatran
  - Acute hemodialysis (only 35% protein bound)
- **Rivaroxaban**
  - Not dialyzable
  - Four factor prothrombin complex concentrate (PCC) at 50 IU/kg reversed all coagulation assay abnormalities in a human volunteer study
  - Treat with PCC or activated factor VIIa
- **Apixaban**
  - Not dialyzable
  - No data, but would treat as would for Rivaroxaban

### Reversal of Warfarin: PCC vs FFP

- Retrospective cohort study
  - 2006-2008 – FFP
  - 2008-2010 – PCC (Octaplex, a 4 factor PCC)
  - Adult patients with INR > 1.5
  - Primary outcome was serious adverse events (death, ischemic stroke, myocardial infarction, heart failure, venous thromboembolism or peripheral arterial thromboembolism) within 7 days
  - Secondary outcomes included time to INR reversal, hospital length of stay and red blood cells transfused within 48 hours

### Reversal of Warfarin: PCC vs FFP

- 148 patients received FFP, 165 patients received Octaplex
- Serious adverse events
  - 19.5% for FFP
  - 9.7% for Octaplex (p=0.014, Relative Risk (RR) 2.0, 95% CI 1.1 to 3.5)
- Median INR reversal
  - 11.8 hours for FFP
  - 5.7 hours using Octaplex (p<0.0001)
  - Mean red cell transfusion
    - 3.2 units for FFP
    - 1.4 for Octaplex (p<0.0001).
Advantages of New Agents vs. VKAs

- **RAPID ONSET OF ACTION**
  - May replace parenteral anticoagulants for selected conditions
  - Eliminates need for two anticoagulant regimen (i.e. heparin and warfarin)
- **PREDICTABLE THERAPEUTIC EFFECT WITH FIXED OR WEIGHT-BASED DOSING**
  - No routine coagulation monitoring required
- **LIMITED OR NO FOOD OR DRUG INTERACTIONS**
- **SHORT HALF-LIFE**
  - Effect wears off more quickly than VKAs
- **NO NEED FOR BRIDGING AC FOR INVASIVE PROCEDURES**

Disadvantages of New Agents vs. VKAs

- **NO ROUTINE COAGULATION MONITORING**
  - Cannot titrate dose
  - Determination of failure of therapy vs. poor compliance
- **SHORT HALF-LIFE**
  - Anticoagulation effect declines quickly if compliance poor
  - Poor compliance may affect efficacy more than with VKA
- **NO CLINICALLY PROVEN ANTIDOTES**
- **NO MONITORING LAB MARKER AVAILABLE TO RELIABLY MEASURE DRUG ACTIVITY IF NEEDED**
- **POTENTIAL DOSE ADJUSTMENT REQUIRED FOR RENAL OR HEPATIC DYSFUNCTION**
- **COST?**

Populations That Should Be Initially Treated with or Remain on Warfarin Rather Than Be Placed on a Newer Oral Anticoagulant

- **ALREADY TAKING WARFARIN WITH EXCELLENT INR CONTROL**
  - RE-LY data demonstrated equivalent efficacy but increased GI bleeding when comparing Dabigatran 150mg bid to Warfarin with excellent control
- **RENAL INSUFFICIENCY**
  - Consider if CrCl < 30 and definitely if < 15
- **MECHANICAL HEART VALVES**
- **PREDISPOSITION TO GI BLEEDING**
- **POOR COMPLIANCE**
  - Concern regarding the quick loss of anticoagulant effect (question this)
- **CAN'T AFFORD NEWER DRUG**

Populations That Should Consider Treating With Newer Oral Anticoagulants

- **THOSE WITH UNEXPLAINED POOR INR CONTROL**
  - RE-LY data demonstrated equivalent efficacy but increased GI bleeding when comparing Dabigatran 150mg bid to Warfarin with excellent control
- **POOR INR CONTROL DUE TO UNAVOIDABLE DRUG INTERACTION**
  - Recurrent antibiotics, Amiodarone, Chemotherapy, APAP, Azathioprine, polypharmacy
- **NEW PATIENTS ON ANTICOAGULATION WITHOUT SIGNIFICANT RENAL INSUFFICIENCY**
- **CAN AFFORD THE NEW DRUGS**

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