New Oral Anticoagulants for extending treatment of DVT
Do they alter the risk benefit ratio?

Anthony J. Comerota, MD, FACS, FACC
Director, JOBST Vascular Institute
Adjunct Professor of Surgery, University of Michigan

Objective:
To determine the benefits and harms of an additional 18 months of warfarin after an non-randomized 6 month treatment period on a VKA

Study Design
- 371 PTS 1st PE: Rx'd for 6 months with VKA
- Randomized: Additional 18 months VKA vs. Placebo
- 24 month follow up
- 1st outcome: Recurrent VTE and Major Bleed

Duration of Anticoagulation for VTE

Risk
- Increased Bleeding
- Reduced Recurrence

Purpose
Decision to give extended anticoagulation

Duration of Anticoagulants

- Recurrent VTE Following Anticoagulation

Unprovoked
All
Provoked

Research

Original Investigation
Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism
The PADIS-PE Randomized Clinical Trial

JAMA 2015; 314 (1) : 31-40

Disclosures
- None
**New Oral Anticoagulants vs. Warfarin**

**Mechanisms of Action**

- Specific direct inhibition of Factor IIa or Xa
  
  (*“Gate-keeper” location in clotting cascade*)

  vs.

- Diffuse variable and indirect inhibition of production of multiple clotting factors via multiple enzyme systems at various levels in the clotting cascade

**Warfarin**

**Mechanism of Action**

- Inhibits the carboxylation of Vit-K dependent clotting factors in the liver
- Metabolized by cytochrome P450 enzyme system

  ...also involved: 2C9, 2C19, 2C8, 3A4

  ...enzymes

- Variant alleles CYP2C9*2 and CYP2C9*3

  Warfarin is involved with no fewer than nine hepatic enzyme systems!

**New Oral Anticoagulants**

**Treatment of Acute Venous Thromboembolism**

A Word About Warfarin (approved 60 years ago!)

**Advantages**

- Rapidly absorbed from GI tract (1 – 4hrs)
- Rapid therapeutic anticoagulation
- Eliminates need for monitoring
- No dose adjustment
- Minimal (if any) interindividual differences
- Minimal drug-drug interaction
- Minimal (if any) food interaction
- Used for short-term and long-term Rx
- No patient education required
- Short half-life (9 – 12 hours)

**Watch**

- “Peak [therapeutic] anticoagulant effect may be delayed 72 – 96 hours”
- “The duration of action of a single dose of warfarin is 2.5 days”

Measure activity of warfarin with a calendar!
Venous Thromboembolism

**Warfarin vs. NOACs**
- Randomized Trials –
  - Ten randomized trials
  - Blinded, adjudicated outcomes
  - 27,005 patients – acute VTE trials
  - 7,901 patients – extended Rx trials
    - 34,906 patients
    - Results remarkably consistent

**NOACs vs. Warfarin for VTE**

Recurrent VTE

![Graph showing NOACs vs. Warfarin for VTE]

*Every NOAC demonstrated noninferiority for recurrence... point estimates favor NOACs!*

**Initial/Long-Term VTE Treatment**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Trial</th>
<th>Relative Risk/Incident Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>10 mg BID x 7d, then 5 mg BID</td>
<td>AMPLIFY</td>
<td>RR 0.31 (95% CI, 0.17 to 0.55)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>15 mg BID x 21d, then 20 mg QD</td>
<td>EINSTEIN-DVT</td>
<td>HR 0.65 (95% CI, 0.33 to 1.30)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>150 mg BID</td>
<td>RE-COVER</td>
<td>HR 0.49 (95% CI, 0.31 to 0.79)</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>60 mg QD</td>
<td>Hokusai-VTE</td>
<td>HR 0.82 (95% CI, 0.45 to 1.48)</td>
</tr>
</tbody>
</table>

**Anticoagulant Related Bleeding w/ VKAs**

<table>
<thead>
<tr>
<th></th>
<th>Initial 3 mos.</th>
<th>After 3 mos.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial[^1^]</td>
<td>1.5% / yr.</td>
<td>0.65% / yr.</td>
</tr>
<tr>
<td>Overall[^2^]</td>
<td>11.0% / yr.</td>
<td>6.3% / yr.</td>
</tr>
</tbody>
</table>


**NOACs vs. Warfarin**

- **Intracranial Bleed** –
  - Risk Reduction with IIa or Xa Inhibitors vs. Warfarin
    - Dabigatran: 59-70%
    - Rivaroxaban: 29%
    - Apixaban: 59%

  On average... 50% less risk of intracranial bleed vs. warfarin

**Prevention of Recurrence**

- **New Oral Anticoagulants** –
  - Dabigatran: IIa Inhibitor
    - Active control (warfarin)
    - Placebo control
  - Rivaroxaban: Xa Inhibitor
    - Placebo control
  - Apixaban: Xa Inhibitor
    - Placebo control
- Two Double Blind Trials –

• 4199 patients

• Study drug:
  6 – 18 months: Dabigatran vs. Warfarin
  6 months: Dabigatran vs. Placebo

• Endpoints:
  Efficacy – Symptomatic recurrence and death
  Safety – Bleeding (Major and CRNM)

Recurrent VTE/Death – Active Control –

Risk

Months Since Randomization

p=0.01

1.8%
1.3%

Acute Coronary Syndrome
Dabigatran – 0.9%
Warfarin – 1.1%
Placebo – 0.2%
p=0.02

(Noninferiority)

Recurrent VTE/Death – Placebo Control –

Risk

Months Since Randomization

p=0.001

p=0.006

p=0.03

11.5%
5.6%
0.4%

Any Bleeding – Active Control –

Risk

Months Since First Dose

p<0.001

26.2%
Major/CRNM
War. – 10.2%
Dab. – 5.6%
p<0.001

Any Bleeding – Placebo Control –

Risk

Months Since First Dose

p<0.003

5.9%
Major/CRNM
Dab. – 5.5%
Plbo. – 1.8%
p=0.001

Einstein-Ext

– Continued Treatment Study –

• 1196 patients with acute DVT Rx’ed 6-12 months

• Randomized: Rivarox 20mg/day vs. Placebo

• Study drug given 6 – 12 months

• Endpoints: Efficacy – Symptomatic recurrent VTE and death
  Safety – Bleeding (Major and CRNM)
**Einstein-Ext**

### - Recurrent VTE -

- **Major/CRNMB**
  - Pbo: 1.2%
  - Riva: 0.0%
  - RR: 0.18 (Superiority)
  - p<0.001 (Superiority)

- **1.3%**

**No. at Risk**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weeks</th>
<th>Placebo</th>
<th>Pbo</th>
<th>Riva</th>
<th>Riva (No. %)</th>
<th>Placebo (No. %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pbo</td>
<td>12</td>
<td>1013</td>
<td>997</td>
<td>52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riva</td>
<td>12</td>
<td>1005</td>
<td>992</td>
<td>37</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Amplify-Ext**

- 2486 patients completing 6-12 months anticoag
- Randomized 1:1:1 twice daily dosing: placebo vs. 2.5mg apixaban vs. 5.0mg apixaban
- Study drugs X 12 months
- **Endpoints:** Efficacy – Symptomatic recurrent VTE and death
  - Safety – Bleeding (Major and CRNM)

**Recurrent VTE/VTE-Related Death**

- **RRR = 81%**
- **p<0.001**

**No. at Risk**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weeks</th>
<th>Placebo</th>
<th>Pbo</th>
<th>2.5 mg Apixaban</th>
<th>5 mg Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>12</td>
<td>1013</td>
<td>1011</td>
<td>276</td>
<td>264</td>
</tr>
<tr>
<td>2.5 mg</td>
<td>12</td>
<td>1005</td>
<td>1003</td>
<td>274</td>
<td>268</td>
</tr>
<tr>
<td>5 mg</td>
<td>12</td>
<td>1005</td>
<td>1003</td>
<td>274</td>
<td>268</td>
</tr>
</tbody>
</table>

**Extended VTE Treatment (Compared to Placebo)**

**Recurrence and VTE-Related Death**

- **Risk Reduction:** 80-92%

**RR**

- **Apixaban 2.5 mg:** RR 0.19 (95% CI, 0.11 to 0.33)
- **Apixaban 5 mg:** RR 0.18 (95% CI, 0.11 to 0.33)
- **Rivaroxaban 20 mg:** RR 0.18 (95% CI, 0.06 to 0.50)
- **Dabigatran 150 mg:** RR 0.09 (95% CI, 0.02 to 0.41)

**Placebo Better**

**Relative Risk (RR)**

- **0.19**
- **0.18**
- **0.18**
- **0.09**
### Extended VTE Treatment (Compared to Placebo)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Trial</th>
<th>Relative Risk/Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>2.5 mg BID</td>
<td>AMPLIFY-EXT</td>
<td>Reduced Dose: RR 1.20 (95% CI: 0.69 to 2.10)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>20 mg QD</td>
<td>EINSTEIN-EXT</td>
<td>Hazard Ratio: HR 5.19 (95% CI: 2.34 to 11.7)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>150 mg BID</td>
<td>RE-SONATE</td>
<td>Hazard Ratio: HR 2.92 (95% CI: 1.52 to 5.60)</td>
</tr>
</tbody>
</table>

### Extended Treatment for VTE

#### Conclusion

1. Recurrent VTE continues to be a major problem
2. NOAC's offer major safety advantage vs. Warfarin
3. Reduced dose Apixaban appears safe vs. placebo
4. We should consider extended Rx in most VTE patients

---