DOACs in Non-AF Conditions: Judicious Use and Management

Kenneth A. Bauer, MD
Professor of Medicine
Harvard Medical School
Boston, MA USA
Disclosures

Janssen – rivaroxaban

BMS – apixaban

Daiichi Sankyo – edoxaban

Instrumentation Laboratory – coagulation diagnostics
Your poll will show here

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or
Open poll in your web browser
Pre-Test Question 2

A 69 year old male on apixaban for afib (CHADSVASC 6) presents for evaluation with severe bleeding for 2 weeks following placement of 4 implants. He has no prior personal or family history of excessive bleeding. Labs show PT 12.9 (nl<12.5), PTT 46.8 (ref range 25.0-36.5). What is your assessment?
Your poll will show here

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Pre-Test Question 3

A 60 year old male weighing 83 kg on long-term warfarin presents to your clinic for evaluation. He has a hx of recurrent VTE and is on chronic hemodialysis for CKD and has developed calciphylaxis requiring the cessation of warfarin. Which of the following would you recommend?
Your poll will show here

1. Install the app from pollev.com/app
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Direct Oral Anticoagulants

Unfractionated Heparin

Low Molecular Weight Heparin

Direct Factor Xa Inhibitors
- Rivaroxaban
- Apixaban
- Edoxaban

Direct Thrombin (IIa) Inhibitors
- Dabigatran etexilate

Fibrin Clot
### Advantages of Direct Oral Anticoagulants

<table>
<thead>
<tr>
<th>Feature</th>
<th>Warfarin</th>
<th>Direct OAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Dosing</td>
<td>Variable</td>
<td>Fixed</td>
</tr>
<tr>
<td>Food effect (vitamin K)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>Many</td>
<td>Few</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Offset</td>
<td>Long</td>
<td>Shorter</td>
</tr>
</tbody>
</table>

Eikelboom and Weitz. Circulation 2010
Direct Oral Anticoagulants have a Wide Therapeutic Window

Diagram showing the relationship between dose (concentration) of anticoagulant and the risk of thrombosis vs. bleeding, with a safe range in the middle.
Direct Oral Anticoagulants: Approval Status in United States

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip Replacement</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>Knee Replacement</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>Stroke Prevention in Atrial Fibrillation</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Venous Thromboembolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extended</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DOACs should never be used in patients with prosthetic heart valves!
### Comparative Properties of Direct Oral Anticoagulants (DOACs)

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran Etexilate</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bioavailability</strong></td>
<td>6-7%</td>
<td>~80%</td>
<td>~66%</td>
<td>~60%</td>
</tr>
<tr>
<td><strong>T (max)</strong></td>
<td>2 h</td>
<td>2-4 h</td>
<td>3 h</td>
<td>1-2 h</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>12-14 h</td>
<td>7-13 h</td>
<td>8-13 h</td>
<td>9-11 h</td>
</tr>
<tr>
<td><strong>Protein Binding</strong></td>
<td>35%</td>
<td>90%</td>
<td>87%</td>
<td>55%</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Twice (or once) daily</td>
<td>Once (or twice) daily</td>
<td>Twice daily</td>
<td>Once daily</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>80% renal</td>
<td>67% renal (1/2 active)</td>
<td>25% renal</td>
<td>35% renal</td>
</tr>
<tr>
<td></td>
<td>33% fecal</td>
<td>75% fecal</td>
<td>65% fecal</td>
<td></td>
</tr>
<tr>
<td><strong>Potential Drug</strong></td>
<td>Potent P-gp inhibitors</td>
<td>Potent CYP 3A4 and P-gp inhibitors</td>
<td>Potent CYP 3A4 and P-gp inhibitors</td>
<td>Potent CYP 3A4 (&lt;4%) and P-gp inhibitors</td>
</tr>
</tbody>
</table>

**Inhibitors:** ketoconazole, ritonavir  
**Inducers:** rifampin, phenytoin, carbamazepine, St. John’s wort
## Rivaroxaban in Orthopedics

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Rivaroxaban (%)</th>
<th>Enoxaparin (%)</th>
<th>HR or RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total VTE</strong> (DVT, PE, death)</td>
<td>4.26</td>
<td>9.43</td>
<td>RR 0.46 (0.39, 0.54)</td>
</tr>
<tr>
<td><strong>Major VTE</strong> (proximal DVT, PE, VTE death)</td>
<td>0.68</td>
<td>2.74</td>
<td>RR 0.25 (0.17, 0.37)</td>
</tr>
<tr>
<td><strong>Symptomatic VTE or death</strong></td>
<td>0.57</td>
<td>1.32</td>
<td>HR 0.42 (0.29, 0.63)</td>
</tr>
<tr>
<td><strong>Major bleeding event</strong></td>
<td>0.39</td>
<td>0.21</td>
<td>HR 1.84 (0.94, 3.62)</td>
</tr>
<tr>
<td><strong>Major or CRNM bleeding event</strong></td>
<td>3.19</td>
<td>2.55</td>
<td>HR 1.25 (1.01, 1.54)</td>
</tr>
<tr>
<td><strong>Major bleeding combined with surgical-site bleeding events</strong></td>
<td>1.80</td>
<td>1.37</td>
<td>HR 1.31 (0.99, 1.73)</td>
</tr>
</tbody>
</table>

# Apixaban in Orthopedics

<table>
<thead>
<tr>
<th></th>
<th>All VTE/Death</th>
<th>Major VTE</th>
<th>Major Bleed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Apix</td>
<td>Enox</td>
<td>Apix</td>
</tr>
<tr>
<td>ADVANCE 1 (TKR)</td>
<td>9.0%</td>
<td>8.9%</td>
<td>2.1%</td>
</tr>
<tr>
<td>ADVANCE 2 (TKR)</td>
<td>15.1%</td>
<td>24.4%</td>
<td>1.1%</td>
</tr>
<tr>
<td>ADVANCE 3 (THR)</td>
<td>1.4%</td>
<td>3.9%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

- Did not meet prespecified criterion for noninferiority vs enoxaparin 30 mg BID in TKR (ADVANCE 1)
- Superior to enoxaparin 40 mg once daily in THR and TKR (ADVANCE 2 & 3)

Summary: Trials of DOACs vs Warfarin

- DOACs at least as effective/safe as warfarin and can be given without monitoring
- Lower stroke risks with dabigatran/apixaban in AF
- Less major bleeding with apixaban and edoxaban
- Slight increase in myocardial infarction rates with dabigatran in AF
- Increase in gastrointestinal bleeding with dabigatran, rivaroxaban, and edoxaban in AF
- In comparison with warfarin, direct oral anticoagulants reduced major bleeding by 28% and intracranial and fatal hemorrhage by 50%.

Dose/Schedules of Doacs in Atrial Fibrillation (US)

**Dabigatran (twice daily)**
- 150 mg BID if CrCl \( \geq 30 \text{ mL/min} \)
- Renal impairment (CrCl 15-29 mL/min) 75 mg BID

**Rivaroxaban (once daily)**
- 20 mg QD (with evening meal) if CrCl \( \geq 50 \text{ mL/min} \)
- Renal impairment (CrCl 15-49 mL/min) 15 mg QD

**Apixaban (twice daily)**
- 5 mg BID
- 2.5 mg BID if any 2: age \( \geq 80 \text{ kg}, \) wt \( \leq 60 \text{ kg}, \) Cr \( \geq 1.5-2.5 \text{ mg/dL} \)

**Edoxaban (once daily)**
- 60 mg QD if CrCl > 50 mL/min;
- “Should not be used” if CrCl > 95 mL/min
- Renal impairment (CrCl 15-50 mL/min) 30 mg QD
Rationale for Selection of Dabigatran 75 mg Twice Daily in Patients With Renal Impairment

Creatinine Clearance
- 75 mg BID, 15.0 mL/min
- 75 mg BID, 29.0 mL/min
- 150 mg BID, 68.6 mL/min

Data on file. Boehringer Ingelheim Pharmaceuticals, Inc.
## Advantages of DOACs vs. Warfarin

<table>
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<tr>
<th>Feature</th>
<th>Warfarin</th>
<th>New OAC</th>
</tr>
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<tbody>
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Eikelboom and Weitz. Circulation 2010
# New Agents for Venous Thrombosis

## Rivaroxaban
- **15 mg b.i.d. for 3 weeks**
- then 20 mg once daily
- Can be used as monotherapy

## Dabigatran
- **150 mg b.i.d.**
- 5 days of parenteral treatment needed **before dabigatran**

## Apixaban
- **10 mg b.i.d. for 7 days**
- then **5 mg b.i.d.**
- Can be used as monotherapy

## Edoxaban
- Daily (60 mg qd; or 30 mg for CrCl 30-49 mL/min or weight<60kg)
- 5 days parenteral (LMWH) treatment needed **before edoxaban**

## FDA Approval Status (for VTE)
- **Approved** for acute treatment and long-term prevention 11/12
- **Approved** for acute treatment and long-term prevention 4/14
- **Approved** for acute treatment and long-term prevention 8/14
- **Approved** for acute treatment 1/15
Recurrent VTE and VTE-related Death

Dabigatran

Rivaroxaban

Apixaban

Edoxaban


Bleeding: Major and Major + CRNM

Major Bleeding
- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban

P for Sup
- NS
- <0.002
- <0.001
- NS

Major and CRNB
- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban

P for Sup
- <0.001
- 0.27
- <0.001
- 0.004

Recurrent VTE/VTE-Related Death* in DOAC Extended Treatment Trials

**AMPLIFY-EXT**
- $P < 0.0001$ (for superiority)
- 2.5 mg BID
  - RR (95% CI): 0.19 (0.11 – 0.33)
- 5 mg BID
  - RR (95% CI): 0.20 (0.11 – 0.34)

**EINSTEIN-EXT**
- $P < 0.0001$
  - (for superiority)
- HR (95% CI): 0.18 (0.09–0.39)

**RE-SONATE**
- $P < 0.0001$
  - (for superiority)
- HR (95% CI): 0.08 (0.02–0.25)

**RE-MEDY**
- Noninferior
- HR (95% CI): 1.44 (0.78–2.64)

* Primary efficacy endpoint in AMPLIFY-EXT was recurrent VTE and all-cause death; in other trials, was recurrent VTE and VTE-related death
Major Bleeding Outcomes in DOAC Extended Treatment Trials

**AMPLIFY-EXT**
- \( P = \text{not significant}^* \)
- **2.5 mg BID**
  - RR (95% CI): 1.20 (0.69–2.10)

**EINSTEIN-EXT**
- **5 mg BID**
  - RR (95% CI): 1.62 (0.96–2.73)
- \( P = 0.11 \) in paper
- HR not in label

**RE-SONATE**
- \( P = 1.0 \) in paper
- HR not in label

**RE-MEDY**
- \( P = 0.06 \) in paper
- HR (95% CI): 0.54 (0.25–1.16)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients With Major Bleeding Event (%)</th>
<th>( P ) value</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.5% (n=4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban 2.5 mg</td>
<td>0.2% (n=2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban 5 mg</td>
<td>0.1% (n=1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.0% (n=0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>0.7% (n=0)</td>
<td>( P = \text{not significant}^* )</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.0% (n=0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>0.3% (n=2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>1.8% (n=25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>0.9% (n=13)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Based on 95% CI
Major + CRNM Bleeding Outcomes in DOAC Extended Treatment Trials

**AMPLIFY-EXT**
- 2.5 mg BID
  - P=not significant*
  - RR (95% CI): 1.20 (0.69–2.10)
- 5 mg BID
  - P=not significant*
  - RR (95% CI): 1.62 (0.96–2.73)

**EINSTEIN-EXT**
- P<0.001 in paper
- HR (95% CI): 5.19 (2.3–11.7)

**RE-SONATE**
- P=0.001 in paper
- HR (95% CI): 2.92 (1.52–5.60)

**RE-MEDY**
- P<0.001 in paper
- HR (95% CI): 0.54 (0.41–0.71)

• Based on 95% CI
CRNM Bleeding Outcomes in DOAC Extended Treatment Trials

**AMPLIFY-EXT**
- **2.5 mg BID**
  - *P* = not significant*
  - RR (95% CI): 1.29 (0.72–2.33)
- **5 mg BID**
  - *P* = not significant*
  - RR (95% CI): 1.82 (1.05–3.18)

**EINSTEIN-EXT**
- *P* value not reported
- HR not reported

**RE-SONATE**
- *P* value not in label
- HR (95% CI): 2.54 (1.34–4.82)

**RE-MEDY**
- *P* value not in label
- HR (95% CI): 0.56 (0.42–0.75)

* Based on 95% CI.
How do DOACs compare to standard therapy in patients with hereditary thrombophilia?

- No data – patients entering trials were not screened for hereditary thrombophilia

- No a priori reason to believe that DOACs will not be effective and safe in patients with hereditary thrombophilia (might be preferable to heparin/LMWH in AT deficiency or warfarin in protein C deficiency)
Now that DOACs are approved for VTE treatment, when should we use them? Wouldn’t use (or be cautious) in:

- Never in pregnancy-associated VTE or post-partum (if breast feeding)
- Massive PE (hemodynamically unstable) or DVT (phlegmasia cerulea dolens) where thrombolysis is a consideration
- Very obese or frail patients (? weight >300 lb or < 100 lb)
- Renal dysfunction (creatinine clearance <30 mL/min) or major drug-drug interactions
- Patients with altered GI anatomy (gastric bypass procedures)
- Would be cautious in "difficult" or highly prothrombotic patients (recurrent VTE on established therapies such as warfarin or LMWH, APLS, active cancer, HIT, etc.)
Ischemic Stroke on Dabigatran

- 48 year old male with PAF, hypertension, hypertrophic cardiomyopathy
- 4 weeks after switch from warfarin to dabigatran: Ischemic right hemispheric stroke
- **Body Weight 153 kg, BMI 44.7**
- CrCl 163 ml/min (70-120 ml/min)
- Admission labs 9 hours after last dabigatran dose, plasma level was 0 ng/ml
- Dabigatran continued x 3 days and serial measurements q2h monitored:
Ischemic Stroke on Dabigatran

Red = peak plasma levels 2 hrs after dose
Gray = trough after 12 hours
Treatment of Acute VTE in Cancer

Control Group
- LMWH
- Vitamin K antagonist (INR 2.0 to 3.0)

CANTHAN OX
- N=146
- Enoxaparin 1.5 mg/kg OD

LITE
- N=200
- Tinzaparin 175 IU/kg OD

CLOT
- N=672
- Dalteparin 200 IU/kg OD then ~150 IU/kg OD

5 – 7 days  1 month  3 months  6 months
CLOT: Recurrent VTE

Risk reduction = 52%
p-value = 0.0017

OAC
TTR 46%
dalteparin
DOAC and VTE in Patients With Cancer

1. Systematic review and meta-analysis

A. VTE Recurrence

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DOA Events</th>
<th>Total</th>
<th>Comparator Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPLIFY 2013</td>
<td>3</td>
<td>81</td>
<td>5</td>
<td>78</td>
<td>15.2%</td>
<td>0.56 [0.13, 2.43]</td>
</tr>
<tr>
<td>EINSTEIN-DVT 2010</td>
<td>4</td>
<td>118</td>
<td>5</td>
<td>89</td>
<td>17.1%</td>
<td>0.59 [0.15, 2.26]</td>
</tr>
<tr>
<td>EINSTEIN-PE 2012</td>
<td>2</td>
<td>114</td>
<td>3</td>
<td>109</td>
<td>9.4%</td>
<td>0.63 [0.10, 3.85]</td>
</tr>
<tr>
<td>HOKUSAI 2013</td>
<td>4</td>
<td>109</td>
<td>7</td>
<td>99</td>
<td>22.0%</td>
<td>0.50 [0.14, 1.77]</td>
</tr>
<tr>
<td>RECOVER I &amp; II 2013</td>
<td>10</td>
<td>173</td>
<td>12</td>
<td>162</td>
<td>36.3%</td>
<td>0.77 [0.32, 1.83]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>595</td>
<td>537</td>
<td></td>
<td>100.0%</td>
<td>0.63 [0.37, 1.10]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>23</td>
<td>32</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.36, \text{df} = 4 \ (P = .99); I^2 = 0$

Test for overall effect: $Z = 1.62 \ (P = .10)$

DOAC and VTE in Patients With Cancer

B. Major bleeding

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DOA Events</th>
<th>DOA Total</th>
<th>Comparator Events</th>
<th>Comparator Total</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPLIFY 2013</td>
<td>2</td>
<td>87</td>
<td>4</td>
<td>80</td>
<td>0.45 [0.08, 2.51]</td>
</tr>
<tr>
<td>EINSTEIN DVT &amp; PE 2013</td>
<td>6</td>
<td>232</td>
<td>8</td>
<td>196</td>
<td>0.62 [0.21, 1.83]</td>
</tr>
<tr>
<td>HOKUSAI 2013</td>
<td>5</td>
<td>109</td>
<td>3</td>
<td>99</td>
<td>1.54 [0.36, 6.61]</td>
</tr>
<tr>
<td>RECOVER I &amp; II 2013</td>
<td>6</td>
<td>159</td>
<td>7</td>
<td>152</td>
<td>0.81 [0.27, 2.47]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>587</td>
<td>527</td>
<td></td>
<td></td>
<td>0.77 [0.41, 1.44]</td>
</tr>
</tbody>
</table>

Total events 19

Heterogeneity: Chi² = 1.40, df = 3 (P = 0.70); I² = 0%
Test for overall effect: Z = 0.81 (P = 0.42)

C. Clinically relevant bleeding

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DOA Events</th>
<th>DOA Total</th>
<th>Comparator Events</th>
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<th>Odds Ratio M-H, Fixed, 95% CI</th>
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<tr>
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<td>88</td>
<td>0.89 [0.41, 1.92]</td>
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<td>1.37 [0.58, 3.24]</td>
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<td>25</td>
<td>99</td>
<td>0.67 [0.34, 1.29]</td>
</tr>
<tr>
<td>RECOVER I &amp; II 2013</td>
<td>23</td>
<td>159</td>
<td>20</td>
<td>152</td>
<td>1.12 [0.59, 2.13]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>587</td>
<td>527</td>
<td></td>
<td></td>
<td>0.85 [0.62, 1.18]</td>
</tr>
</tbody>
</table>

Total events 85

Heterogeneity: Chi² = 4.04, df = 4 (P = 0.40); I² = 1%
Test for overall effect: Z = 0.96 (P = 0.34)


<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban</th>
<th>Enoxaparin/VKA</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>%</td>
<td>n/N</td>
</tr>
<tr>
<td><strong>Recurrent VTE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>16/316</td>
<td>5.1</td>
<td>20/281</td>
</tr>
<tr>
<td>No cancer</td>
<td>70/3834</td>
<td>1.8</td>
<td>75/3850</td>
</tr>
<tr>
<td><strong>Major bleeding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>9/316</td>
<td>2.8</td>
<td>14/278</td>
</tr>
<tr>
<td>No cancer</td>
<td>31/3820</td>
<td>0.8</td>
<td>58/3832</td>
</tr>
</tbody>
</table>

Different cancer population than the CLOT Trial  (~2-fold higher recurrence rate on warfarin)
8,101 hospitalized patients with medical illness from 52 countries at risk for VTE treated for 35 ± 4 days with rivaroxaban vs enoxaparin (10 ± 4 d) followed by placebo. Ultrasound at d 10 ± 4 and d 35 ± 4.

Rivaroxaban, 10 mg QD x 35 ± 4 days

Primary Efficacy: asymptomatic/symptomatic DVT, non-fatal PE, and VTE-related death at 10 and 35 days

Primary Safety: Major and CRNM bleeding

Enoxaparin 40 mg QD x 10 ± 4 days, then placebo for total 35 ± 4 days

Approximately 45% acute infectious disease; 33% heart failure; 28% acute respiratory insufficiency; only 7% active cancer

Cohen AT et. NEJM 2013
Primary Post-Hospital Prophylaxis of VTE
Rivaroxaban vs Enoxaparin/Placebo: MAGELLAN

Primary efficacy at d 10 non-inferiority and at d 35 superiority

- RR 0.77; P = 0.02
  - For Sup
- P < 0.001

Important Events
- Symp DVT, non-fatal PE, VTE-related death
  - 16 vs 14 events
- Symp DVT, non-fatal PE, VTE-related death
  - 42 vs 59 events

Major/CRNM Bleeding at d 10
- Major Bleeding
  - 24 vs 11 events
  - P = 0.003
  - Fatal Bleeding
  - 5 vs 1

Major/CRNM Bleeding at d 350
- Major Bleeding
  - 19 vs 4 events
  - P = 0.0004
  - Fatal Bleeding
  - 2 vs 0

Cohen AT et. al. NEJM 2013
Comparison of Properties of Direct Oral Anticoagulants to Vitamin K Antagonists

<table>
<thead>
<tr>
<th>Features</th>
<th>Warfarin</th>
<th>DOACs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Dosing</td>
<td>Variable</td>
<td>Fixed</td>
</tr>
<tr>
<td>Effect of diet</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Many</td>
<td>Few</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Half-life</td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td>Specific Reversal Agent</td>
<td>Yes</td>
<td>Not for FXa Inhibitors</td>
</tr>
</tbody>
</table>
**Idarucizumab: A specific reversal agent for the anticoagulant activity of dabigatran**

- Humanized Fab fragment
  - Binds with high-affinity to dabigatran/metabolites
- Primarily renal excretion
- Short half-life ($t_{1/2}$)
  - Initial $t_{1/2}$ 47 min, terminal $t_{1/2}$ 10.3 hours
- No interaction with other drugs
- Reduces dabigatran-induced bleeding in animal models
- Immediate, complete, and sustained reversal of dabigatran activity in normal volunteers
Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.
REVERSE-AD: Multicenter, ongoing, open-label, single-arm phase III study

Group A: Uncontrolled bleeding + dabigatran-treated

Group B: Emergency surgery or procedure + dabigatran-treated

5 g idarucizumab (two separate infusions of 2.5 g)

Reverses up to the 99th percentile of dabigatran levels measured in RE-LY

N=300

0–15 minutes

0–24 hours

90 days follow-up

Hospital arrival

Blood samples

Pre-1st vial

Pre-2nd vial

~20 min

1 h

2 h

4 h

12 h

24 h

30 d

90 d
Maximum % reversal of the anticoagulation effect of dabigatran based on central laboratory assessment of dTT or ECT within 4 hours after idarucizumab

dTT and ECT show linear correlations with wide range of dabigatran concentrations

Glund S et al, Lancet 2015
RE-VERSE AD: Secondary Endpoints

- Cessation of bleeding in Group A: determined by local investigator
- Hemostasis during procedure in Group B: assessed by local investigator as normal or mildly, moderately, or severely abnormal
- Adjudicated post-treatment thrombotic events to 90 days

- Mortality
- Time to complete reversal and duration of reversal
- Serial dabigatran levels
- Local and central laboratory aPTT and TT
- Use of blood products and other therapies
- Restart of antithrombotic therapy
- Modified Rankin scores (entry and 90 days) for ICH
## Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A</th>
<th>Group B</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>n=51</td>
<td>n=39</td>
<td>N = 90</td>
</tr>
<tr>
<td>Indication for dabigatran stroke prevention in A Fib</td>
<td>47/51</td>
<td>39/39</td>
<td>86/90</td>
</tr>
<tr>
<td>Age median, range (years)</td>
<td>77 (48–93)</td>
<td>76 (56–93)</td>
<td>76.5 (48–93)</td>
</tr>
<tr>
<td>Creatinine clearance median, range (mL/min)</td>
<td>51.5 (15.8–186.8)</td>
<td>60.1 (11.5–171)</td>
<td>57.6 (11.5–186.8)</td>
</tr>
<tr>
<td>Patient-reported time since last dose, median (hours)</td>
<td>15.2</td>
<td>16.6</td>
<td>15.4</td>
</tr>
<tr>
<td>Elevated dTT at baseline</td>
<td>40/51</td>
<td>28/39</td>
<td>68/90</td>
</tr>
<tr>
<td>Elevated ECT at baseline</td>
<td>47/51</td>
<td>34/39</td>
<td>81/90</td>
</tr>
<tr>
<td>Elevated dTT or ECT at baseline</td>
<td>47/51</td>
<td>34/39</td>
<td>81/90</td>
</tr>
</tbody>
</table>
RESULTS: Primary endpoint in Group A: dTT and ECT
Reversal of dabigatran with idarucizumab
**RESULTS: Primary Endpoints**

- Median maximum reversal within 4 hours was 100% for both dTT and ECT (95% CI, 100–100), evident after first vial of idarucizumab

- dTT normalized in 98% and 93% of Group A and B patients, respectively*

- ECT normalized in 89% and 88% of Group A and B patients, respectively*

*Similar results with central laboratory aPTT and TT

*calculated for patients with elevated levels at baseline
Secondary Endpoints: Clinical Outcomes

- **Group A**
  - 51 Patients
  - Assessable in 38 patients
  - Median local investigator-determined time to bleeding cessation 11.4 hours*

- **Group B**
  - 39 Patients
  - Surgery performed in 36 patients
  - Intraoperative hemostasis:
    - 33 normal
    - 2 mildly abnormal
    - 1 moderately abnormal

*Assessment of bleeding cessation may be difficult in internal bleeding into confined space such as intramuscular or intracranial bleeding.
Safety

- No cases of hypersensitivity were observed

- Five thrombotic events occurred
  - 1 early event (DVT + PE) within 72 hours of idarucizumab administration
  - 4 patients had events after 72 hours of idarucizumab administration (DVT, DVT+PE+LA thrombus, MI, ischemic stroke)
  - None of these 5 patients was receiving any antithrombotic therapy when the events occurred

- 18 deaths occurred (9 in each Group)
  - Related to presenting index event and comorbidities
Management of Major Bleeding in Patients on Dabigatran

Discontinue/hold dabigatran

Supportive Care (IV fluids, packed RBCs)

Activated charcoal (if ingested in last 2 hours)

Localization/management of bleeding site (if possible)

Administer idarucizumab

   In life-threatening or uncontrolled bleeding

   For emergency surgery/urgent procedures (if judged to have clinically significant plasma levels of dabigatran)

No need to consider administration of PCCs, activated PCCs, or rVIIa or to employ dialysis
Characteristics of PRT4445 (Andexanet)


41 kD recombinant, genetically engineered version of human Factor Xa
- Retains high affinity for FXa inhibitors while minimizing interactions with other coagulation or regulatory proteins
- Catalytic activity eliminated by substitution of active site serine by alanine
- Gla domain removed to eliminate incorporation into prothrombinase complex
- N terminal residues retained

Predictable PK, Terminal half-life ~6 hours
Andexanet: Restores function of native coagulation system

Inhibited Prothrombinase Complex

Active Prothrombinase Complex
Antifactor Xa Activity Before and After Andexanet

- Anti-Xa levels reduced
- **Apixaban:** Andexanet vs. placebo (94% vs. 21% P<.001) bolus
- **Rivaroxaban:** Andexanet vs. placebo (92% vs. 18% P<.001) bolus
- **Apixaban:** Andexanet vs. placebo (92% vs. 33% P<.001) infusion
- **Rivaroxaban:** Andexanet vs. placebo (97% vs. 45% P<.001) infusion

NEJM 2015
Assessing Intensity of Anticoagulation Effects

Clinical applicability:

- **INR** for apixaban/rivaroxaban/edoxaban is extremely variable depending on reagent
- **TT** for dabigatran is very sensitive, even to small concentrations of dabigatran
- Chromogenic anti-factor Xa assay and dilute thrombin time provide good measures for the Xa inhibitors and dabigatran, but not widely available

<table>
<thead>
<tr>
<th></th>
<th>Apixaban/Rivaroxaban/Edoxaban</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Present (Qualitative test)</td>
<td>PT only with selected reagent</td>
<td>Thrombin time</td>
</tr>
<tr>
<td>Quantitative Test</td>
<td>Chromogenic anti-factor Xa</td>
<td>Dilute thrombin time or Ecarin Clotting Time</td>
</tr>
<tr>
<td>Sensitivity: PT vs aPTT</td>
<td>PT &gt; aPTT</td>
<td>TT &gt; aPTT &gt; PT</td>
</tr>
<tr>
<td>PT Ratio</td>
<td>May be used to establish presence or absence of anticoagulant</td>
<td></td>
</tr>
</tbody>
</table>
Challenges in using reversal agents for major/life-threatening bleeding in association with DOACs

Clinical scenario dictates the therapeutic intervention required

- Can supportive measures suffice or invasive procedures/surgery be delayed until the DOAC has been cleared from the blood?

Quantitative assays for DOACs are not widely available. If they are, how long does it take for result to return? Rapid point-of-care tests could be helpful in guiding management.
For intra-cerebral bleeding, early presentation to a healthcare facility, prompt diagnosis, and prompt administration of an effective reversal agent will be critical to improve outcomes. Will smaller community hospitals stock these drugs given the frequency of use and cost?

Major/life-threatening bleeds on anticoagulation invariably occur at sites of anatomic lesions. This patient population tends to be elderly with comorbidities. These factors, rather than the ability to reverse the anticoagulant, often determine clinical outcomes and mortality.
## Periprocedural Management of DOACs
### Timing of Interruption of DOACs Before Surgery or Invasive Procedures

<table>
<thead>
<tr>
<th>Calculated CrCl, mL/min</th>
<th>Half-life, h</th>
<th>Timing of Last Dose Before Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Standard Risk of Bleeding&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dabigatran&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>13 (11-22)</td>
<td>24 h</td>
</tr>
<tr>
<td>&gt;50-≤80</td>
<td>15 (12-34)</td>
<td>24 h</td>
</tr>
<tr>
<td>&gt;30-≤50</td>
<td>18 (13-23)</td>
<td>2 d</td>
</tr>
<tr>
<td>≤30</td>
<td>27 (22-35)</td>
<td>4 d</td>
</tr>
<tr>
<td>Rivaroxaban&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;30</td>
<td>12 (11-13)</td>
<td>24 h</td>
</tr>
<tr>
<td>≤30</td>
<td>Unknown</td>
<td>2 d</td>
</tr>
<tr>
<td>Apixaban&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>24 h</td>
</tr>
</tbody>
</table>

<sup>a</sup> Examples: cardiac catheterization, ablation therapy, colonoscopy without removal of large polyps, uncomplicated laparoscopic procedures

<sup>b</sup> Examples: major cardiac/cancer/urologic/vascular surgery, insertion of pacemakers/defibrillators, neurosurgery, large hernia surgery
Adoption of Institutional Protocols/Clinical Pathways for DOACs to Achieve Optimal Outcomes: An Individualized Approach

Components: Patient Preference, Patient Selection, Drug Interactions, Compliance, Follow-up (e.g., DVT - ED to clinic), Monitoring (i.e., medication refills)

1. Direct oral anticoagulant ordered
2. Anticoag Pharmacy screening, inclusion + exclusion criteria, patient assessment
   - Entered into database
   - Appropriate:
     - Drug dispensed
   - Not appropriate:
     - Physician notified, alternative management

Adapted from Jonathan Halperin and Mary Cushman
Your poll will show here

1. Install the app from pollev.com/app
2. Make sure you are in Slide Show mode

Still not working? Get help at pollev.com/app/help
or
Open poll in your web browser
A 69 year old male on apixaban for afib (CHADSVASC 6) presents for evaluation with severe bleeding for 2 weeks following placement of 4 implants. He has no prior personal or family history of excessive bleeding. Labs show PT 12.9 (nl<12.5), PTT 46.8 (ref range 25.0-36.5). What is your assessment?
Your poll will show here

1. Install the app from pollev.com/app
2. Make sure you are in Slide Show mode

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or
Open poll in your web browser
A 60 year old male weighing 83 kg on long-term warfarin presents to your clinic for evaluation. He has a hx of recurrent VTE and is on chronic hemodialysis for CKD and has developed calciphylaxis requiring the cessation of warfarin. Which of the following would you recommend?
Your poll will show here

1. Install the app from [pollev.com/app](http://pollev.com/app)

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[Open poll in your web browser](http://pollev.com/app)