3rd Annual Symposium

PULMONARY EMBOLISM
What Is Known, and What We Need to Know

State-of-the-Art and Scientific Update

June 23–24, 2017
Royal Sonesta Boston
40 Edwin H. Land Boulevard
Cambridge, MA
Direct Oral Anticoagulants (DOACs) and Other Heparin Alternatives

Rachel P. Rosovksy, MD, MPH
Disclosures

• Janssen: Research Support
• BMS: Research Support
Case

- Thanksgiving Day, 30F felt strain in right calf. She thought muscle cramp but did not resolve with stretching out. She was on oral contraceptive pills and had two recent trips (Haiti and Mexico).
- She then developed SOB and presented to medical attention.
- Ultrasound showed DVT in right lower extremity. CTA: PE
- She was admitted to outside hospital for five days. Initially placed on low-molecular-weight heparin as bridge to Coumadin. On fifth day, her INR 1.4.
- What would you do?
Historical Perspective

- 1st documented description and treatment of DVT in Middle Ages.
- Pain & swelling in calf which progressed to leg ulcers.

Time Line

Direct oral agents → 2010
Direct Oral Anticoagulants (DOACs)

- Direct Thrombin Inhibitor
  - Pradaxa: Dabigatran
- Factor Xa inhibitors
  - Xarelto: Rivaroxaban
  - Eliquis: Apixaban
  - Savaysa: Edoxaban
What makes a new standard of care?

• Effective
• Safe
• Simple and reliable
• Adaptable and scalable
• Patient satisfaction
Table 2. Efficacy Outcome of Recurrent VTE with Use of Non–Vitamin K Antagonist Oral Anticoagulants in Comparison With Vitamin K Antagonists in the Treatment of Acute VTE

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>n/N (%)</th>
<th>RR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>59/2691 (2.3)</td>
<td>0.84 (0.60–1.18)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>60/2553 (2.4)</td>
<td>1.09 (0.76–1.57)</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>130/4118 (3.2)</td>
<td>0.89 (0.70–1.13)</td>
</tr>
<tr>
<td>Rivaroxaban†</td>
<td>86/4150 (2.1)</td>
<td>0.90 (0.68–1.20)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; RR, relative risk; and VTE, venous thromboembolism.

*RR was recalculated from the hazard ratio for optimal comparison (dabigatran [from RE-COVER II pooled analysis], edoxaban, and rivaroxaban [combined data from EINSTEIN-DVT and EINSTEIN-PE study]).

†Efficacy outcome for EINSTEIN studies was recurrent VTE, and not combined recurrent VTE or VTE-related death.
DOACs: Are they effective?

- **Dabigatran**
  - Estimated Cumulative Risk (%)
  - Months since Randomization

- **Rivaroxaban**
  - Cumulative Event Rate (%)
  - Days

- **Apixaban**
  - Patients with VTE or VTE Related Death (%)
  - Days

- **Edoxaban**
  - Adjusted Recurrent VTE (%)
  - Days
## Table 3. Safety Outcomes of Bleeding With Use of Non–Vitamin K Antagonist Oral Anticoagulants in Comparison With Vitamin K Antagonists in the Treatment of Acute Venous Thromboembolism

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Major Bleeding or Clinically Relevant Nonmajor Bleeding</th>
<th>Major Bleeding</th>
<th>ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence, n/N (%) RR* (95% CI)</td>
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<td>Incidence, n/N (%) RR* (95% CI)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>115/2691 (4.3) 0.44 (0.36–0.55)</td>
<td>15/2691 (0.6) 0.31 (0.17–0.55)</td>
<td>3/2691 (0.1) 0.50 (0.13–2.01)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>136/2553 (5.3) 0.63 (0.51–0.77)</td>
<td>37/2553 (1.4) 0.73 (0.48–1.10)</td>
<td>2/2553 (0.1) 0.40 (0.08–2.06)</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>349/4118 (8.5) 0.81 (0.71–0.94)</td>
<td>56/4118 (1.4) 0.84 (0.59–1.21)</td>
<td>5/4118 (0.1) 0.28 (0.10–0.75)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>388/4150 (9.3) 0.94 (0.82–1.07)</td>
<td>40/4150 (1.0) 0.55 (0.38–0.81)</td>
<td>3/2419 (0.1) 0.25 (0.07–0.88)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; ICH, intracranial hemorrhage; and RR, relative risk.

*RR recalculated from the hazard ratio for optimal comparison (dabigatran [from RE-COVER II pooled analysis], edoxaban, and rivaroxaban [combined data from EINSTEIN-DVT and EINSTEIN-PE study]). ICH includes both fatal and nonfatal ICH with RR calculated from each study.
DOACs: Are they safe?

- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban
Direct Oral Anticoagulants

Are they simple and reliable?

- can be given in fixed doses
- do not require routine monitoring
- have fewer food or drug interactions
- are more predictable than warfarin
Patient satisfaction?

- Rivaroxaban significantly higher treatment satisfaction (convenience, effectiveness, and global satisfaction) compared with vitamin K antagonists.

Effective, safe, simple and reliable and patients are satisfied

All approved for the treatment of DVT and PE
Key differences between DOACs dosing in treatment of acute VTE

**Rivaroxaban**
- **15 mg twice daily for 21 days**
- **20 mg once daily**

**Apixaban**
- **10 mg twice daily for 7 days**
- **5 mg twice daily**

**Edoxaban**
- Parenteral agent with UFH or LMWH for 5-10 days
- **60 mg once daily** (30 mg once daily if CrCl 15-50 cc/min or weight < 60 kg or on P-gp inhibitors)

**Dabigatran**
- Parenteral agent with UFH or LMWH for 5-10 days
- **150 mg twice daily**

**Colors**
- **Red**: need higher dose initially
- **Purple**: need parenteral agent initially
- **Green**: once daily dosing
- **Blue**: twice daily dosing

Rosovsky, Merli. TVIR, submitted
<table>
<thead>
<tr>
<th>Key Points:</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism Action</td>
<td>Direct Thrombin Inhibitor</td>
<td>Factor Xa Inhibitor</td>
<td>Factor Xa Inhibitor</td>
<td>Factor Xa Inhibitor</td>
</tr>
<tr>
<td>Time to Peak</td>
<td>1.5 hrs</td>
<td>2-4 hrs</td>
<td>3-4 hrs</td>
<td>1-2 hrs</td>
</tr>
<tr>
<td>Half Life</td>
<td>12-17 hrs</td>
<td>9-13 hrs</td>
<td>12 hrs</td>
<td>10-14 hrs</td>
</tr>
<tr>
<td>Special considerations</td>
<td>Avoid if CrCL &lt;30 mL/min or Child-Pugh class B and C.</td>
<td>Avoid if CrCL &lt;30 mL/min or Child-Pugh class B and C.</td>
<td>Avoid if CrCL &lt;15 mL/min or Child-Pugh class B and C.</td>
<td>Avoid if CrCL &lt;15 mL/min or Child-Pugh class B and C.</td>
</tr>
<tr>
<td></td>
<td>Avoid if dyspepsia, upper GI symptom.</td>
<td>Must be taken with food.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>P-glycoprotein (P-gp)</td>
<td>P-gp and CYP 3A4/5</td>
<td>P-gp and CYP 3A4/5</td>
<td>P-gp and min. CYP 3A4/5</td>
</tr>
<tr>
<td>Measurement</td>
<td>ECT, dTT</td>
<td>Anti-Xa</td>
<td>Anti-Xa</td>
<td>Anti-Xa</td>
</tr>
<tr>
<td>Reversal Agent</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

ECT: Eucarin clot time
Case

- 30 F on OCP and recent travel with INR 1.4
- Change to DOAC
- Things to consider
  - pregnancy, cancer, bleeding, kidney and liver functions, lupus anticoagulant
Cautions with the DOACs

- Only approved reversal agent is for dabigatran
- No monitoring for effect
  - Adherence & Compliance
- Renal and hepatic failure
- Reimbursement issues
  - COST (warfarin $5/mo vs $250-350/mo)
- Post marketing bleeding rates
- Clinician familiarity
- Lack of guidelines
  - bleeding complications
Cautions with the DOACs

- Lack of data on patients at extreme weights.
  - ISTH suggests DOAC not be used: BMI >40 kg m-2 or weight >120 kg.
- Due to lack of antidote**, these new agents may not be appropriate for patient at high initial bleeding risk.
  - major trauma or surgery
- Unclear role in extensive DVT or massive PE
  - Patients excluded because often required advanced therapies.
- Have not been evaluated in conjunction with thrombolytic therapy.

*DVT= deep vein thrombosis
**PE= pulmonary embolism
***ISTH – International Society of Thrombosis and Hemostasis
Long Term Anticoagulation
After any thrombolysis (systemic or CDT), what is your preferred choice of long term anticoagulant?

A. Bridge to Coumadin
B. LMWH
C. Arixtra
D. Direct oral anticoagulant (DOAC)
Advantages with the DOACs

- Oral
- No need for monitoring (creatinine)
- No need for titration or dose adjustments
- Short onset
- Short half life
- Predictable absorption and metabolism
- Few drug-drug interactions
- Few dietary restrictions
- Convenience
In the absence of direct comparisons between NOACs ...no preference for one NOAC over another NOAC.”
DOACs: Important Questions

• How to switch from one agent to another
• Peri-operative/procedure management: how long to hold medication
Switching to/from DOAC: Review package insert

Table 15 Switching to DOACs

<table>
<thead>
<tr>
<th>Warfarin to DOAC</th>
</tr>
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<tbody>
<tr>
<td>Dabigatran&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rivaroxaban&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Apixaban&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Edoxaban&lt;sup&gt;a&lt;/sup&gt;</td>
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LMWH to DOAC

- Dabigatran
- Rivaroxaban | Start DOAC within 0–2 h of the time of next scheduled dose of LMWH
- Apixaban
- Edoxaban

(iv) UFH to DOAC

- Dabigatran<sup>a</sup>
- Rivaroxaban<sup>a</sup> | Start DOAC immediately after stopping iv UFH
- Apixaban<sup>a</sup>
- Edoxaban<sup>a</sup> | Start edoxaban 4 h after stopping iv UFH

As a general rule, we suggest that as INR drops below 2.5, a DOAC can be started.
As a general rule, we suggest that each DOAC can be started within 30 min after stopping (iv) UFH.

<sup>a</sup> Recommendations adapted from company’s package insert

Peri-operative/procedure management? How long to hold medication?

• ½ life of the drug
• Bleeding risk of the procedure
• Bleeding and thrombotic risk of the patient
• Current dose
• Renal function
How long to hold DOAC for procedures?

<table>
<thead>
<tr>
<th>Table 11: Cessation and resumption of DOAC for TT [46, 47, 126, 127]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cessation</strong></td>
</tr>
<tr>
<td><strong>Real function (nL/min)</strong></td>
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<tr>
<td>Dalteparin (BID dosing)</td>
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<tr>
<td>Rivaroxaban (Once daily dosing)</td>
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<tr>
<td>Apixaban (BID dosing)</td>
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<tr>
<td>Edoxaban (Once daily dosing)</td>
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</table>

*Look at package inserts*
Take Home Points

• DOACs have similar efficacy and mortality profiles as warfarin, many have better bleeding profile. **THEY ARE NOW FIRST LINE.**

• No head to head trials with DOACs -- which one to use depends on patient factors and preferences.

• Important for clinicians to understand when and how to use them and their limitations.
Thank you


Figure 2. Management of Bleeding on a DOAC

Initial Questions
Is the patient actively bleeding?
What is the location and severity of the bleed?
Can local hemostatic measures be applied or is a surgical intervention or procedure required?
What DOAC is the patient taking and when was the last dose?
Does the patient have renal failure or liver disease which may affect metabolism or clearance of DOAC?
Is the patient on an antithrombotic or alternative medication that may further increase risk of bleeding?
Does the patient have comorbidities that may increase the risk of bleeding?
Is the patient hemodynamically stable?

Initial Testing
Complete Blood Count
Comprehensive Metabolic Panel to assess kidney and liver function
Coagulation tests: PT, PTT, INR

Minor
- Local hemostatic measures
- Consider discontinuation of DOAC
- Surgical or procedural intervention if necessary

Moderate *
- Local hemostatic measures
- Monitor closely
- Discontinue DOAC
- Surgical or procedural intervention if necessary
- Blood transfusion support if necessary

Severe
- Place in ICU and monitor closely
- Hemodynamic support if necessary
- Blood transfusion support: EBC, platelets, FFP if necessary
- Discontinue DOAC
- Activated charcoal if last dose <6 hours

* In many circumstances, may need to employ severe bleeding strategies
PTT - Partial Thromboplastin Time
DOAC - direct oral anticoagulant

PCC - Prothrombin Complex concentrate
DDAVP - desmopressin

Rosovsky, Merli. TVIR, submitted
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BEVYXXA safely and effectively. See full prescribing information for BEVYXXA.

BEVYXXA (betrixaban) capsules, for oral use
Initial U.S. Approval: 2017

INDICATIONS AND USAGE
BEVYXXA is a factor Xa (FXa) inhibitor indicated for the prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to residual or severe restricted mobility and other risk factors for VTE. (1)

DOSAGE AND ADMINISTRATION
The recommended dose of BEVYXXA is an initial single dose of 100 mg, followed by 80 mg once daily, taken at the same time each day with food. The recommended duration of treatment is 35 to 42 days. (2)

Reduce dose for patients with severe renal impairment. (2.2)

Reduce dose for patients with moderate or severe restricted mobility and other risk factors for VTE. (2.3)

CONTRAINDICATIONS
Active pathological bleeding (1)
Concomitant use should not be made in patients treated with beprineline or undergoing spinal puncture. The risk of these events may be increased by the use of inducing spinal catheters or the concomitant use of medical products affecting hemostasis. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. (2.2)

WARNINGS AND PRECAUTIONS
Risk of Bleeding: Use caution in patients with previously fatal bleeding, promptly evaluate signs and symptoms of blood loss. (3.1)

Severe Renal Impairment: Increased risk of bleeding events; reduce BEVYXXA dose (2.3, 3.1)

Concomitant P-gp Inhibitors: Increased risk of bleeding events; reduce BEVYXXA dose (2.3, 3.1)

ADVERSE REACTIONS
Most common adverse reactions (incidence >5%) in bleeding. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Portola Pharmaceuticals at 1-855-767-7167 or FDA at 1-888-FDA-1088 or www.fda.gov/medwatch

Missed Dose
Reduce dose. (2.2)

Drug Interactions
P-gp inhibitors increase the blood levels of betrixaban. Reduce BEVYXXA dose. (7.2)

Anticoagulants: Avoid concurrent use. (7.2)

Dosage Forms and Strengths
Capsules: 40 mg and 80 mg (5)

Full Prescribing Information: Contents *

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dose
2.2 Severe Renal Impairment
2.3 Use with P-gp Inhibitors
2.4 Mixed Dose
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Risk of Bleeding
5.2 Spinal/Epidural Anesthesia or Puncture
5.3 Use in Patients with Severe Renal Impairment
5.4 Use in Patients on Concomitant P-gp Inhibitors
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
7 DRUG INTERACTIONS
7.1 Inhibitors of P-gp 
7.2 Anticoagulants, Antiplatelets, and Thrombolytics
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Pediatric Use
8.4 Geriatric Use
8.5 Renal Impairment
8.6 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

DOSAGE FORMS AND STRENGTHS
Capsules: 40 mg and 80 mg (5)

CONTRAINDICATIONS
• Active pathological bleeding
• Concomitant use should not be made in patients treated with beprineline or undergoing spinal puncture. The risk of these events may be increased by the use of inducing spinal catheters or the concomitant use of medical products affecting hemostasis. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures.

WARNINGS AND PRECAUTIONS
• Risk of Bleeding: Use caution in patients with previously fatal bleeding, promptly evaluate signs and symptoms of blood loss.
• Severe Renal Impairment: Increased risk of bleeding events; reduce BEVYXXA dose.
• Concomitant P-gp Inhibitors: Increased risk of bleeding events; reduce BEVYXXA dose.

ADVERSE REACTIONS
Most common adverse reactions (incidence >5%) in bleeding.

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Reduce dose.

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