Gotta Catch Them All! The Pokemon Approach to Understanding Direct Oral Anticoagulants
Shannon Finks, PharmD, FCCP, BCPS

Live Activity Handout
4 slides per page

freeCE
Gotta Catch Them All! The Pokemon Approach to Understanding Direct Oral Anticoagulants

ACTIVITY DESCRIPTION
Direct oral anticoagulants (DOACs) are recognized by guidelines as first-line options for the treatment of venous thromboembolism and prevention of stroke and systemic embolism in nonvalvular atrial fibrillation. Now that multiple DOACs have been FDA approved for these indications, and their use is wide-spread, it is challenging to ensure patient safety as each agent has slightly different pharmacokinetic considerations with its use. This program will address safety and efficacy with each agent, initial recommendations for dosing and adjustments based on renal considerations, drug interactions, and age and weight. Common risk factors for bleeding will be identified as well as options in support of the management of bleeding, if it should occur, are proposed.

TARGET AUDIENCE
The target audience for this activity is pharmacists and nurses in hospital, community, and retail pharmacy settings.

LEARNING OBJECTIVES
After completing this activity, the pharmacist will be able to:

• Differentiate among the pharmacotherapeutic options available for the treatment of non-valvular atrial fibrillation and venous thromboembolism
• Apply knowledge of clinical trial data and guidelines in order to determine the most appropriate anticoagulant for individualized patients
• Based on risks for bleeding and other risk characteristics, recommend appropriate modifications and dose adjustments of direct oral anticoagulants

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Professor of Clinical Pharmacy, University of Tennessee College of Pharmacy

ABOUT THE AUTHOR
Dr. Shannon Finks, PharmD., FCCP, BCPS is a Professor of Clinical Pharmacy at the University of Tennessee College of Pharmacy. She received her Doctor of Pharmacy degree from The University of Tennessee College of Pharmacy and completed a pharmacy practice residency at Methodist Hospitals of Memphis. Dr. Finks has practiced for fifteen years in the area of cardiology. She is a Fellow of the American College of Clinical Pharmacy and a Board Certified Pharmacotherapy Specialist with Added Qualifications in Cardiology. Dr. Finks has served as a national faculty member for the American College of Clinical Pharmacy Updates in Therapeutics: The Pharmacotherapy Preparatory and Recertification Course since 2012. Her current practice includes Cardiology Service at the VA Hospital where she co-precepts students and residents in the cardiology intensive care unit. Throughout her career she has mentored numerous students and residents and takes great pride in fostering continued education among pharmacists. Dr. Finks has received multiple teaching awards, including the Most Influential Professor Award from the University of Tennessee College Of Pharmacy and The University of Tennessee Alumni Association Outstanding Teacher Award. Dr. Finks is well published in the medical literature and has been invited to present locally, regionally, and nationally on numerous cardiovascular related topics.

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Objectives for Pharmacists

• Differentiate among the pharmacotherapeutic options available for the treatment of non-valvular atrial fibrillation and venous thromboembolism
• Apply knowledge of clinical trial data and guidelines in order to determine the most appropriate anticoagulant for individualized patients
• Based on risks for bleeding and other risk characteristics, recommend appropriate modifications and dose adjustments of direct oral anticoagulants

Modern Nomenclature

Players
• TSOAC = Target Specific
• NOAC = New, Novel, Non-Vit K, No

Term de jure
• DOAC = Direct Oral Anticoagulant
Timeline for OACs

1954 Coumadin

October 19, 2010 dabigatran

November 4, 2011 rivaroxaban

December 28, 2012 apixaban

January 8, 2015 edoxaban

October 19, 2010 dabigatran

November 4, 2011 rivaroxaban

December 28, 2012 apixaban

January 8, 2015 edoxaban

June 23, 2017 betrixaban

How often do you use/see a DOAC used in preference to VKA?

a) 0-25% of the time
b) 26-50% of the time
c) 51-75% of the time
d) 76-100% of the time

This is NOT a poll question.

GLORIA™-AF Registry

Advancement?

1950s

2017
Comparisons in favor of DOACs

- Efficacy as good or better than warfarin in VTE and AF
- Just as safe or safer than warfarin
- Immediate onset
- No INR monitoring required

Major Efficacy Outcomes of DOACs

<table>
<thead>
<tr>
<th>Condition</th>
<th>RE-LY (Dabigatran 150 bid)</th>
<th>ROCKET-AF (Rivaroxaban 20 mg/d)</th>
<th>ARISTOTLE (Apixaban 5 mg bid)</th>
<th>ENGAGE-AF (Edoxaban 60 mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/SEE</td>
<td>(0.66) Non-inferior</td>
<td>(0.79) Non-inferior</td>
<td>(0.51) Non-inferior</td>
<td></td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>(0.76) NS</td>
<td>(0.50) NS</td>
<td>(0.54)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic Stk</td>
<td>(0.26)</td>
<td>(0.59)</td>
<td>(0.51)</td>
<td></td>
</tr>
</tbody>
</table>

Efficacy of DOACs (as a class effect)

<table>
<thead>
<tr>
<th>Stroke or systemic embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOAC/events</td>
</tr>
<tr>
<td>RE-LY</td>
</tr>
<tr>
<td>ROCKET-AF</td>
</tr>
<tr>
<td>ARISTOTLE</td>
</tr>
<tr>
<td>ENGAGE-AF</td>
</tr>
<tr>
<td>Combined (random)</td>
</tr>
</tbody>
</table>

N=71,683

Efficacy of DOACs (as a class effect)

Secondary efficacy and safety outcomes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Post-Dabigatran (events)</th>
<th>Post-Warfarin (events)</th>
<th>RR (95% CI)</th>
<th><em>p</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>86/5729</td>
<td>71/5721</td>
<td>1.20 (0.87-1.63)</td>
<td>0.28</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>138/5729</td>
<td>74/5711</td>
<td>1.87 (1.4-2.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All-case mortality</td>
<td>202/5729</td>
<td>213/5721</td>
<td>1.00 (0.78-1.28)</td>
<td>0.985</td>
</tr>
<tr>
<td>Serious bleeding</td>
<td>40/5729</td>
<td>24/5711</td>
<td>1.71 (1.08-2.71)</td>
<td>0.023</td>
</tr>
</tbody>
</table>

N=71,683
Major Safety Outcomes of DOACs

<table>
<thead>
<tr>
<th>NVAF Outcome (RR)</th>
<th>RE-LY (Dabigatran 150 mg bid)</th>
<th>ROCKET-AF (Rivaroxaban 20 mg qd)</th>
<th>ARISTOTLE (Apixaban 5 mg bid)</th>
<th>ENGAGE-AF (Edoxaban 60 mg bid)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH</td>
<td>(0.4)  ( VS ) (0.67)</td>
<td>(0.42)  ( VS ) (0.47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>NS</td>
<td>(0.69)  ( VS ) (0.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRNM Bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI bleeding</td>
<td>(1.19-1.89)</td>
<td>(1.02 vs 1.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VTE Treatment Outcome (RR)

<table>
<thead>
<tr>
<th>RECOVER I/II (Dabigatran 150 bid)</th>
<th>EINSTEIN-DVT and IPE (Rivaroxaban 15 mg BID x 21, then 20 mg qd)</th>
<th>AMPLIFY (Apixaban 10 mg BID x 6, then 5 mg bid)</th>
<th>Holmquist-VTE (Edoxaban 60 mg/d)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>NS</td>
<td>(Einstein PE)</td>
<td>NS</td>
</tr>
<tr>
<td>Major + CRNM bleeding</td>
<td>(1.02 vs 1.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Safety (as a DOAC Class Effect)

Differences in Practice Perspective

a) Efficacy and safety
b) Pharmacokinetics/ Need for monitoring/follow up
c) Patient cost/Health-care system cost
d) Opportunity for reversal
e) Patient preference

Comparisons *worth notice!*

- Pharmacokinetic differences among the DOAC class
- Indication based dosing
- Varying degrees of renal clearance
- Different dose adjustments based on indications, drug interactions, renal clearance, weight and age
- Risk for GI bleeding
- Limited reversal
- Stopping for procedures or switching among agents complicated
Pharmacokinetic Considerations

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (Eliquis)</th>
<th>Edoxaban (Savaysa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA</td>
<td>DTI</td>
<td>Factor Xa inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administration</td>
<td>BID</td>
<td>QD*</td>
<td>BID</td>
<td>QD*</td>
</tr>
<tr>
<td>Peak effect (hr)</td>
<td>3</td>
<td>2-4</td>
<td>3</td>
<td>1-2</td>
</tr>
<tr>
<td>Half-life</td>
<td>12-17 hours</td>
<td>6-9 hours; 5-13</td>
<td>8-15 hours; 9-14</td>
<td>9-10 hours; 10-14</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>80%</td>
<td>36%</td>
<td>27%</td>
<td>50%</td>
</tr>
<tr>
<td>Drug-drug intx*</td>
<td>PGP</td>
<td>PGP and IA4</td>
<td>PGP and IA4</td>
<td>PGP</td>
</tr>
<tr>
<td>Reversal agent</td>
<td>Idarucizumab (Praxbind)</td>
<td>Andexanet-alpha</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Food increases bioavailability at higher doses; therefore, > 10 mg should be taken with food

Dosing Considerations

1. VTE Treatment
2. A. Fib
3. VTE Prevention

Dosing Adjustments in VTE

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (Eliquis)</th>
<th>Edoxaban (Savaysa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing VTE</td>
<td>150 mg BID (after at least 5 days IV anticoagulation)</td>
<td>15 mg BID x 21 days, then 20 mg daily with food</td>
<td>10 mg BID x 7 days, then 5 mg BID</td>
<td>60 mg daily (after at least 5 days IV anticoagulation)</td>
</tr>
<tr>
<td>Renal</td>
<td>No adjustments</td>
<td>No adjustments</td>
<td>No adjustments*</td>
<td>Reduce to 30 mg daily if CrCl 15-50 ml/min; weight &lt; 60 kg, or taking P-gp inhibitor</td>
</tr>
</tbody>
</table>

*Food increases bioavailability at higher doses; therefore, > 10 mg should be taken with food

Renal Dosing Adjustments in NVAF

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (Eliquis)</th>
<th>Edoxaban (Savaysa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>150 mg BID</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl 15-30 ml/min:</td>
<td>75 mg BID</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl 15-50 ml/min:</td>
<td>15 mg BID with evening meal*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl &lt;15 ml/min or on dialysis: not recommended</td>
<td>20 mg QD with evening meal*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduce to 2.5 mg BID with ≥ 2 of the following: ≥ 80 years, weight ≤ 60 kg, or SCr ≥ 1.5 mg/dL</td>
<td>Reduce to 2.5 mg BID with ≥ 2 of the following: ≥ 80 years, weight ≤ 60 kg, or SCr ≥ 1.5 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reg dosing in HD except if age ≥ 80 or wt ≤ 60 kg, then 2.5 mg</td>
<td>Reg dosing in HD except if age ≥ 80 or wt ≤ 60 kg, then 2.5 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl &gt;95 ml/min or &lt;15 ml/min: do not use</td>
<td>CrCl &gt;95 ml/min or &lt;15 ml/min: do not use</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Food increases bioavailability at higher doses; therefore, > 10 mg should be taken with food

Dosing Adjustments by Age/Weight

<table>
<thead>
<tr>
<th>Drug</th>
<th>NVAF (European)</th>
<th>VTE (Pradaxa)</th>
<th>Apixaban (Eliquis)</th>
<th>Edoxaban (Savaysa)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong> (Pradaxa)</td>
<td>European dosing includes 110 mg in those ≥ 80 years</td>
<td>Reduce to 2 mg BID with ≥ 2 of the following: ≥ 80 years, Weight ≤ 60 kg, or SCR ≥ 1.5 mg/dL.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong> (Xarelto)</td>
<td></td>
<td></td>
<td>Reduce to 2.5 mg BID with ≥ 2 of the following: ≥ 80 years, Weight ≤ 60 kg, or SCR ≥ 1.5 mg/dL.</td>
<td></td>
</tr>
<tr>
<td><strong>Apixaban</strong> (Eliquis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **Edoxaban** (Savaysa) | | | | |}

- NVAF: Reduce to 30 mg daily if CrCl 15-50 ml/min, weight ≤ 60 kg, or taking P-gp inhibitor.

Real world dosing observations in AF

N=14,865 patients receiving dabigatran, rivaroxaban, or apixaban

**Potential Overdose**
- 43% received standard dose
  - should have been decreased based on renal function
- **Greater risk of major bleeding** with no reduction of stroke
  - (11.29 vs. 5.06 major bleeding events/100 person years, HR 2.19, 95% CI 1.07-4.46)

**Potential Underdose**
- 13.3% received reduced dose
  - No label indication for reduced dose (i.e. age alone)
- Patients receiving apixaban had higher risk of stroke and no fewer major bleeds
  - 2.57 vs. 0.54 cerebrovascular events/100 person years, HR 4.87, 95% CI, 1.30-18.26)

Hepatic Disease Considerations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hepatic*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong> (Pradaxa)</td>
<td>Not recommended in severe disease (Child-Pugh C)</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong> (Xarelto)</td>
<td>Avoid in Child-Pugh B or C for hepatic disease associated with coagulopathy</td>
</tr>
<tr>
<td><strong>Apixaban</strong> (Eliquis)</td>
<td>Avoid use in severe disease (Child-Pugh C)</td>
</tr>
<tr>
<td><strong>Edoxaban</strong> (Savaysa)</td>
<td>Not recommended in moderate or severe disease (Child-Pugh B or C)</td>
</tr>
</tbody>
</table>

*Hepatic recommendations are not different among the indications

DOAC Drug Interactions: P-gp

Drug diffusion from intestinal lumen through terminal membrane into enteroocyte. P-gp pumps drug out of cell back into intestinal lumen.

P-gp inhibition
- P-gp activity reduced; less drug pumped out of systemic exposure.
- Less systemic exposure.

P-gp induction
- P-gp activity increased; more drug pumped out of systemic exposure.

DOAC Drug Interactions

AF Guidelines- DOACs first line

VTE Guidelines- DOACs first line

ISMP Quarter Watch/FAERS
Bleeding Observations from Trial Data

• Major bleeding with a DOAC is less severe in nature and required less intensive management than those with standard VKA therapy
  • Most bleeding events require supportive care only
• ICH and hemorrhagic stroke significantly less with DOACs
• GI bleeding is higher than VKA with dabigatran 150 mg, rivaroxaban, and edoxaban.
  • Increased risk for GIB when used for AF
  • No increase in GIB in treatment of the VTE population
• While randomized comparisons between the DOACs are not available, GI bleeding seems to occur least in patients receiving apixaban
• Risk factors for major bleed are similar among the DOACs

DOAC reversal agents

• Idarucizumab - October 16, 2015
  • Accelerated approval
  • For reversal of dabigatran (Pradaxa)
    • For life threatening bleeding or when reversal is necessary prior to emergency surgery
    • 5 g (2.5g per vial) IV infusion or 2 bolus injections
    • RE-VERSE AD
    • Reversed the anticoagulant effect of dabigatran in more than 89% of patients within 4 hours
    • Clinical pathways needed; $3500 per dose

Bleeding Risk Factors

<table>
<thead>
<tr>
<th>Bleeding Risk Factors</th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (Eliquis)</th>
<th>Edoxaban (Savaysa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old age, worse renal function, and concomitant aspirin or NSAID</td>
<td>Older age, prior GI bleeding, anemia at baseline, lower creatinine clearance, and aspirin use</td>
<td>Older age, prior hemorrhage, prior stroke or TIA, diabetes, lower creatinine clearance and use of aspirin or NSAID</td>
<td>Dose reductions to 30 mg in those with moderate renal impairment, weight &lt;60 kg, or in those with P-gp inx was associated with bleeding</td>
<td></td>
</tr>
</tbody>
</table>

Upcoming reversal agents

Andexanet Alpha (AndexXa)

• Modified protein extracted from human factor Xa
• Reverses indirect and direct factor Xa inhibitors with no coagulant activity
• Rivarox/apixaban/edoxaban
• Enoxaparin
• ANNEXA-R and ANNEXA-A
• Bolus ± infusion
• FDA delayed approval August 2016, requesting more info:
  • manufacturing, edoxaban, and enoxaparin

Ciraparantag (PER977)

• A synthetic water soluble compound originally synthesized to bind to and neutralize UFH/LMWH
• Also binds to target specific Xa and Xa inhibitors
• Dabigatran/rivarox/apix/edox
• UFH/LMWH/fondaparinux

Cost Effectiveness

Direct and Indirect costs
- Initial hospital stay
- Follow up visits
- Loss of work
- Cost of bleeding events
  - Several Markov pharmacoeconomic models have indicated that apixaban may be the most cost effective option

Drug Cost
- VKA ($4) vs. DOAC ($300)
- Need for bridging agents ($1100 enoxaparin)

AWP DOACs

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (Eliquis)</th>
<th>Edoxaban (Savaysa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 day supply</td>
<td>150 mg BID. U.S.: $333.57, Canada: $106.80</td>
<td>10, 15, or 20 mg once daily. U.S.: $332.27, Canada: $92.02</td>
<td>2.5 mg BID or 5 mg BID. U.S.: $359.92, Canada: $103.68</td>
<td>60 mg or 30 mg once daily. U.S.: $291.30, Canada: $92.02</td>
</tr>
</tbody>
</table>

Savings card
- Pradaxa savings card can reduce out-of-pocket cost by up to $2400 per year for U.S. patients with private insurance. Free 30 day supply: www.pradaxa.com
- Xarelto CarePath savings card can reduce out-of-pocket cost to U.S. patients with private insurance to $10 per month ($3400 max annual) (www.xarelto.com).
- Eliquis copay card can reduce out-of-pocket cost for U.S. patients with private insurance to $10 per month (www.eloquis.com).
- Savaysa savings card can reduce out-of-pocket cost to U.S. patients with private insurance to $4 per month (www.savaysa.com).

Importance of Patient Preference in Treatment Decisions

Shared Decision Making
- Improved adherence
- Ownership of one's health
- Improved satisfaction

Partnership
- Improved health outcomes
- Quality improvement

Advancement in Care

- DOACs represent an advancement in practice beyond that of traditional anticoagulation with VKA
- Guidelines support these agents as first line approaches in VTE and prevention of systemic embolism and stroke in NVAF

1950s 2017
There is no one perfect OAC!

- Difference in efficacy/safety
- Difference in daily dosing/adherence
- Difference in need for INR follow up vs. none
- Difference in renal clearance
- Difference in drug-drug interactions
- Difference in bleeding location (GI vs. ICH)
- Difference in reversal availability
- Difference in cost and patient preference

Agent selection should be individualized based on shared decision-making after discussion of the absolute and RRs of stroke and bleeding, and the patient’s values and preferences (i.e. risk factors, cost, tolerability, potential for drug interactions, and other clinical characteristics including TTR).

Case Study #1

A 46-year-old woman (weight 70 kg) with chronic kidney disease (CrCl estimated <30 ml/min) without insurance is diagnosed with pulmonary embolism and subcutaneous enoxaparin 1 mg/kg twice daily is initiated in the hospital. The patient expresses concern over her ability to pay for her prescriptions. She is willing to arrange transportation for monthly checkups. Your anticoagulation services have an average time in therapeutic range of 72%. Based on clinical evidence and patient preference which anticoagulant would you recommend?

Case Study #2

A 46-year-old woman (weight 70 kg) with chronic kidney disease (CrCl estimated <30 ml/min) is diagnosed with pulmonary embolism. Your anticoagulation services have an average time in therapeutic range of 45%. The patient has prescription coverage. She travels frequently due to her job and expresses concern about keeping multiple monitoring appointments. Based on clinical evidence and patient preference which anticoagulant is best to recommend?

Questions?