The Direct Oral Anticoagulants: Practical Considerations

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Disclosure

• Occasional consultant to:
  – BMS, Pfizer, Daiichi Sankyo, Janssen, Boehringer Ingelheim, Portola
# 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>Phase III complete</td>
<td>✓</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>Knee Replacement</td>
<td>Phase III complete</td>
<td>✓</td>
<td>✓</td>
<td>-</td>
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<tr>
<td>Stroke Prevention in Atrial Fibrillation</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Venous Thrombosis Treatment</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Acute Extended</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Extended</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Oncology</td>
<td>-</td>
<td>-</td>
<td>Phase II complete</td>
<td>Phase IV planned</td>
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</table>

✓ = approved by US FDA
### DOACs for Venous Thrombosis

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• 15 mg b.i.d. for 3 weeks</td>
<td>• 150 mg b.i.d.</td>
<td>• 10 mg b.i.d. for 7 days</td>
<td>• Daily (60 mg; or 30 mg for renal impairment or low weight)</td>
</tr>
<tr>
<td></td>
<td>• then 20 mg once daily</td>
<td>• 5 days of parenteral treatment needed <em>before dabigatran</em></td>
<td>• then 5 mg b.i.d.</td>
<td>• 5 days parenteral (LMWH) treatment needed <em>before edoxaban</em></td>
</tr>
<tr>
<td></td>
<td>• Can be used as monotherapy</td>
<td>• Can be used as monotherapy</td>
<td>• Can be used as monotherapy</td>
<td></td>
</tr>
</tbody>
</table>

**FDA Approval Status (for VTE)**

- **Rivaroxaban**: Approved Nov 2012
- **Dabigatran**: Approved Apr 2014
- **Apixaban**: Approved Aug 2014
- **Edoxaban**: Approved Jan 2015
DOACs: Barriers to Use

• Lack of antidote

• Uncertainty about lab measurement and procedures

• Negative Heart Valve Study
  ➢ (concern re: other highly pro-thrombotic states)

• Cost
Anticoagulation and Bleeding

• **Axiom**: Since warfarin effect can be ‘reversed’ and DOAC effect cannot, bleeding outcomes will be worse in patients taking DOACs.
What is the Risk of Death after Major Warfarin-associated Bleeding?

• Meta-analysis of 33 studies
  – 4374 patient-years of oral vitamin K antagonist therapy

• Case-fatality rate after warfarin-associated major bleeding: 13.4%

## Case Fatality Rate after Major Bleeding: Warfarin vs. DOACs

<table>
<thead>
<tr>
<th>Study</th>
<th>Warfarin Major Bleeds/Fatal bleeds</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROCKET AF</td>
<td>386/55 14%</td>
</tr>
<tr>
<td>Dabigatran systematic review</td>
<td>407/53* 13%</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>462/55 12%</td>
</tr>
<tr>
<td>ENGAGE-AF</td>
<td>524/59 11.3%</td>
</tr>
<tr>
<td>Dresden Registry</td>
<td>N/A</td>
</tr>
</tbody>
</table>

* estimated from paper
# Case Fatality Rate after Major Bleeding: Warfarin vs. DOACs

<table>
<thead>
<tr>
<th></th>
<th>Warfarin Major Bleeds/Fatal bleeds</th>
<th>New agent Major Bleeds/Fatal bleeds</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ROCKET AF</strong></td>
<td>386/55 14%</td>
<td>395/27 7%</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>407/53* 13%</td>
<td>627/57* 9.1%</td>
</tr>
<tr>
<td>systematic review</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ARISTOTLE</strong></td>
<td>462/55 12%</td>
<td>327/34 10%</td>
</tr>
<tr>
<td><strong>ENGAGE-AF</strong></td>
<td>524/59 11.3%</td>
<td>418/32 7.7%</td>
</tr>
<tr>
<td><strong>Dresden Registry</strong></td>
<td>N/A</td>
<td>5.1%</td>
</tr>
</tbody>
</table>

Major Bleeding PLUS Death within 30 days

Hylek at al. J Am Coll Cardiol. 2014 May 27;63(20):2141-7
Fatal Bleeding among >100,000 patients in 12 RCTs
## Pro-hemostatic Measures Used Infrequently

<table>
<thead>
<tr>
<th>Agent</th>
<th>Total Patients at Risk</th>
<th>Number given PCC or rVIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>dabigatran(^1)</td>
<td>12,091</td>
<td>13</td>
</tr>
<tr>
<td>rivaroxaban(^2)</td>
<td>7,061</td>
<td>4</td>
</tr>
<tr>
<td>apixaban(^3)</td>
<td>9,120</td>
<td>5</td>
</tr>
</tbody>
</table>

In all studies, median follow-up was approximately 2 years.

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3 Manuscript in press; European Heart Journal.
FDA Drug Safety Communication: FDA study of Medicare patients finds risks lower for stroke and death but higher for gastrointestinal bleeding with Pradaxa (dabigatran) compared to warfarin

This information is in follow-up to the FDA Drug Safety Communication: Update on the risk for serious bleeding events with the anticoagulant Pradaxa (dabigatran) that was issued on November 2, 2012.

Safety Announcement

[05-13-2014] In its ongoing review of the blood thinner Pradaxa (dabigatran), the U.S. Food and Drug Administration (FDA) recently completed a new study in Medicare patients comparing Pradaxa to the blood thinner warfarin (Coumadin, Jantoven, and generics), for risk of ischemic


Quality and Outcomes

Characterizing Major Bleeding in Patients With Nonvalvular Atrial Fibrillation: A Pharmacovigilance Study of 27,467 Patients Taking Rivaroxaban

- January 2013 to March 2014:
  - US Department of Defense electronic health care records
  - queried for major bleeding

- 27,467 patients on rivaroxaban
  - Major bleed rates similar to RCT data
  - 88.5% of major bleeds were GI
  - 14/478 MB episodes were fatal (< 3%) prior to d/c

Anticoagulation and Bleeding

• **Axiom:** Since warfarin effect can be ‘reversed’ and DOAC effect cannot, bleeding outcomes will be worse in patients taking DOACs.
How to Explain the Favorable Bleeding Outcome Data for DOACs

• Fewer major bleeds (especially intracranial)

• Short half-life

• Warfarin ‘reversal’ often does not translate to a favorable outcome
When confronted by a bleeding patient, ask:

1. Is the drug present in significant quantities?

2. Is reversal really needed?

3. If reversal is needed, what is the best strategy to follow?
Lab Measurement for DOACs at UWMC and HMC

- Dabigatran: dilute thrombin time ("DTI assay" calibrated for dabigatran)

- Rivaroxaban and apixaban: anti-Xa assay (calibrated for a particular DOAC)

- “expected” trough: ~ 50 ng/mL
- “expected” peak: 150 – 250 ng/mL

Overview of DOAC-associated Bleeding

- Evidence base for use of any reversal strategy is poor
- Use a standardized approach for all anticoagulated patients
- Get interventionalists involved early in major bleeding
- Pre-clinical data suggests PCC (prothrombin complex concentrate) or rVIIa may be helpful

- Above all, do not panic – supportive care may be the best option
Per 977

• Small, water-soluble molecule that binds to anticoagulants neutralizing their anticoagulant activity
• Reported to bind and neutralize heparin, fondaparinux, LMWH and DOACs
• Does not bind endogenous coagulation factors

http://www.perosphere.com
Figure 1. Effect of PER977 on Whole-Blood Clotting Time.

Shown are the mean whole-blood clotting times after administration of a single oral 60-mg dose of edoxaban, followed 3 hours later by a single intravenous dose of 25 mg, 100 mg, or 300 mg of PER977 or placebo.
Andexanet (a FXa decoy)
Rivaroxaban – Reversal of anti-Xa effect

Crowther et al. ASH abstract 2013
Idarucizumab

• monoclonal antibody fragment that binds dabigatran with an affinity 350 times that of thrombin.

• binds free and thrombin-bound dabigatran and neutralizes its activity
Healthy volunteer study: immediate, dose-dependent reversal of dabigatran anticoagulation

'Data shown as mean ± SD
Glund S et al. AHA 2013; abstract 17765

'Normal upper reference limit': mean+2SD of 86 predose measurements from a total of 51 subjects,
Idarucizumab for Dabigatran Reversal “RE-VERSE AD”

• Group A: overt, uncontrollable or life-threatening bleeding (51 patients)

• Group B: required surgery or other invasive procedures that could not be delayed for at least 8 hours (39 patients)
Anticoagulant Effect vs. Time

Clinical Outcomes

• Group A
  – 3 of 51 patients died from bleeding within 30 days

• Group B (36 patients underwent a procedure)
  – normal intraoperative hemostasis: 33
  – mildly abnormal hemostasis: 2
  – moderately abnormal hemostasis: 1

• No evidence of pro-thrombotic or immunogenic effect

Issues with Antidotes

1. Availability
2. Cost
3. Need
4. Toxicities
What do we know about Peri-procedural DOAC use?
Pharmacokinetic Profile of a DOAC

Apixaban 10 mg in 21 healthy volunteers

Adapted from Frost C et al. World Congress of Clinical Pharmacology and Therapeutics, July, 2008, Quebec, Canada (poster T2M102).
### DOACS:
Procedure and Interruption Data from RCTs

<table>
<thead>
<tr>
<th>Trial</th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>dabigatran</td>
<td>0.5</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>warfarin</td>
<td>0.5</td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>rivaroxaban</td>
<td>0.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>warfarin</td>
<td>0.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>apixaban</td>
<td>1.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>warfarin</td>
<td>1.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Stroke or Systemic Embolism**
  - RE-LY: 0.5
  - ROCKET-AF: 0.3
  - ARISTOTLE: 0.4

- **Major Bleeding**
  - RE-LY: 5.1
  - ROCKET-AF: 0.99
  - ARISTOTLE: 1.6

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Procedures and Interruptions on DOACS: Summary

• Many procedures can be performed safely without DOAC interruption
  – Need more data to select patients and procedures

• Short-term interruption of DOAC (in AF) is associated with low 30-day risk of stroke
  – Bridging likely not needed (except for patients who cannot take oral medication)
Procedures and Interruptions on DOACS: Summary

• For patients whose procedure requires interruption
  – 24 – 48 hours likely sufficient if renal function normal
  – Longer interruptions if renal impairment and/or high-risk procedure

• More data anticipated from P.A.U.S.E.*
  – Prospective cohort study with standardized interruption schedule

* NCT 02228798
What Patients should NOT receive a DOAC?
Mechanical Heart Valves

Dabigatran versus Warfarin in Patients with Mechanical Heart Valves

John W. Eikelboom, M.D., Stuart J. Connolly, M.D., Martina Brueckmann, M.D., Christopher B. Granger, M.D., Arie P. Kappetein, M.D., Ph.D.,

available at NEJM.org.

This article was published on September 1, 2013, at NEJM.org.

DOI: 10.1056/NEJMoa1300615
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Re-ALIGN

• Multi-center clinical trial in which dabigatran was monitored and the dose adjusted to keep the trough level elevated

• Designed to provide guidance on dosing for Phase III clinical trial
Re-ALIGN

• initial dabigatran dosed to keep trough > 50 ng/mL:
  – 150 mg BID in 15% - CrCl < 70 mL/min
  – 220 mg BID in 54% - CrCl 70 to 109 mL/min
  – 300 mg BID in 31% - CrCl > 110 mL/min

• Dose adjusted based on trough
  – Dabigatran increased in 39 of 162 patients
  – Dabigatran stopped in 13 patients due to trough less than 50 ng/mL at 200 mg BID
A  First Thromboembolic Event

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th></th>
<th></th>
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<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>168</td>
<td>156</td>
<td>126</td>
<td>108</td>
<td>73</td>
<td>44</td>
<td>15</td>
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<tr>
<td>Dabigatran</td>
<td>84</td>
<td>82</td>
<td>66</td>
<td>55</td>
<td>40</td>
<td>22</td>
<td>9</td>
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Days

Probability of No Event
B First Bleeding Event

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>168 days</td>
<td>168</td>
<td>84</td>
</tr>
<tr>
<td>129 days</td>
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<td>73</td>
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<td>103 days</td>
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<td>86 days</td>
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<td>58 days</td>
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<td>38</td>
</tr>
<tr>
<td>32 days</td>
<td>32</td>
<td>22</td>
</tr>
<tr>
<td>11 days</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>6 days</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

Probability of No Event vs Days

- Dabigatran
- Warfarin
Summary of Re-ALIGN

– Even very high doses of dabigatran failed to prevent valve thrombosis

– These doses are effective in other settings and bleeding was higher than with warfarin

– Therefore not due to an inadequate anticoagulant effect
Implication of these findings?

• Perhaps single-target inhibition of the coagulation cascade is not adequate in the face of strong prothrombotic stimuli
  
  – ? Antiphospholipid antibodies
  – ? Heparin-induced thrombocytopenia
  – ? Foreign-surface associated thrombosis
  – ? Cancer associated thrombosis

• For these conditions, we should await evidence of efficacy before *routinely* recommending DOACs
Other Reasons Not to Use DOACs In Cancer Patients

- Virtually no experience in patients with thrombocytopenia.

- Interactions with many chemotherapy agents unknown.

- Proper RCT will be impossible if DOACs become standard for cancer-associated VTE.
Upcoming Randomized Trial: Dalteparin vs. Edoxaban x 6 months

- Active cancer + VTE
- Target Sample Size = 1300
- Primary Outcome: recurrent VTE OR major bleeding (composite endpoint)
- NCT01164046
Summary

• New anticoagulants represent an evolutionary step in our care of patients with, or at risk of, thrombosis.
• Compared to warfarin, the risk of fatal bleeding was lower with DOACs in large RCTs.
• Cost and concerns about efficacy in selected populations are valid reasons to continue to use warfarin.
• Antidotes are being developed, but the lack of an antidote should not be a major consideration in 2015.
• Measurement of DOAC effect is possible.
• DOACs will likely eliminate the need for perioperative ‘bridging’.