The Direct Oral Anticoagulants: Practical Considerations

David Garcia, MD
University of Washington
Disclosures for David Garcia, MD

In compliance with ACCME policy, ASH requires disclosures to the session audience:

- **Consultancy:** Alexion; Boehringer Ingelheim; Bristol-Meyers Squibb; Daiichi Sankyo; Genzyme; Incyte; Janssen; Pfizer; Portola
- **Research Funding:** Daiichi Sankyo; Incyte; Janssen; Portola

**Speakers’ Bureau:** None

**Promotional Presentations:** None

**Discussion of off-label drug use:** None
Outline

• Measurement vs. Monitoring

• Reversal

• Peri-procedural Interruption
1940: Karl Link identifies dicoumarol, a toxic element causing hemorrhagic disease of cattle.
The amazing pill that keeps Ike alive

By Robert C. Toth

The small pill that helps keep President Eisenhower alive and active may be the forerunner of a pill that will add years of happiness and activity to our lives.

The tasteless, aspirin-sized pill that Ike takes in the morning—usually six times a week but sometimes seven—is said to be almost literally keeping him alive. He has swallowed more than a thousand of them since his heart attack in 1955. They are peach-colored, white or red, depending on whether they contain 5, 10 or 25 milligrams of Coumadin—a substance that can kill a rat in a matter of minutes.

Coumadin is an anti-coagulant drug; it discourages blood from clotting. It can cause a small animal to bleed to death internally. If the drug is given in large enough doses, it can turn a normal human being into a
## Direct Oral Anticoagulants [DOACs]: 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 Thrombosis Treatment</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>
<tr>
<td>Oncology</td>
<td>-</td>
<td>-</td>
<td>Phase II complete</td>
<td>Phase IV planned</td>
</tr>
</tbody>
</table>

✓ = approved by US FDA
DOACs:
Alternatives to vit. K antagonists in atrial fibrillation

Circulation. 2014 Dec 2;130(23):2071-104.
Atrial fibrillation: DOACs reduce all-cause mortality by 10% compared to warfarin

DOACs should now be the ‘default’ choice for patients with DVT and/or PE

Chest. 2016;149(2):315-352
Why DOACs are preferred for *most patients* with Venous Thrombosis

- More convenient
  - No routine monitoring or dose adjustment
  - No dietary (and few drug-drug) interactions
  - Simplified peri-procedural anticoagulation

- As effective as warfarin

- Safer than warfarin
Fatal Bleeding among >100,000 patients in 12 Randomized Controlled Trials

When should a DOAC *not* be the first choice?

- Pro-thrombotic states: e.g. cancer
- Severe renal impairment (CrCl < 30 ml/min)
- Moderate to severe hepatic impairment
- Clinically significant drug interactions
- Extremely high body weight (> 120 kg?)
- Prohibitive cost
The folly of monitoring

Schematic of drug effect: warfarin vs DOACs

Anticoagulant Effect (or drug level) vs Dose

Peak & trough levels with DOACs

INR on warfarin
Measuring DOACs: When

<table>
<thead>
<tr>
<th>Detection of clinically relevant levels</th>
<th>Detection of expected on-therapy levels</th>
<th>Detection of excessive levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgent or emergent invasive procedure</td>
<td>Distinguish nonadherence from break-through thrombosis</td>
<td>Suspected overdose or possible drug interaction</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>Diminished/changing renal function</td>
<td></td>
</tr>
</tbody>
</table>
Lab Measurement for DOACs

• DOACs can (but do not always) prolong “traditional” clotting times (PTT or PT)

• Thrombin time (TT) is very sensitive to (even low concentrations of) dabigatran – a normal thrombin time excludes dabigatran
Best tests for DOACs

• Dabigatran: dilute thrombin time (*calibrated for dabigatran*)

• FXa inhibitors: anti-Xa assay (*calibrated for a particular DOAC*)

• “expected” trough: ~ 50 ng/mL
• “expected” peak: 150 – 250 ng/mL
Measuring DOACs: How

Cuker et al JACC 2014; doi: 10.1016/j.jacc.2014.05.065
Overview of Anticoagulant-associated Bleeding

• **Evidence** for any reversal strategy is poor

• Use a **standardized approach** for all anticoagulated patients

• DOACs
  – Consider idarucizumab or andexanet, if available
  – Pre-clinical data suggests PCC (prothrombin complex concentrate) or rVIIa **may** be helpful
  – Do not panic – **supportive care may be the best option**
## Case Fatality Rate after Major Bleeding: Warfarin vs. DOACs

<table>
<thead>
<tr>
<th></th>
<th>Warfarin Major Bleeds/Fatal bleeds</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROCKET AF</td>
<td>386/55</td>
</tr>
<tr>
<td></td>
<td>14%</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>407/53*</td>
</tr>
<tr>
<td>systematic review</td>
<td>13%</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>462/55</td>
</tr>
<tr>
<td></td>
<td>12%</td>
</tr>
<tr>
<td>ENGAGE-AF</td>
<td>524/59</td>
</tr>
<tr>
<td></td>
<td>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><strong>Dabigatran</strong></td>
<td>407/53* 13%</td>
<td>627/57* 9.1%</td>
</tr>
<tr>
<td><strong>systematic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>review</strong></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</strong></td>
<td>N/A</td>
<td>5.1%</td>
</tr>
<tr>
<td><strong>Registry</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For more precise (and pooled) estimates, see: 
DOACs: The Reversal Agents
Idarucizumab: specific reversal agent for dabigatran
Healthy volunteer study: immediate, dose-dependent reversal of dabigatran anticoagulation

Glund S et al. AHA 2013; abstract 17765
Idarucizumab: The “RE-VERSE AD” Study

• 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)
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

Idarucizumab

• Approved by US FDA in fall 2015
Andexanet: (a FXa decoy)
Rivaroxaban in healthy volunteers
Andexanet Reversal

End of Bolus

End of Infusion

- Placebo (n=9)
- 210 mg bolus only (n=6)
- 420 mg bolus only (n=6)
- 600 mg bolus only (n=6)
- 720 mg bolus + 240 mg infusion (n=6)

Siegal D. et al NEJM 2015
ANNEXA-4: Andexanet for FXa-associated bleeding

**Efficacy Measurements**
- Change in anti-FXa activity
- Clinical hemostatic efficacy through 12 hours

**Safety Measurements**
- Thrombotic events
- Antibodies to FX, FXa, andexanet
- 30-day mortality

Conclusions

• Andexanet bolus plus 2 hour infusion rapidly reversed anti-fXa activity

• Effective hemostasis observed in 79% of patients

• Thrombotic events occurred at rates consistent with the high risk profile of the patients

Connolly et al. NEJM. 2016 epub.
US FDA requests additional information

- additional data to support inclusion of edoxaban and enoxaparin in the label
- needs to finalize its review of Portola’s post-marketing commitments
Considerations for reversal agents

1. Availability

2. Cost

3. Need (Shelf life)

4. Unanticipated Toxicities?
Case

• Your patient has a history of unprovoked pulmonary embolism 8 months ago.

• She takes apixaban but now needs to undergo a screening colonoscopy.

• How will you manage her apixaban treatment around the procedure?
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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>warfarin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>apixaban</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>warfarin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or Systemic Embolism</td>
<td>0.5</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>5.1</td>
<td>0.99</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Temporary interruption of DOACs

Communicate with the patient and providers involved

‘Bridging’ with parenteral anticoagulants is not necessary

Consider:
• Current renal function
• Half-life of DOAC
• Bleeding risk

Spyropoulos A. Blood. 2012
Summary

• DOACs now the **first choice** for many patients with VTE or AF (but not mechanical heart valve patients)

• Effect of DOACs can be **measured**

• Reversal agents are here (or coming soon) – but will likely be used infrequently

• DOACs simplify perioperative anticoagulation and can be safely interrupted for short time periods