How I use and reverse novel oral coagulants

Ryan Zarychanski MD MSc FRCPC
Disclosures

FINANCIAL DISCLOSURE

Grants/Research Support: Pfizer / Bayer / CIHR

Speaker bureau/Honoraria: Bayer

Consultant: None

Scientific advisory board: None
Objectives

1. Review properties and uses of the novel oral anticoagulants (NOACs)
2. Discuss reversal strategies for oral anticoagulants
3. Present concepts related to therapeutic monitoring of NOACs
Treatment of atrial fibrillation and VTE has changed!

<table>
<thead>
<tr>
<th>1970 to 2000</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Warfarin reigned supreme: anticoagulant of choice (afib)</td>
<td>• Warfarin no longer the ‘go to’ blood thinner (afib)</td>
</tr>
<tr>
<td>• 6 months was ‘standard’ (VTE)</td>
<td>• 3 months is ‘standard’ (VTE)</td>
</tr>
<tr>
<td>• Thrombophilia testing was the rage</td>
<td>• Thrombophilia testing recognized as unhelpful</td>
</tr>
</tbody>
</table>
Traditional management of VTE

Initial treatment

- LMWH or UFH*

5-7 days

Long-term therapy

- VKA** (INR† 2.0-3.0)

>3 months

*UFH = unfractionated heparin

**VKA = vitamin K antagonist

†INR = international normalization ratio
## Conventional Management

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Effective</td>
<td>• Requires multiple injections</td>
</tr>
<tr>
<td>• Familiar</td>
<td>• INR monitoring</td>
</tr>
<tr>
<td>• Facilitates outpatient therapy</td>
<td>• Plus...all the burdens of warfarin</td>
</tr>
</tbody>
</table>
Why Don Houston likes warfarin

1. Strong evidence base for its use
2. Highly effective anticoagulant in a broad range of indications
3. No significant off-target toxicities
4. Profoundly inexpensive
Why we dislike warfarin

1. Brutal pharmacodynamics
2. Unfavourable pharmacokinetics
3. Drug interactions
4. Requirement for monitoring
Novel oral anticoagulants (NOACs)

**Direct thrombin inhibitor**
Dabigatran (Pradaxa®)

**Direct Factor Xa inhibitor**
Rivaroxaban (Xarelto®)
Apixaban (Eliquis®)
Edoxaban

*Others are coming...*
# Novel oral anticoagulants (NOACs)

<table>
<thead>
<tr>
<th><strong>Dabigatran</strong> (Pradaxa)</th>
<th><strong>Rivaroxaban</strong> (Xarelto)</th>
<th><strong>Apixaban</strong> (Eliquis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Oral direct thrombin inhibitor</td>
<td>• Oral direct Factor Xa inhibitor</td>
<td>• Oral direct Factor Xa inhibitor</td>
</tr>
<tr>
<td>• little food interaction</td>
<td>• little food interaction</td>
<td>• little food interaction</td>
</tr>
<tr>
<td>• Half life 12-17 hrs</td>
<td>• Half-life 5-13 hrs</td>
<td>• Half-life ~12 hrs</td>
</tr>
</tbody>
</table>

**Approved for:**

- DVT prophylaxis in orthopedic surgery
- Atrial fibrillation
- DVT/PE treatment

- DVT prophylaxis in orthopedic surgery
- Atrial fibrillation
- DVT/PE treatment
- DVT prophylaxis in orthopedic surgery
- Atrial fibrillation
- DVT/PE treatment
# Novel oral anticoagulants (NOACs)

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Interactions</strong></td>
<td>P-gp</td>
<td>CYP 3A4 &amp; P-gp</td>
<td>CYP 3A4 &amp; P-gp</td>
</tr>
<tr>
<td><strong>Renal Elimination</strong></td>
<td>80%</td>
<td>33%</td>
<td>27%</td>
</tr>
</tbody>
</table>

**P-gp/CYP 3A4 inhibitors:** -azole antifungals, HIV protease inhibitors, tacrolimus, cyclosporine, verapamil, quinidine

**P-gp/CYP 3A4 Inducers:** rifampin, phenytoin, carbamazepine, St. John’s Wart
NOACs in non-valvular atrial fibrillation
# NOACs for non-valvular Atrial Fibrillation

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Dabigatran**      | • Oral direct thrombin inhibitor  
                     • little food interaction  
                     • Half life 12-17 hrs  
                     • 150 mg BID  
                     • 110 mg BID if at increased risk of bleeding  
                     • CrCl < 30; don’t use |
| **Rivaroxaban**     | • Oral direct Factor Xa inhibitor  
                     • little food interaction  
                     • Half-life 5-13 hrs  
                     • 20 mg OD  
                     • CrCl 30-49 ml/min  
                     • 15 mg OD |
| **Apixaban**        | • Oral direct Factor Xa inhibitor  
                     • little food interaction  
                     • Half-life 12 hrs  
                     • 5 mg BID  
                     • 2.5 mg BID: If any 2 are present: age ≥80, weight < 60 kg, or creatinine ≥ 133  
                     • CrCl 15-24: limited data  
                     • CrCl < 15: don’t use |

ALL AGENTS ARE HEALTH CANADA APPROVED & Part 3 EDS in Manitoba
New Anticoagulants vs. Warfarin

Stroke or Systemic Embolism

**ROCKET AF**

- Mean CHADS$_2$ Score: 3.5
- p = 0.12

**RE-LY**

- Mean CHADS$_2$ Score: 2.1
- p = 0.3 (D110 mg)
- p < 0.001 (D150 mg)

**ARISTOTLE**

- Mean CHADS$_2$ Score: 2.1
- p = 0.01
New Anticoagulants vs. Warfarin

All-Cause Mortality

ROCKET AF

- Rivaroxaban (n=7,081)
- Warfarin (n=7,090)

p = 0.152

RE-LY

- D110 mg (n=6,015)
- D150 mg (n=6,076)
- Warfarin (n=6,022)

p = 0.131 (D110 mg)

p = 0.052 (D150 mg)

ARISTOTLE

- Apixaban (n=9,120)
- Warfarin (n=9,081)

p = 0.047
In Summary:

NOACs vs. warfarin in NV atrial fibrillation

1. NOACs are better than warfarin to prevent stroke in non-valvular atrial fibrillation
2. ~10% reduction in relative risk of death compared to warfarin for all NOACs
3. Lower rate of intracranial bleeding compared to warfarin
4. NOAC is preferred to warfarin as first line therapy
NOACs and VTE (PE/DVT)
**NOACs for the treatment of DVT/PE**

<table>
<thead>
<tr>
<th><strong>Dabigatran</strong> (Pradaxa)</th>
<th><strong>Rivaroxaban</strong> (Xarelto)</th>
<th><strong>Apixaban</strong> (Eliquis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral direct thrombin inhibitor</td>
<td>Oral direct Factor Xa inhibitor</td>
<td>Oral direct Factor Xa inhibitor</td>
</tr>
<tr>
<td>little food interaction</td>
<td>little food interaction</td>
<td>little food interaction</td>
</tr>
<tr>
<td>Half life 12-17 hrs</td>
<td>Half-life 9 hrs</td>
<td>Half-life 12 hrs</td>
</tr>
<tr>
<td>Subcutaneous LMWH x 7 days</td>
<td>15 mg BID x 3 weeks</td>
<td>10 mg BID x 7 days</td>
</tr>
<tr>
<td>Then dabigatran 150 mg BID</td>
<td>Then 20 mg OD for at least 9 weeks</td>
<td>Then 5 mg BID for at least 11 weeks</td>
</tr>
</tbody>
</table>

*Use limited due to the need for S/Q injections*

- **CrCl** <30 – don’t use
- **CrCL** 30-50; No adjustment
- **CrCl** <25 – don’t use
- **CrCL** 25-50; No adjustment
## NOACs for the treatment of DVT/PE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
<th>Patients</th>
<th>Recurrent VTE</th>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong> (Pradaxa)</td>
<td>Oral direct thrombin inhibitor, little food interaction, half life 12-17 hrs</td>
<td>1274</td>
<td>No difference</td>
<td>No difference</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong> (Xarelto)</td>
<td>Oral direct Factor Xa inhibitor, little food interaction, half-life 9 hrs</td>
<td>8281</td>
<td>No difference</td>
<td>No difference</td>
</tr>
<tr>
<td><strong>Apixaban</strong>  (Eliquis)</td>
<td>Oral direct Factor Xa inhibitor, little food interaction, half-life 12 hrs</td>
<td>5395</td>
<td>No difference</td>
<td>Decreased major bleeding with NOAC</td>
</tr>
</tbody>
</table>
In Summary: NOACs vs. warfarin for VTE

1. As good as warfarin with less major bleeding

2. No need for multiple ER visits or for dalteparin injections if rivaroxaban or apixaban is used

3. All agents are approved for treatment of DVT and PE in Canada
All great...but what if the patient bleeds!
Bleeding and anticoagulants: Warfarin

64 y.o. man on warfarin for atrial fibrillation. Presents with type B dissection.

- Acute renal failure (anuric)
- Hemodynamically stable
- INR 3.4

How would you reverse warfarin?
Pharmacologic treatment/reversal of bleeding on warfarin

- 10 mg IV vitamin K
- Prothrombin concentrates
  - Octaplex
  - Beriplex

**Dose of Prothrombin Complex**
- INR <3.0: 40 mL (1000 IU)
- INR 3-5: 80 mL (2000 IU)
- INR >5: 120 mL (3000 IU)

*Consider dose increase if > 100 kg

**If no bleeding or urgency, then just give 2 mg of vitamin K orally**
Prothrombin Concentrates (Octaplex / Beriplex)*

Concentrate of vitamin K dependent factors (II, VII, IX, X)

Appealing features:

• Virus inactivated
• Reconstitute from powder => quicker than thawing/giving FFP
• Small volume to administer
• No blood group matching required
• Cost is comparable

* Contraindicated in HIT
64 y.o. man on dabigatran for atrial fibrillation. Presents with lower GI bleed.
• Blood pressure 90/60 mmHg
• INR 1.4; aPTT 46 sec

How would you manage the bleeding?

Would you reverse dabigatran?

...Do you need to?
Bleeding and anticoagulants: Dabigatran

Initiate resuscitation measures:

- Bolus isotonic crystalloids
- RBC transfusion (target > 70 g/L)
- Activating Massive Transfusion Protocol if appropriate
- Local hemostatic measures /endoscopy
- Collect baseline labs
- CBC, aPTT, INR

...remember the half life is 12-17 hours
Bleeding and anticoagulants: Dabigatran

Idarucizumab

- Monoclonal antibody with 350 X higher affinity over thrombin
- 5 gram dose results in immediate and complete reversal of dabigatran
- No safety concerns yet identified
Bleeding and anticoagulants: Dabigatran

Idarucizumab

Indications:

1. Emergency surgery/urgent procedures
2. Life-threatening bleeding
Are reversal agents for NOAC the ‘cavalry’ we’ve been waiting for?

<table>
<thead>
<tr>
<th>RE-LY Trial (afib)</th>
<th>Warfarin</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality from Intracranial bleeding</td>
<td>36% (32/90)</td>
<td>35% (13/37)</td>
</tr>
</tbody>
</table>

You don’t have to reverse a bleed that doesn’t happen!
Mortality after a major bleeding event: Are NOACs really more dangerous?

Figure 1: Major Bleeding Following by Death Within 30 Days

Figure: Thirty-day mortality rate after a major bleeding event.

Cl = confidence interval; HR = hazard ratio.
Mortality after a major bleeding event: Are NOACs really more dangerous?

Table 1  Event Rates and HRs and 95% CIs for Bleeding Events

<table>
<thead>
<tr>
<th>Events (Rate)</th>
<th>Rivaroxaban (n = 7,111)</th>
<th>Warfarin (n = 7,125)</th>
<th>HR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal safety endpoint</td>
<td>1,475 (14.91)</td>
<td>1,449 (14.52)</td>
<td>1.03 (0.96-1.11)</td>
<td>0.442</td>
</tr>
<tr>
<td>Major</td>
<td>395 (3.60)</td>
<td>386 (3.45)</td>
<td>1.04 (0.90-1.20)</td>
<td>0.576</td>
</tr>
<tr>
<td>Hemoglobin/hematocrit drop</td>
<td>305 (2.77)</td>
<td>254 (2.26)</td>
<td>1.22 (1.03-1.44)</td>
<td>0.019</td>
</tr>
<tr>
<td>Transfusion</td>
<td>183 (1.65)</td>
<td>149 (1.32)</td>
<td>1.25 (1.01-1.55)</td>
<td>0.044</td>
</tr>
<tr>
<td>Critical organ bleeding</td>
<td>91 (0.82)</td>
<td>133 (1.18)</td>
<td>0.69 (0.53-0.91)</td>
<td>0.007</td>
</tr>
<tr>
<td>Death</td>
<td>27 (0.24)</td>
<td>55 (0.48)</td>
<td>0.50 (0.31-0.79)</td>
<td>0.003</td>
</tr>
<tr>
<td>Nonmajor clinically relevant</td>
<td>1,185 (11.80)</td>
<td>1,151 (11.37)</td>
<td>1.04 (0.96-1.13)</td>
<td>0.345</td>
</tr>
<tr>
<td>Minimal</td>
<td>258 (2.35)</td>
<td>226 (2.03)</td>
<td>1.16 (0.97-1.39)</td>
<td>0.102</td>
</tr>
</tbody>
</table>

Event rates/100 patient-years.
REVERSAL AGENTS are coming very soon. (Andexanet alpha)

Until such agents are available:
• Can you wait it out? (half life 9-12 hours)

• **Prothrombin concentrates recommended** based on non-clinical, laboratory outcomes of uncertain relevance
  • **Dose:** 50 units/kg based on in vitro studies

• Consider tranexamic acid
  • 1 g IV bolus, then 1 gram over 8 hours
In Summary:

Antidotes for NOACs

**Idarucizumab (Praxbind)**
Dabigatran specific inhibitor
Available – June 2016

**Andexanet alfa**
Direct and indirect FXa inhibitor (e.g. heparins, fondaparinux, apixaban, rivaroxaban)
*NOT available yet*

**Aripazine (PER977)**
The ‘universal reverser...’
FXa inhibitor & oral direct thrombin inhibitor
Very groovy indeed
*Still in development*
Take Home Messages

1. In non-valvular atrial fibrillation, NOACs are preferred to warfarin (reduced stroke, mortality, and intracranial hemorrhage)

2. In VTE management, NOACs (rivaroxaban/apixaban) are as effective as warfarin and associated with less major bleeding

3. Reversal agent for dabigatran has arrived. Consider using for:
   • Life-threatening bleeding
   • Very urgent procedures

The net clinical benefit of reversal agents remains uncertain
Questions?

rzarychanski@cancercare.mb.ca
4. A 75 y.o. female with HTN, diabetes and non-valvular atrial fibrillation. Creatinine 130 mmol/L. Estimated creatinine clearance is 34 ml/min. Weight 65 kg

What agent should you use to treat her atrial fibrillation?

A. Warfarin (INR 2-3)  
B. Rivaroxaban 20 mg OD  
C. Rivaroxaban 15 mg OD  
D. Apixaban 5 mg BID  
E. Apixaban 2.5 mg BID
4. A 75 y.o. female with HTN, diabetes and non-valvular atrial fibrillation. Creatinine 130 mmol/L. Estimated creatinine clearance is 34 ml/min. Weight 65 kg

What agent should you use to treat her atrial fibrillation?
A. Warfarin (INR 2-3)
B. Rivaroxaban 20 mg OD
C. Rivaroxaban 15 mg OD
D. Apixaban 5 mg BID
E. Apixaban 2.5 mg BID