Impact of new (direct) oral anticoagulants in patient blood management

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1325-1350
Objectives

By the end of this presentation, you should be able to:

1. List new direct oral anticoagulants (DOACs) and their mechanism of action
2. Determine how to manage the DOACs perioperatively
3. Develop an approach to the management of bleeding in patients on DOACs
Case: Mrs. CC

• 76 F with non-valvular atrial fibrillation
  ▫ Poor LV function, Hypertension, Diabetes
  ▫ Creatinine clearance 50 mL/min
  ▫ No history of bleeding

• What would you recommend for stroke prophylaxis?
  A. apixaban (Eliquis)
  B. dabigatran (Pradaxa)
  C. rivaroxaban (Xarelto)
  D. warfarin
  E. I don’t know
Why New Anticoagulants?

• The problems with warfarin
  ▫ Drug interactions
  ▫ Diet interactions
  ▫ Long onset of action
  ▫ Long offset of action
  ▫ Narrow therapeutic window
  ▫ Regular lab monitoring
DOACs in AF: Meta-analysis

- apixaban (ARISTOTLE), dabigatran (RE-LY), rivaroxaban (ROCKET) trial data (N=44,563)

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Miller et al. Am J Cardiol 2012;110:453-60
<table>
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<tr>
<th>Indications</th>
<th>apixaban (Eliquis®)</th>
<th>dabigatran (Pradax®)</th>
<th>rivaroxaban (Xarelto®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thromboprophylaxis</strong></td>
<td><strong>Yes</strong></td>
<td><strong>Yes</strong></td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>after THA, TKA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stroke prevention in AF</strong></td>
<td><strong>Yes</strong></td>
<td><strong>Yes</strong></td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td><strong>DVT/PE treatment</strong></td>
<td>No</td>
<td>No</td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td><strong>ACS</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Other indications</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Medical/surgical thromboprophylaxis
- Mechanical heart valves
- Cancer, pregnancy

# ODB supported
Direct Thrombin Inhibitor e.g. dabigatran

Factor Xa Inhibitor e.g. rivaroxaban, apixaban

Oral Vitamin K antagonists e.g. warfarin
Deficiency in factors 2, 7, 9 and 10

12 → 11 → 9 → 8 → 10 → 5 → 2 → 1

Thrombin (IIa) Fibrinogen
<table>
<thead>
<tr>
<th>Property</th>
<th>dabigatran</th>
<th>rivaroxaban</th>
<th>apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target of inhibition</strong></td>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td><strong>Time to peak</strong></td>
<td>1-2 hrs</td>
<td>2-4 hrs</td>
<td>1-2 hrs</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>12-17 hrs</td>
<td>9-12 hrs</td>
<td>8-15 hrs</td>
</tr>
<tr>
<td><strong>Renal elimination</strong></td>
<td>&gt;80%</td>
<td>33% of active drug</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Liver metabolism</strong></td>
<td>Very little</td>
<td>33% (CYP3A4, 2J2)</td>
<td>75% (CYP3A4)</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Twice daily</td>
<td>Once daily</td>
<td>Twice daily</td>
</tr>
</tbody>
</table>
Case: Mrs. CC

- She is in fact on dabigatran 150 mg po BID
- Her creatinine clearance has decreased from 65 mL/min to 50 mL/min in the past year.

- Do you think she requires lab monitoring of her anticoagulant?
  A. Yes
  B. No
Dabigatran levels (RE-LY)

- Plasma concentrations obtained from 9,183 patients
  - 112 ischemic strokes
  - 323 major bleeds
- Dependent on renal function, age, weight, female gender
  - Not on ethnicity, geography, ASA, clopidogrel use
- Risk of ischemic events inversely related to trough dabigatran concentrations, with age and previous stroke as covariates
- Major bleeding increased with increased trough dabigatran levels, age, aspirin use, diabetes

Reilly et al. JACC September 2013;epub ahead of print
Dabigatran levels (RE-LY)

- Trough levels varied up to 5 fold with standard dosing
- Is there a subset of individuals that may benefit from measuring plasma levels?

Reilly et al. JACC 2013;epub ahead of print
“No lab monitoring required”

Lab monitoring might be helpful in certain situations...

• Extremes of weight – is it the right dose?

• Older age

• Renal (dabigatran) / liver dysfunction (apixaban) – do you adjust the dose?

• Drug interactions

• Dual/triple antithrombotic therapy

• Adherence check and education
Lab monitoring is necessary...

- Pre-procedure safety – elective, urgent particularly in the setting of renal/hepatic dysfunction

- Suspected underdose or overdose

  - Acute thromboembolic event
  - Bleeding
Dabigatran monitoring

**aPTT**
- Peak: 1.5-2.0x normal PTT
- May predict excess

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van Ryn – Thromb Haemost 2010;103:1116-27
Rivaroxaban monitoring

- Not linear
- Sensitivity varies with reagent
- Must be calibrated for rivaroxaban

Rivaroxaban monitoring

Anti-Xa assay

Harenberg – Sem Thromb Hemost 2012;38:178-84
Apixaban Monitoring

PT

Anti-Xa Assay

Barrett et al. Thromb Haemost 2010;104:1263-71
# Options for Laboratory Monitoring

## Monitoring of drug level

<table>
<thead>
<tr>
<th>Drug</th>
<th>Assay/Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>dabigatran</td>
<td>Hemoclot®</td>
</tr>
<tr>
<td>Factor Xa inhibitors</td>
<td>Anti-Xa assay</td>
</tr>
</tbody>
</table>

*Correlation with clinical outcomes unknown*

## Qualitative assessment of reversal

<table>
<thead>
<tr>
<th>Drug</th>
<th>Test/Assay</th>
</tr>
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<tbody>
<tr>
<td>dabigatran</td>
<td>aPTT</td>
</tr>
<tr>
<td>Factor Xa inhibitors</td>
<td>PT (not ideal)</td>
</tr>
</tbody>
</table>
Case: Mrs. CC

- Unfortunately, she is admitted with a hip fracture

- In addition to holding her dabigatran, how will you manage pre-op dabigatran?
  A. Administer 10mg IV Vitamin K
  B. Administer 10mg IV Vitamin K and PCCs
  C. Wait 12 hours
  D. Wait 2 days
  E. Wait until the PTT is normal
**dabigatran - elective procedure**

<table>
<thead>
<tr>
<th>Renal Function (CrCL, mL/min)</th>
<th>Half-life (hr)</th>
<th>Last dose pre-procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Std risk</strong></td>
</tr>
<tr>
<td>≥ 50</td>
<td>14-17h</td>
<td>2 days (skip 2 doses)</td>
</tr>
<tr>
<td>30 - 49</td>
<td>16-18h</td>
<td>3 days (skip 4 doses)</td>
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* Use of dabigatran contraindicated if CrCl < 30 mL/min

### Oral Xa inhibitors - Elective procedure

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<tr>
<th>Renal Function (CrCL, mL/min)</th>
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<th>High risk</th>
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<tr>
<td>* Use contraindicated if CrCl &lt; 30 mL/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rivaroxaban (OD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 30</td>
<td>8-9h</td>
<td>2 days (skip 1 dose)</td>
<td>3 days (skip 2 doses)</td>
<td></td>
</tr>
<tr>
<td>apixaban (BID)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 50</td>
<td>7-8h</td>
<td>2 days (skip 2 doses)</td>
<td>3 days (skip 4 doses)</td>
<td></td>
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<tr>
<td>30-50</td>
<td>17-18h</td>
<td>3 days (skip 4 doses)</td>
<td>4 days (skip 6 doses)</td>
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When is it safe to do surgery?

- Dabigatran
  - If PTT normal, unlikely to be significant bleeding risk
  - Hemoclot® Assay helpful (if available)

- Rivaroxaban & apixaban
  - We do not know that a normal PT = no bleeding risk
  - Make sure you know the performance of your local institutional assays
  - Anti-Xa assay for rivaroxaban/apixaban helpful (if available)
Case: Mrs. CC

- Unfortunately, she is admitted with a hip fracture

- How will you manage pre-op dabigatran?
  - Hold dabigatran and...
    A. Administer 10mg IV Vitamin K
    B. Administer 10mg IV Vitamin K and PCCs
    C. Wait 12 hours
    D. Wait 2 days
    E. Wait until the PTT is normal
      - consider bleeding risk / clearance / urgency of surgery
Case: Mrs. CC

- Her last dose was 24 hours ago. Her PTT is normal.
- She goes to OR the next AM without complications.

- How will you manage her post-op DVT prophylaxis?
Post-Procedure Management

- Dictated almost entirely by bleeding risk (vs. the risk of thrombosis)
- Consider starting a prophylaxis dose until bleeding risk ↓
  - Dabigatran 150mg OD
  - Rivaroxaban 10mg OD
- Or LMWH until bleeding risk ↓

DVT prophylaxis with LMWH or prophylactic dose of NOAC

Restart NOAC at therapeutic doses

NOAC (stop 1-2 days preop if renal function normal)
Case: Mrs. CC

- The story ends there but what if...
- She came back a few weeks later with ICH

After discontinuing the drug and supportive care (fluids, monitoring), how would you treat this patient?

A. Antifibrinolytic (tranexamic acid, EACA)
B. Frozen plasma
C. Prothrombin complex concentrates
D. Activated prothrombin complex concentrates
E. Recombinant factor VIIa
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Miller et al. Am J Cardiol 2012;110:453-60
Management of Bleeding on DOACs

• Discontinue drug
  ▫ Check time of last dose
  ▫ Estimate half-life of drug (based on renal/liver function)
  ▫ Estimate anticoagulant activity (labs)

• General measures
  ▫ Local hemostasis (compression, angiography, surgery)
  ▫ Crystalloids for hemodynamic support
  ▫ RBC and plt transfusion as needed
  ▫ Do not use FP (plasma) unless factor deficiency too
Management of Bleeding on DOACs

- **dabigatran**
  - Activated charcoal if < 2 hours: in vitro study showing 99.9% adsorbed
  - Hemodialysis removed 62% at 2 hr and 68% at 4 hr

- **rivaroxaban and apixaban**
  - Activated charcoal
  - Not removed by hemodialysis

van Ryn et al. ASH abstract 2009
Management of Bleeding on DOACs

• If life-threatening bleeding??
• NO ANTIDOTE!

• Options
  ▫ ?? Tranexamic acid: locally/topically/systemic
  ▫ ?? Prothrombin complex concentrates
  ▫ ?? FEIBA (activated PCCs, mainly VIIa)
  ▫ ?? Recombinant factor VIIa
Reversal with PCCs

- Dabigatran 150 mg PO BID or rivaroxaban 20 mg QD x 2½ days in 12 healthy volunteers treated with PCC 50 units/kg

Reversal of dabigatran and rivaroxaban

- 10 healthy male subjects
- One dose of dabi 150mg or riva 20mg
- Measured in vitro tests
- dabigatran
  - Low doses PCC or FEIBA normalized ETP (higher doses caused over correction)
  - Higher doses FEIBA required to normalize lag time

Marlu et al. Thromb Haemost 2012;epub May 25
dabigatran = Direct Thrombin
Inhibitor

Factor Xa Inhibitor

e.g. rivaroxaban, apixaban

Thrombin

Fibrinogen

Potential specific antidotes in development – not yet available

Antidote aDabi-Fab r-Antidote

Patient with bleeding on dabigatran

- Last dose?
- CBC, creatinine, aPTT*

If aPTT ≥40 sec, consult TE or Transfusion Medicine

Mild bleeding
- Local hemostatic measures
- Hold dabigatran

Moderate-severe Bleeding*
- Manage bleeding (compression, surgery)
- Fluid → diuresis
- Transfuse RBCs or platelets if needed (follow Sunnybrook guidelines)
- Oral charcoal if dose <2 hrs before

Life-threatening Bleeding*
- Contact Transfusion Medicine or Thromboembolism
- Tranexamic acid (1g bolus then 1g over 8h)
- Hemodialysis might be helpful
- Consider FEIBA

*DO NOT TRANSFUSE plasma to reverse ↑ aPTT

*Provides qualitative assessment
Patient with bleeding on rivaroxaban

- Last dose?
- CBC, creatinine, PT*

If PT $\geq 15$ sec, consult TE or Transfusion Medicine

**Mild bleeding**
- Local hemostatic measures
- Hold dabigatran

**Manage bleeding** (compression, surgery)
- Fluid $\rightarrow$ diuresis
- Transfuse RBCs or platelets if needed (follow Sunnybrook guidelines)
- Oral charcoal if dose $<2$ hrs before

**Threatening Bleeding**
- Contact Transfusion Medicine or Thromboembolism
- Tranexamic acid (1g bolus then 1g over 8h)
- Consider PCC

*DO NOT TRANSFUSE plasma to reverse ↑ PT

*Provides qualitative assessment

Update Regularly
Summary
New Direct Oral Anticoagulants

12 → 11 → 9 → 8

Factor Xa Inhibitor e.g. Rivaroxaban, Apixaban

10 → 5 → 2 → 1

Direct Thrombin Inhibitor e.g. Dabigatran

7

Thrombin (IIa) Fibrinogen
What we are still learning...

- How to monitor effects of DOACs
- What to do in the perioperative setting: consider half-life / clearance / bleeding risk
  - Which lab tests might be useful
- How to manage bleeding
  - No antidote or proven reversal agent (yet)
Thank You!