New Oral Anticoagulants in Everyday Practice:
Addressing Common Clinical Scenarios and Questions…
not covered by the big trials

James Douketis, MD, FRCPC
Specialty: Internal Medicine
Professor, Department of Medicine, McMaster University, Staff, General Internal Medicine and Vascular Medicine
St. Joseph's Health Care, Hamilton, ON
Faculty/Presenter Disclosure

• Faculty Name: Dr James Douketis
• Relationships with commercial interests:
  ▪ Consulting Fees/Honoraria: Scientific advisor for Bristol-Myers Squibb-Pfizer, Bayer, Boehringer-Ingelheim, Biotie, Medicine.ca
  ▪ Officer, Director, Or In Any Other Fiduciary Role:
  ▪ Clinical Trials: NIH, CIMR, HSF, Portola Pharmaceuticals
  ▪ Ownership/Partnership/Principal:
  ▪ Intellectual Property Rights:
  ▪ Other Financial Benefit:
Disclosure of Commercial Support

• This program has NOT received any financial support
• This program has been created solely by Thrombosis Canada without the input of any commercial or non-commercial organization

Potential for conflict(s) of interest:
• Dr. James Douketis has received funding from Bayer Canada whose product(s) are being discussed in this program.
• The following companies make thrombolytic agents that may be mentioned in this talk:
  Bayer Canada, Bristol-Myers Squibb-Pfizer, Boehringer-Ingelheim
Mitigating Potential Bias

• This program has been created solely by Thrombosis Canada, a registered non-profit, non-commercial organization.

• This program has been peer reviewed by Thrombosis Canada and the College of Family Physicians of Canada.

• No commercial or other non-commercial organization have had any input to the content of this program.

• No commercial or other non-commercial organization have been present at or privy to any discussions, meetings, or other activities related to the content of this program.
Learning Objectives

After attending this session, participants will:

• Have an approach to the management of NOAC-treated patients who need an elective or urgent surgery/procedure and the use and interpretation of coagulation tests in the perioperative setting;

• Have an approach to the management of NOAC-treated patients with minor or more serious bleeding;

• Be able to address common "what ifs" relating to NOAC use.
Preoperative Management of Patients Receiving New Anticoagulants: Which drugs, what doses?

- **Dabigatran**
  - DVT prophylaxis….150 mg or 220 mg OD
  - AF…………………110 mg or 150 mg BID

- **Rivaroxaban**
  - DVT prophylaxis….10 mg OD
  - VTE treatment………15 mg BID x 3 weeks, 20 mg OD x 9 weeks
  - AF…………………… 20 mg OD (15 mg OD if CrCl 30-50 mL/min)

- **Apixaban**
  - DVT prophylaxis…. 2.5 mg BID
  - AF……………………5 mg BID (2.5 mg BID if 2/3 of: age>80, wt <60, creat >133)
Pros and Cons of NOACs

Pros:
- Rapid onset
- Predictable effect
- Specific target
- Few food / drug interactions
- Short half-life

Cons:
- Renal elimination
- Difficult to monitor
- Potential for overuse
- High cost
- Short half-life
- No antidote

Rapid onset
Predictable effect
Specific target
Few food / drug interactions
Short half-life
Case #1:  
**Minor Procedure**

- A 68 year old female on apixaban for SPAF (normal renal function) needs 2 dental extractions that will include local anesthetic injections…

How do you manage peri-procedure?

She also takes ASA to prevent a first heart attack and stroke. Is this appropriate?
ACCP 2012 Recommendation: In patients who require minor dental surgery and are receiving VKA therapy, we suggest either continuing VKA with co-administration of an oral prohemostatic agent or stopping VKAs 2-3 days before the procedure instead of alternative strategies (Grade 2C).

Recommendations for NOACs?
- No evidence-based guidelines
- Probably reasonable to continue apixaban and give pro-hemostatic mouthwash
- Equally reasonable to stop 24 hours before procedure
Combining NOACs and Antiplatelet Drugs

- Increased risk for bleeding with dabigatran and AP drugs
  - concomitant use of a single antiplatelet drug increased risk of major bleeding: HR = 1.60 (95% CI: 1.42-1.82)
  - concomitant use of two antiplatelet drugs conferred higher risk for major bleeding: HR = 2.31 (95% CI:1.79-2.98)

- Increased risk for bleeding with apixaban and ASA

Clinical Guide Sources

• NOACs and Perioperative Management

• Related Guides:
  ▪ Dabigatran
  ▪ Rivaroxaban
  ▪ Apixaban
Case #2: Elective Surgery

- 78-year old female with atrial fibrillation receiving dabigatran, 150 mg BID
- CHADS score = 4 (prior TIA, age >75 yrs, hypertension)
- Scheduled for elective hip replacement and is to receive spinal/epidural anesthesia
- weight = 65 kg
- serum creatinine = 120 umol/L
- CrCl = 35 mL/min (moderate renal insufficiency)
What to do pre-operatively with dabigatran?

1. Stop dabigatran 1 day before surgery (skip 2 doses)
2. Stop dabigatran 4 days before surgery (skip 8 doses)
3. Stop dabigatran 5 days before surgery and administer therap-dose LMWH bridging (enox. 1 mg/kg BID) starting 3 days pre-op.
4. Stop dabigatran 5 days before surgery and administer low-dose LMWH bridging (dalt. 5000 IU OD) starting 3 days pre-op.
## Pre-operative Management of Dabigatran

<table>
<thead>
<tr>
<th>Renal function (CrCl)</th>
<th>Estimated half-life (hrs)</th>
<th>Stop dabigatran</th>
<th>Before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50 mL/min (mild dysfunction or normal)</td>
<td>14-17</td>
<td>2-3 days</td>
<td>1 day</td>
</tr>
<tr>
<td>30 to &lt;50 mL/min (moderate dysfunction)</td>
<td>18-24</td>
<td>4 days</td>
<td>2-3 days</td>
</tr>
<tr>
<td>&lt;30 mL/min (severe dysfunction)</td>
<td>&gt;24</td>
<td>&gt;5 days</td>
<td>2-5 days</td>
</tr>
</tbody>
</table>

High Bleeding-Risk Surgery/Procedures

- Urologic: TURP, bladder resection, nephrectomy or kidney biopsy (untreated damage after TURP and urokinase release)
- Pacemaker or ICD implantation (separation of infraclavicular fascia and no suturing of unopposed tissues)
- Colonic polyp resection, especially >1-2 cm sessile polyps (bleeding occurs at transected stalk after hemostatic plug release); ERCP and sphincterotomy
- Vascular organ surgery: thyroid, liver, spleen
- Bowel resection (bleeding at anastomosis site)
- Major surgery: cancer surgery, arthroplasty, reconstructive
- Cardiac, intracranial or spinal surgery (small bleeds can have serious clinical consequences)
Effect of Dabigatran on aPTT after Interruption

What to do post-operatively?
(N.B. bleeding as expected)

1. Resume dabigatran 150 mg BID on evening after surgery
2. Resume dabigatran, 150 mg BID, 24 hrs after surgery (evening of 1\textsuperscript{st} post-op day)
3. Resume dabigatran, 150 mg BID, on 3\textsuperscript{rd} post-op day.
4. Start low-dose LMWH bridging (dalt. 5000 IU daily) within 24 hrs post-op and resume dalteparin, 150 mg BID, on 3\textsuperscript{rd} post-op day.
# Post-operative Management of Dabigatran

<table>
<thead>
<tr>
<th>Surgery Type</th>
<th>Suggested Approach</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major (or high bleed risk) surgery</td>
<td>resume 150 mg BID 48-72 hrs post-op</td>
<td>substitute 75 or 150 mg dose <em>once-daily</em> for 2-3 days</td>
</tr>
<tr>
<td>Minor (or low bleed risk) surgery</td>
<td>resume 150 mg BID 24 hrs post-op</td>
<td>resume 24-48 hrs post-op</td>
</tr>
</tbody>
</table>

Anticoagulant Interruption in RE-LY Patients

- 4,591 (25% of all) patients studied with *first* treatment interruption for a surgery/procedure (8% urgent)

- Surgery/procedure types:
  - 22% diagnostic (e.g., colonoscopy)
  - 10% pacemaker/ICD insertion
  - 10% dental
  - 9% cataract
  - 6% joint replacement
  - 43% other surgery (minor/major)

Perioperative Dabigatran Management in RE-LY

• Pre-operative
  ▪ patients either STOPPED dabigatran 24 hrs pre-op or according to specific nomogram
  ▪ last dose dabigatran given 49 hrs (range: 35-85) pre-op
  ▪ last dose warfarin given 114 hrs (range: 87-114) pre-op

• Post-operative
  ▪ anticoagulation resumed at discretion of treating physician, when hemostasis secured

Anticoagulant Interruption in RE-LY

Major Bleeding

- Any surgery/procedure: No significant difference in bleeding
  - dabigatran, 110 mg...... 3.8%
  - dabigatran, 150 mg...... 5.1%
  - warfarin.................... 4.6%

- Urgent surgery/procedure: No significant difference in bleeding
  - dabigatran, 110 mg...... 17.8%
  - dabigatran, 150 mg...... 17.7%
  - warfarin.................... 21.6%

- Incidence of stroke or TE low (<0.5%) and not significantly different between treatment arms

Clinical Guide Sources

• NOACs and Perioperative Management
• NOACs and Laboratory Monitoring

• Related Guides:
  ▪ Dabigatran
  ▪ Rivaroxaban
  ▪ Apixaban
Case #3: Urgent Surgery

- 60-year old woman with bioprosthetic mitral valve and atrial fibrillation on rivaroxaban 20 mg OD, falls and fractures her hip.
- Presents to ER on Friday at 1PM and requires urgent (ideally within 24 hrs) hip repair...her last rivaroxaban dose was 4 hrs ago.
- INR = 1.8
- weight = 65 kg, creatinine = 100 umol/L, CrCL = 52 mL/min

What do you do to get her ready for surgery?

Is it OK to use NOACs with bioprosthetic valve?
What to do pre-operatively?

1. Give 30 IU/kg PCC and take to OR that evening
2. Give 4 units FFP and take to OR that evening
3. Wait 24 hrs after last rivaroxaban dose and take to OR (on Sat. AM)
4. Wait 2 days after last rivaroxaban dose and take to OR.
5. Wait 5 days after last dose and take to OR
Correlation between PT and Plasma Rivaroxaban Levels

Step 1: prothrombin time (PT)
- if elevated PT, likely some rivaroxaban effect
- if normal PT, no significant rivaroxaban effect
- PT not good to reflect apixaban anticoagulant effect!

Step 2: anti-factor Xa assay
- more precise measurement, but…
- not widely-available

What about Dabigatran’s Effect on Coagulation Tests?

**Hemoclot test**

- Linear fit: $y = 31.44 + 0.1437x$
- 95% Prediction interval

**PT (INR)**

- Equation: $y = 1.047 + 0.00246x$
- $r^2 = 0.8459$

**Thrombin time**

- Equation: $y = 2.4040 + 0.05851x$
- $r^2 = 0.8568$

**aPTT**

- Equation: $y = 0.86 + 0.06873x^{1/2}$
- $r^2 = 0.8514$
Peri-procedure Laboratory Monitoring of Dabigatran

- **Step 1: partial thromboplastin time (aPTT)**
  - if elevated aPTT, likely some dabigatran effect
  - if normal aPTT, no significant dabigatran effect

- **Step 2: thrombin time (TT) or Hemoclot test (dilute TT)**
  - if normal TT (<30 sec) no dabigatran effect but TT is too sensitive and detects clinically unimportant levels…avoid TT!
  - Hemoclot test is more precise but, not widely available

Case #4: *Minor bleeding*

- 82-yr female, fully independent, with AF was switched from warfarin to apixaban, 2.5 mg BID, due to recurrent bruising
- ‘petit’ body habitus, frail skin, weight = 55 kg

Presents with ‘red eye’ – what do you do with apixaban?

Patient ask you about a family member with a mechanical aortic valve who want to take a NOAC instead of warfarin?

N.B. reduced apixaban dose since 2 of:

1) wt <60 kg;
2) >80 yrs;
3) creatinine >133 umol
NOACs for Mechanical Heart Valves?

- Phase 2 (RE-ALIGN) trial assessed dabigatran (150 mg or 300 mg BID) after mechanical aortic/mitral valve replacement vs warfarin (INR: 2.5-3.5)
- Trial stopped (252 patients recruited) due to increased stroke/valve thrombosis and bleeding

...why more clots in mechanical heart valve patients?
What is the Mechanism for NOAC-associated Valve Thrombosis?

Intrinsic Pathway
- XIIa
- XIa
- IX
- IXa
- X
- Xa
- Thrombin (IIa)

Extrinsic Pathway (tissue factor)
- VIIa
- TFPI

Direct Activation:
- apixaban/rivaroxaban

Inhibitors:
- dabigatran

Clot Formation:
- Thrombin-Fibrin Clot
Case #5: 
**Serious bleeding**

- 74-year-old male with AF and hypertension, type 2 diabetes, obesity presents with upper GI bleed on Friday, 5PM
  - BP = 100/60 mmHg, HR = 110/min
  - Hgb = 72 g/L
  - aPTT = 59, INR = 1.3, TT >150 sec
  - CrCl = 55 mL/min

- Receiving dabigatran, 150 mg BID (last dose at 11AM)

---

**How to manage the bleeding?**

---

**After bleeding resolves, would you change from dabigatran to another NOAC or to warfarin?**
Summary of (Non-clinical) Studies Assessing PCCs/rfVIIa to Reverse NOAC Effect

• Relationship between anticoagulation and prediction of cessation of bleeding not well understood with NOACs

• PCCs and rFVIIa may be effective at least with dabigatran and rivaroxaban-induced bleeding…*but no clinical data!*

• Many study limitations:
  - animal data may not be reflective of clinical practice
  - healthy volunteer studies do not induce bleeding
  - lack of clinical data in urgent clinical situations
Clinical Guide Sources

- NOACs and Bleeding
- Related Guides:
  - Dabigatran
  - Rivaroxaban
  - Apixaban
Pooled analysis of 5 RCTs
Is a major bleed worse in dabigatran- or warfarin-treated patients?

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Mortality dabigatran*</th>
<th>Mortality warfarin*</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with major bleeds, n**</td>
<td>627</td>
<td>407</td>
<td></td>
</tr>
<tr>
<td>Age &lt;75 years</td>
<td>8.4%</td>
<td>12.9%</td>
<td>0.62 (0.34–1.12)</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>9.8%</td>
<td>13.2%</td>
<td>0.72 (0.42–1.25)</td>
</tr>
<tr>
<td>CrCl ≥50 mL/min</td>
<td>9.6%</td>
<td>13.2%</td>
<td>0.69 (0.42–1.15)</td>
</tr>
<tr>
<td>CrCl &lt;50 mL/min</td>
<td>8.9%</td>
<td>12.9%</td>
<td>0.66 (0.34–1.29)</td>
</tr>
<tr>
<td>ASA</td>
<td>8.8%</td>
<td>10.0%</td>
<td>0.86 (0.38–2.04)</td>
</tr>
<tr>
<td>No ASA</td>
<td>9.5%</td>
<td>14.0%</td>
<td>0.64 (0.41–1.02)</td>
</tr>
</tbody>
</table>

*Data combined from dabigatran 150 mg and 110 mg BID groups. Only first major bleed included. Analysis not adjusted for covariates

**1,121 major bleeds in 1,034 patients

Take-home Messages

Approach to perioperative management based on:
- drug half-lives (9-17 hrs) and rapid peak effect (1-3 hrs)
- effect of renal function
- surgery/procedure type and risk for bleeding

Use and interpretation of coagulation tests:
- rivaroxaban: PT (screen), anti-factor Xa (quantitative)
- apixaban: anti-factor Xa
- dabigatran: aPTT (screen), dilute TT/Hemoclot (quantitative)
...More Take-home Messages

Approach to bleeding based on:
- treat as any anticoagulant-related bleed (if minor or major)
- PCC may be helpful if life-threatening bleeding

Approach to patients with CAD who are taking NOAC:
- use ASA only if coronary stent/recent ACS
- avoid ASA for primary prevention
Final Take-home Messages!

Other ‘what ifs’:

- **OK** to use NOACs for:
  - most valvular HD (except mod-to-severe mitral stenosis?)
  - bioprosthetic HV (assuming another indication for NOAC)

- **not OK** to use NOACs for:
  - any mechanical HV (RCT-proven harm)
  - splanchnic/UE vein thrombosis (other treatments)
  - superficial thrombosis (other proven treatments)
  - cancer-associated VTE (unless exceptional circumstances)
Question Period