Management of Bleeding and Practical Management of New Oral Anticoagulants

Anna Rahmani
October 2, 2014
CONFLICT OF INTEREST: NONE
Overview:

- Background on the new oral anticoagulants (NOACs)
- Approved NOACs in Canada
- Perioperative management of NOACs
- Laboratory Monitoring
- Management of Bleeding
**warfarin**

- multiple interaction with food, alcohol and other drugs
- require frequent laboratory monitoring
- narrow therapeutic window
- quality of anticoagulation is calculated by estimating total proportion of time that INR is within therapeutic range (TTR)
- TTR is estimated to be at 64%

**Heparin**

- parenteral administration
- need for frequent monitoring
- Heparin-induced Thrombocytopenia
- LMWH are limited due to their parenteral administration, limitation of use in extreme obesity and in renal failure
Characteristics of an ideal anticoagulant

- Orally administered
- Once a day dosing
- Fixed dose
- Rapid onset and off-set of action
- Wide therapeutic range
- No need for therapeutic monitoring
- Low propensity for food and drug interaction
- Predictable pharmacodynamics and pharmacokinetics.
New Oral Anticoagulants

- Rivaroxaban (Xarelto)
- Apixaban (Eliquis)
- Edoxaban (Savaysa)
- Betrixaban (phase III)
- Dabigatran (Pradaxa)
Extrinsic Pathway (Tissue factor)

- VII
- TF-Villa Complex

Common Pathway
- Xa
- Ca^{2+} Phospholipids

Intrinsic Pathway (Contact Activation)

- Xlla
- Xla
- IXa
- VIIIa

Activated protein C

- Fibrinogen (I)
- Fibrin (Ia)
- Stable clot, Fibrin cross linked

Platelet aggregation
- Loose platelet plug

Platelet activation
- vWF adheres platelets to injury
Rivaroxaban
Apixaban
Edoxaban
Betrixaban

Extrinsic Pathway (Tissue factor)

VII

TF-Villa Complex

Intrinsic Pathway (Contact Activation)

XIIa
Xla
IXa
VIIla

Common Pathway

Xa

Ca²⁺ + Phospholipids

Va

Activated protein C

Fibrinogen (I)

Fibrin (Ia)

XIIIa

Stable clot, Fibrin cross linked

Prothrombin (II)

Platelet aggregation
Loose platelet plug

Platelet activation

vWF adheres platelets to injury

Dabigatran
<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Edoxaban</th>
<th>Apixaban</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of Action</strong></td>
<td>Direct factor Xa inhibitor</td>
<td>Direct thrombin inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>80%</td>
<td>62%</td>
<td>50%</td>
<td>6.5%</td>
</tr>
<tr>
<td><strong>Renal Excretion</strong></td>
<td>30%</td>
<td>50%</td>
<td>25%</td>
<td>80%</td>
</tr>
<tr>
<td><strong>Peak Serum concentration</strong></td>
<td>2.5 - 4 hrs</td>
<td>1-2 hrs</td>
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</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>5 - 9 hrs</td>
<td>9 - 11 hrs</td>
<td>12 hrs</td>
<td>12 - 17 hrs</td>
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</tbody>
</table>

- Lack reversibility
- No reliable laboratory tests
- Depend on renal excretion
DABIGATRAN

Dabigatran vs. warfarin in patients with atrial fibrillation

**RE-LY** (NEJM Sep 17, 2009 361:1139)

Dabigatran vs. warfarin in patients with mechanical heart valves.

**RE-ALIGN** (NEJM Sep 27, 2013 369:1206)

Dabigatran etexilate vs. enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomized, double-blind, non-inferiority trial

**RE-NOVATE** (The Lancet Sep 15 2007 370:949)

Oral Dabigatran vs. enoxaparin for thromboprophylaxis after primary total hip arthroplasty

**RE-NOVATE II** (Journal of Thrombosis and Haemostasis Jan 12, 2011 105:721)

Oral Dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial

**RE-MODEL** (Journal of Thrombosis and Haemostasis Aug 2007 5:2178)

Dabigatran vs. warfarin in the treatment of acute venous thromboembolism

**RE-COVER** (NEJM Dec 10, 2009 361:2342)
Dabigatran vs, warfarin in patients with mechanical heart valves.

**RE-ALIGN** (NEJM Sep 27, 2013 369:1206)

- Phase 2, dose validation study looking at use of dabigatran in patient with mechanical heart valves in Mitral or Aortic position.

- Trial was terminated prematurely due to excessive rate of bleeding and thromboembolic events in the dabigatran group.
**RIVAROXABAN**

Rivaroxaban vs. warfarin in nonvalvular atrial fibrillation

**ROCKET AF** *(NEJM Sep 8, 2011 365: 883)*

Rivaroxaban in patients with a recent acute coronary syndrome

**ATLAS ACS 2-TIMI 51** *(NEJM Jan 5, 2012 366: 9)*

Rivaroxaban vs. enoxaparin for thromboprophylaxis after hip arthroplasty

**RECORD 1** *(NEJM June 26, 2008 358:2765)*

Extended duration rivaroxaban vs. short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomized controlled trial

**RECORD 2** *(The Lancet July 5, 2008 372: 31)*

Rivaroxaban vs. enoxaparin for thromboprophylaxis after total knee arthroplasty.

**RECORD 3** *(NEJM June 26, 2008 358: 2776)*

Rivaroxaban vs. enoxaparin for thromboprophylaxis after total knee arthroplasty: a randomised trial

**RECORD 4** *(The Lancet May 5, 2009 373:1673)*

Oral rivaroxaban for symptomatic venous thromboembolism

**EINSTEIN** *(NEJM Dec 23, 2010 363: 2499)*
APIXABAN

Apixaban vs. warfarin in patients with atrial fibrillation

ARISTOTLE  (NEJM Sep 1, 2011 365: 981)

Apixaban an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: Results of the apixaban for prevention of acute ischemic and safety events (APPRAISE) trial

APPRAISE  (Circulation March 24, 2009 119: 2877)

Apixaban with antiplatelet therapy after acute coronary syndrome


Apixaban in patients with atrial fibrillation

AVERROSES  (NEJM March 3, 2011 364: 806)

Apixaban vs. enoxaparin for thromboprophylaxis after hip replacement

ADVANCE-3  (NEJM Dec 23, 2010 363:2487)

Apixaban vs. enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial

ADVANCE-2  (The Lancet March 6, 2010 375: 807)

Apixaban for the treatment of acute venous thromboembolism

AMPLIFY  (NEJM Aug 29, 2013 369: 799)

Apixaban vs. enoxaparin for thromboprophylaxis in medically ill patients

ADOPT  (NEJM Dec 8, 2011 365: 2167)
EDOXABAN

Edoxaban vs. warfarin in patients with atrial fibrillation
**ENGAGE-TIMI 48** *(NEJM Oct 10, 2013)*

Edoxaban vs. Warfarin for the treatment of symptomatic venous thromboembolism.
**HOKUSAI-VTE** *(NEJM Nov 28, 2013)*

Edoxaban for prevention of venous thromboembolism after major orthopaedic surgery.
*Orthopaedic research and reviews*  May 2012
Current indications for clinical use

• *Non-valvular* atrial fibrillation

• Venous thromboembolism

• Post-operative hip and knee arthroplasty prophylaxis
<table>
<thead>
<tr>
<th></th>
<th>DABIGATRAN</th>
<th>RIVAROXABAN</th>
<th>APIXABAN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-valvular Atrial Fibrillation</strong></td>
<td><strong>YES</strong></td>
<td><strong>YES</strong></td>
<td><strong>YES</strong></td>
</tr>
<tr>
<td><strong>DVT and PE</strong></td>
<td><strong>YES</strong></td>
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<td><strong>Total Hip and knee arthroplasty</strong></td>
<td><strong>YES</strong></td>
<td><strong>YES</strong></td>
<td><strong>YES</strong></td>
</tr>
</tbody>
</table>

NOACs are contraindicated in pregnancy and in treatment of mechanical heart valves (RE-ALIGN).
Non-valvular atrial fibrillation
| **Dabigatran**  
RE-LY                                | **Rivaroxaban**  
ROCKET-AF                          | **APIXABAN**  
ARISTOTLE                        |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Double blind comparison between the two doses, but unblinded comparison between warfarin and dabigatran</td>
<td>Double-blind, double dummy</td>
<td>Double-blind, double dummy</td>
</tr>
</tbody>
</table>
| 110 mg BID non-inferior to warfarin  
150 mg BID superior to warfarin at TTR 64% | 20 mg QD non-inferior to warfarin at TTR 55% | 5 mg BID superior to warfarin  
TTR 62% |
| Mean CHADS  
20% of patients with stroke or TIA | Mean CHADS  
~ 54% of patient with stroke or TIA | Mean CHADS  
20% of pt with stroke or TIA |
| Higher rate of GI bleed  
Higher incidence of dyspepsia | Higher rate of GI bleed | Lower rate of Bleed |
| Lower rate of intracranial bleed  
Lower rate of hemorrhagic stroke | Lower rate of intracranial bleed  
Lower rate of hemorrhagic stroke | Lower rate of intracranial bleed and hemorrhagic stroke |

**NOTE:** As compare to warfarin and not to each other
<table>
<thead>
<tr>
<th><strong>Dabigatran</strong></th>
<th><strong>Rivaroxaban</strong></th>
<th><strong>Apixaban</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher rate of MI</td>
<td>Similar MI profile</td>
<td>Similar MI profile</td>
</tr>
<tr>
<td>Limited to patients with CrCl &gt; 30cc/min</td>
<td>Limited to patients with CrCl &gt; 30cc/min</td>
<td>Limited to patients with CrCl &gt; 25cc/min Some data on Stage III CKD</td>
</tr>
<tr>
<td>BID dosing Longer half-life</td>
<td>QD dosing Shorter half-life Increased event rate during transition to coumadin</td>
<td>BID dosing Longer half life</td>
</tr>
<tr>
<td>Must be stored in original packaging and used within 120 days</td>
<td>Can be dispensed in blister pack</td>
<td>Can be dispensed in blister pack</td>
</tr>
<tr>
<td>No reversing agent</td>
<td>No reversing agent</td>
<td>No reversing agent</td>
</tr>
<tr>
<td>Cost ~ $110/month</td>
<td>Cost ~$100</td>
<td>Cost ~ $190</td>
</tr>
</tbody>
</table>

**NOTE:** As compare to warfarin and not to each other
## Non-valvular Atrial Fibrillation

### As compared to warfarin

<table>
<thead>
<tr>
<th>Drug</th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or systemic embolism</td>
<td>150 mg BID superior 110 mg BID non-inferior</td>
<td>20 mg QD non-inferior</td>
<td>5 mg BID superior</td>
</tr>
<tr>
<td><strong>Hemorrhagic stroke</strong></td>
<td>Superior 110 mg 150 mg</td>
<td>Superior</td>
<td>Superior</td>
</tr>
<tr>
<td><strong>Safety endpoint:</strong></td>
<td>Major bleed</td>
<td>110 mg superior</td>
<td>Decrease critical and fatal bleeding</td>
</tr>
<tr>
<td><strong>Intracranial bleed</strong></td>
<td>superior</td>
<td>Superior</td>
<td>Superior</td>
</tr>
</tbody>
</table>
NOACs in Real Life

- All three new oral anticoagulants are approved for prevention of stroke and systemic embolism in non-valvular atrial fibrillation by Health Canada.

- Let’s have a look beyond the excellent results.

- Direct comparison of requires very large numbers.
Indirect Comparisons of New Oral Anticoagulant Drugs for Efficacy and Safety When Used for Stroke Prevention in Atrial Fibrillation

Gregory Y. H. Lip, MD,*† Torben Bjerregaard Larsen, MD, PhD,†‡ Flemming Skjøth, PhD,†‡ Lars Hvilsted Rasmussen, MD, PhD†‡

Birmingham, United Kingdom; and Aalborg, Denmark
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Table 2
Risk Differences and Confidence Intervals, in Relation to Differences in the Study Populations at Baseline

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>RE-LY (N = 18,113)</th>
<th>ROCKET-AF (N = 14,264)</th>
<th>ARISTOTLE (N = 18,201)</th>
<th>RE-LY vs. ROCKET-AF</th>
<th>RE-LY vs. ARISTOTLE Percent Point (% Study 1; % Study 2)</th>
<th>ROCKET-AF vs. ARISTOTLE Percent Point (% Study 1; % Study 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs*</td>
<td>71.5 ± 8.7</td>
<td>73 [65-78]</td>
<td>70 [63-76]</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Female, %</td>
<td>36.4</td>
<td>39.7</td>
<td>35.2</td>
<td>—</td>
<td>1.1 (0.2; 2.2)</td>
<td>4.5 (3.3; 5.5)</td>
</tr>
<tr>
<td>CHADS2, mean</td>
<td>2.2</td>
<td>3.5</td>
<td>2.1</td>
<td>—</td>
<td>1.26 (1.28; 1.28)</td>
<td>—</td>
</tr>
<tr>
<td>CHADS2 3-6, %</td>
<td>32.5</td>
<td>87.0</td>
<td>30.2</td>
<td>—</td>
<td>56.7 (55.9; 57.6)</td>
<td>—</td>
</tr>
<tr>
<td>Paroxysmal AF, %</td>
<td>32.8</td>
<td>17.6</td>
<td>15.3</td>
<td>—</td>
<td>15.2 (14.3; 16.1)</td>
<td>2.3 (1.5; 3.1)</td>
</tr>
<tr>
<td>Prior stroke, TIA,</td>
<td>20.0</td>
<td>54.8</td>
<td>19.4</td>
<td>—</td>
<td>35.3 (34.3; 36.3)</td>
<td>—</td>
</tr>
<tr>
<td>or systemic embolism, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19.4 (13.9; 16.0)</td>
<td>—</td>
</tr>
<tr>
<td>Heart failure, %</td>
<td>32.0</td>
<td>62.5</td>
<td>35.4</td>
<td>—</td>
<td>27.0 (26.0; 28.1)</td>
<td>—</td>
</tr>
<tr>
<td>Prior myocardial infarction, %</td>
<td>16.6</td>
<td>17.3</td>
<td>14.2</td>
<td>—</td>
<td>2.4 (1.6; 3.1)</td>
<td>3.1 (2.3; 3.9)</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>23.3</td>
<td>40.0</td>
<td>25.0</td>
<td>—</td>
<td>14.9 (13.9; 16.0)</td>
<td>—</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>78.9</td>
<td>90.5</td>
<td>87.5</td>
<td>—</td>
<td>3.1 (2.9; 3.7)</td>
<td>—</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin, %</td>
<td>39.8</td>
<td>36.5</td>
<td>30.9</td>
<td>—</td>
<td>8.8 (7.8; 9.8)</td>
<td>5.5 (4.5; 6.6)</td>
</tr>
<tr>
<td>Vitamin K antagonist, %</td>
<td>49.6</td>
<td>62.4</td>
<td>57.2</td>
<td>—</td>
<td>7.5 (8.5; 6.5)</td>
<td>5.3 (4.2; 6.3)</td>
</tr>
</tbody>
</table>

*Table includes only patients aged ≥65 years at entry to the trial. **The CHADS2 study population in efficacy endpoints summarized in Online Table 2. **Relative safety of dabigatran, apixaban, and rivaroxaban.
All NOACs compared to warfarin

- Lower stroke and systemic embolism by 21%
- Lower hemorrhagic stroke by 53%
- Lower intracranial bleeding by 51%
Primary efficacy endpoint

- For preventing stroke and systemic embolism:
  - Apixaban ~ Dabigatran (both doses)
  - Apixaban ~ Rivaroxaban
  - Rivaroxaban ~ Dabigatran 110mg
Primary Safety Endpoint

• Major bleeding was significantly lower with Apixaban compared with Dabigatran 150 mg BID (26%) and Rivaroxaban (34%)

• GI (41%) and extracranial bleed (26%) significantly less with Apixaban compared with Dabigatran 150 mg BID

• Dabigatran 110mg BID had less major bleed and intracranial bleed when compared to rivaroxaban
LIMITATIONS

• Different patient population
• Difference in definition of safety endpoints, mainly major bleeding
• Unblinded Dabigatran trial vs. Double blinded trial of Rivaroxaban and apixaban
LIMITATIONS

• Can not adjust for patient demographics and stroke risk (i.e. ROCKET-AF had a higher risk population)

• Can not adjust for the differences in warfarin control between the trials
IN CLINIC
From clinical trials to everyday clinical practice
Basic assessment for initiation or transition from warfarin to one of the new oral anticoagulants

- Age
- Creatinine Clearance
  - >50cc/min
  - 30 - 50 cc/min
- Weight
- Labile INR vs. Good TTR (57 -72% good and >72% excellent)
- Compliance
- Bleeding history
- GI history
  - Angiodysplasia, diverticulosis, PUD
- **Patient preferences**
  - Drug cost
  - Lack of reversibility
- Awareness of free samples provided to patients with financial difficulty
- Ask patient to wear a MEDICAL ALERT BRACELET
Age

• Dabigatran:
  • 150 mg BID <75 yrs if no other co-morbidities**
  • 110 mg BID for >75 yrs with impaired renal function

**150mg dose is associated with higher rate of bleed in >75 yrs

• Apixaban:
  • 2.5mg BID dose is recommended for age >80; weight of less than 60 kg or serum creatinine >133 umol/L
Contraindications to NOACs

- Prosthetic heart valves
- Creatinine clearance of less than 30 ml/min
- Pregnant or breast feeding
- Phospholipid antibody syndrome
- Disorders of haemostats (von Willebrand disease/coagulation factor deficiency)
- Acute hepatitis, chronic active hepatitis, liver cirrhosis (Child-Pugh class B and C)
Drug Interactions

- Rivaroxaban and Apixaban: CYP3A4 and P-gp
  - Azole antifungals
  - Protease inhibitors (HIV)
  - Rifampin / carbamazepine / phenytoin, phenobarbital
- Dabigatran: p-Glycoprotein
  - Verapamil
  - Amiodarone / dronedarone
  - Ketoconazole /itraconazole / voriconazole / posaconazole
  - Quinidine
Current indications for clinical use

- *Non-valvular* atrial fibrillation
- Venous thromboembolism
- Post-operative hip and knee arthroplasty prophylaxis
Venous Thromboembolism
<table>
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<tr>
<td><strong>Non-valvular</strong></td>
<td>YES</td>
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<td><strong>Atrial Fibrillation</strong></td>
<td>YES</td>
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NOACs are contraindicated in pregnancy and in treatment of mechanical heart valves (RE-ALIGN).
Einstein-PE
Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism

Randomization

Rivaroxaban 15mg BID
3 weeks

Rivaroxaban 20mg daily

Enoxaparin BID for 5 days and warfarin INR range 2-3

N = 4833

primary end point of:
Symptomatic recurrent VTE

Randomized, open label study
AMPLIFY

Oral Apixaban for the Treatment of Acute Venous Thromboembolism

Randomization

N = 5400

Apixaban 10mg BID for 7 days → Apixaban 5mg BID

Enoxaparin BID for 5 days and warfarin INR range 2-3

primary end point of: Symptomatic recurrent VTE

Randomized Double-Blind Study
Dabigatran vs. Warfarin in the Treatment of Acute Venous Thromboembolism

Randomized, double-blind, non inferiority trial

N = 2564

Randomization

LMWH BID for 5-10 days

LMWH BID for 5-10 days and warfarin INR range 2-3

Dabigatran 150mg BID

primary end point of:
Symptomatic recurrent VTE at 6 months
There was no statistically significant difference in risk of recurrent VTE or all-cause mortality between these NOACs. Apixaban appears to be associated with lower risk of bleeding than the other NOACs.
No significant difference in risk of mortality or recurrent VTE. Therefore, no difference in efficacy for treatment of acute VTE, but apixaban was shown to have better safety profile.
Everyday clinical practice

Pros

- Does not involve any teaching.
- Early discharge from emergency room
- Option of outpatient treatment of VTE without need for immediate follow up.
Everyday clinical practice

Cons

- Appropriate initiation
- Lack of education and true understanding of disease state by the patients.
- Lack of reassessment by health professionals (nurse/physician) to determine treatment response.
- Special authority not immediately available
- Patients with financial difficulty might stop or under-dose their NOACs.
Everyday clinical practice

• No clear data on management of patients who might be diagnosed with malignancy

• Age and creatinine

• Lack of laboratory monitoring in cases of bleeding and or treatment failure
Perioperative Management of NOACs
Peri-operative management of NOACs

- The timing of preoperative NOAC interruption to ensure minimal or no residual anticoagulant effect at surgery is based on:
  1. The elimination half-life of the NOAC
  2. Patient renal function (based on calculated CrCl ml/min)
  3. Bleeding risk associated with planned surgery
# Preoperative Interruption of NOACs

<table>
<thead>
<tr>
<th>Renal Function:</th>
<th>Low Bleeding Risk</th>
<th>High Bleeding Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CrCl &gt;50 ml/min</td>
<td>CrCl 30-49 ml/min</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>24 hrs</td>
<td>48 -72 hrs</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>24 hrs</td>
<td>48 hrs</td>
</tr>
<tr>
<td>Apixaban</td>
<td>24 hrs</td>
<td>48 hrs</td>
</tr>
</tbody>
</table>
### Postoperative Resumption of NOACs

<table>
<thead>
<tr>
<th></th>
<th>Low Bleeding Risk</th>
<th>High Bleeding Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td>resume 24 hr after surgery</td>
<td>Resume 48-72 hrs after surgery*</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>resume 24 hr after surgery</td>
<td>Resume 48-72 hrs after surgery*</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>resume 24 hr after surgery</td>
<td>Resume 48-72 hrs after surgery*</td>
</tr>
</tbody>
</table>

* Consider DVT prophylaxis and/or alternatives such as IV heparin
Indwelling Epidural Catheters

• Dabigatran not recommended in patients with indwelling catheters.

• Rivaroxaband and Apixaban:
  • Avoid use if possible
  • traumatic or repeated puncture: delay for 24 hours.
Laboratory Monitoring
Monitoring anticoagulation with NOACs

- Acute bleed
- Urgent surgery
- Adherence
- Treatment failure with recurrence or extension of thromboembolism
## Laboratory Tests

<table>
<thead>
<tr>
<th></th>
<th>RIVAROXABAN</th>
<th>APIXABAN</th>
<th>DABIGATRAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT / INR</td>
<td>PT: Neoplasmin reagent</td>
<td>Not recommended</td>
<td>Insensitive</td>
</tr>
<tr>
<td></td>
<td>INR: Not recommended</td>
<td></td>
<td></td>
</tr>
<tr>
<td>aPTT</td>
<td>maybe prolonged but not as sensitive as PT</td>
<td>Insensitive</td>
<td>Somewhat sensitive may underestimated levels</td>
</tr>
<tr>
<td>Anti-Xa Assay</td>
<td>Too sensitive Modified anti-Xa for Rivaroxaban available</td>
<td>Rotachrom Heparin Anti-Xa assay</td>
<td>Insensitive</td>
</tr>
<tr>
<td>Thrombin Time (TT)</td>
<td>Insensitive</td>
<td>Insensitive</td>
<td>Oversensitive HEMOCLOT more suitable</td>
</tr>
</tbody>
</table>
New oral anticoagulants: a practical guide on prescription, laboratory testing and peri-procedural/bleeding management.  
**Expected Overall Test Patterns:**

<table>
<thead>
<tr>
<th></th>
<th>DABIGATRAN</th>
<th>RIVAROXABAN</th>
<th>APIXABAN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Significant anticoagulant effect unlikely:</strong></td>
<td>aPTT &amp; TT normal</td>
<td>PT normal (if a sensitive assay is used)</td>
<td>PT normal (if a sensitive assay is used)</td>
</tr>
<tr>
<td><strong>Anticoagulant effect present (screening tests):</strong></td>
<td>TT prolonged aPTT prolonged</td>
<td>PT prolonged</td>
<td>PT prolonged (apixaban present in excess)</td>
</tr>
<tr>
<td><strong>Drug effect likely (confirmatory tests):</strong></td>
<td>HEMOCLOT prolonged (dilute thrombin clotting time assay)</td>
<td>Modified Rivaroxaban anti-Xa positive</td>
<td>Rotachrom Heparin Anti-Xa assay</td>
</tr>
</tbody>
</table>
Management of NOAC-related Bleeding
Management of NOAC-related Bleeding: General Principles

- Drug Discontinuation
- Baseline laboratory assessment
- Assess renal function
Management of NOAC-related Bleeding: General Principles

- Initiate supportive measures:
  1. Identify source of bleeding
     - Surgical, radiological, endoscopic assessment, keeping in mind risk of procedure-related bleeding in an anti-coagulated patient.
  2. Initiate of IV supportive therapy if indicated
     - Enhance renal clearance with hydration
     - Provide pRBC if appropriate
     - Consider platelet transfusion if patient on anti-platelet therapy
Management of NOAC-related Bleeding:
General Principles

- Activated Charcoal
  - should only be considered in patients who have established time line, with last oral dose within 2 hours of presentation

- Hemodialysis
  - can be considered with Dabigatran only
Management of NOAC-related Bleeding: General Principles

- Administration of Hemostatic agents:
  - activated prothrombin complex concentrate (aPCC)
  - recombinant factor VIIa
On Horizon

ANDEXANET ALPHA

- Recombinant Factor Xa inhibitor antidote.
- It binds and sequesters the direct Factor Xa inhibitors in blood.
- Preclinical and phase one studies suggest Andexanet alpha can be a potential universal reversal agent for all factor Xa inhibitors.
Thank you.