Laboratory Tests for Anticoagulants which Do Not Require Routine Monitoring

Ponnudurai Kuperan
FRCP FRCPA FRCPPath
Department of Haematology
Tan Tock Seng Hospital
Anticoagulants Currently in use

- Unfractionated Heparin (UFH)
- Low Molecular Weight Heparin (LMWH)
- Vitamin K Antagonists (Warfarin)
- Direct Oral Anticoagulants (DOAC)
  - Dabigatran
  - Rivaroxaban
  - Apixaban
Conventional Anticoagulants

Target Sites

- Factor IX
- Factor X
- Factor VII
- Factor Xa
- Factor IIa (Thrombin)
- Factor II (Prothrombin)
- Antithrombin
- Fibrinogen
- Fibrin

Heparin
LMWH
Fondaparinux

Antithrombin

Warfarin

Factor IX

Factor X

Factor VII

FIXa

FVIIa

Antithrombin

Factor II (Prothrombin)

Factor IIa (Thrombin)
<table>
<thead>
<tr>
<th><strong>UFH</strong></th>
<th><strong>LMWH</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable Non-Specific binding to</td>
<td>No Significant Non-Specific Binding</td>
</tr>
<tr>
<td>- Plasma Proteins</td>
<td>- Endothelial Cells</td>
</tr>
<tr>
<td>- Endothelial Cells</td>
<td>- Monocytes</td>
</tr>
<tr>
<td>- Monocytes</td>
<td>- Platelet Factor 4</td>
</tr>
<tr>
<td>Highly Variable Anticoagulant Effect in Different Individuals</td>
<td>Predictable Anticoagulant Effect</td>
</tr>
</tbody>
</table>

- Needs Monitoring
- Weight Adjusted Dose Possible
Monitoring of UFH

- Given by Continuous IV Infusion
- APTT between 1.5-2.5 times normal
- Anti-Xa Level 0.3-0.7 U/ml
UFH
Cleared mainly by RE System

LMWH
Mostly Cleared by Kidneys

UFH → AT →
• Xa
• Thrombin
• IXa/XIa

LMWH → AT →
• Xa
• Thrombin
• IXa/XIa
LMWH and Increased Risk of Bleeding

- Elderly
- Obese/Underweight/Children
- Renal Failure
- Pregnancy
- Concomittent other Medications
LMWH (SC)

Peak Plasma Level 3-4 Hours

Anti-Xa Level

- Treatment Once Daily: 1.0-2.0 IU/ml
- Prophylactic Once Daily: 0.2-0.5 IU/ml
- Treatment Twice Daily: 0.6-1.2 IU/ml

Varies with Different Preparations
LMWH and Laboratory Monitoring

“Therapeutic Range” has been Suggested
Have Not Been Validated in Clinical Trials

Peak Level or Trough Level

Generally Peak Level but
Renal Failure $\rightarrow$ Increased Accumulation
Pregnancy $\rightarrow$ Enhanced Clearance

High Trough Level $\geq 0.5\text{U/ml}$ Higher Risk of Bleeding

No Consensus on Dose Adjustment
LMWH Anti-Xa Level is “Reliable”

• Collected after 4 hours of a Dose

• Plasma separated within 1 hour of Collection

• Assay Done within 2-4 hours of Collection

• If not done soon → Frozen at -20ºC

Plasma should be Platelet-free (<10x10⁹/L)
Effect sites of anticoagulation agents. The new oral anticoagulation agents directly inhibit one of two major targets in the coagulation cascade. Rivaroxaban and apixaban directly inhibit factor Xa, and dabigatran directly inhibits thrombin. The parenteral anticoagulants that inhibit factor Xa include low-molecular-weight heparin (LMWH) and fondaparinux by antithrombin (AT)-dependent binding. Parenteral direct thrombin inhibitors include argatroban, bivalirudin, and desirudin that also directly inhibit thrombin independent of AT.
<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of Action</strong></td>
<td>Direct Thrombin Inhibitor</td>
<td>Direct Xa Inhibitor</td>
<td>Direct Xa Inhibitor</td>
</tr>
<tr>
<td><strong>Onset of Action</strong></td>
<td>1-3 hours</td>
<td>1-3 hours</td>
<td>1-3 hours</td>
</tr>
<tr>
<td><strong>Renal Clearance</strong></td>
<td>80%</td>
<td>33%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Half Life</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl &gt;80ml/min</td>
<td>11 hours</td>
<td>9 hours</td>
<td>9 hours</td>
</tr>
<tr>
<td>CrCl 50-80ml/min</td>
<td>14 hours</td>
<td>9 hours</td>
<td>9 hours</td>
</tr>
<tr>
<td>CrCl 30-50ml/min</td>
<td>15-17 hours</td>
<td>10-15 hours</td>
<td>10-14 hours</td>
</tr>
</tbody>
</table>
Laboratory Assessment of Novel Oral Anticoagulants

- **Wide** therapeutic window
- **Predictable** pharmacokinetic profiles
- **Fixed dose** therapy

**Routine** laboratory assessment/monitoring is **not required**

Patients Treated Under Clinical Trials **vs** Unselected Routine Patients
Intrinsic Pathway

H. M. W. K.
Prekallikrein
XII, XI, IX, VIII

Extrinsic Pathway

Tissue Factor
VII

Plalet Phospholipid Surface

X, V, II
Ca++

Fibrinogen

Fibrin

APTT

PT
Add activator of VII + Phospholipid + Ca²⁺

Sensitivity of the Reagent Varies
APTT

Add activator of XII + Phospholipid + Ca++

Plasma → Platelets → Red cells

Fibrin clot

Sensitivity of the Reagent Varies

Time
Add Thrombin

Sensitivity of the Reagent Varies
DOAC and Coagulation Tests

Depends on

- Reagents used
- Type of Assays used

Results Vary from Lab to Lab
## DOAC and Routine Coagulation Tests

<table>
<thead>
<tr>
<th></th>
<th>PT</th>
<th>aPTT</th>
<th>TCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>↑</td>
<td>↑↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>↑↑↑</td>
<td>↑</td>
<td>-</td>
</tr>
<tr>
<td>Apixaban</td>
<td>(↑)</td>
<td>(↑)</td>
<td>-</td>
</tr>
</tbody>
</table>
Qualitative Tests (PT/APTT/TCT)

- TCT is **very sensitive** to Dabigatran
- **Normal PT/ APTT** Does Not exclude the presence of Residual drug effect
- **Prolonged PT/ APTT** Probably indicates Drug effect
DOAC and Coagulation Tests

Patient Presents with Major Bleeding

- ? Overdosage
- ? Another Cause

Patient Presents with an Ischaemic Stroke

- ? Underdosage
- ? Not related
  - ? Thrombolytic therapy

Patient needs Urgent Surgery

- ? Any Residual Drug Effect
- ? Drug Level High
Laboratory Assessment of Novel Oral Anticoagulants

- Monitoring
  - X

- Qualitative Tests
  - Very Minimal Drug Effect

- Quantitative Assay
  - Low Level
  - High Level
DOAC and Qualitative Tests

• May help clinicians with decision making in certain clinical situations

• Normal TCT excludes presence of Dabigatran effect

• Rivaroxaban and Apixaban - PT/ APTT/ TCT – NOT reliable

• Anti Xa assay is the only Reliable test
Below on-therapy, on-therapy, and above on-therapy ranges for DOACs. Therapeutic ranges for the DOACs have not been established.

Adam Cuker, and Deborah Siegal Hematology
2015;2015:117-124
Direct Oral Anticoagulants and Surgery

- **Urgency of Surgery**
- **Residual Drug Effect**
- **Risk of bleeding with the surgery**

- **Time of Last Dose**
- **Renal Function**
Patients on DOAC admitted with Bleeding

- FBC
- Creatinine Clearance
- PT/APTT/TCT
- **Quantification** of Drug Level
  - Dilute Thrombin Time
  - Anti-Xa Assay
  
  *if surgery contemplated*
Dabigatran

Normal TCT No drug effect

Drug level < 30 ng/ ml – Low drug level
> 30 ng / ml – Significant drug level
Rivaroxaban/ Apixaban

Normal PT/APTT  Does NOT exclude drug effect

PT/APTT Prolonged  - Probable drug effect present

Drug level  < 30 ng/ml  Low drug level
          >30ng/ml  Significant drug level
DOAC and Laboratory Tests

• May help clinicians with decision making in certain clinical situations

• Most Appropriate test to be used

• The Interpretation of the Results

• Assessment of Renal function is Mandatory
Thank You For Your Attention