Novel Oral Anticoagulants and Laboratory Testing

All you need to know

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Outline

• Current novel oral anticoagulants (NOACs) and their actions
• Effects on routine coagulation tests
• Effects on specialized coagulation testing
• Measuring drug levels and role of monitoring
Targets for anticoagulants

Adapted from Weitz and Bates, 2005; Ansell et al 2008; Hirsh et al 2008 Weitz et al 2008
**Current NOACs in Singapore and their approved indications**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE prophylaxis for major orthopaedic surgery</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>DVT treatment</td>
<td></td>
<td>✔️</td>
<td></td>
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<tr>
<td>Extended VTE treatment</td>
<td></td>
<td>✔️</td>
<td>✔️</td>
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<tr>
<td>Stroke prevention in atrial fibrillation</td>
<td>✔️</td>
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<td></td>
</tr>
</tbody>
</table>
70, Male

- Chronic atrial fibrillation on dabigatran
- Admitted for pneumonia
- Prothrombin time – 15 seconds (10.2 – 12.1s)
- Activated partial thromboplastin time – 55 seconds (28.5 – 36.1 s)
- Thrombin time – 200 seconds
- Fibrinogen – 3.2 gm/L
Dabigatran and PT
Dabigatran on aPTT

![Graph showing the relationship between initial blood sample dabigatran concentration and time, with cut-off values of 67ng/mL and 200ng/mL.](image)

- CK prest (STA) $R^2=0.99$
- Cephascreen (STA) $R^2=0.99$
- Synthasil (ACL TOP) $R^2=0.99$
- Actin FS (BCS) $R^2=0.96$
- PTT-A (STA) $R^2=0.99$

Interpreting global coagulation tests in the presence of dabigatran

<table>
<thead>
<tr>
<th>Test</th>
<th>Effects of dabigatran</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin time</td>
<td>↑</td>
<td>Exponential increase at higher concentrations</td>
</tr>
<tr>
<td>Activated partial thromboplastin time</td>
<td>↑</td>
<td>Increase levels off at higher concentration</td>
</tr>
<tr>
<td>Thrombin time</td>
<td>↑↑</td>
<td>Very sensitive to dabigatran. May however be assay dependent</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>↔</td>
<td>Mostly not affected</td>
</tr>
</tbody>
</table>
Female, 55

- Deep vein thrombosis associated with heparin induced thrombocytopenia. On rivaroxaban.
- Admitted for knee pain
- Prothrombin time – 11.2 seconds (10.2 – 12.1 s)
- APTT – 39 seconds (28.5 – 36.1s)
Rivaroxaban started

Warfarin started

INR – done at SGH

PT sent to TTSH
## Interpreting global coagulation tests in the presence of rivaroxaban

<table>
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<tr>
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<tbody>
<tr>
<td>Prothrombin time</td>
<td>↑ or ↔</td>
<td>Highly dependent on assay</td>
</tr>
<tr>
<td>Activated partial thromboplastin time</td>
<td>↑</td>
<td>Variable increase</td>
</tr>
<tr>
<td>Thrombin time</td>
<td>↔</td>
<td>Not affected</td>
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<tr>
<td>Fibrinogen</td>
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Commonly used thromboplastin for PT/INR measurement in Singapore and their sensitivity to rivaroxaban

<table>
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<tr>
<th>Thromboplastin</th>
<th>Sensitivity</th>
<th>Institutions using the thromboplastin#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplastin</td>
<td>Sensitive, PT/INR prolonged</td>
<td>Tan Tock Seng Hospital, National University Hospital, Ng Teng Fong General Hospital, Kandang Kerbau Women and Children’s Hospital</td>
</tr>
<tr>
<td>Innovin</td>
<td>Insensitive, minimal effect on PT/INR result</td>
<td>Singapore General Hospital, Changi General Hospital, Khoo Teck Puat General Hospital, Raffles Hospital, Parkway Group Hospitals, Thomson Medical Centre</td>
</tr>
</tbody>
</table>
Apixaban and Prothrombin Time

The graph illustrates the relationship between the concentration of apixaban (ng/mL) and the prothrombin time (sec). The data points are represented by different lines, each corresponding to a specific test method:

- **Triniclot PT Excel S** ($r^2=1.00; 2xCT=154; CV=1.1$)
- **RecombiPlas Tin 2G** ($r^2=1.00; 2xCT=300; CV=0.6$)
- **Triniclot PT Excel** ($r^2=0.97; 2xCT=459; CV=2.4$)
- **Neoplastin Cl+** ($r^2=0.99; 2xCT=511; CV=0.8$)
- **Neoplastin R** ($r^2=0.99; 2xCT=740; CV=0.9$)
- **Triniclot PT HTF** ($r^2=0.88; 2xCT=1,105; CV=1.9$)
- **Innovin** ($r^2=0.94; 2xCT=1,387; CV=0.7$)
Interpreting global coagulation tests in the presence of apixaban

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Specialized Coagulation Tests and the NOACs

General guidance

• Test potentially affected by NOACs
  – Lupus anticoagulant
  – Protein C
  – Protein S
  – Antithrombin III

• Specific assays may not be affected by NOACs
Specialized Coagulation Tests and the NOACs

• Unless assay used is known, best to avoid testing in the presence of NOACS to prevent false positive results

• NOACs can be withheld for duration of action before testing (>72 hours)
Testing for plasma NOAC levels

• Dabigatran – Hemoclot assay available in TTSH
• Rivaroxaban - Anti-Xa chromogenic assay (STA-Liquid Anti-Xa, STA-Rivaroxaban Calibrator, Diagnostica Stago, France) – available in TTSH
• Apixaban – currently not available in Singapore
Measuring NOAC levels

• Monitoring of anti-Xa level usually not indicated.
• May be considered in the following instances:
  – Prior to surgical intervention where residual NOAC effect is not desired
  – Bleeding patients where NOAC effect needs to be excluded
  – In patients with overdose of NOACs where consideration may be given for alternate methods of clearance if levels remains high
  – In patients developing a thrombotic event when compliance is doubted
Take home message..

• NOACs affect various coagulation tests
• Sensitivity varies with each assay used
• Ideally, each laboratory should establish its own sensitivity
• When in doubt, call your lab..
Thank you!