Dabigatran etexilate, more commonly referred to by its trade name Pradaxa, is a novel, oral, direct thrombin inhibitor currently licensed for anticoagulation of selected patients with atrial fibrillation (AF) or for post-orthopaedic prophylaxis of venous thromboembolism.

**Monitoring dabigatran (Pradaxa)**

The newer anticoagulants, such as Pradaxa, have predictable dose-related activity and few drug or dietary interactions. Unlike warfarin, they do not need continuous monitoring to maintain the patient within a therapeutic window by dose adjustment. Some patients in some clinical scenarios may benefit from assessment of the degree of anticoagulation induced by this drug. These include:

- the bleeding patient (assessing for over-anticoagulation)
- patients with failure of efficacy (checking for compliance)
- prior to surgery (looking for safety to proceed)
- patients with renal impairment (assessing drug accumulation).

Routine coagulation tests (APTT, INR/PT) are not indicative of the anticoagulant effect of Pradaxa. The ECT is not routinely available in clinical practice, although some laboratories have chosen to employ this test. Requests for ECT for monitoring must be discussed with the laboratory in advance. Currently Melbourne Pathology and Cabrini Pathology only perform the TCT and not the ECT.

Although an elevated TCT is a useful adjunct to assessing the degree of anticoagulant effect in a patient, it alone does not predict the actual “in vivo” bleeding risk for an individual. Many factors will contribute to adequate haemostasis including recent cessation or re-introduction of warfarin, vitamin K depletion or liver disease, thrombocytopenia and exposure to anti-platelet drugs.

**When to stop dabigatran (Pradaxa) before procedures**

The drug-free interval before invasive procedures depends on the:

- nature of the procedure
- renal function of the patient

Pradaxa is predominantly renally cleared (80%). The drug has a short half-life (13 hrs) in patients with normal renal function but longer than 24 hours in patients with poor renal function (CrCl <30 mL/min).

**The eGFR and serum creatinine are not necessarily good indicators of renal function in certain patient groups** (elderly patients, low weight patients) and caution is recommended in these patients.

Calculation of the creatinine clearance (CrCl) using the Cockcroft-Gault equation, adjusting for gender and lean body weight, is recommended using either medical software or according to the following formula:

\[
CrCl(\text{mL/min}) = \text{Constant} \times \left( \frac{140 - \text{Age}}{\text{Weight (kg)}} \right) \times 1.23
\]

where constant is 1.0 for males and 0.85 for females.
MINOR PROCEDURES
Patients can continue Pradaxa for any procedure if this procedure is deemed to be safely performed on therapeutic warfarin.
In a patient with adequate renal function (CrCl >50mL/min), ceasing the drug at least 24 hours prior to a minor procedure is recommended.
In a patient with renal impairment, cease the drug a minimum of 2 days prior to minor procedures.

<table>
<thead>
<tr>
<th>Renal Function (CrCL mL/min)</th>
<th>Half-life (hours), mean (range)</th>
<th>Timing of Discontinuation Prior to Procedure (Minimum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 80</td>
<td>13 (11 – 22)</td>
<td>24 hours</td>
</tr>
<tr>
<td>50 – 80</td>
<td>15 (12 – 34)</td>
<td>24 hours</td>
</tr>
<tr>
<td>30 – 50</td>
<td>18 (13 – 23)</td>
<td>≥ 48 hours</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>27 (22 – 35)</td>
<td>48 – 120 hours</td>
</tr>
</tbody>
</table>

* Examples: electrophysiology procedures, cardiac catheterisations, no additional patient-specific risk factors.

When to restart dabigatran (Pradaxa) after procedures
The anticoagulant effect of the drug takes effect quickly, within 2 hours after oral administration. Once the on-going bleeding risk for the individual is determined to be low the drug can be recommenced at usual dose. For minor procedures this is commonly the following day.

For major procedures or patients at risk of rebleeding this may be longer and should be determined by the surgeon in consultation with the managing physician.

MAJOR PROCEDURES
Discussion with a perioperative physician or anaesthetist and haematologist well in advance of surgery is recommended to create the appropriate pre and post-operative plan. For surgery with a higher bleeding risk, cease Pradaxa at least 2 – 4 days prior to the procedure. In patients with poor renal function a longer period of dose interruption will be indicated.

A TCT performed on the day prior to surgery can guide whether it is safe to proceed. A normal TCT following cessation of Pradaxa indicates that there is no significant residual anticoagulant effect and surgery can proceed safely. A prolonged TCT suggests there may be residual Pradaxa effect and that surgery may need to be delayed, where possible, until the TCT has returned to normal.

Prolonged interruption of dabigatran
If the patient is considered at high risk of post-operative thrombosis but maintains a concurrent high risk for bleeding, a short-acting and/or reversible anticoagulant is recommended to manage this period of care such as intravenous unfractionated heparin (UFH) or a LMWH such as Enoxaparin (Clexane). Consultation with a haematologist is suggested for complex cases. Of note, many of these patients may not fit the criteria for on-label use of dabigatran and reassessment of their long-term anticoagulation may be required.
Experience with management of bleeding is limited. Unfortunately there is no known antidote for dabigatran (Pradaxa). It cannot be reversed with plasma, Prothrombinex-VF, protamine or vitamin K. Novoseven® (recombinant Vlla) may also not be effective. Treatment is supportive until the effect of the drug has worn off.

**FOR LIFE-THREATENING BLEEDING:**

The efficacy and safety of strategies using prothrombinex, FFP and/or Novoseven® are clinically unproven. Beneficial effects cannot be readily confirmed by currently available laboratory testing. Data about their use is limited however they may be considered when all other attempts to manage haemorrhage have failed.

**PTX-VF®** (Prothrombinex-VF 50 units/kg IV) followed by 3 – 4 x 300mL units of AB or group specific FFP (fresh frozen plasma) may be tried initially in cases of severe bleeding.

**Novoseven®** (rVIIa 90mcg/kg IV) may be considered in cases of severe bleeding but its short half-life, lack of proven efficacy, risk of thrombotic complications and expense need to be considered.

**FOR MODERATE TO SEVERE BLEEDING:**

1. Support the patient
   - Maintain adequate venous access
   - Obtain FBE, valid Group + Screen and baseline coagulation studies (APTT, PT/INR, fibrinogen) including a TCT (thrombin time). This may help to determine if there are other potentially treatable contributors to bleeding and allow the patient to be supported appropriately with blood products
   - Provide haemodynamic support with fluids
   - Maintain/promote diuresis
   - Transfuse with blood products as indicated by degree/rate of haemorrhage and haemodilution
   - Consider the role of surgical or radiological intervention for a bleeding site.

2. Notify the haematologist.

3. Reduce the plasma levels of dabigatran (Pradaxa)
   - Consider oral charcoal if Pradaxa ingested within last 2 hours and clinically safe to proceed, or charcoal haemofiltration if available
   - Haemodialysis can reduce the plasma levels by 60%+ within 2 hours.

**FOR MINOR BLEEDING IN NON-CRITICAL SITES:**

1. Delay subsequent doses of Pradaxa
2. Local measures (immobilisation, compression and elevation)
3. Tranexamic acid mouth wash can be employed for bleeding in the oral cavity.

### PATIENT WITH BLEEDING ON DABIGATRAN (PRADAXA)

<table>
<thead>
<tr>
<th>Life threatening bleeding</th>
<th>Moderate to severe bleeding</th>
<th>Mild bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>■ Consideration of recombinant factor Vlla or PCCs or aPCCs*</td>
<td>■ Symptomatic treatment</td>
<td>■ Delay next dose of Pradaxa or discontinue treatment as appropriate</td>
</tr>
<tr>
<td>■ Charcoal filtration*</td>
<td>■ Mechanical compression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Surgical intervention</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Fluid replacement and haemodynamic support</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Blood product transfusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Oral charcoal application* (if Pradaxa ingestion &lt;2 hours before)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Haemodialysis</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from van Ryn et al. Throm Haemost 2010; 103: 1116-27.

*Recommendation is based only on limited non-clinical data; there is no experience in volunteers or patients

PCCs: Prothrombin Complex Concentrates (PTX-VF®), aPCCs: activated Prothrombin Complex Concentrates (FEIBA®)
Further Reading / References:

Dr Lachlan Hayes
MBBS, FRACP, FRCPA
Haematology
Dr Hayes graduated from the University of Adelaide and trained at the Royal Melbourne Hospital, the Austin Hospital and the Royal Children's Hospital. He obtained combined fellowship with both the Royal Australasian College of Physicians and the Royal College of Pathologists of Australasia in 2008.
He is heavily involved in teaching, specifically in the areas of anticoagulation, blood bank/transfusion, obstetric haematology and management of haematological malignancies in the elderly.
Dr Hayes joined Melbourne Pathology in 2008 and is the Director of the Clinical Haematology Service at Northern Health. He has appointments at the Austin Hospital and also practices privately.

Dr Ellen Maxwell
MBBS, FRACP, FRCPA
Medical Director & Director Of Haematology
Dr Maxwell is a University of Melbourne graduate who completed combined fellowships with the College of Physicians and the College of Pathologists in 1997.
She trained initially at the Austin and Repatriation Medical Centres and later at the Alfred Hospital where she developed a keen interest in coagulation and transfusion medicine.
Dr Maxwell is a member of the Clinical Practice Improvement Subcommittee (ANZSBT), Victorian Blood User Group (Chair), the National Blood Transfusion Committee, Serious Transfusion Incident Reporting Working Group (DHS Victoria), RCPA Haematology Advisory Committee and Pathology Update Haematology Subcommittee (Chair).
Dr Maxwell was appointed Medical Director at Melbourne Pathology in September 2009.