THE (CLINICAL) TRIALS AND TRIBULATIONS OF DABIGATRAN – MANAGEMENT OF SURGICAL AND BLEEDING PATIENTS

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Dabigatran (Pradaxa) is an oral direct thrombin inhibitor which was fully funded from 1 July 2011 in New Zealand for use in atrial fibrillation (AF) and postoperative orthopaedic DVT prophylaxis. The decision to offer dabigatran as an alternative to warfarin in AF followed similar FDA approval in the United States and is based on the RE-LY study (NEJM 2009; 361: 1139) of 18,000 patients in which dabigatran 150mg twice daily had similar rates of major bleeding to warfarin and less cerebrovascular accidents. Dabigatran has a reported half-life of 12 to 14 hours (when CrCl > 50ml/min) and is primarily renally excreted. The dose is fixed with no interval monitoring; a dose reduction is recommended in patients over 80 years and use is contraindicated when CrCl < 30ml/min.

There is no specific reversal agent with proven efficacy should a bleeding event occur and the management of major bleeding episodes in clinical trials has not been specifically reported to date. During the first month of use in New Zealand there were several admissions to hospital with bleeding events. These were primarily in patients over 80 years; renal dysfunction and errors in transition from warfarin to dabigatran were common. The management of bleeding, surgical procedures, and interpretation of coagulation tests will be discussed based on this recent clinical experience and the limited published data which is available.

Two appendices follow.

Guidelines for testing and perioperative management of dabigatran - for possible inclusion into local management protocols

The following guidelines have been prepared by PHARMAC with the assistance of practicing specialists in response to requests for information. They are provided to assist clinical services to develop their own guidelines in accordance with local procedures and should not be adopted without appropriate review.

Testing for dabigatran anticoagulant effect

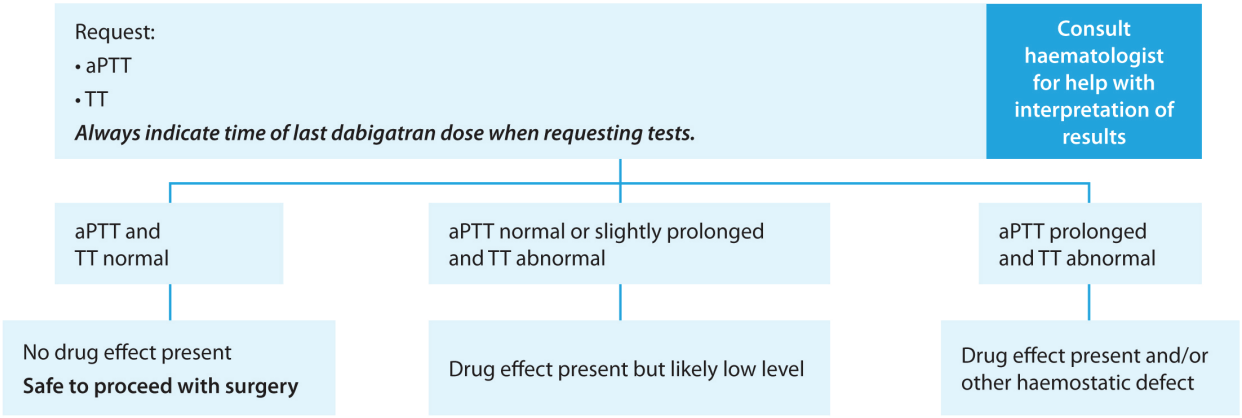
Routine testing is not required during treatment with dabigatran. However, testing may be required in:

- patients with moderate or severe reduction of renal function;
- the perioperative setting; or
- in the event of bleeding.

Tests that can measure the anticoagulant effect of dabigatran exist but are not yet well understood. Note that INR (international normalised ratio) is relatively insensitive to dabigatran with only supra-therapeutic concentrations of dabigatran resulting in an INR of approximately 2.0.[a] Advice should also be sought from local laboratories on the sensitivity of the coagulation tests used as these may differ and will affect test results.[b]

The recommended tests for assessing the effect of dabigatran are:[ac]

- **Activated partial thromboplastin time (aPTT)**
  - Moderately sensitive but has reduced responsiveness at higher doses.
  - Result approximately twice baseline value at dabigatran treatment doses of 150 mg bid but varies for different test brands.
  - Result of >80 seconds at trough (when the next dose is due) is associated with a higher bleeding risk.
- **Thrombin time (TT)**
  - Very sensitive with linear dose-response relationship.
  - Significantly raised at therapeutic doses.



Other tests which can be done to guide the treatment of a patient on dabigatran include:

- **Fibrinogen assay**
  - May be useful to monitor for disseminated intravascular coagulation (DIC) and determining whether replacement treatment is required.
  - Note that reagents vary in responsiveness to dabigatran for fibrinogen assays and some brands may give misleading results.[b]
  - If fibrinogen concentration is below ~1.5 g/L (note this is dependent on assay reagents), a dose of 1 bag of Cryoprecipitate per 30 kg body weight will increase fibrinogen by approximately 1 g/L.
- **Platelet count**
  - Useful to determine whether replacement is required.
  - Transfusion of Platelet Concentrate is indicated where the platelet count is below 70-80 X 10^9 /L.
  - If the patient has been treated with an anti-platelet agent, a dose of 1 to 2 bags of Platelet Concentrate is appropriate for adults.
- **Ecarin clotting time (ECT) (if available)**
  - Sensitive with a linear dose-response relationship.
  - Result increased 2-4 times at dabigatran doses of 150 mg bid.
- **Haemoclot® thrombin inhibitor assay (if available)**
  - Sensitive with a linear dose-response relationship.
  - Clotting time from 30 to 75 seconds at dabigatran dose of 220 mg/day.

Perioperative management of dabigatran

Semi-acute or elective surgery

- Assess the risk of bleeding against the risk of thrombosis when considering discontinuing anticoagulation.
- For minor procedures, dabigatran may not need to be discontinued.
- **If dabigatran does need to be stopped, it is important to plan ahead as there is no treatment available to immediately reverse dabigatran.**
- Dabigatran is primarily renally excreted; therefore, the timing of discontinuation is dependent on the patient's renal function. Renal function should be checked at the pre-admission clinic and the patient should be given clear instructions about when to stop dabigatran treatment.

Renal function (CrCl, mL/min)	Half-life of dabigatran (hours)[d]	Timing of discontinuation after last dose of dabigatran before surgery	
		Standard risk of bleeding	High risk of bleeding[e]
> 80	13 (11-22)	24 hours	2-4 days
> 50 to ≤ 80	15 (12-34)	24 hours	2-4 days
> 30 to ≤ 50	18 (13-23)	At least 2 days (48 hours)	4 days
≤ 30[f]	27 (22-35)	2-5 days	> 5 days

- If there is a risk of thrombosis, consider bridging anticoagulant therapy.

Urgent surgery

- Stop dabigatran.
- Check full blood count, electrolytes (including calcium), renal function and coagulation screen including aPTT, TT and fibrinogen assay. Indicate time of last dabigatran dose when requesting test.
- Consider delaying surgery if appropriate until coagulation screen (aPTT, TT and fibrinogen assay) is normal or until sufficient time has elapsed for drug clearance.
- Where urgent life-saving surgery cannot be delayed, consult with Haematology Service over measures (for e.g. recombinant factor VIIa) to control bleeding prior to and during the surgery.

Re-starting dabigatran after surgery

The appropriate time to re-start dabigatran after surgery will be determined by the nature of the surgery, the urgency for restarting thromboprophylaxis and the haemostatic state of the patient. Discussion with a Haematologist is appropriate to determine individual case management.

In elective situations where the wound is stable and haemostasis is satisfactory, it is suggested that dabigatran is re-started with a single capsule (75 mg, 110 mg or 150 mg depending on the indication) 1–4 hours after surgery with the usual daily dose commenced the following day.

A delay in restarting dabigatran will be appropriate if the wound is not stable and clinically significant wound losses are still present. Short term use of an alternative reversible anticoagulant (bridging anticoagulation) may be appropriate where thromboprophylaxis is required but the risks from wound bleeding are increased. The risk for thrombosis should be assessed.

[a] van Ryn et al. Thromb Haemost 2010 Jun; 103(6): 1116-27.

[b] Lindahl et al. Thromb Haemost 2011 Feb; 105(2): 371-8.

[c] Dabigatran Medsafe datasheet 11 February 2011.

[d] Stangier et al. Clin Pharmacokinet 2010; 49: 259-268, geometric mean (range).

[e] Types of surgery associated with a high risk of bleeding (or in major surgery where complete haemostasis may be required) including but not limited to cardiac surgery, neurosurgery, abdominal surgery, or surgeries involving a major organ. Other procedures such as spinal anaesthsia may also require complete haemostatic function. Other important determinants of bleeding risk include advancing age, co-morbidities (eg, major cardiac, respiratory, or liver disease) and concomitant use of anti-platelet therapy.

[f] Dabigatran is contraindicated for use in patients with CrCl ≤30 ml/min. CrCl = creatinine clearance.

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Guidelines for Acute Reversal Dabigatran

Introduction:

Dabigatran (Pradaxa) is a direct thrombin inhibitor with a half-life of 12-14 hours, significantly prolonged with renal impairment.

THERE IS NO SPECIFIC REVERSAL AGENT FOR DABIGATRAN. In the event of bleeding, consider:

1. The standard measures for support of coagulation and the haemodynamic state which would be used in ANY haemorrhagic episode.

2. Additional measures to attempt to reverse the effect of Dabigatran **IF** the bleeding is significant and standard measures are insufficient. Noted these measures are based on animal data ONLY with no published data about bleed management at this time.

All Bleeds

1. Cease dabigatran therapy.
2. Semi-urgent surgery should be delayed wherever possible.
3. Consider oral charcoal if within 2 hours of ingestion of Dabigatran tablet.
4. Check FBC, full coagulation screen including: TCT, request Dabigatran level (1 purple and 3 blue tubes); calculate CrCl.
5. Crossmatch.
6. Consider vitamin K IV (deficiency is common in the elderly and treat any residual warfarin effect).

Mild Bleeding

- Haemodynamically stable, no organ/limb compromise; no transfusion needed
  1. Local measures to control bleeding
  2. If CrCl <30ml/min or marked dabigatran accumulation (see tests) then time to resolution of coagulopathy may be prolonged: discuss with haematology and consider interventions discussed in "moderate bleeding".

Moderate Bleeding

- Moderate bleeding, GI bleed requiring transfusion, reduction in Hb >30g/L, bleeding in critical area or organ where arrest of haematoma development is critical.

- All moderate bleeds:
  1. Fluid resus / promote diuresis.
  2. Transfuse RBCs and FFP where appropriate.
  3. Platelets if <80x10^{12}/L or anti-platelet agent (aspirin or clopidogrel).
  4. Tranexamic acid 1g IV or oral (unproven but relatively low risk of thrombotic complications).
  5. Consider Prothrombinex 50iu/kg – benefit UNCERTAIN, limited animal data only.

- CrCl >30ml/min., dabigatran levels in expected range (see notes):
- Reasonable to support until levels fall, expected time 12 to 24 hours.

- CrCl <30ml/min and/or evidence of significant dabigatran accumulation:
- Consider haemofiltration or haemodialysis in addition to above (DCCM).

Life-threatening Bleeding

1. Intra-cerebral bleed with reduced GCS:

   Prothrombinex 25iu/kg and rFVIIa – <70kg – 4mg, >/= 70kg 6mg, followed by second dose of rFVIIa after two hours if unchanged.
   Note uncertain but increased prothrombotic risk and efficacy based on animal studies.

2. Massive Bleeding:

   Massive transfusion protocol and Prothrombinex 25iu/kg and rFVIIa – <70kg – 4mg, >/= 70kg 6mg, followed by repeat dose of rFVIIa after 2 hours if unchanged.

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Guidelines for Acute Reversal Dabigatran

Interpretation of laboratory tests:

This is NOT straightforward as unlike the INR and warfarin, there is no clear linear correlation between test results and bleeding risk. The therapeutic range is uncertain and thought to be wide.

APTT: moderately sensitive but levels in the range of 50 to 80 can mean acceptable or high levels. Some evidence that APTT>80 has higher risk of bleeding

PR: less sensitive. PR prolongation >1.5 suggests higher levels of dabigatran. Note potential for warfarin effect if soon after transition, or possible vitamin K deficiency

dTCT: very sensitive. Significantly prolonged in any patient on dabigatran therefore levels >80s seen with low or high levels.

If APTT and PR are normal: levels likely to be low
If APTT <50, PR<1.5 then levels probably low OR moderate

The laboratory has a Dabigatran assay which should not be performed for routine monitoring but may be used as a guide as part of the management of unplanned surgery / procedures or bleeding. This needs to be interpreted in the context of the time of last dose. There is no clear therapeutic range. Published data suggests that peak levels with chronic therapy are on average 0.18ug/ml (range 0.06-0.4) and trough levels are on average 0.09ug/ml (range 0.03-0.2). We will get more experience of how to interpret these results, however if the level is <0.1 and CrCl is >30ml/min then the levels should fall over 12 to 24 hours. The threshold for dialysis or haemofiltration to remove Dabigatran from plasma is UNCLEAR however will need to be interpreted in the context of the type of bleed, and renal function.

There is NO published clinically acceptable level of Dabigatran, or coagulation test results, at which surgery is SAFE. The results will need to be interpreted in the context of the type of surgery and the urgency of the procedure. Ideally waiting until the APTT and PR are normal, and dTCT is mildly prolonged or normal is appropriate.

Starting Dabigatran when converting from warfarin: The INR must be <2 before Dabigatran is started. In lower risk patients (including uncomplicated atrial fibrillation) wait 2 – 4 days after stopping warfarin and check the INR is <2 before starting Dabigatran.