Dabigatran (Pradaxa) Guidelines

Dabigatran is a new anticoagulant for reducing the risk of stroke in patients with atrial fibrillation. Dabigatran is a direct thrombin inhibitor, similar to warfarin, without requiring INR monitoring and dose adjustments.

Choosing between warfarin and dabigatran can depend on patient considerations and preferences. This document gives guidelines for choosing between these therapies, perioperative management, and management of bleeding.

Who is an appropriate candidate for dabigatran?
- Only FDA approved indication: Non-valvular atrial fibrillation, as an alternative to warfarin, for stroke prevention.
- Creatinine clearance > 30ml/min.
- Patients with unstable INRs (time in therapeutic range < 60%) have the greatest benefit from dabigatran.
- Compliant with medications as the dosing is twice daily.

Who is not an appropriate candidate for dabigatran?
- Patients who are well controlled on warfarin derive the least benefit from a change to dabigatran.
- Creatinine clearance < 30ml/min.
- Documented history of PUD, GI bleeds (or risk of), or significant GERD.
- Taking rifampin
- Patient concerns about higher drug costs. Most members will pay a higher Brand co-pay for dabigatran and a lower generic co-pay for warfarin. Average monthly costs are about $200 with dabigatran and $10 with warfarin.

About the drug
- Mechanism of action - direct thrombin inhibitor.
- Rapid absorption and peak activity in 2 – 4 hours.
- Half life 12 – 17 hours.
- Renal excretion, the drug will accumulate if creatinine clearance < 30 ml/min
- There are no interactions with food and low potential for drug-drug interactions.
● Appears to be susceptible to humidity and has a 30-day expiration once the bottle has been opened (pills must remain in manufactured bottle, and cannot be placed in pill boxes/trays or repackaged).

● Prescribing authority for Dabigatran (Pradaxa) is restricted to cardiology and heme/onc.

Contraindications and precautions

● In HealthPartners, at this time (June 2011) dabigatran can only be ordered by our Cardiology and Hematology/Oncology colleagues. If you have a patient with atrial fibrillation for whom you believe this would be the preferred therapeutic choice, please contact the on-call cardiologist. If you’re thinking of using it for another purpose you could also call the on-call hematologist.

● It should not be used in patients with bleeding or falls risks.

● It should not be used in patients with CrCl < 15 ml/min or on dialysis.

● It has not been studied in pregnancy or valvular heart disease.

● It is not approved for venous thromboembolic disease, DVT prophylaxis or bridging for procedures.

● Anti-platelet agents were allowed in the RE-LY trial, but these increase the risk for hemorrhage.

● Absorption can be affected by p-glycoprotein inhibitors and inducers. Rifampin decreases the AUC of dabigatran and should be avoided. Other p-glycoprotein inhibitors such as ketoconazole, verapamil, amiodarone, quinidine, and clarithromycin do not require dose adjustments.

● Patients must not chew, break or open capsules as this can result in increased exposure.

Dosing

● 150mg PO bid in patients with creatinine clearance (CrCl) > 30ml/min.

● 75mg PO bid was approved for patients with CrCl of 15-30ml/min, but there is no clinical experience with this dose and it should be used with caution.

Monitoring and laboratory studies

● Baseline labs: CBC, Platelets, LFTs, Scr, INR & aPTT

● Routine monitoring is not required.

● The drug prolongs the PTT, INR, thrombin time (TT) by inhibiting thrombin activity.

● Ecarin clotting time and dilute thrombin time can be used to evaluate plasma levels, but these are not widely available.

● If the TT is normal there is no dabigatran in the sample.
Side effects
- Dyspepsia in 11.8% in the RE-LY trial
- Myocardial infarction was higher in the dabigatran group, but this was not statistically significant. Data suggests that warfarin may have an intrinsic protective property against MI, as opposed to the non-warfarin anticoagulants.
- Major bleeding risk similar to warfarin (3.32% per year)
- Intracranial bleeding was less with dabigatran (0.30% per year with dabigatran versus 0.74% per year with warfarin).

Perioperative management
- The duration for which the drug needs to be held prior to a procedure depends on renal function and risk of bleeding during the procedure.
  - CrCl > 50 ml/min – discontinue dabigatran at least 24 hours prior to the procedure, but if high risk for bleeding (major surgery) stop 2 – 4 days prior.
  - CrCl 50-30 ml/min – stop 48 hours prior to the procedure, if high risk for bleeding stop for 4 days.
  - CrCl < 30 - hold drug for 2 – 5 days and > 5 days for high risk bleeding.

In patients at high risk of bleeding a thrombin time can be checked 6 – 12 hours prior to surgery – if normal there is no dabigatran present. Please note that the thrombin time does not accurately reflect plasma concentrations of dabigatran and is not useful to predict bleeding risk.

Restarting
- Timing of resumption of dabigatran must be adjusted according to bleeding risk.
  The anticoagulant effect occurs within 1 – 3 hours after drug ingestion.

Converting from or to Warfarin
When converting patients from warfarin therapy to Pradaxa, discontinue warfarin and start Pradaxa when the international normalized ratio (INR) is below 2.0.
When converting from PRADAXA to warfarin, adjust the starting time of warfarin based on creatinine clearance as follows:
  - For CrCl >50 mL/min, start warfarin 3 days before discontinuing PRADAXA.
  - For CrCl 31-50 mL/min, start warfarin 2 days before discontinuing PRADAXA.
  - For CrCl 15-30 mL/min, start warfarin 1 day before discontinuing PRADAXA.
  - For CrCl <15 mL/min, no recommendations can be made.

Because PRADAXA can contribute to an elevated INR, the INR will better reflect warfarin’s effect after PRADAXA has been stopped for at least 2 days.
Converting from or to Parenteral Anticoagulants

- For patients currently receiving a parenteral anticoagulant, start PRADAXA 0 to 2 hours before the time that the next dose of the parenteral drug was to have been administered or at the time of discontinuation of a continuously administered parenteral drug (e.g., intravenous unfractionated heparin).
- For patients currently taking PRADAXA, wait 12 hours (CrCl ≥ 30 mL/min) or 24 hours (CrCl < 30 mL/min) after the last dose of PRADAXA before initiating treatment with a parenteral anticoagulant [see Clinical Pharmacology (12.3)].

Guidelines for the Management of Bleeding

- There is no specific agent to reverse the drug.
- Plasma will not work as the drug will inhibit thrombin in transfused plasma.
- The only way to remove the drug is dialysis.
- There is very little data to help guide us in managing bleeding complications on the drug.

Lab testing

- CBC, Platelet count, LFT, aPTT, INR, TT and fibrinogen activity.
- If TT is normal no drug is present.
- Repeat testing every 4 hours until bleeding has stopped

Note: All clotting times will be abnormal on dabigatran. We are not yet sure if our fibrinogen testing is reliable on the drug, it may be low, this is under investigation.

For minor bleeding

- Stopping the drug will decrease the bleeding risk. Decisions about stopping can be based on the risk of stroke and the severity of the bleeding. Factors to consider include the duration of the drug effects (1-2 days in patients with normal renal function) and the onset of action when restarting (peak activity within 2-4 hours).
- Use local measures to control the site bleeding
- Keep hydrated
- Replace fluids and blood products as needed

For severe or life-threatening bleeding

- Stop the drug
- Control of bleeding site and supportive care of patient
- Activated charcoal administered if the drug has been given within 2 hours.
- Consider dialysis, can remove 60% of the drug
  1. Need to contact IR for placement of an IJ Quinton
  2. Contact renal team, to set up a machine and staff for the dialysis
- Blood transfusion
  1. Transfuse RBCs to keep Hgb above 9 or 10
  2. After the 4th unit of RBCs start giving RBCs and Plasma on a 1:1 ratio (to avoid a dilutional coagulopathy)
  3. Cryoprecipitate, give 10 units after the 8th unit of RBCs, 4th unit of Plasma – May not need cryo if fibrinogen activity is > 100 mg/dl
- Recombinant activated Factor VII - dose of 20-40mcg/kg, or 2mg if <100 kg and 4
mg if > 100 kg. This should be considered if bleeding is life-threatening.

I have included recombinant activated Factor VII (rFVIIa) as an option to help with clot formation at the site bleeding. It does not reverse the drug and the correct dose is unknown. Thrombosis is a potential side effect of rFVIIa.

**Note:** Recombinant activated Factor VII and prothrombin complex concentrates have not been evaluated for reversal of bleeding in humans, but did reduce blood loss in a rat model.

**References:**
5. ICSI Antithrombotic Therapy Supplement Guideline, April 2011
   - [ICSI Antithrombotic Therapy Supplement Guideline](http://www.imehealthpartners.com)

**Questions:** Please reply to this e-mail, and your questions(s) will be directed to the author of this Pearl, Dr. Colleen Morton and Peter Marshall, Pharm. D.

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