

Recommendations on Use of Dabigatran in Atrial Fibrillation

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Endorsed by the the Section of Hematology/Oncology and Section of Cardiology, University of Manitoba -- October 2012

Introduction

Dabigatran (Pradax® in Canada, Pradaxa® in U.S.) is one of three new oral agents which are the vanguard of a new era of anticoagulant therapy. New oral agents are anticipated to revolutionize the prevention and management of thromboembolic disorders. All health care professionals caring for patients on anticoagulation will need to be aware of these agents, as routine anticoagulation management and monitoring will be very different.

These recommendations have been developed to aid health professionals in making appropriate use of this new agent, and to highlight potential problems. The intent is to maximize positive outcomes and ensure patient safety.

This document is not intended to compare dabigatran to other new oral anticoagulants that are or may eventually be approved for use for atrial fibrillation (e.g. rivaroxaban and apixaban). Many, but not all, of the comments listed below that refer to the role of dabigatran compared to warfarin may be applicable to the other new oral anticoagulants.

Dabigatran is eligible (as is rivaroxaban) for coverage under the Manitoba Pharmacare Program effective September 24, 2012 for stroke prevention in atrial fibrillation. It is listed under EDS Part III, which requires the prescriber to call Pharmacare for approval prior to dispensing. The specific Pharmacare Criteria are:

“For patients with non-valvular atrial fibrillation (AF) who require Pradax for the prevention of stroke and systemic embolism AND in whom:

- a) Anticoagulation is inadequate following a reasonable trial of warfarin; OR
- b) Anticoagulation with warfarin is contraindicated or not possible due to inability to regularly monitor via International Normalized Ratio (INR) testing (i.e. no access to INR testing services at a laboratory, clinic, pharmacy, and at home)”

Indication

Dabigatran is indicated in Canada for prevention of stroke or systemic embolization in patients with atrial fibrillation for whom anticoagulation is appropriate (i.e. where CHADS2 score ≥ 1 and bleeding risk is acceptable).

At this time, it should NOT be used in patients with atrial fibrillation who have mechanical heart valves or significant valve disease, as those patients have not been studied.

CHADS2 Score

Congestive heart failure or LVEF < 35% = 1 point

Hypertension = 1 point

Age \geq 75 years = 1 point

Diabetes = 1 point

Stroke or TIA in past = 2 points

In a large randomized non-blinded trial of patients with CHADS2 score of ≥ 1 , dabigatran 150mg b.i.d. demonstrated superior efficacy to warfarin in preventing stroke or systemic embolism (36% relative risk reduction). Dabigatran at the standard dose of 150 mg b.i.d. demonstrated statistically equivalent safety overall for major bleeding. Compared to warfarin, GI bleeding largely from the lower GI tract was more frequent with dabigatran, but intracranial hemorrhage was significantly less frequent.

Contraindications

Dabigatran is CONTRAINDICATED in patients:

- with creatinine clearance <30ml/min
- with active bleeding
- with very high risk of bleeding (essentially the same consideration of bleeding risk should apply as with warfarin)
- during concomitant use of ketoconazole
- who are pregnant or breastfeeding, on basis of lack of safety data and presumed hemorrhagic risk for the fetus or infant

Advantages and Disadvantages of Dabigatran compared to Warfarin for Atrial Fibrillation:

Advantages

- moderately superior efficacy
- no monitoring required
- few significant drug interactions
- no diet interaction
- more rapid onset of anticoagulant effect (and offset after stopping)
- lower risk of intracranial hemorrhage

Disadvantages

- twice daily dosing
- accumulates in renal insufficiency
- greater risk of GI intolerance
- greater risk of lower GI bleeding
- no validated assay available if monitoring is desired (see below)
- no antidote in the event of bleeding
- possibly less benefit in protecting against myocardial infarction
- higher cost
- impossible to confirm adequate anticoagulation or compliance (see Monitoring section)

Dose

The standard dose for most patients with normal renal function is 150 mg b.i.d.

For patients in whom the risk of bleeding is of particular concern, the 110 mg b.i.d. dose may be used, on the basis of a lower bleeding risk than warfarin. This advantage is modest, and for some patients the risk of bleeding is too high to consider any anticoagulation.

In the U.S., a dose of 75 mg b.i.d. is approved for use in poor renal function (Cl_{cr} 15 – 30 mL/min) or combination of a drug interaction and moderate renal function (Cl_{cr} 30 – 50 mL/min). Canadian regulators have not approved the 75 mg dose. This patient population is more likely to have unstable renal function and to be at higher risk of excess accumulation of dabigatran. For these reasons, the use of 75 mg capsules (indicated in Canada for orthopedic prophylaxis) should not be used “off label” for atrial fibrillation.

Renal Insufficiency

Dabigatran is predominantly cleared by the kidneys, hence the drug accumulates in renal insufficiency. The half life increases from about 13 hours when creatinine clearance is above 80 ml/min, to about 27 hours when creatinine clearance is less than 30 ml/min.

A current measurement of renal function (e.g. eGFR or Cockcroft Gault based) is mandatory before initiating any patient on dabigatran. Monitoring of renal function should be done periodically if renal function is expected to change, or if the patient is exposed to illnesses or drug treatments that may alter renal function. If renal function declines, dose adjustment or discontinuation of dabigatran are appropriate. Health Canada recommends that eGFR be checked at least once a year in patients > 75 yrs of age or with moderate renal dysfunction.

Recommendations

Patients in whom use of dabigatran is appropriate:

Dabigatran should be considered as a good alternative to warfarin for patients with atrial fibrillation, in particular cases:

- where INR has been difficult to stabilize (on the basis that dabigatran’s advantage in terms of efficacy accrues to populations with poorer INR control). Whether it is advantageous for patients whose INR is unstable due to poor adherence to medication is less clear as discussed below
- who have higher stroke risk as defined by higher CHADS₂ or CHADS-Vasc scores (on basis of greater absolute stroke risk, and therefore greater absolute benefit)
- where INR monitoring is problematic (e.g. poor venous access, or patient travels frequently or lives in remote location). Note that use of finger-poke point-of-care INR test devices (e.g. CoaguChek XS) are an alternative solution to this problem
- who have had embolic events despite warfarin (on basis of superior efficacy overall with the 150 mg b.i.d. dose)

- before and after elective cardioversion or EP procedure, when long term anticoagulation is not indicated (CHADS2 score <1)

It is not clear whether dabigatran offers an advantage to patients with a propensity to miss doses. The anticoagulant effect of dabigatran is much shorter lived than that of warfarin, so missing one or two doses will leave them unprotected; at the same time these patients are likely to have unstable INR results and have poorer outcomes with warfarin as well.

Subgroup analysis of the major atrial fibrillation trial provided evidence that dabigatran was successfully used around the time of cardioversion; hence this appears to be an appropriate off-label indication for the use of the dabigatran. Use of dabigatran as a 'bridge' during interruption of warfarin therapy at time of surgery has not been formally evaluated; low molecular weight heparin has been better studied for this purpose and is recommended when a 'bridge' is felt to be appropriate.

Patients in whom use of dabigatran is not recommended:

Until more data are available, we recommend dabigatran NOT be preferred to warfarin in patients who have:

- renal insufficiency (estimated creatinine clearance 30-50 ml/min) or unstable renal function (on basis that drug accumulates in renal insufficiency)
- a history of untreated GI bleeding or propensity to lower GI bleeding
- weight less than 50kg. Consider reduced dose for smaller or frail individuals.
- age less than 16, as dabigatran has not been studied in children
- a record of stable anticoagulation control on warfarin maintaining more than 65% of INR results within therapeutic range (on basis of analysis showing no advantage accrues to populations with high quality INR control on warfarin)
- difficulty to swallow whole capsules. Capsules cannot be opened as this may dramatically affected drug absorption and increase risk of bleeding

Additionally, we recommend patients ≥ 80 yrs have special attention paid to their renal function. The Canadian product monograph recommends that they receive a lower dosage of 110 mg twice daily. This lower dose should also be considered in patients especially above 75 yrs with at least one other risk factor for bleeding.

Serum creatinine should be measured and estimated creatinine clearance (eGFR) calculated for every patient before dabigatran is prescribed. Creatinine levels should be monitored periodically in those with unstable renal function, and at least annually in the elderly.

Dabigatran has not been studied at this time for management of patients with acute coronary syndromes, ventricular thrombus, or mechanical heart valves and is not recommended for those patients. In general, "off label" use is discouraged until evidence is available supporting the use of dabigatran in these contexts. This caution also extends to other new oral anticoagulants (e.g. apixaban and rivaroxaban).

Monitoring

Dabigatran acts as a direct thrombin inhibitor. No monitoring has been validated for this agent and monitoring in general is not recommended. Dabigatran was given without monitoring or dose adjustment in the pivotal clinical trials.

The INR increases somewhat but is not very sensitive to the effect of dabigatran and cannot be used to assess or adjust dosing. In healthy volunteers on standard doses of dabigatran the INR is typically mildly elevated (about 1.2 – 1.8). **DABIGATRAN DOSE SHOULD NOT BE ADJUSTED TO ACHIEVE AN INR OF 2 TO 3 AS IS THE PRACTICE FOR WARFARIN.** Because of the influence on INR values, warfarin cannot be monitored if co-administered with dabigatran. In addition, a normal INR does not guarantee that the patient is no longer fully anticoagulated.

The aPTT is more sensitive to dabigatran, but different aPTT reagents vary in their sensitivity to the drug's effect. A normal aPTT makes it unlikely that therapeutic or supertherapeutic dabigatran levels are present in a bleeding patient for whom no history is available, and suggests that the drug effect has largely worn off in a patient previously taking it. However, beyond this, the aPTT does not reliably determine whether dabigatran levels are too high or too low.

Assays such as thrombin time or ecarin clotting time can be used to monitor dabigatran, but it should be noted that their clinical utility is not established. These assays are not available in any Manitoba laboratory at this time.

Management of surgery or procedures in patients on dabigatran

Prior to surgery or invasive procedures in any patient receiving dabigatran, an eGFR should be estimated. Dabigatran should be stopped 4 days before the procedure if the intervention is associated with a high bleeding risk OR if spinal/epidural analgesia is to be used OR if the eGFR is less than 80ml/min. Otherwise, dabigatran should be stopped at least 2 days before the procedure.. If the eGFR is < 50 mL/min, a longer period than 4 days (e.g. 6 days) should be considered, especially if the potential for catastrophic bleeding is high (e.g. neuraxial procedures).

It is reasonable to extrapolate that minor dental procedures and extractions may be performed in patients receiving dabigatran, with use of topical tranexamic acid (5% solution in saline, 15ml rinse and expectorate QID), as this is effective in warfarin-anticoagulated patients. It is recommended that the dental practitioner not ask the patient to stop dabigatran prior to minor dental procedures.

Management of bleeding on dabigatran

The most important consideration to minimize risk of bleeding is appropriate selection of patients and appropriate dosing of dabigatran. In published case reports, bleeding occurred in many cases when the patient was either a poor candidate for the drug because of renal insufficiency, or when the 150 mg dose strength was inappropriately given.

There is no specific antidote for the anticoagulant effect of dabigatran, and no good trials are available to guide recommendations for therapy of bleeding that occurs in a patient receiving dabigatran. Consultation is recommended. The following recommendations are based on general principles of hemostasis.

As in any bleeding patient, any correctable cause for bleeding should be addressed (e.g. vitamin K deficiency, thrombocytopenia, coagulation factor deficiency). Topical measures (direct pressure, fibrin sealant, hygroscopic hemostatic powders) should be employed where possible. Local measures for hemostatic control should also be used where appropriate (e.g. vessel embolization or ligation). Unlike warfarin, Vitamin K will not reverse the effects of dabigatran. Likewise, protamine has no effect to correct hemostasis in patients on dabigatran. Despite the lack of a specific antidote, it is notable that in the RE-LY trial, the case fatality rate of major bleeding episodes was lower in dabigatran-treated patients than in warfarin-treated patients.

Renal function should be assessed in any bleeding patient. The half-life of dabigatran is about 12 hours in the presence of normal renal function, so if the patient can be supported the bleeding effect should resolve in that time frame. However, with creatinine clearance < 30 mL/min, half life is \geq 24 hrs. Hemodialysis will remove about 2/3 of circulating dabigatran and can be considered if bleeding occurs in the context of renal failure, or if an overdose of the drug has been ingested.

If the drug was ingested within 2 hours of presenting to the emergency room, activated charcoal should be administered to reduce drug absorption.

There are limited animal data and no good clinical data to guide management of severe or life-threatening bleeding. Agents such as prothrombin complex concentrates (octaplexTM or BeriplexTM) and recombinant Factor VIIa (NiasaseTM) may be considered. Consultation with the Hematologist on-call is recommended (and necessary to access these hemostatic products).

Fresh frozen plasma should be used in preference to colloid and crystalloid solutions in major hemorrhage that necessitates massive transfusion, so as to avoid a superimposed dilutional coagulopathy. Plasma however does not reverse the effect of dabigatran as it does the effect of warfarin.

Other adjunctive measures that may be given to improve hemostasis non-specifically include DDAVP 20 mcg by slow i.v. infusion, and tranexamic acid (1 g i.v. or 1.5 g p.o. TID).

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