DABIGATRAN (PRADAXA®)

Thrombosis Canada
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OBJECTIVE:

To provide an overview of the mechanism of action, licensed indications, dosing regimens, and side effects of dabigatran.

MECHANISM OF ACTION:

Dabigatran is an oral direct thrombin (factor IIa) inhibitor. By binding reversibly to the active site of thrombin, dabigatran attenuates thrombin activity and reduces fibrin formation.

INDICATIONS:

Dabigatran is currently licensed in Canada for the following indications:

- Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.
- Treatment of venous thromboembolism events (deep vein thrombosis [DVT], pulmonary embolism [PE]) and prevention of recurrent DVT and PE.
- Prevention of DVT and PE after elective hip or knee replacement surgery.

DOSING:

1. **Prevention of stroke and systemic embolism in atrial fibrillation**: 110 mg twice daily (BID) or 150 mg BID. Patients aged 80 years and older or at higher risk of bleeding, including those 75 years of age or older with 1 risk factor for bleeding (e.g. clinical risk factor such as coagulation disorder, thrombocytopenia, functional platelet defect or recent bleed or invasive procedure; bacterial endocarditis, moderate renal impairment with creatinine clearance [CrCl] 30-50 mL/min; co-medication with NSAIDS, antiplatelet agents, selective serotonin re-uptake inhibitors, selective serotonin norepinephrine re-uptake inhibitors, or P-gp inhibitors [see Special Considerations: Drug Interactions below]) should be treated with a dose of 110 mg BID. All other patients should receive 150 mg BID. There is no recommended dose adjustment for patients with moderate renal impairment (CrCl 30 to 50 mL/min). Dabigatran is contraindicated in patients with CrCl <30 mL/min.
2. **Treatment of DVT and PE**: Dabigatran 150 mg BID is started after 5 to 10 days of initial treatment with a parenteral anticoagulant. Dose adjustment to 110 mg BID is recommended in patients as listed under Prevention of Stroke and Systemic Embolism in Atrial Fibrillation (above) but this regimen has not been evaluated in a venous thromboembolism (VTE) treatment clinical trial.

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There is no recommended dose adjustment in patients with moderate renal impairment (CrCl 30 to 50 mL/min). Dabigatran is contraindicated in patients with CrCl <30 mL/min.

3. **Thromboprophylaxis after hip or knee arthroplasty:** Start with 110 mg 1-4 hours after surgery (and establishment of hemostasis) and increase to 220 mg once daily starting the day after surgery; the 220 mg daily dose is continued for at least 10 days and up to 35 days. Patients with moderate renal impairment (CrCl 30-50 ml/min) may take a one-time dose of 75 mg followed by 150 mg daily.

MONITORING:

Laboratory monitoring of the anticoagulant effect of dabigatran is not recommended during routine clinical use. Periodic clinical assessment is important to determine and reinforce adherence, review comorbidity and medication changes, drug-drug interactions, and provide education. Furthermore, for most patients, at least yearly assessment of creatinine clearance is recommended. The creatinine should be measured more frequently in patients with an abnormal value at baseline or at risk of worsening renal function. [See **Clinical Resource: Direct Oral Anticoagulant (DOAC) Follow-Up Checklist for Clinicians; Direct Oral Anticoagulation (DOAC) Monitoring Checklist for Pharmacists**]

The prothrombin time/international normalized ratio (PT/INR) does not provide a reliable measure of the anticoagulant activity of dabigatran. The activated partial thromboplastin time (aPTT) is prolonged by dabigatran but the prolongation of the aPTT is reagent-dependent and the values plateau with higher dabigatran concentrations. Nonetheless, a prolonged aPTT with a sensitive reagent indicates the presence of dabigatran and a normal test renders high dabigatran levels unlikely. The thrombin clotting time (TCT) is the most sensitive assay for the presence of dabigatran. It is always prolonged in the presence of dabigatran, but it should not be used to monitor the anticoagulant activity. The dilute thrombin clotting time (commercially available as the Hemoclot® assay) shows a linear response with dabigatran plasma concentration. The ecarin clotting time also exhibits a linear response with dabigatran concentrations. However, these tests are not widely available and a therapeutic range for either test has not been established. [See the **Clinical Guide: NOACs/DOACs: Coagulation Tests**]

ADVERSE EFFECTS:

The major adverse effect of dabigatran is bleeding; concomitant use of antiplatelet drugs or strong P-glycoprotein inhibitors (see below under Special Considerations: Drug Interactions) increases this risk. Dabigatran should be avoided in patients with indwelling epidural catheters or recent spinal punctures in order to reduce the risk of epidural or spinal hematomas. Dabigatran may be associated with dyspepsia in up to 10% of users; the frequency of this complication can be reduced by having patients take the drug with meals. Dyspepsia usually resolves with time and may improve with the use of an anti-ulcer medication such as a proton pump inhibitor, but caution is advised as the absorption of dabigatran is decreased when co-administered with antacids containing aluminum, magnesium, or calcium.

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PERI-PROCEDURAL MANAGEMENT:

See **Clinical Guide: NOACs/DOACs: Peri-Operative Management** and the **Tool: Perioperative Anticoagulant Management**.

SPECIAL CONSIDERATIONS:

Administration and storage: Dabigatran may be taken with or without food. Capsules should be swallowed whole. The capsule should not be crushed, chewed or opened before swallowing. Capsules should be stored in their blister package to protect them from moisture.

Bleeding: Idarucizumab, a humanized antibody fragment against dabigatran, is now available as an antidote for dabigatran in situations of life-threatening or uncontrolled bleeding due to dabigatran. Idarucizumab, which is given as an intravenous bolus dose of 5 grams, rapidly reverses the anticoagulant effect of dabigatran. Approaches to the management of bleeding can be found in the **Clinical Guide: NOACs/DOACs: Management of Bleeding** and the **Tool: Bleed Management**.

Drug Interactions: Dabigatran absorption is decreased by agents that increase gastric pH (i.e. antacids containing magnesium or aluminum); however, there is no contraindication to concurrent use of proton pump inhibitors, though diminished clinical effect may occur.

Selective serotonin re-uptake inhibitors (SSRIs) increased the relative risk of bleeding by 50-100% and selective serotonin norepinephrine re-uptake inhibitors (SNRIs) increased bleeding by 100% in atrial fibrillation on dabigatran. Concomitant use of these drugs should be undertaken with caution.

Because dabigatran etexilate is a substrate of the P-glycoprotein transport system, potent inhibitors or inducers are expected to alter plasma levels of dabigatran.

a) *Inhibitors of P-glycoprotein:* Drugs that inhibit this transport system can increase systemic exposure to dabigatran. Concomitant use of the strong P-glycoprotein inhibitors (e.g. ketoconazole, dronedarone) is contraindicated. Caution is advised if taken with moderate inhibitors (e.g. cyclosporine, itraconazole, ritonavir, nelfinavir, saquinavir, tipranavir, posaconazole, and tacrolimus). Patients who are taking the P-glycoprotein inhibitors verapamil and quinidine should take the dabigatran dose 2 hours prior to a dose of verapamil or quinidine. No dosage adjustment to dabigatran is recommended for patients concurrently taking these interacting medications for atrial fibrillation or VTE treatment, but dose reduction to 150 mg once daily is recommended by the manufacturer for thromboprophylaxis in hip or knee replacement.

b) *Inducers of P-glycoprotein*: Drugs that induce P-glycoprotein can decrease the systemic exposure to dabigatran. Co-administration with potent inducers such as carbamazepine, phenytoin, rifampin, and Saint John's wort should be avoided.

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Renal and hepatic dysfunction: Dabigatran is contraindicated in patients with CrCl <30 mL/min. Dose modification is not needed in patients with hepatic impairment, but dabigatran should be used with caution in those with cirrhosis or baseline coagulopathy who are at high risk of bleeding.

Mechanical heart valves: Dabigatran is contraindicated in patients with mechanical heart valves due to increased rates of thrombotic and bleeding complications when compared to warfarin.

Pregnancy and breast feeding: Dabigatran crosses the placenta and should not be used in pregnancy. Small amounts of dabigatran were found in the breast milk of two women treated with a single oral dose of dabigatran 220 mg. The impact of repeated dosing and potential effects on nursing infants of women taking dabigatran is unknown.

Pediatrics: Dabigatran is not recommended for use in anyone under the age of 18 until ongoing studies establish the pharmacokinetics, pharmacodynamics, safety, and efficacy of dabigatran.

Cancer-associated thrombosis: No randomized trials comparing the use of dabigatran and LMWH for cancer-associated thrombosis have been published. Dabigatran should be avoided until safety and efficacy data is published. Further information can be found in the **Clinical Guide: Cancer and Thrombosis.**

Post percutaneous coronary intervention (PCI): Although there is no specific indication for dabigatran in this setting, the REDUAL PCI study suggests that in patients with nonvalvular atrial fibrillation undergoing percutaneous coronary intervention (PCI) for coronary artery disease, dual therapy with clopidogrel or ticagrelor and dabigatran (110 mg or 150 mg BID) is associated with significant reduction in major and clinically relevant non-major bleeding (15.4% in the 110-mg dual-therapy group as compared with 26.9% in the triple-therapy group [hazard ratio, 0.52; 95% confidence interval [CI], 0.42 to 0.63] and 20.2% in the 150-mg dual-therapy group as compared with 25.7% in the corresponding triple-therapy group [hazard ratio, 0.72; 95% CI, 0.58 to 0.88]) and similar risks of thrombosis when compared to triple therapy with warfarin, clopidogrel or ticagrelor, and ASA.

OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES, RESOURCES, AND TOOLS:

- Cancer and Thrombosis
- NOACs/DOACs: Comparison and Frequently Asked Questions
- NOACs/DOACs: Coagulation Tests
- NOACs/DOACs: Management of Bleeding
- NOACs/DOACs: Peri-Operative Management
- Stroke Prevention in Atrial Fibrillation
- Thromboprophylaxis: Orthopedic Surgery
- Clinical Resource: Direct Oral Anticoagulant (DOAC) Follow-Up Checklist for Clinicians
- Clinical Resource: Direct Oral Anticoagulation (DOAC) Monitoring Checklist for Pharmacists
- Tool: Perioperative Anticoagulant Management Algorithm
- Tool: Bleed Management

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