CLOT

Is Dabigatran (Pradaxa®) an Option for Your Patient?
(Note: A generic product is on the market. Availability on provincial formularies varies by province)

Indications
- Non-Valvular Atrial Fibrillation (NVAF)* to prevent stroke & systemic embolism
- Acute VTE treatment & prevention of recurrent VTE [for deep vein thrombosis (DVT) and pulmonary embolism (PE)]
- Prevention of venous thromboembolic events (VTE) in elective total hip or knee replacement surgery (THR, TKR)
  * CCS definition: AF without mechanical heart valves or without moderate/severe mitral stenosis (rheumatic and non-rheumatic)

Requirements - NOTE: Dabigatran accumulates in renal dysfunction.
- Stable creatinine clearance (CrCl) 30 mL/min or more

Contraindications
- Mechanical heart valves
- Dabigatran, like other anticoagulants, is contraindicated in patients at high risk for bleeding
- Pregnant/Breastfeeding: Safety & dosing has not been studied. Use is NOT recommended
- Drug Interactions: Significant drug interactions involving P-glycoprotein - See below.

Potential Limitations
- Not recommended in hemodynamically unstable acute PE or those requiring thrombectomy or thrombolysis
- Not recommended in antiphospholipid syndrome with a history of thrombosis (especially triple positive)
- Drug Interactions: AVOID rifampin, select azole antifungals & anticonvulsants, HIV protease inhibitors, glecaprevir/pibrentasvir, ticagrelor, St. John’s Wort, and other strong P-gp inducers and inhibitors as there is minimal knowledge of clinical outcomes
- Rapid decline in anticoagulant effect after a missed dose; adherence is critical
- Limited data supporting the use in extremes of weight (under 50 kg; over 120 kg or BMI > 40)
- Less than 18 years of age: Safety and dosing has not been established
- Acute treatment of VTE: Must be preceded by 5-10 days of parenteral anticoagulant
- Dyspepsia
- AF: dabigatran 150mg BID showed higher GI bleed rate than warfarin, but no difference in overall bleeding events
- Product monograph indicates must remain in original blister package or manufacturer’s bottle. Recent data indicates stability outside of the manufacturer’s packaging, but the clinical implications of this storage are not yet known

May offer an advantage over warfarin if:
- Difficulty stabilizing on warfarin for reasons other than poor medication adherence
- INR monitoring is problematic (e.g. poor venous access, frequent travel, remote location).
- AF: superior reduction in rate of stroke and systemic embolism with dabigatran 150 mg bid, lower rate major bleeding with 110 mg bid, lower intracranial hemorrhage with both doses vs. warfarin
- Availability of idarucizumab for emergency surgery/urgent procedures or life-threatening/ uncontrolled bleeding

Dosing Recommendations

<table>
<thead>
<tr>
<th>Indication</th>
<th>CrCl 50 mL/min or greater</th>
<th>CrCl 30–49 mL/min</th>
<th>CrCl less than 30mL/min</th>
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</thead>
<tbody>
<tr>
<td>Stroke Prevention in Non-Valvular Atrial Fibrillation</td>
<td></td>
<td></td>
<td>Contraindicated</td>
</tr>
<tr>
<td></td>
<td>• 150 mg BID</td>
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<td></td>
<td>• 110 mg BID if ≥ 80 years of age. Also consider if &gt;75 years old and ONE or more risk factor for bleeding (e.g. CrCl 30 - 49 mL/min, on antiplatelets, or interacting medication, etc.)</td>
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<td>Acute DVT/PE Treatment</td>
<td>Parenteral Anticoagulant x 5-10 days, then dabigatran as per AF dosing</td>
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<tr>
<td>Hip &amp; Knee Replacement</td>
<td>110 mg initial dose*, then 220 mg once daily x 10 (THR) to 28-35 days (THR)</td>
<td>75 mg initial dose*, then 150 mg once daily x 10 (TKR) to 28-35 days (THR)</td>
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* 110 mg BID dose not studied for VTE treatment, but is suggested as per AF indication above
*Initiate 1-4 h after surgery once hemostasis secured. If not started day of surgery, initiate with 220 mg once daily
Monitoring Patients on Dabigatran

- CrCl should be determined at baseline and at least annually. Monitor more frequently if older than 75y, with renal dysfunction (CrCl <60 mL/min), or when a decline in renal function suspected
- Monitor for symptoms and signs of bleeding
- No routine coagulation testing required. NOTE: INR is not useful for monitoring. Do not target INR 2 to 3.
- If excess anticoagulation suspected, or to determine presence of dabigatran, an aPTT or more specifically a Thrombin Time (TT) may be considered. Normal values indicate little to no dabigatran present; however, a normal aPTT does not exclude presence of residual dabigatran. Specialized testing (e.g. dilute TT, Hemoclot™) may not be widely available, and should only occur in consultation with an expert in anticoagulation.

Switching Between Agents 1

From warfarin to dabigatran:
- Discontinue warfarin and start dabigatran once INR is less than 2

From non-warfarin anticoagulant (oral or parenteral - e.g. LMWH, rivaroxaban, apixaban, edoxaban) to dabigatran:
- Start dabigatran 0 - 2 hours before the next scheduled dose of non-warfarin anticoagulant was to be administered
- For agents administered by continuous infusion, stop the infusion and start dabigatran at the same time

From dabigatran to warfarin:
- Start warfarin and only discontinue dabigatran once INR is 2 or greater

Management of Bleeding Episodes with Dabigatran

- Idarucizumab (Praxbind™) is a rapid acting, target specific antidote, administered as an IV infusion / IV bolus for life threatening/uncontrolled bleeding or for emergency surgery/urgent procedures 8
- Vitamin K, protamine, tranexamic acid, and/or plasma will not reverse drug effects
- In the event of major hemorrhagic complications, discontinue dabigatran and refer patient for urgent assessment and locally developed management strategies
- PCC/activated PCC may reverse anticoagulant effect 10, but the effect of these agents on bleeding outcomes is limited

Anticoagulation around Invasive Procedures 11 (e.g. surgery, elective day procedures, major dental procedures)

- As with warfarin, very low risk bleed procedures (such as dental extraction) do not require withholding dabigatran
- Management plans should be made in consultation with the provider performing the procedure
- Renal function significantly impacts clearance of dabigatran. If the recommendations below cannot be met, consultation with an expert in anticoagulation management is encouraged.
- Due to the onset/offset time of dabigatran, peri-procedural use of LMWH is not required

Pre-Procedure - If required, stop dabigatran before procedure as follows:

<table>
<thead>
<tr>
<th>Renal function# (CrCl mL/min)</th>
<th>Last intake of drug prior to procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Bleeding Risk</td>
<td>High Bleeding Risk*</td>
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<tr>
<td>80 or more</td>
<td>at least 24 hours</td>
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<tr>
<td>50 - 79</td>
<td>at least 36 hours</td>
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<tr>
<td>30 - 49</td>
<td>at least 48 hours</td>
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# If CrCl less than 30 mL/min, dabigatran is contraindicated: Hold drug at least 5 days 4
* Make a careful decision (i.e. hold longer) for patients undergoing major surgery, spinal puncture, or other regional anaesthesia in whom complete hemostasis is required. Consult specialist in these high risk patients/procedures.

For an interactive perioperative management algorithm, see Thrombosis Canada website: http://thrombosiscanada.ca/?page_id=502&calc=perioperativeAnticoagulantAlgorithm

Post Procedure: Resumption should not be initiated until adequate hemostasis has been achieved and clinical situation allows (usually 1 -3 days). NOTE: Full therapeutic effect occurs approximately 2 hours after ingestion.

References:
9. Pradaxa® Full Prescribing Information (Boehringer Ingelheim Pharmaceuticals, Inc. USA),July 2020.