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Is Dabigatran (Pradaxa®) an Option for Your Patient?

(Note: A generic product is on the market. Availability on provincial formularies varies by province)

Indications[1]

- ❑ 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)[2]

Requirements[1] - NOTE: Dabigatran accumulates in renal dysfunction.

- ❑ Stable creatinine clearance (CrCl) 30 mL/min or more

Contraindications[1,2]

- ❑ Mechanical heart valves [1,3]
- ❑ 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[1]

- ❑ 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)[4]
- ❑ 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[5]
- ❑ Product monograph indicates must remain in original blister package or manufacturer's bottle.[1] Recent data indicates stability outside of the manufacturer's packaging, but the clinical implications of this storage are not yet known[6]

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[5]
- ❑ Availability of idarucizumab for emergency surgery/urgent procedures or life-threatening/ uncontrolled bleeding.[7,8]

Dosing Recommendations[1]

Indication	CrCl 50 mL/min or greater	CrCl 30–49 mL/min	CrCl less than 30mL/min
Stroke Prevention in Non-Valvular Atrial Fibrillation	• 150 mg BID • 110 mg BID if ≥ 80 years of age. Also consider if >75 years old and ONE or more risk factor for bleeding (e.g. CrCl 30 - 49 mL/min, on antiplatelets, or interacting medication, etc.)		Contraindicated
Acute DVT/PE Treatment	Parenteral Anticoagulant x 5-10 days, then dabigatran as per AF dosing#		
Hip & Knee Replacement	110 mg initial dose*, then 220 mg once daily x 10 (TKR) to 28-35 days (THR)	75 mg initial dose*, then 150 mg once daily x 10 (TKR) to 28-35 days (THR)	

110 mg BID dose not studied for VTE treatment, but is suggested as per AF indication above[1]

*Initiate 1-4 h after surgery once hemostasis secured. If not started day of surgery, initiate with 220 mg once daily

 Collaborative Learning on Thrombosis (CLOT) – Canadian Prairie pharmacists with an interest in thromboembolic disorders

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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

From dabigatran to non-warfarin anticoagulants (oral or parenteral): (e.g. LMWH, rivaroxaban, apixaban, edoxaban)

- CrCl 30 mL/min or greater: Give 1st dose of non-warfarin anticoagulant 12 hours after the last dose of dabigatran
- CrCl Less than 30 mL/min: Give 1st dose of non-warfarin anticoagulant 24 hours after the last dose of dabigatran[9]

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:

Renal function# (CrCl mL/min)	Last intake of drug prior to procedure	
	Low Bleeding Risk	High Bleeding Risk*
80 or more	at least 24 hours	at least 48 hours
50 - 79	at least 36 hours	at least 72 hours
30 - 49	at least 48 hours	at least 96 hours

If CrCl less than 30 mL/min, dabigatran is contraindicated: Hold drug at least 5 days[1]

* 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:

1. Product Monographs: a) Pradaxa® Product Monograph (Boehringer Ingelheim Canada), March 23, 2020. b) Apo-Dabigatran Product Monograph (Apotex, Inc. Canada), July 30, 2020. **2.** Andrade JG et al. Can J Cardiol 2020; 36: 1847-1948. **3.** Eikelboom JW, et al. N Engl J Med 2013;369(13):1206-14. **4.** Direct oral Anticoagulants in Obese Patients. Thrombosis Canada Website: https://thrombosiscanada.ca/wp-content/uploads/2020/06/DOACS-in-Obesity_24June2020.pdf. Accessed March 15, 2021. **5.** Connolly SJ, et al. N Engl J Med 2009;361(12):1139-51. **6.** Wang EH, et al. Can J Hosp Pharm 2015;68(1): 16-21. **7.** Pollack CV, et al. N Engl J Med 2017;377:431-441. **8.** Praxbind™. Product Monograph Including Patient Medication Information. (Boehringer Ingelheim, Burlington, Ontario). April 29,2016. **9.** Pradaxa® Full Prescribing Information (Boehringer Ingelheim Pharmaceuticals, Inc. USA),July 2020. **10.** Eerenberg ES, et al. Circulation 2011;124(14):1573-9. **11.** Steffel J, et al. Eur Heart J 2018; 39:1 330-1393.