Mechanism of Action: Direct Thrombin Inhibitor

BACKGROUND
Dabigatran is a direct thrombin inhibitor (DTI) that is administered orally. It inhibits both free and clot-bound thrombin. It is currently indicated for the prevention of thromboembolic events in patients with non-valvular atrial fibrillation only, but these indications are expected to expand in the future.

Dabigatran is indicated in Canada for:
• prevention of stroke and systemic embolism in patients with atrial fibrillation, in whom anticoagulation is appropriate
• prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip replacement (THR) or total knee replacement (TKR) surgery
• treatment of venous thromboembolism events (deep vein thrombosis [DVT], pulmonary embolism [PE]) and prevention of recurrent DVT and PE

Place in Therapy at UHN
Dabigatran is approved at UHN for:
• prevention of stroke and systemic embolism in patients with atrial fibrillation and a CHADS2 score equal to or greater than 1.

Dose for ATRIAL FIBRILLATION
• Usual dose: 150 mg orally twice daily
• Low dose: 110 mg orally twice daily (recommended for patients over 75 years old)

Pharmacologic Profile and Laboratory Monitoring
• There is no specific antidote. Reversal of anticoagulant effect is theoretically possible with factor VIIa, but clinical data are lacking.
• Dabigatran prolongs the activated partial thromboplastin time (aPTT) in a non-linear manner and it “plateaus” at high concentrations.
• Thrombin time (TT) is very sensitive to dabigatran therapy and displays a linear dose-response relationship at therapeutic concentrations.
• NORMAL aPTT and/or TT are good indicators that there is little or no anticoagulant activity of dabigatran present. However, high aPTT or TT do not correlate with degree of anticoagulation and are therefore not useful for routine monitoring.
• Serum creatinine, creatinine clearance (CrCl) at baseline and every 6-12 months

Onset: immediate

Peak Effect: 0.5-2 hours

Bioavailability: 3–7% in capsule; may increase by 75% if capsule is breached

Half Life: 12–17 hours with normal kidney function

Elimination: 80% is excreted unchanged in urine; consequently, half life and potency increase in patients with renal dysfunction. It is contraindicated in patients with severe renal impairment.

Contraindications
• high bleeding risk
Cardiac Diseases and Therapies
ATRIAL FIBRILLATION
DABIGATRAN CLINICIAN SUMMARY

Recent GI bleed, extensive stroke within the last 6 months, patients with bleeding disorders
• concomitant use with ketoconazole
• severe renal impairment (CrCl) less than right hip # 2* unwitnessed fall at NH. ORIF Feb 14. intra-op SVT during extubation and again in PACU, both episodes broke with adenosine (given 11mg total). 30 mL/min

Precautions
• Concomitant use of antiplatelet agents
  – Caution is advised in patients already taking other antiplatelet agents, e.g., Aggrenox®, ASA, clopidogrel, prasugrel, ticagrelor, etc.
• Liver Disease
  – Patients with Child-Pugh classification B and C, or with serum liver function tests higher than 2x upper limit of normal (ULN), or with hepatitis A, B and C were excluded from atrial fibrillation (AF) trials.
• Pharmacokinetic drug interactions
  – Concomitant use with strong P-glycoprotein (P-gp) inhibitors, such as itraconazole, tacrolimus, cyclosporine, ritonavir, tipranavir, nelfinavir and saquinavir, has not been studied and may increase bleeding risk.
  – Although no dose adjustment is recommended, caution is advised in using dabigatran with other P-gp inhibitors, e.g., amiodarone, and P-gp inducers, e.g., rifampin. A summary of studied drug interactions affecting dabigatran blood concentrations is provided below. However, this list is not all-inclusive.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on dabigatran concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td></td>
</tr>
<tr>
<td>Antacids*</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td></td>
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<tr>
<td>Clarithromycin</td>
<td></td>
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<tr>
<td>Pantoprazole</td>
<td></td>
</tr>
<tr>
<td>Rifampicin</td>
<td>(combined use should be avoided)</td>
</tr>
<tr>
<td>Verapamil*</td>
<td></td>
</tr>
<tr>
<td>Quinidine</td>
<td></td>
</tr>
</tbody>
</table>

*Give 2 hours prior to dabigatran

Adverse Effects
• bleeding
• dyspepsia

Administration
• The capsule should be swallowed whole and not crushed, chewed or opened to avoid unintentional increase in bioavailability and risk of bleeding.
• Can be taken with or without food.

SWITCHING TO DABIGATRAN from OTHER AGENTS
• Switching from intermittent parenteral anticoagulants, e.g., low molecular weight heparin (LMWH)
Patients on intermittent parenteral anticoagulants who are switching to dabigatran can do so 0–2 hours before the NEXT dose of the parenteral anticoagulant is due.

- **Switching from continuous parenteral anticoagulants**, e.g., heparin infusions
  - If switching to dabigatran from continuous infusions, e.g., heparin infusion, administer the first dose of dabigatran at the time of discontinuation.
- **Switching from warfarin**
  - Due to its faster onset, patients should be initiated on dabigatran only when the INR is less than 2.0 after warfarin discontinuation.

**SWITCHING FROM DABIGATRAN to OTHER AGENTS**
- **Switching to intermittent parenteral anticoagulants**, e.g., LMWHs
  - Patients on dabigatran who are switching to parenteral anticoagulants (e.g., LMWHs), for the indication of continued anticoagulation for the prevention of stroke, should wait 12 hours before switching.
- **Switching to warfarin**
  - Due to its delay in reaching therapeutic INR, warfarin should be started 2-3 days before dabigatran discontinuation in patients with creatinine clearances greater than 30 mL/min.

**NEURAXIAL ANESTHESIA AND DABIGATRAN**

For patients whose procedures involve spinal/neuraxial blockade, the timing of discontinuation should be determined through consultation with Anaesthesia and the patient’s surgeon

There is limited experience with the use of a DTI in the setting of neuraxial anesthesia. The ASRA guidelines from 2010 (3rd edition) state the following: "Although there have been no reported spinal hematomas, the lack of information regarding the specifics of block performance and the prolonged half-life warrants a cautious approach."

Based on its pharmacokinetic properties and to be consistent with current guidelines for other anticoagulation agents, we recommend the following at UHN

- **Discontinue the drug 5 days prior to neuraxial intervention.** This will ensure adequate time for cessation of action of the drug in the majority of patients (see table below).

  **Note:** May need to consider bridging for select patients at very high risk of stroke.

- The **first dose** of dabigatran may be administered **not earlier than 6 hours** following spinal anesthesia, lumbar plexus block or epidural catheter removal.
- Dabigatran should **not** be administered to a patient with an indwelling epidural catheter and should **not** be administered until 6 hours after the removal of an epidural catheter.
- Indwelling neuraxial (spinal, epidural or lumbar paravertebral/lumbar plexus) catheters are **not** recommended during active dabigatran therapy. Due to the fast onset of action and prolonged half life of the drug, there will be no adequate window to safely remove an epidural/lumbar plexus catheter while a patient is on this drug.
- Neuraxial anesthesia (spinal, epidural or lumbar plexus block) should likely not be performed on a patient receiving therapeutic doses of dabigatran if the drug has not been withheld for the recommended period of time or the aPTT is outside of the normal range. In case of urgent/emergency surgery, a benefit/risk analysis should be performed. If a neuraxial technique is
strongly indicated over other alternatives, consider an attempt of reversal with Factor VIIa and confirm a normal aPTT or TT before neuraxial block. Hematology advice may be warranted in such instances, as there are risks of overcorrection with this approach.

**PERIPROCEDURAL/PERIOPERATIVE MANAGEMENT**

**ELECTIVE SURGICAL PROCEDURES**

Consider both the risk of bleeding in the patient and the surgical bleeding risk.


Hold dabigatran as per patient’s creatinine clearance:

<table>
<thead>
<tr>
<th>Calculated Creatinine Clearance</th>
<th>Procedures with low risk of bleeding*</th>
<th>Procedures with moderate to significant risk of bleeding*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater or equal to 50 mL/min</td>
<td>24 hours</td>
<td>2 to 4 days</td>
</tr>
<tr>
<td>Between 30 to 50 mL/min</td>
<td>At least 2 days</td>
<td>4 days</td>
</tr>
<tr>
<td>Less than 30 mL/min</td>
<td>2 to 5 days</td>
<td>At least 5 days</td>
</tr>
</tbody>
</table>

* see list of procedures and bleed risk under UHN Periprocedural Hemostasis Policy

Note: Cardiac catheterizations may be considered a procedure with a low or high risk of bleeding. Please check with the interventionalist or cardiac triage.

**When Is Bridging Required?**

As per UHN Periprocedural Hemostasis Policies, consult hematology for discussion of bridging anticoagulation in patients with:

- mechanical heart valves
- Atrial fibrillation with prior neurologic event
- Recent (less than 3 months ago) venous thromboembolism
- Intracardiac thrombus
- Antiphospholipid syndrome

**When to Resume Dabigatran Post-procedure**

Time to resume dabigatran depends on the postoperative risk of bleeding.

When dabigatran has been withdrawn for an invasive procedure, therapy can be restarted 1 day after hemostasis is established post-procedure. (usually 48 hours for a procedure with a low risk of bleeding and 72 hours for a procedure with an intermediate or high risk of bleeding).

For procedures such as major abdominal surgery or urologic surgery with incomplete hemostasis, dabigatran should only be resumed when there is no drainage or other evidence of active bleeding.
ACUTE CORONARY SYNDROMES
For patients who arrive in the emergency department on dabigatran and who need treatment for acute coronary syndrome:

Check aPTT, if aPTT is:
• greater than 1.5 x ULN, repeat every 4 hours until less than 1.5 x ULN, then start heparin or other anticoagulation
• greater than 1.2 but less than 1.5 x ULN start unfractionated heparin without loading dose or start fondaparinux or low-molecular-weight heparin
• less than 1.2 x ULN, proceed as with any patient not on dabigatran

Percutaneous Coronary Intervention: Use activated clotting time (ACT) and administer unfractionated heparin per ACT according to usual practice.

ASPIRIN THERAPY
Always re-assess indication for ASA when starting dabigatran. If it was previously prescribed for the sole indication of stroke prevention in atrial fibrillation, ensure ASA is discontinued when dabigatran is initiated.

MANAGEMENT OF BLEEDING COMPLICATIONS/REVERSAL OF DABIGATRAN
• Contact poison control for most up to date guidelines
• Idarucizumab (Dabigabind) antidote awaiting FDA approval pending approval, limited clinical data regarding reversal; expert opinion indicates:
  – for overdose, activated charcoal may be effective but must be given within 1-2h
  – Hemodialysis removes some dabigatran; however it’s use for managing bleeding complications has not been established
  – Maintain diuresis
  – Supportive measures for severe bleeding:
    ▪ transfusion of blood products
    ▪ Hematology consult should be obtained for assistance with administration of blood products and reversal agents
    ▪ administration of reversal agents such as Activated Factor VII (NovoSeven®) or Activated Prothrombin complex concentrates (FEIBA®)
    ▪ Refer to UHN Bleeding Management Pathway for Patients Receiving Dabigatran, below.
REFERENCES


UHN BLEEDING MANAGEMENT PATHWAY FOR PATIENTS RECEIVING DABIGATRAN

**Notes:**
- \( t_{1/2} \) is 11-17 hours in normal renal function
- 80% of drug is cleared via the kidneys

**Patient with bleeding on dabigatran**

**Obtain:**
- CBC
- creatinine
- aPTT

**aPTT demonstrates presence of dabigatran in the absence of coagulopathy**

If aPTT >40 sec, consult Hematology.

**Minor bleeding**
- Hold dabigatran
- Supportive care

**Moderate-severe bleeding**
- Supportive Care (compression, surgery)
- Fluid → diuresis
- Transfuse PRBCs
- Oral charcoal if last dose <2 hours before

**Life-threatening bleeding**
- Invoke Massive Transfusion Protocol
- Consider Factor VIIa
- Hemodialysis might be helpful

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1. Do not transfuse FFP to reverse \( \uparrow \) aPTT
2. Refer to UHN Clinical Policy 3.130.004, Massive Transfusions
3. Factor VIIa (off label) dose per Hematology

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**Updated by:** Amanda Chan, BScPhm, ACPR, Jessica Koo, BScPhm, ACPR – February 2015
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The contents of this Handbook are approved and endorsed by the UHN Cardiovascular Subcommittee of the Pharmacy and Therapeutics Committee.

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Notice to Healthcare Providers:

The Pharmacotherapy Handbook is intended to be used as a tool to aid in the appropriate prescribing and administration of cardiovascular formulary agents.

This information in this Handbook is intended for use by and with experienced physicians and pharmacists. The information is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about Cardiovascular illness and the treatments in question.

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