

# Management of Dabigatran in Adults



Dabigatran is an oral anticoagulant that acts as a direct thrombin inhibitor. It is approved as an alternative to warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Dabigatran is **not approved** for other indications, such as prevention or treatment of pulmonary embolism or deep vein thrombosis.

## INITIATION OF THERAPY

Patient-specific considerations for initiation of dabigatran therapy include the following:

- **Indication for therapy.** Patients must have non-valvular atrial fibrillation with risk factors that warrant therapeutic anticoagulation (i.e., CHADS<sub>2</sub> score  $\geq$  1).
- **Renal function.** A baseline serum creatinine is required for drug dosing (see table below).
- **Oral intake.** Patients must be able to swallow capsules. Dabigatran capsules may not be opened or crushed, as this significantly increases bioavailability and thus risk of bleeding.
- **Cost of therapy.** Whether patients can afford dabigatran must also be considered, as costs may exceed \$200 per month.

**TABLE 1. Initial Dabigatran Dose**

Renal Function <sup>a</sup> (CrCL ml/min)	> 30	15- 30	< 15
Recommended Starting Dose <sup>b</sup>	150 mg BID	75 mg BID	Do not use
<sup>a</sup> For the purpose of dabigatran dosing, renal function should be estimated by the Cockcroft-Gault method. It is not appropriate to use the CrCL (MDRD method) automatically reported in the WebCIS lab section . Cockcroft-Gault equation: $CrCl = [(140 - \text{age}) \times \text{weight (kg)}] / (\text{SCr} \times 72)$ (x 0.85 if female)			
<sup>b</sup> The median weight of patients treated with dabigatran in RE-LY was 82.5±19.4 kg. No information is available on its safety and efficacy in overweight or obese patients and anti-Xa levels are not useful for guiding drug dosing.			

## CONVERSION TO DABIGATRAN

**TABLE 2. Converting to Dabigatran**

Agent	Conversion Instructions
Heparin	Start dabigatran at the time the heparin infusion is turned off.
Enoxaparin	Start dabigatran at the time the next dose of enoxaparin was to be administered (may overlap by up to 2 hours). If enoxaparin was adjusted for renal function, dabigatran may also require dose adjustment (see Table 1 above).
Warfarin	Discontinue warfarin and start dabigatran when the INR is < 2.0.

## CONVERSION FROM DABIGATRAN

The following recommendations are based on the approved labeling for the use of dabigatran in patients with atrial fibrillation. Considering the risk of stroke and embolism in each patient (i.e., CHADS<sub>2</sub> score, cardioversion), it may be reasonable to continue dabigatran until the INR is 2–3.

These guidelines do not reflect the practice of overlapping parenteral anticoagulants and warfarin for 5 days in the treatment of pulmonary embolism (PE) or deep vein thrombosis (DVT). Dabigatran is **NOT** approved at this time for the treatment of PE or DVT. Overlapping beyond the number of days recommended below may be considered on an individual basis assessing the risk of embolism and bleeding. (*Jaff M. Circulation. 2011;123:00.*)

**TABLE 3. Converting Dabigatran to Warfarin**

Renal Function (CrCL mL/min)	Conversion Instructions <sup>a</sup>
> 50	Start warfarin and overlap with dabigatran for 3 days. Discontinue dabigatran on day 4.
31 – 50	Start warfarin and overlap for 2 days with dabigatran. Discontinue dabigatran on day 3.
15 – 30	Start warfarin and overlap for 1 day with dabigatran. Discontinue dabigatran on day 2.
< 15	Start warfarin and overlap for 1 day with dabigatran. Discontinue dabigatran on day 2. This patient should not resume dabigatran therapy. <sup>b</sup>

<sup>a</sup> Dabigatran may contribute to an elevated INR for up to 2 days after discontinuation.  
<sup>b</sup> No data exist in patients with CrCL < 15 mL/min or in patients on hemodialysis. Recommendations are extrapolated from pharmacokinetic data and comparison of relative risks and benefits.

**TABLE 4. Converting Dabigatran to Parenteral Anticoagulants (Heparin, Enoxaparin)**

Renal Function (CrCL mL/min)	Conversion Instructions <sup>a</sup>
≥ 30	Start parenteral anticoagulant 12 hours after last dabigatran dose.
< 30	Start parenteral anticoagulant 24 hours after last dabigatran dose.

<sup>a</sup> Methods for converting dabigatran to heparin have not been studied and are based on the pharmacokinetics of the drug. Clinical decisions should be made based on patient-specific risk of bleeding vs. thromboembolism.

## PERIOPERATIVE MANAGEMENT

**TABLE 5. Discontinuation of Dabigatran Prior to Inpatient or Outpatient Procedures**

Renal Function (CrCL mL/min)	Half-life (hours), mean (range)	Timing of Discontinuation Prior to Procedure (Minimum)	
		Standard Risk of Bleeding <sup>a</sup>	High Risk of Bleeding <sup>b</sup>
> 80	13 (11 – 22)	24 hours	2 – 4 days
50 – 80	15 (12 – 34)	24 hours	2 – 4 days
30 – 50	18 (13 – 23)	≥ 48 hours	≥ 4 days
< 30	27 (22 – 35)	48 – 120 hours	≥ 5 days

<sup>a</sup> Examples: electrophysiology procedures, cardiac catheterizations, no additional patient-specific risk factors.  
<sup>b</sup> Examples: surgery involving major organs, procedures requiring complete hemostasis (e.g., spinal anesthesia), or when additional patient-specific risk factors are present.  
*Adapted from van Ryn, J. Thromb Haemost. 2010 Jun;103(6):1116-27.*

### Bridging with Parenteral Anticoagulants for Procedures

For patients at high risk of thromboembolic events in whom invasive procedures are planned, some clinicians may wish to bridge with parenteral anticoagulants (e.g., unfractionated heparin, enoxaparin). The necessity for this depends on a patient's risk for thromboembolism while off anticoagulation, and for bleeding if on anticoagulants. This may be performed by (1) converting dabigatran to the desired parenteral anticoagulant as described in Table 4, and (2) continuing to hold dabigatran for the minimum amount of time recommended in Table 5, based on an individual patient's renal function and risk of bleeding. Parenteral anticoagulation may then be discontinued prior to the planned procedure according to usual standards of care.

## DENTAL PROCEDURES

Many dental procedures can be safely performed on full-dose dabigatran, as the risk of complications is considered similar to that of therapeutic anticoagulation with warfarin. Consider the risk of bleeding versus risk of thromboembolism when deciding to hold doses of dabigatran. Dental procedures which require partial or complete reversal of anticoagulation with warfarin may require temporary discontinuation of dabigatran.

## ADVERSE EFFECTS

Compared to warfarin, more patients discontinue dabigatran due to its adverse effects. The most common non-hemorrhagic adverse effects are GI-related and may include dyspepsia, nausea, upper abdominal pain, and diarrhea. Although overall bleeding rates between dabigatran and warfarin are similar in clinical trials, dabigatran is associated with a greater risk of gastrointestinal bleeding compared to warfarin (i.e., 1.5% per year with dabigatran vs. 1.1% per year with warfarin) (*N Engl J Med.* 2009; 361(12):1139-51).

### Management of Dabigatran-Related Bleeding Events

There is no pharmacologic antidote for dabigatran, so management of hemorrhagic complications is primarily supportive. Dabigatran is mostly excreted in the urine (80%), so appropriate diuresis must be maintained in order to promote adequate drug clearance. An outline for supportive management of dabigatran-related bleeding events based on bleeding severity is provided in Table 6.

**If patients require pharmacologic therapy to manage hemorrhagic complications, a Hematology/Coagulation consult is also required.**

**TABLE 6. Management of Dabigatran-Related Bleeding Events**

Bleeding Severity	Management Recommendations
Mild – Moderate	Delay next dose or discontinue dabigatran.
Severe or Life-threatening	<p><i>Consider any of the following based on bleeding severity:</i></p> <ul style="list-style-type: none"> <li>• Symptomatic treatment</li> <li>• Mechanical compression</li> <li>• Surgical intervention</li> <li>• Fluid replacement and hemodynamic support</li> <li>• Blood product transfusion</li> <li>• Oral activated charcoal (if last dabigatran dose ingested within 2 hours) Dose: Liquid charcoal with sorbitol 50 g PO x 1 dose</li> <li>• Hemodialysis</li> </ul> <p><i>Also consider in the following order (may initiate while hematology/coagulation consult is obtained):</i></p> <ol style="list-style-type: none"> <li>1. Prothrombin complex concentrate (Profilnine®) 50 units/kg IV x 1 ± fresh frozen plasma (2-4 units)</li> </ol> <p><i>Hematology/Coagulation consult <u>must</u> be obtained prior to the following:</i></p> <ol style="list-style-type: none"> <li>2. Recombinant factor VIIa (NovoSeven®) 90 mcg/kg IV x 1</li> <li>3. Fresh frozen plasma (as much as tolerated)</li> <li>4. Hemodialysis</li> </ol> <p>To investigate potential causes of the bleeding event, obtain the following: serum creatinine, PT, aPTT, thrombin clotting time (TCT), CBC (platelets).</p>

*Adapted from van Ryn. Thromb Haemost. 2010 Jun;103(6):1116-27; www.clotconnect.org (Author: Stephan Moll, MD)*

## PATIENT EDUCATION

### **Management of Missed Doses**

If a dose of dabigatran is not taken at the scheduled time, the dose should be taken as soon as possible. If it is less than 6 hours from the time the next dose is due, skip the dose and resume dabigatran with the next scheduled dose. The dose of dabigatran should not be doubled to make up for a missed dose.

### **Management of a Doubled Dose**

If a doubled dose is taken, the patient should be advised to skip the next scheduled dose. After skipping one scheduled dose, patients should resume their prescribed dabigatran dose approximately 12 hours from the skipped dose.

### **Storage Instructions**

Dabigatran must be stored in its original packaging with the bottle tightly sealed to ensure potency of the medication. Do not remove dabigatran from the original packaging until it is time for the next scheduled dose, as the drug begins to degrade as early as one day. Doses left out of the manufacturer's packaging should be discarded.

Dabigatran is only good for 60 days after the bulk packaging has been opened. Any doses remaining after 60 days from opening the packaging should be discarded along with the bulk bottle.

It may be preferable that patients get their dabigatran supplied in unit-dose blister packs to avoid these storage issues.