UNC HEALTH CARE GUIDELINE

Management of Dabigatran in Adults

Dabigatran (Pradaxa®) 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 any other indications at this time, including the prevention or treatment of deep vein thrombosis or pulmonary embolism.

INITIATION OF THERAPY

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

- **Indication for therapy**. Patients must have non-valvular atrial fibrillation and risk factors that warrant therapeutic anticoagulation (i.e., $CHADS_2$ 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 at discharge must also be considered, as costs may exceed $200 per month.

TABLE 1. Initial Dabigatran Dose

Renal Function[a] (CrCL ml/min)	**> 30**	**15 – 30**	**< 15**
Recommended Starting Dose[b]	**150 mg BID**	**75 mg BID**	**Do not use**

[a] 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-age) x weight (kg)] / (SCr x 72) (x 0.85 if female)
[b] 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).
Rivaroxaban	Start dabigatran at the time the next dose of rivaroxaban was to be administered. For patients at greater risk of stroke[a] who have normal renal function, starting dabigatran up to 12 hours after the last dose of rivaroxaban may be considered.
Warfarin	Discontinue warfarin and start dabigatran when the INR is < 2.0.

[a] Recommendations are adapted from the approved labeling for rivaroxaban as well as pharmacokinetic data, so patient-specific risks of stroke and bleeding should be considered. Examples of increased stroke risk include recent cardioversion or ablation, higher $CHADS_2$ score, and conditions that may increase baseline risks of thromboembolism (e.g., medically ill).

CONVERSION FROM DABIGATRAN

The following recommendations are based on the approved labeling for the use of dabigatran in patients with atrial fibrillation. Taking into consideration the risk of stroke and embolism in each individual patient (i.e., $CHADS_2$ score, cardioversion), it may be reasonable to continue dabigatran until the INR is 2–3 when bridging to warfarin.

These guidelines do not reflect the practice of overlapping parenteral anticoagulants and warfarin for 5 days in the treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE). Dabigatran is **NOT** approved at this time for the treatment of DVT or PE. 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**[a]
> 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.[b]

[a] Dabigatran may contribute to an elevated INR for up to 2 days after discontinuation.
[b] 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**[a]
≥ 30	Start parenteral anticoagulant 12 hours after last dabigatran dose.
< 30	Start parenteral anticoagulant 24 hours after last dabigatran dose.

[a] 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.

Converting Dabigatran to Rivaroxaban

The approved labeling for rivaroxaban recommends administration of the drug once daily with the evening meal. Therefore, rivaroxaban should be started 12 hours after the last morning dose of dabigatran.

PERIOPERATIVE MANAGEMENT

TABLE 5. Discontinuation 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[a]	High Risk of Bleeding[b]
> 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

[a] Examples: electrophysiology procedures, cardiac catheterizations, no additional patient-specific risk factors.
[b] 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 to Procedures with Parenteral Anticoagulants
For patients at high risk of thromboembolic events in whom inpatient 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. Consider risk of bleeding versus risk of thromboembolism when deciding to hold doses of dabigatran for a dental procedure.

ADVERSE EFFECTS

Compared to warfarin, more patients discontinue dabigatran due to 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*).

The following section outlines strategies for the management of dabigatran-related bleeding events.

MANAGEMENT OF 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 with dabigatran, **a Hematology/Coagulation consult is required**.

TABLE 6. Management of Dabigatran-Related Bleeding Events

Bleeding Severity	Management Recommendations
Mild	Delay next dose or discontinue dabigatran.
Moderate	*Consider any of the following based on bleeding severity:* • Symptomatic treatment • Mechanical compression • Surgical intervention • Fluid replacement and hemodynamic support • Blood product transfusion • Oral activated charcoal (if previous dose ingested within 2 hours) Dose: Liquid charcoal with sorbitol 50 g PO x 1 dose *If hemostasis is not achieved with the strategies outlined above, consider the administration of 2-4 units of fresh frozen plasma (FFP). Obtain a Hematology/Coagulation consult for further recommendations.*
Severe or Life-threatening	*Consider any of the strategies outlined above based on bleeding severity. In the setting of acute renal failure, initiation of hemodialysis may be considered for the purpose of facilitating drug elimination. No agent has been shown to successfully reverse the anticoagulant effects of dabigatran or treat dabigatran-related bleeding events. However, the interventions below may be considered.* *A Hematology/Coagulation consult must be obtained prior to the following*: 1. Prothrombin Complex Concentrate (PCC) a. Low risk for thrombotic complications: Consider activated prothrombin complex concentrate (aPCC) (FEIBA®) 50 units/kg x 1.[a] b. High-risk for thrombotic complications: Consider non-activated prothrombin complex concentrate (PCC) (Profilnine®) 50 units/kg x 1. 2. Recombinant factor VIIa (NovoSeven®) 45-90 mcg/kg IV x 1.[b] After several hours, additional doses of 45-90 mcg/kg IV may be considered (with Hematology/Coagulation guidance) based on bleeding severity and degree of hemostasis achieved. 3. Fibrinolytic therapy (e.g., tranexamic acid, aminocaproic acid) may also be considered. 4. Fresh frozen plasma (as much as tolerated) 5. Hemodialysis To investigate potential causes of the bleeding event, obtain the following: serum creatinine, PT, aPTT, thrombin clotting time (TCT), CBC (platelets).

[a] Both activated PCC (FEIBA®) and recombinant factor VIIa (NovoSeven®) are associated with thrombotic complications, so the risk of bleeding versus thrombosis must be considered.

[b] A starting dose of 45-90 mcg/kg was chosen based review of clinical trials and case series as well as a dose-related risk of thromboembolic complications. *Ann Pharmacother 2010;44:718-26*; *N Engl J Med 2010;363:1791-800.*

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

P A T I E N T E D U C A T I O N

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 capsules are sensitive to moisture and should be stored in the original bulk bottle or blister pack until it is time for the next scheduled dose. The bottle should be tightly closed between doses, as the drug begins to degrade in as early as one day when exposed to moisture. Doses left out of the manufacturer's packaging should be discarded. Patients should be advised against storing dabigatran capsules in any other container, including pill boxes or organizers.

Dabigatran capsules retain their potency inside the original bulk bottle for 4 months after it has been opened. Any doses remaining after 4 months should be discarded along with the bulk bottle. It may be recommended that patients get their dabigatran supplied in unit-dose blister packs to avoid these storage issues.