Periprocedural Management and Approach to Bleeding in Patients Taking Dabigatran

Jeffrey I. Weitz, MD; Daniel J. Quinlan, MBBS; John W. Eikelboom, MBBS

Case Presentation: A 78-year-old man with atrial fibrillation, hypertension, and a history of ischemic stroke 2 years earlier presents to the emergency department with hematemesis and melena. He is taking dabigatran (150 mg twice daily) for stroke prevention, and his last dose was taken 12 hours earlier. His hemoglobin is 5.9 g/dL, platelet count is 185 × 10^9/L, and calculated creatinine clearance is 26 mL/min. The activated partial thromboplastin time (aPTT) is 83 s and the thrombin time (TT) is >150 s. How would you manage this patient?

The Randomized Evaluation of Long-Term Anticoagulant Therapy trial conducted in 18 113 patients with atrial fibrillation demonstrated that, compared with warfarin, dabigatran at a dose of 150 mg twice daily for stroke prevention, and his last dose was taken 12 hours earlier. His hemoglobin is 5.9 g/dL, platelet count is 185 × 10^9/L, and calculated creatinine clearance is 26 mL/min. The activated partial thromboplastin time (aPTT) is 83 s and the thrombin time (TT) is >150 s. How would you manage this patient? The Randomized Evaluation of Long-Term Anticoagulant Therapy trial conducted in 18 113 patients with atrial fibrillation demonstrated that, compared with warfarin, dabigatran at a dose of 150 mg twice daily reduced the risk of stroke or systemic embolism by one third and was associated with a similar rate of major bleeding; at a dose of 110 mg twice daily, the risk of stroke or systemic embolism with dabigatran was similar to that with warfarin, but dabigatran reduced the risk of major bleeding by one fifth.1 Both doses of dabigatran reduced the risk of intracranial bleeding by two thirds compared with warfarin. The risk of stroke was consistently reduced in all of the patient subgroups, but in those over the age of 75 years, the higher dose of dabigatran was associated with an increased risk of extracranial bleeding.2

Patient Selection
Prescribing guidelines for dabigatran vary by country and should be reviewed before starting the drug. The majority of atrial fibrillation patients with ≥1 additional risk factor for stroke are eligible for dabigatran. Absolute contraindications are uncommon, but include impaired renal function with a calculated creatinine clearance <15 mL/min in the United States or <30 mL/min in the rest of the world. Dabigatran has not been evaluated in patients with valvular atrial fibrillation or mechanical heart valves and should not be used in such patients. Because ≥80% of the drug is cleared unchanged by the kidneys, dabigatran may accumulate in patients with renal impairment. Consequently, the creatinine should be measured and the creatinine clearance calculated (eg, using the Cockcroft-Gault formula3) in all patients before commencement of dabigatran. Outside of the United States, dabigatran is contraindicated or should be used with caution in conjunction with potent inhibitors or inducers of P-glycoprotein (eg, ketoconazole, quinidine, and rifampicin).

Dose Selection
Dabigatran dose selection is country specific and is influenced by patient age, estimated creatinine clearance, and bleeding risk. The 150 mg twice-daily dose of dabigatran is the most effective for stroke prevention and is appropriate for the majority of patients. Although not approved in the United States, the 110 mg twice-daily dose of dabigatran may be considered for patients >75 or 80 years of age and for those whose creatinine clearance is between 30 and 50 mL/min.4,5 In the United States, the 75-mg twice-daily dose is available for patients with a creatinine clearance of 15 to 30 mL/min and for those with moderate renal impairment (creatinine clearance of 30–50 mL/min) who are receiving concomitant treatment with potent in-
hibitors of P-glycoprotein that increase dabigatran levels (eg, dronedarone and ketoconazole).6

**Laboratory Monitoring**

Routine monitoring of the anticoagulant effect of dabigatran is unnecessary because the drug produces a predictable and stable anticoagulant effect.7 However, coagulation monitoring can be of value in emergency situations to determine the presence or absence of dabigatran, to plan the timing of invasive procedures in relation to treatment interruption, for assessment of adherence, and to help evaluate the cause of ischemic stroke or bleeding.

The aPTT can be used to determine the presence or absence of dabigatran in the circulation.8 Although the aPTT reaches a plateau with dabigatran concentrations >250 ng/mL and results can vary depending on the reagent and coagulumeter used for aPTT determination, a normal aPTT indicates the absence of a significant dabigatran effect,9 whereas an aPTT >2.5 times the control 8 to 12 hours after dabigatran dosing is suggestive of excess anticoagulant activity. Figure 1 highlights the effect of varying degrees of renal impairment on the pharmacodynamic effect of dabigatran as determined by the aPTT.

Dabigatran also prolongs the TT, but this test is too sensitive for routine use because even negligible concentrations of dabigatran affect the results. Nonetheless, a normal TT indicates complete absence of circulating dabigatran. Because the effect of dabigatran on the prothrombin time/international normalized ratio is unpredictable, this test should not be used to monitor the drug.10 However, with high concentrations of dabigatran, both the aPTT and international normalized ratio will be prolonged.

The dilute TT assay (Hemoclot, Hyphen BioMed) performed with internal dabigatran calibrators provides an accurate measure of dabigatran drug levels.11 The Hemoclot assay is commercially available in Canada and Europe, but it is not approved for patient use in the United States. Because of its simplicity and low cost, the dilute TT is likely to become the preferred test for measuring dabigatran levels. Ecarin-based coagulation assays can also be used to determine drug concentrations, but these tests are currently restricted to research settings.

A key consideration in the interpretation of coagulation test results is the timing of dabigatran administration relative to blood sampling. Results from samples collected within 2 hours of dabigatran dosing can be twice those in blood obtained 8 or 12 hours after the same dose (peak and trough levels, respectively). In the absence of bleeding, trough levels provide the best assessment of the adequacy of dabigatran dosing.

**Periprocedural Management**

Dabigatran need not be stopped in patients undergoing minor procedures where the risk of bleeding is low. Such procedures include dental cleaning or extraction, skin biopsy, or cataract extraction. Ideally, such procedures should be performed ≥10 hours after dosing so that dabigatran levels are at their lowest. Like all anticoagulants, dabigatran must be withheld for an appropriate time before surgery or other invasive procedures associated with a moderate or high risk of bleeding. The timing of stopping depends on the renal function because the half-life of dabigatran is prolonged as the creatinine clearance declines12 (Figure 2). For procedures associated with a moderate risk of bleeding, dabigatran should be held for 2 to 3 half-lives, whereas it should be held for 4 to 5 half-lives before procedures associated...
with a high risk of bleeding. Examples of procedures with a moderate risk of bleeding include pacemaker or implantable cardioverter-defibrillator implantation and colonoscopic resection of polyps, particularly those that are sessile and have a broad base. Procedures associated with a high risk of bleeding include urologic procedures, such as transurethral prostate resection, major abdominal or pelvic surgery for cancer, joint replacement surgery, cardiac surgery, and neurosurgery.

If urgent surgery or intervention is required, the risk of bleeding must be weighed against the clinical need for the procedure. Ideally, surgery should be delayed for ≥1 half-life after the last dose of dabigatran or until the aPTT is normal or near normal. If the procedure is performed 2 to 4 hours after the last dose of dabigatran, the risk of bleeding is increased and strategies to reduce bleeding may be required.

The timing for reinitiating dabigatran after surgery depends on the bleeding risk. Dabigatran should be restarted when hemostasis is secure and the risk of bleeding is deemed to be acceptably low. When resuming dabigatran it is important to remember that the drug has a rapid onset of action with peak levels achieved 1.5 hours after dabigatran ingestion. If therapeutic doses of dabigatran cannot be restarted within 24 hours of surgery, thromboprophylaxis should be considered according to usual practice. If dabigatran-treated patients present with acute coronary syndrome and require percutaneous coronary intervention, they should be switched to heparin or another parenteral anticoagulant; ideally, this should be done 1 half-life after the last drug ingestion or when the aPTT is <1.5 times control.

**Treatment of Bleeding**

Unlike warfarin and heparin, there is no specific antidote for dabigatran, although a dabigatran-directed neutralizing antibody is under development. In view of the reduced risk of intracranial, life-threatening, and fatal bleeding with dabigatran compared with warfarin, we believe that the absence of an antidote is an insufficient reason to deprive patients of the benefits of dabigatran.

The management of bleeding complications in patients receiving dabigatran should be individualized based on the location and severity of the hemorrhage. In all cases, the drug should be discontinued and, if possible, local measures should be applied to stop the bleeding in anticipation of a rapid offset of the anticoagulant effect of dabigatran. In patients with normal renal function, approximately half of the steady-state drug level remains 12 hours after stopping the drug; this decreases to one quarter at 24 hours. Therefore, it is important to verify the time of the last dabigatran dose. For minor bleeding episodes, such as epistaxis or hematuria, holding 1 to 2 doses of dabigatran until the bleeding resolves is often sufficient. In cases of suspected overdose, oral activated charcoal may be helpful if administered within 2 to 4 hours of dabigatran ingestion, although its benefit has yet to be established in patients.

For moderate-to-severe bleeding, concomitant antplatelet drugs should be stopped if possible because their concomitant use with anticoagulants increases the risk of bleeding. The serum creatinine level should be measured and the creatinine clearance calculated because the half-life of dabigatran depends on renal function and the drug can accumulate in patients with renal impairment. To assess the anticoagulant effect of dabigatran and determine the drug level, the aPTT should be determined.

Maintained diuresis may help to facilitate renal clearance of dabigatran. Transfusion support (packed red cells, fresh-frozen plasma, and platelets) should be administered as indicated.

With severe or life-threatening bleeding, nonspecific hemostatic agents (eg, nonactivated or activated prothrombin complex concentrates [PCCs] or recombinant activated factor VII) may be considered in an attempt to control bleeding, although evidence of their efficacy in humans is limited. Administration of nonactivated PCC containing all 4 vitamin K-dependent procoagulant proteins to rabbits given a dabigatran overdose reversed injury-induced bleeding and restored the time to hemostasis to control levels but did not normalize the aPTT or other coagulation as-
The lack of an effect of PCC on dabigatran-induced prolongation of the aPTT after PCC administration.17 Consequently, lack of effect of PCCs and their effect on tests of coagulation17; consequently, lack of reversal of abnormal coagulation tests does not preclude a beneficial effect of procoagulants on bleeding. Unlike the PCCs in Europe and Canada, which contain all 4 vitamin K-dependent procoagulant proteins, those currently available in the United States contain little or no factor VII: the effect of these so-called 3-factor concentrates on dabigatran-induced bleeding in animals and humans is unknown. Consequently, until 4-factor PCCs are available, the 3-factor products should be supplemented with plasma or low doses (eg, 15–30 µg/kg) of recombinant activated factor VII (NovoSeven, NovoNor-disk, Bagsvaerd, Denmark); alternatively, Factor Eight Inhibitor Bypassing Activity (FEIBA VH; Baxter, Vienna, Austria), an activated PCC, or therapeutic doses (eg, 90 µg/kg) of recombinant activated factor VII may be better choices. Appropriate doses of these hemostatic agents are provided in Figure 3. In general, it is preferable to wait ≥30 minutes to assess the effect of each therapy before initiating the next.

**Figure 3.** Proposed algorithm for management of moderate-to-severe bleeding and life-threatening bleeding episodes in patients treated with dabigatran. *Recommendations are based on limited nonclinical data only. PCC indicates prothrombin complex concentrates (nonactivated); rFVIIa, recombinant activated factor VII. Moderate-to-severe bleeding indicates a reduction in hemoglobin ≥5 g/dL, transfusion of ≥2 U of red cells, or symptomatic bleeding in critical area (ie, intracranial, intracranial, intraspinal, intra-articular, or pericardial bleeding). Life-threatening bleeding indicates symptomatic intracranial bleed, reduction in hemoglobin ≥5 g/dL, transfusion of ≥4 U of red cells, hypotension requiring inotropic agents, or bleeding requiring surgical intervention.

**Case Resolution**

In the case presented, renal failure resulted in dabigatran accumulation and prolonged its half-life. Dabigatran was stopped and 8 U of packed red blood cells, 12 U of platelets, 10 U of fresh-frozen plasma, and 8 U of cryoprecipitate were administered. Because of ongoing bleeding, 40 IU/kg of PCC (Beriplex P/N, CSL Behring, Marburg, Germany) were given, which promptly reduced the blood loss. The patient was stabilized and eventually discharged home on a reduced dose of dabigatran, 75 mg twice daily. Regular assessments of renal function were scheduled and the patient remained free of any further bleeding events.

**Acknowledgments**

We are grateful to Drs Joanne Van Ryn, Andreas Clemens, and Martina Brueckmann for their helpful comments on the final draft of the article, but the authors are responsible for the content of the article.

**Sources of Funding**

This article was supported in part from grants from the Heart and Stroke Foundation (T-6537) and the Canadian Institutes of Health Research (MOP-102735). Dr Weitz is the recipient of the Canada Research Chair (Tier I) in Thrombosis and the Heart and Stroke Foundation of OntarioJ. Fraser Mustard Chair in Cardiovascular Research, and Dr Eikelboom is the recipient of the Canada Research Chair (Tier II) in Cardiovascular Medicine.

**Disclosures**

Dr Weitz has served as a consultant and has received honoraria from Boehringer Ingelheim, BMS, Pfizer, Bayer, Janssen Pharmaceuticals, and Daiichi Sankyo. Dr Eikelboom has received honoraria and research support from Boehringer Ingelheim, BMS, Pfizer, Bayer, Janssen Pharmaceuticals, and Daiichi Sankyo. Dr Quinlan has no disclosures.
References
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Circulation. 2012;126:2428-2432
doi: 10.1161/CIRCULATIONAHA.112.123224
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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