Maine Medical Center
Guideline for the Management of Bleeding on Dabigatran (Pradaxa®)

Key Background

- Dabigatran is a direct thrombin (factor IIa) inhibitor. As such, clotting factor replacement is not as effective in stopping bleeding as it is in settings with factor deficiency. There is currently no strong evidence that FFP, recombinant Factor VIIa, or prothrombin complex concentrates can reduce the bleeding induced by dabigatran.[1] **[R]** The prolonged clotting time with dabigatran is a reflection of thrombin inhibition rather than a clotting factor deficiency.[6,7] *The role of FFP is in the avoidance of a dilutional coagulopathy following massive transfusion rather than in reversing the anticoagulant effect of dabigatran.* **[R]**
- Idarucizumab (Praxbind) is a monoclonal antibody developed to bind both bound and unbound dabigatran in the plasma. Idarucizumab rapidly and completely reverses the effects of dabigatran as measured by several laboratory markers of prolonged coagulation due to dabigatran. This agent should be resurved for major or life-threatening hemorrhage.[2] [B]

General Care for All Patients

- Hold dabigatran,[1,3] **[R]**
- Obtain laboratory studies including CBC, CMP, aPTT, thrombin time, fibrinogen[1,3,7] **[R]**.
  - If the thrombin time is normal, this indicates an absence of dabigatran
- Evaluate for anatomic defects explaining hemorrhage,[1,3] **[R]**
- Use local measures to control bleeding,[1,3] **[R]**
- Consider the need for surgical intervention, embolization to control bleeding,[1,3] **[R]**
- Consider the need for Pharmacy/Hematology/Nephrology consults based on the degree of bleeding (see below).[1,2] **[R]**

For Patients with Mild Bleeding

- Continue "General Care for All Patients" listed above, and:
- Delay next dabigatran dose or discontinue dabigatran treatment if appropriate,[1,3] **[R]**
- Supportive care / symptomatic treatment.[1,3] **[R]**

For Patients with Moderate Bleeding

- Discontinue dabigatran,[1,3] **[R]**
- Supportive care / symptomatic treatment,[1,3] **[R]**
- Activated charcoal at standard doses if last dose of dabigatran is within 2 hours,[1,3,4] **[R]**
- Maintain adequate diuresis with fluid replacement and hemodynamic support as needed,[1,3-6] **[B]**
- Transfuse RBCs as needed to maintain HgB above 8 gm/dL,[3,6] **[R]**
- If more than 4 units of RBCs are required, transfuse RBCs/plasma 1:1 to avoid a dilutional coagulopathy,[8] **[B]**
- See also Maine Medical Center *Massive Transfusion Protocol,*
- Consultation with nephrology for consideration of dialysis.[1,5,8] **[B]**

For Patients with Severe/Life Threatening Bleeding OR Urgent Surgery/Procedure that cannot be delayed by 8 hours

- Continue "General Care," and "Moderate to Severe Bleeding" measures above, and:
- Mandatory consult with pharmacy (741-7933) for consideration of idarucizumab
- Idarucizumab 5 gm (2 x 2.5 gm doses) given 15 minutes apart to completely reverse dabigatran[2] **[B]**
- Consider nephrology consult if patient in AKI and/or CrCL <50 mL/min

Grade R Evidence = Consensus Statement from Consensus Report or Narrative Review

Supporting Evidence

1. van Ryn J, Stangier J, Haertter S, Liesenfeld K-H, Wienen W, Feuring M, Clemens A. Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor: Interpretation of coagulation assays and reversal of anticoagulant activity. *Thrombosis and Haemostasis* 2010; 103(6): 1116-1127. [**Level of Evidence: R**]

2. Pollack CV, Reilly PA, Eikelboom J, Glund S, Verhamme P, et al. Idarucizumab for Dabigatran Reversal. *New Engl J Med* 2015; doi: 10.1056/NEJMoa1502000. **[Level of Evidence: B]**

3. Hankey GJ, Eikelboom JW. Dabigatran etexilate – A new oral thrombin inhibitor. *Circulation* 2011; 123: 1436-1450. [**Level of Evidence: R**]

4. van Ryn J, Sieger P, Kink-Eiband M, et al. Adsorption of dabigatran etexilate in water or dabigatran in pooled human plasma by activated charcoal in vitro. In: 51st ASH Annual Meeting and Exposition. New Orleans, LA: American Society of Hematology; 2009. Available at: http://ash.confex.com/ash/2009/webprogram/Paper21383.html (Accessed 2011 Oct 4). [**Level of Evidence: R**]

5. Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. *Clinical Pharmacokinetics* 2008; 45(5): 285-295. [**Level of Evidence: A**]

6. Stangier J, Rathgen K, Stahle H, et al. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate *Clinical Pharmacokinetics* 2010; 49: 259-268. [**Level of Evidence: B**]

7. Institute for Clinical Systems Improvement (ICSI). Antithrombotic therapy supplement. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2011 Apr. 75 p. Available at: http://www.guideline.gov/content.aspx?id=32824&search=antithrombotic+therapy+supplement. Accessed 10-10-11. [**Level of Evidence: R**]

8. Institute for Clinical Systems Improvement (ICSI). Dabigatran: Consensus-based statement on emergency care of bleeding. Bloomington (MN): Institute for Clinical Systems Improvement; 2011 Sept. Available at: http://www.icsi.org/dabigatran__consensus-based_statement_on_emergency_care_of_bleeding_protocol/dabigatran__consensus-based_statement_on_emergency_care_of_bleeding__protocol_.html
Accessed 10-10-11. [**Level of Evidence: R**]

9. Stangier J, Stahle H, Rathgen K, Fuhr R. Pharmacokinetics and pharmacodynamics of the direct oral thrombin inhibitor dabigatran in healthy elderly subjects. *Clinical Pharmacokinetics* 2008; 47: 47-59. [**Level of Evidence: B**]

10. van Ryn J, Ruehl D, Priepke H, et al. Reversibility of the anticoagulant effect of high doses of the direct thrombin inhibitor daigatran , by recombinant Factor VIIa or activated prothrombin complex concentrate. *Haematologica* 2008; 93 (Suppl 1): 148. [**Level of Evidence: R**]

11. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate. A randomized, placebo-controlled, crossover study in healthy subjects. *Circulation* 2011; 124: 00-00. [**Level of Evidence: A**]

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Evidence Grading

Primary Reports of New Data Collections

A Randomized, controlled trial

B Cohort study

C Non-randomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity/specificity of a diagnostic test
- Population-based descriptive study

D Cross-sectional study
- Case series
- Case report

Reports that Synthesize or Reflect Upon Collections of Primary Reports

M Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

R Consensus statement
- Consensus report
- Narrative review

X Medical opinion