Maine Medical Center
Guideline for the Management of Bleeding on
RIVAROXABAN (XARELTO®) or APIXABAN (ELIQUIS®)

Key Background

- Rivaroxaban and apixaban are direct factor Xa inhibitors. As such, replacing clotting factor(s) is not as effective in stopping bleeding as it is in settings with factor deficiency. There is currently no strong evidence that FFP, Factor VIIa, or Kcentra (4-factor prothrombin complex concentrate) can reduce the bleeding induced by rivaroxaban or apixaban.[1] **[R]**
- Fresh frozen plasma will not reverse the anticoagulation effect of rivaroxaban or apixaban as the drug will inhibit factor Xa in the infused plasma. The prolonged clotting time with rivaroxaban and apixaban is a reflection of factor Xa inhibition rather than a clotting factor deficiency.[2,6] *The role of FFP is in the avoidance of a dilutional coagulopathy following massive transfusion rather than in reversing the anticoagulant effect of rivaroxaban.* **[R]**

General Care for All Patients

- Hold rivaroxaban/apixaban,[1,2] **[R]**
  - The half-life of rivaroxaban is 5-9 hours, but approaches 11-13 hours in the elderly. The half-life of apixaban is 8 hours for the 2.5 mg dose and 15 hours for the 5 mg dose[7,11].
- Obtain laboratory studies including CBC, aPTT, INR*, CMP, fibrinogen activity,[3,4] **[C,R]**
- Evaluate for anatomic defects explaining hemorrhage,[1,2] **[R]**
- Use local measures to control bleeding,[1,2] **[R]**
- Consider the need for surgical intervention, embolization to control bleeding,[1,2] **[R]**
- Consider the need for Hematology consult.[1,2] **[R]**

**Typical therapeutic doses of rivaroxaban are associated with an INR <1.7. There is limited experience available for apixaban and laboratory testing. Anti-factor Xa assays have not been standardized to the new anticoagulants[9].*

For Patients with Mild Bleeding

- Continue "General Care for All Patients" listed above, and:
- Delay next rivaroxaban/ apixaban dose,[1,2] **[R]**
- Discontinue rivaroxaban/apixaban treatment if appropriate,[1] **[R]**
- Supportive care / symptomatic treatment.[1,2] **[R]**

For Patients with Moderate to Severe Bleeding

- Discontinue rivaroxaban/apixaban,[1,2] **[R]**
- Supportive care / symptomatic treatment,[1,2] **[R]**
- Activated charcoal at standard doses if last dose of rivaroxaban/apixaban within 1-2 hours,[7,10] **[R]**
- Maintain adequate diuresis with fluid replacement and hemodynamic support as needed,[1,7,8] **[B]**
- Transfuse RBCs as needed to maintain HgB above 8 gm/dL,[1,2] **[R]**
- If more than 4 units of RBCs are required, transfuse RBCs/plasma 1:1 to avoid a dilutional coagulopathy **[B]**
- See also Maine Medical Center *Massive Transfusion Protocol*

*Hemodialysis is not effective for the removal of rivaroxaban/apixaban due to high protein binding.

For Patients with Severe/Life Threatening Bleeding

- Continue "General Care," and "Moderate to Severe Bleeding" measures above, and:
- Consider Kcentra (25 units/kg) to help with clot formation at the site of bleeding.[5] **[R]**
- As a last resort, consider recombinant activated Factor VII (20 mcg/kg) [1,7] **[R]**
- **NOTE:** The strength of the evidence for these interventions is weak and limited.

Supporting Evidence

1. Kaatz SC, Kouides PA, Guidance on the emergent reversal of oral thrombin and factor Xa Inhibitors. Am J Hematol 2012;87:S141–S145. [**Level of Evidence: R**]

2. Bauer KA. Reversal of antithrombotic agents. Am J Hematol 2012;87:S119-S126. **[Level of Evidence: R]**

3. Lindhoff-Last E, Samama MM, Ortel T, Weitz JI, Spiro TE. Assays for Measuring Rivaroxaban: Their Suitability and Limitations. Ther Drug Monit 2010;32:673-679. **[Level of Evidence: R]**

4. Samama MM, Martinoli JL, LeFlem L, et al. Assessment of laboratory assays to measure rivaroxaban – an oral, direct factor Xa inhibitor. Thromb Haemost 2010;103:815-825. **[Level of Evidence: R]**

5. 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]**

6. 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]**

7. Food and Drug Administration. Advisory committee briefing book: rivaroxaban. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM138385.pdf (accessed 2012 Aug 3) **[Level of Evidence: R]**

8. Kubitza D, Becka M, Mueck W, et al. Effects of renal impairment on the pharmacokinetics, pharmacodynamics, and safety of rivaroxaban, an oral, direct Factor Xa inhibitor. Br J Clin Pharmacol 2010;70:703-712. **[Level of Evidence: B]**

9. Tripodi A. The laboratory and the direct oral anticoagulants. Blood 2013;121:4032-5. **[Level of Evidence: R]**

10. Eliquis® (apixaban) tablets for oral use package insert. Bristol-Myers Squibb Company, Princeton, NJ, December 2012. **[Level of Evidence: R]**

11. Frost C, Nepal S, Wang J, et al. Safety, pharmacokinetics and pharmacodynamics of multiple oral doses of apixaban, a factor Xa inhibitior, in healthy subjects. Br J Clin Pharmacol 2012;75:476-87. **[Level of Evidence: C]**

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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