



Commonwealth of Massachusetts
Board of Registration in Medicine
Quality and Patient Safety Division

Advisory
“New” Anticoagulants

October 2014

Background

The Quality and Patient Safety Division (QPSD) has received Safety and Quality Review (SQR) reports illustrating the challenges associated with caring for patients being treated with the newer types anticoagulants (i.e. Factor Xa inhibitors and direct thrombin inhibitors). This advisory is issued to share some of the lessons learned by the reporting health care facilities and to support health care facilities in their efforts to assure safe and effective anticoagulation management. While some references are provided, this advisory does not include a comprehensive review of the literature; nor is it intended to provide specific recommendations for evidence-based practice.

Publication of this Advisory does not constitute an endorsement by the Board of any studies or practices described in the Advisory and none should be inferred.

Overview

Factor Xa inhibitors and direct thrombin inhibitors (including dabigatran, rivaroxaban, fondaparinux and apixaban) have been approved for stroke prevention in non-valvular atrial fibrillation (AF), and for venous thromboembolism (VTE) prophylaxis and/or treatment of deep venous thrombosis (DVT) and pulmonary embolus (PE).¹ The oral formulations of the Factor Xa inhibitors and direct thrombin inhibitors are used in outpatient and inpatient settings. Fondaparinux, an injectable direct thrombin inhibitor, is used primarily in the inpatient setting in place of heparin or low molecular weight heparin. Currently, there are additional anticoagulants in varying stages of clinical trials for Food and Drug Administration (FDA) approval.

As with any new medication or technology, providers must understand the indications, limitations and potential complications of these new types of anticoagulants in order to maximize patient safety.^{2,3}

Case Examples and Lessons Learned

Case One: An elderly patient was admitted to the hospital for treatment of sepsis and started on fondaparinux (Arixtra) for DVT prophylaxis. Fondaparinux was held for three days before PICC line placement, but the patient had persistent bleeding from the site despite compression and Vitamin K administration. The patient developed symptomatic anemia and required a blood transfusion.

¹ Please see FDA website for specific approval history, label information, medication guides and any post-market safety information: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.

² Wanat, MA. Novel Oral Anticoagulants: A review of new agents. Postgrad Med. 2013; 125(4):103-114.

³ Hylek, EM. Gaps in Translation from Trials to Practice: Non-vitamin K Antagonist oral anticoagulants (NOACs) for stroke prevention in atrial fibrillation. Throm Haemost. 2014; 111:1-6.

Lessons Learned: Surveys of nurses and non-orthopedic providers at the facility revealed inadequate awareness of fondaparinux, including drug method of action, indications and precautions for use. The hospital revised its anticoagulation protocols to include guidance on Factor Xa and direct thrombin inhibitors. “Alerts” for these medications were added to the CPOE system and “tip” cards given to physicians and nurses. Educational programs on anticoagulation management, with particular focus on these new anticoagulants, were provided to the medical and nursing staff.

Case Two: An elderly patient was admitted to the hospital for vascular surgery. The patient had atrial fibrillation and was being treated with dabigatran (Pradaxa) for stroke prevention. Dabigatran was held four days before surgery and was not restarted post-operatively due to the surgeon’s concerns about bleeding risk. On the fourth postoperative day, the patient suffered an embolic stroke.

Lessons Learned: The health care facility’s findings from review of this case identified the need for a multidisciplinary approach to perioperative anticoagulation management, particularly with the growing number of pharmaceutical options both for treatment of atrial fibrillation and VTE prophylaxis. Formal guidelines for perioperative anticoagulation were developed. Members from the Cardiology and Pharmacy service now participate in a multi-disciplinary team approach to post-operative care and stroke prevention.

Areas for Health Care Facility Systems Review

The areas described below provide topics and references as support for internal discussion and review of health care facility anticoagulation protocols and prescribing patterns. While oral anticoagulation medications are frequently used in the outpatient setting, they also are initiated on inpatient units or during care transitions, and must be considered during pre- and post-operative care.

1. **Stroke and bleeding risk assessment:** Algorithms and models for assessing risk are used to guide treatment and identify patients requiring more intensive monitoring. They can be used in the context of collaborative efforts between surgeons, cardiologists, primary care physicians and pharmacists, and can be valuable in identifying those patients who may be at risk for stroke or bleeding. For example, there are a variety of tools used to help providers determine the risk of stroke and bleeding in patients with atrial fibrillation.^{4,5} In addition to atrial fibrillation, identification of patients with higher thrombotic risks, such as recent VTE or coagulation abnormalities, is essential, as these patients may require more aggressive treatment and monitoring.

Providers should discuss stroke and bleeding risks with patients before starting or stopping an anticoagulant, and before clinical transitions such as in the peri-operative period. When prescribing these medications, careful medical record documentation and medication reconciliation practices will facilitate communication between providers.

2. **Patient characteristics and choice of anticoagulation therapy:** The direct thrombin inhibitors and Factor Xa inhibitors differ significantly from Vitamin K antagonists in terms of their onset of action, half-life, drug-drug interactions, and need for monitoring. Full prescribing information should be consulted as there is dosage and cautionary information provided for use in specific populations. Careful consideration should be given to patients that are elderly and/or have decreased renal function, low

⁴ Strobeck, JE. Stroke Prevention in Atrial Fibrillation: Managing the risks in light of new oral anticoagulants. Cardiovasc Drugs Ther. 2012; 26:331-338. (p 332-3)

⁵ Lip, GYH. Implications of the CHA₂DS₂-VASC and HAS-BLED Scores for Thromboprophylaxis in Atrial Fibrillation. Amer J of Med. 2011; 124:111-4

body weight, bleeding tendencies, or a history of poor medication compliance. Current research studies should be reviewed.

Drug interactions: As with all new and existing medications, frequent review of potential drug interactions is recommended. For example, strong dual inhibitors or inducers of CYP3A4 and P-glycoprotein (e.g., ketoconazole, rifampin) may reduce or increase the anticoagulant effect of some of these medications. The inability to reliably measure the biological effect of the newer types of anticoagulants makes it difficult to detect or evaluate the impact of a drug interaction.

3. **Non-adherence or poor medication compliance:** Without routine anticoagulation monitoring that is required for warfarin, the provider is reliant upon the completeness and reliability of the patient's medication history. Non-adherence, late initiation, partial adherence or early discontinuation of medications are all potential confounders for stroke and VTE prevention.⁶ Decisions about anticoagulants started or changed during inpatient stays must consider potential barriers to compliance in the outpatient setting. Some points to consider when engaged in discharge planning for patients:
 - a. Systematic reviews of multiple efforts to improve compliance have shown that even complex, multi-faceted interventions result in modest, often transient, improvements.⁷ Pharmacist-led anticoagulation management clinics can improve outcomes and reduce drug errors and complications.⁸
 - b. The top reasons cited by patients for not filling prescriptions for medications for chronic diseases, or discontinuing without discussing with their provider, were financial hardship, fear or experience of side effects, general concerns about medications, and lack of perceived need for the medication.⁹
4. **Managing transitions:** Transitions in care, whether due to changes in location or clinical status, pose significant challenges for patient care and safety. When patients are transitioning from one anticoagulant to another, or modifying treatment regimens in pre- or post-operative settings, there are many factors to assess such as medication half-life, drug interactions, renal function, and stroke and bleeding risks. The introduction of these new types of anticoagulants, and the frequent updates in the literature with regard to their efficacy and safety contribute to the complexity.
 - a. Numerous references and algorithms for are available for providers, most notably the ACC-AHA 2012 guidelines for the management of peri-operative antithrombotic therapy and drug prescribing information.¹⁰
 - b. Standardization of surgical anticoagulation with input and guidance from pharmacy, cardiology and hematology should be part of a surgical quality program.¹¹ While management of

⁶ Rodriguez, RA. Non-adherence to New Oral Anticoagulants: a reason for concern during long-term anticoagulation? J Thromb Haemost. 2013; 11:390-94.

⁷ Blaschke, TF. Insights Arising from Studies on the Unreliable Link between Prescribed and Actual Drug Dosing Histories. Ann Rev Pharm and Tox. 2012; 52:275-301. (p 295)

⁸ Dobesh, PP. Role of the Pharmacist in Achieving Performance Measures to Improve the Prevention and Treatment of Venous Thromboembolism. Pharmacotherapy. 2013; 33(6):650-64. (p 660)

⁹ McHorney, CA. Frequency of and reasons for medication non-fulfillment and non-persistence among American adults with chronic disease in 2008. Health Expectations. 2010; 14:307-320. (p 312)

¹⁰ Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(2 Suppl)

¹¹ Dobesh, PP. Role of the Pharmacist in Achieving Performance Measures to Improve the Prevention and Treatment of Venous Thromboembolism. Pharmacotherapy 2013;33(6):650–664.

anticoagulation has typically been based on the individual surgeon's preference, this practice should be discouraged.

- c. Redesigning computerized provider order entry for preop/postop anticoagulation protocols for different at-risk populations, including electronic hard stops, can help promote consistent performance and assessment. Consistent monitoring of surgical anticoagulation prophylaxis will inform the surgical department of the patient outcomes related to the redesigned systems and help to identify opportunities for improvement.
5. **Bleeding risk:** While Vitamin K, plasma and cryoprecipitate are effective treatments for bleeding related to warfarin and heparin, there are no antidotes for the direct thrombin and Factor Xa inhibitors in case of uncontrollable bleeding. Several reversal agents are currently in trials.
- a. Hemodialysis can remove dabigatran but its effectiveness is not clear.¹² Oral activated charcoal may remove unabsorbed medication from the GI tract.
 - b. FDA black box warnings exist for the risk of spinal/epidural hematoma in patients taking dabigatran, rivaroxaban, fondaparinux or apixaban and receiving concurrent neuraxial anesthesia or lumbar puncture.
 - c. The result of a qualitative test, such as the PT or aPTT or thrombin time, can indicate whether anticoagulation is supratherapeutic, therapeutic or subtherapeutic, but cannot be used to determine the plasma concentration of the drug or assess compliance.^{13,14}

Conclusion

New anticoagulants, both Factor Xa and direct thrombin inhibitors, are important additions to the prevention and management of stroke and VTE. Providers can improve quality of care with thorough understanding of their limitations and risks, including lack of reversal agents and monitoring tests, drug interactions, and peri-operative challenges. Careful attention should be paid to the patient's risk factors and history of medication compliance. When serious unexpected patient outcomes occur, a thorough review of the patient's anticoagulation management should be conducted, with reporting to the FDA Medwatch program, as appropriate.¹⁵

Healthcare facilities can improve patient safety with standardized surgical anticoagulation protocols, provider and staff education, and facilitation of interdisciplinary collaboration during clinical and pharmaceutical transitions.

Additional Resources

Institute for Safe Medication Practices (Medication Safety Alerts): <http://www.ismp.org/>

Apostolakis S, Sullivan RM, Olshansky B, Lip GY. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin. *Chest*. 2013; 144(5): 1555-1563.

Bapilonia K, Trujillo T. The role of prothrombin complex concentrates in reversal of target specific anticoagulants. *Thromb J*. 2014; 12:8.

¹² Pradaxa prescribing information, Boehringer-Ingelheim. Accessed 7/2/14 at <http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf>

¹³ Baglin, T. Clinical Use of New Anticoagulant Drugs: dabigatran and rivaroxaban. *British J Haem*. 2013; 163:160-7.

¹⁴ Wanat, MA. New Oral Anticoagulants: a review of new agents. *Postgraduate Medicine*, 2013; 125(4):103-114.

¹⁵ FDA Medwatch Program: <https://www.accessdata.fda.gov/scripts/medwatch/>

Baron, TH. New anticoagulant and antiplatelet agents: A primer for the gastroenterologist. Clin Gastroent and Hepatology. 2014; 12:187-195.

Dager WE. Developing a management plan for oral anticoagulant reversal. Am J Health Syst Pharm. 2013 May 15; 70(10 Suppl): S21-31.

Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(2 Suppl).

Gallego P, Apostolakis S, Lip G. Bridging evidence-based practice and practice-based evidence in periprocedural anticoagulation. Circulation. 2012; 126:1573-1576.

Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2438–88.

Pfeilschifter W, Luger S, Brunkhorst R, et al. The gap between trial data and clinical practice—an analysis of case reports on bleeding complications occurring under dabigatran and rivaroxaban anticoagulation. Cerebrovasc Dis. 2013; 35:115-119.

Ross B, Miller MA, et al. Clinical Experience of Life-Threatening Dabigatran-Related Bleeding at a Large Tertiary Care, Academic Medical Center: a case series. J Med Toxicol. (2014) 10:223-228.

Schulman S. How I treat with anticoagulants in 2012: new and old anticoagulants, and when and how to switch. Blood. 2012; 119(13):3016-23.

Steiner T, Bohm M, Dichgans M et al. Recommendations for the emergency management of complications associated with the new direct oral anticoagulants (NOAC), apixiban, dabigatran and rivaroxaban. Clin Res Cardiol. 2013 Jun; 102(6): 399-412.

Strobeck, JE. Stroke Prevention in Atrial Fibrillation: Managing the risks in light of new oral anticoagulants. Cardiovasc Drugs Ther. 2012; 26:331-338. (p 332-3)

Wann LS, Curtis AB, Ellenbogen KA. 2011 ACCF/AHA/HRS Focused update on the management of patients with atrial fibrillation (Update on Dabigatran): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011; 123:1144-1150.

Wysokinski WE, McBane RD. Periprocedural bridging management of anticoagulation. Circulation. 2012;126:486-490.

Drug prescribing information:

Pradaxa (dabigatran), Boehringer-Ingelheim. <http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing%20Information/Pradaxa/Pradaxa.pdf>

Xarelto (rivaroxaban), Janssen Pharmaceuticals. http://www.xareltohcp.com/sites/default/files/pdf/xarelto_0.pdf#zoom=100

Arixtra (fondaparinux), GSK. http://www.gsksource.com/gskprm/en/US/adirect/gskprm?cmd=ProductDetailPage&product_id=1244136744215&featureKey=600552#nlmhighlights

Eliquis (apixiban), Bristol-Myers Squibb. http://packageinserts.bms.com/pi/pi_eliquis.pdf