

Emerging Treatment Options

for the Reversal of
Oral Anticoagulant Therapy

THE EXPERTS ADDRESS QUESTIONS ABOUT REVERSAL OF ORAL ANTICOAGULANTS

Oral anticoagulant therapy is widely used to prevent thromboembolism in patients with non-valvular atrial fibrillation (AF), patients undergoing major orthopedic surgery, and patients with acute coronary syndrome. Excessive anticoagulation can lead to bleeding, thus maintaining balance between the risk for thromboembolism and the risk for bleeding when using oral anticoagulant therapy is needed.

Reversal of the effects of oral anticoagulants sometimes is needed for patients who develop active bleeding or require an urgent invasive procedure or surgery or in case of an overdose. Intervention using fresh frozen plasma, various clotting factor concentrates, and, in warfarin-treated patients, vitamin K may be needed to achieve more rapid reversal of anticoagulation than can be achieved by withholding the anticoagulant alone. Limited clinical data are available, leaving large gaps in knowledge about the optimal reversal strategy. The clinical studies performed to date evaluating various strategies are fraught with methodologic limitations.

Recognizing this gap in knowledge and the challenges that pharmacists face in developing reversal strategies, ASHP Advantage is coordinating a series of learning opportunities related to emerging treatment options related to the reversal of oral anticoagulant therapy. These opportunities are designed to build on each other to provide an overview of the topic, as well as practical issues to consider when developing a reversal strategy in various situations. The educational activities involve live and on-demand formats, and faculty members are nationally recognized experts in anticoagulation and thrombosis management. The series is supported by an educational grant from CSL Behring.

A Midday Symposium, Emerging Treatment Options for the Reversal of Oral Anticoagulant Therapy, was conducted and simultaneously webcast on December 3, 2012, at the 47th ASHP Midyear Clinical Meeting and Exhibition in Las Vegas, Nevada. Attendees submitted questions about unresolved issues related to oral anticoagulant reversal, and these questions served as the guide for Initiative Chair Edith A. Nutescu, Pharm.D., FCCP, and William E. Dager, Pharm.D., BCPS (AQ-Cardiology), when they developed content for a live webinar held on March 20, 2013. This webinar and emerging literature are the primary sources of content explored in the two e-newsletters that are part of the educational initiative.

If you missed the Midyear symposium, it is now available as a web-based activity and is approved for 2 hours of continuing pharmacy education. Its on-demand format is convenient because it may be completed at any time. For more information and to access the web-based activity, go to the web portal at www.ashpadvantage.com/reversal.

FACULTY ROUNDTABLE

Visit the Emerging Treatment Options for the Reversal of Oral Anticoagulant Therapy web portal or [click here](#) to listen to Dr. Edith A. Nutescu and fellow faculty Drs. William E. Dager and James S. Kalus discuss important issues related to the topic. The discussion is available in four parts:

- Issues related to warfarin reversal (14 min)
- Laboratory assays to measure coagulation (10 min)
- Balancing bleeding and thrombosis risk (11 min)
- Reversal of target-specific oral anticoagulants (10 min)

Sign up to be notified of updates related to this educational initiative. The second e-newsletter in this series will address other frequently asked questions about this topic, such as the dosing of clotting factor concentrates for oral anticoagulant reversal in obese patients and the timing of restarting anticoagulant therapy after reversal.

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FREQUENTLY ASKED QUESTIONS

Q Has the introduction of the new oral anticoagulants dabigatran, rivaroxaban, and apixaban reduced the need for reversal?

A Approval by the Food and Drug Administration (FDA) of target-specific oral anticoagulants—so called because they act on specific targets in the coagulation cascade in contrast to warfarin, which inhibits hepatic production of the vitamin K-dependent clotting factors II, VII, IX, and X—has been eagerly awaited in the United States. These agents do not require routine laboratory monitoring, but, as with other anticoagulants, a risk for bleeding is associated with their use. Reversal of target-specific oral anticoagulants may be needed, and it may be more of a problem than warfarin reversal because there is less clinical experience to date with these agents than warfarin, which has been used for more than 60 years.

In October 2010, the direct thrombin (factor IIa) inhibitor dabigatran was approved by FDA to reduce the risk of stroke and systemic embolism in patients with non-valvular AF.¹ The direct factor Xa inhibitor rivaroxaban was approved by FDA in July 2011 for prophylaxis of venous thromboembolism (VTE) in patients undergoing knee or hip replacement surgery.² The agency has since expanded the approved uses of rivaroxaban to include prevention of stroke and systemic embolism in patients with AF in November 2011 and treatment of VTE in November 2012.^{2,3}

In late December 2012, the direct factor Xa inhibitor apixaban was approved by FDA to reduce the risk of stroke and systemic embolism in patients with AF.^{4,5} Studies of anticoagulant reversal are more limited for apixaban than for rivaroxaban and dabigatran. Data from *in vitro* research of the effects of clotting factor concentrates in human blood containing apixaban suggest a possible role in reversal but do not provide insight about which type of available products might be most effective.⁶ Reversal strategies used for rivaroxaban are likely to prove useful for apixaban because both agents are direct factor Xa inhibitors with a similar low reliance on the kidneys for elimination of the drug, although clinical experience with reversal of apixaban is needed to verify this theory.⁷

The introduction of the target-specific oral anticoagulants has not been without problems. Dabigatran was a more common cause of serious, disabling, or fatal injury reported to the FDA MedWatch adverse event reporting program than warfarin in 2011, although the rate of major bleeding was similar with the two drugs in the RELY study of patients with AF.^{8,9} Dabigatran was associated with a lower rate of intracranial bleeding and a higher rate of gastrointestinal (GI) bleeding than warfarin in the RELY study.⁹ In cases of oral anticoagulant-related bleeding reported to the FDA

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MedWatch program in the second quarter of 2012 (the most recent period for which data are available), dabigatran was associated with a fivefold higher risk of death than warfarin after adjusting for age, gender, and the type and source of the report.¹⁰ These differences in MedWatch data may reflect reporting biases (i.e., a greater tendency to report problems with the newer drug).¹¹ Postmarketing reports of serious bleeding in patients receiving dabigatran prompted FDA to conduct an analysis of insurance claims and administrative data that revealed that the rates of GI and intracranial bleeding associated with new use of dabigatran do not appear to be higher than the rates of bleeding associated with new use of warfarin.^{11,12}

In the second quarter of 2012, rivaroxaban was associated with a larger number of serious injury reports to the FDA MedWatch program and a nearly twofold higher risk of death in cases of bleeding compared with warfarin.¹⁰ An unexpectedly large number of thromboembolic events associated with rivaroxaban were reported.¹⁰ Apixaban data were not collected because the drug was not yet approved by FDA.

Approval of rivaroxaban for reducing the risk of myocardial infarction and stroke in patients with acute coronary syndrome was denied by FDA in June 2012 and again in March 2013 because of a lack of data for patients who withdrew from clinical trials and concerns about the risk for bleeding.^{13,14} Postmarketing pharmacovigilance is needed for all three target-specific oral anticoagulants to assess safety in a real-world setting outside of clinical trials. Clinical experience is needed to ascertain the optimal approach to reversing these agents.

Q What advice can you provide for improving the management of patients requiring reversal of oral anticoagulant therapy in health systems?

A A coordinated systems-based oral anticoagulant reversal plan is needed to provide prompt intervention and optimize outcomes in patients with bleeding, an urgent need for an invasive procedure or surgery, or an overdose.¹⁵ A multidisciplinary team of stakeholders involved in caring for such patients should be convened:

- Emergency and trauma physicians;
- Hematologists and nephrologists;
- Pharmacists, nurses, and other pertinent staff (e.g., technicians, billing representatives)
- Intensivists, including neuro-intensivists;
- Neurosurgeons and other surgeons;
- Clinical laboratory staff;
- Blood bank representatives;
- Risk managers; and
- Health informatics professionals.

This team should make recommendations to appropriate decision-making groups about formulary inclusion and

stocking of clotting factor concentrates and other reversal products so that these agents are readily available when needed and treatment delays are avoided.

Clinical and operational guidelines should be developed to facilitate efficient reversal of oral anticoagulants. These guidelines should address patient risk assessment (i.e., risk for thrombosis and bleeding, urgency of the need for intervention); selection, dosing, and monitoring of reversal agents; and appropriate laboratory tests for assessing coagulation status. Clinical and operational guidelines should be sufficiently flexible to accommodate a variety of patient scenarios and clinical judgment. The guidelines should be made available in a centralized location that is easy for clinicians to access, possibly by incorporating them into the institutional health informatics system and clinical decision support tools. The guidelines should identify key individuals who can serve as a resource within the institution, as well as their contact information.

The oral anticoagulant reversal plan should be comprehensive and meet all of the needs of the patient. For example, hemodialysis may be used to remove dabigatran, so arrangements should be established to quickly provide hemodialysis or transfer patients requiring dabigatran reversal to a facility where hemodialysis is available. Policies and procedures should be developed to facilitate transitions of care, including communication with the staff at facilities receiving a transferred patient about his or her clinical status (especially the time elapsed since the last oral anticoagulant dose and any reversal agents administered). Local emergency medical services personnel should be informed about the plan so that they are aware of institutional capabilities and approaches to anticoagulant reversal.

Recent and Upcoming Publications

Here is a list of recently published articles to help clinicians remain abreast of new developments related to oral anticoagulant reversal. In addition, a supplement to the *American Journal of Health-System Pharmacy* based on the proceedings of the Emerging Treatment Options for the Reversal of Oral Anticoagulant Therapy symposium held on December 3, 2012, is slated for publication in the May 15, 2013, issue.

- Dager WE, Gosselin RC, Kitchen S et al. Dabigatran effects on the international normalized ratio, activated partial thromboplastin time, thrombin time, and fibrinogen: a multicenter, in vitro study. *Ann Pharmacother.* 2012; 46:1627-36.
- Dager WE, Gosselin RC, Roberts AJ. Reversing dabigatran in a life-threatening bleed occurring during cardiac ablation with factor eight inhibitor bypassing activity. *Crit Care Med.* 2013 Mar 7. [Epub ahead of print]
- Levy JH, Faraoni D, Spring JL et al. Managing new oral anticoagulants in the perioperative and intensive care unit setting. *Anesthesiology.* 2013 Feb 14. [Epub ahead of print]
- Siegal DM, Cuker A. Reversal of novel oral anticoagulants in patients with major bleeding. *J Thromb Thrombolysis.* 2013 Feb 7. [Epub ahead of print]
- Tsu LV, Dienes JE, Dager WE. Vitamin K dosing to reverse warfarin based on INR, route of administration, and home warfarin dose in the acute/critical care setting. *Ann Pharmacother.* 2012; 46:1617-26.

Q What types of concentrated clotting factor products are available in the United States and how do they differ? What criteria should be used for formulary decisions?

A Various products containing one or more vitamin K-dependent clotting factors in a more concentrated form compared with fresh frozen plasma are available in the United States. Concentrated clotting factor products include three- and four-factor prothrombin complex concentrate (PCC) products, recombinant factor VIIa (rFVIIa), and activated PCC (aPCC, also known as anti-inhibitor factor complex, factor VIII inhibitor bypassing activity, or FEIBA).

The three-factor PCC products contain inactivated clotting factors II, IX, and X and only small amounts of factor VII in an inactivated form. Four-factor PCC products contain larger amounts of inactivated clotting factor VII than three-factor PCC products as well as clotting factors II, IX, and X in an inactivated form. No four-factor PCC products currently are available in the United States, although several products are under review by the FDA. The content of three- and four-factor PCC products from different manufacturers varies.¹⁶ Activated PCC contains clotting factor VII in an activated form and clotting factors II, IX, and X primarily in an inactivated form. Various combinations of clotting factor products (e.g., three-factor PCC plus rFVIIa) have been used to "build" a four-factor PCC containing all four vitamin K-dependent clotting factors.¹⁷

The optimal approach to using concentrated clotting factor products for anticoagulant reversal is the subject of debate. Local practices and clinician experience and preferences may enter into formulary decisions.

Formulary decisions about clotting factor concentrates should take into consideration the patient mix and product efficacy, safety, cost, and availability. Ideally, the choice among available products should be based on well-conducted clinical studies comparing the efficacy and safety of clotting factor concentrates for oral anticoagulant reversal using outcomes data instead of laboratory coagulation assays that serve as surrogate endpoints alone, but such data are lacking to date. Data currently available suggest that aPCC may be useful for dabigatran reversal and four-factor PCC may be useful for reversal of rivaroxaban and apixaban, although it should be noted that well-designed clinical trials have not been conducted.^{15,17-20} The prothrombotic potential of clotting factor concentrates is a concern, especially products that contain activated clotting factors.¹⁷ Since clotting factor concentrates have an effect on bleeding within minutes, an option for minimizing thrombosis risk in situations where sufficient time is available may be to administer incremental doses of the factor product and repeat patient assessment until the desired effect on bleeding is achieved.

Uses of clotting factor concentrates other than anticoagulant reversal (e.g., clotting factor replacement therapy for patients with hemophilia) should be considered

in making formulary decisions. Although efficacy and safety are more prominent concerns than cost, clotting factor concentrates are costly budget items, especially when used to treat patients with hemophilia because of the large dosing requirements. Contract prices and quantity discounts should be considered in formulary decisions. The cost of building a four-factor PCC for anticoagulant reversal may exceed that of aPCC.¹⁷

Q What progress has been made in developing antidotes to the new oral anticoagulant agents?

A Antidotes to dabigatran, rivaroxaban, and apixaban currently are not available but considerable progress has been made in developing them. A humanized antibody fragment specific for dabigatran, Fab (Boehringer Ingelheim Pharma GmbH & Co, Biberach, Germany), has been developed for use as an antidote.^{21,22} Its affinity for dabigatran is approximately 350 times higher than its affinity for thrombin. In *in vitro* studies of human plasma, Fab had no effect on thrombin generation or coagulation assays, although it is structurally similar to thrombin. In a dose-ranging study of animals with experimentally-induced supratherapeutic dabigatran levels and bleeding, intravenous administration of Fab produced a rapid, dose-dependent decrease in blood loss that was maintained for 6 hours after the largest dose. *Ex vivo* coagulation assays (activated partial thromboplastin time, thrombin time, and ecarin clotting time) were reversed by Fab in these animals. Phase 1 testing of this potential antidote is in progress.

A protein, PRT064445 (also known as PRT4445), which binds to direct factor Xa inhibitors (e.g., rivaroxaban, apixaban, the investigational agent betrixaban) and indirect factor Xa inhibitors (e.g., fondaparinux), has been developed for use as an antidote through recombinant DNA technology in Chinese hamster ovary cells by Portola Pharmaceuticals (South San Francisco, CA).²³ The recombinant protein reversed the factor Xa inhibition from rivaroxaban, apixaban, and betrixaban in a dose-dependent manner and corrected the prolongation of clotting times caused by these factor Xa inhibitors in *ex vivo* studies.²³ Hemostasis was restored by PRT064445 in animal models of blood loss associated with factor Xa inhibitors.²³

The protein was safe and well tolerated in 32 healthy volunteers who participated in a phase 1 study of PRT064445.²⁴ Reversal of anticoagulation from a factor Xa inhibitor was rapid (within 5 minutes) and sustained for 3 hours in *in vitro* tests of PRT064445.²⁴ A phase 2 study of the safety and efficacy of PRT064445 for reversal of direct factor Xa inhibitors in healthy volunteers began in December 2012 and is expected to be completed in 2013.^{24,25} The pharmacodynamics, pharmacokinetics, and dosing required for anticoagulant reversal will be explored.

A synthetic small molecule antidote known as PER977 developed by Perosphere Inc. (Mount Kisco, NY) has

been tested in human plasma and animals.²⁶ In an *ex vivo* study of human plasma, the anti-factor Xa activity of rivaroxaban and apixaban at 100% and 200% of the therapeutic peak plasma concentrations was completely reversed by PER977 in a dose-dependent manner. In an *in vivo* study of rats given overdoses of rivaroxaban, apixaban, or dabigatran using a standard tail transection bleeding model, PER977 decreased bleeding by more than 90% after 30 minutes to within the normal range for rats without anticoagulation. No procoagulant effects were observed in human plasma or the animal study.

Potential advantages of PER977 over other antidotes include reversal of both dabigatran and factor Xa inhibitors, which can be beneficial in situations where the identity of the target-specific oral anticoagulant is unknown.²⁷ Stability at room temperature allowing the product to be stocked in am-

balances and other places where refrigeration is not available is a potential advantage over biological products that require refrigeration, such as the monoclonal antibody PRT064445.²⁷ Phase 1 testing of PER977 will begin later this year.



Additional ASHP Advantage Educational Activities

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For complete information about educational activities that are part of this initiative, visit www.ashpadvantage.com/reversal. There is no charge for the activities, and ASHP membership is not required.

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