Antidote Treatments for the Reversal of Direct Oral Anticoagulants

Summary

- There are three intravenous antidotes currently under development for the reversal of direct oral anticoagulants.

- Idarucizumab is a humanized, monoclonal antibody fragment that reverses the direct thrombin inhibitor dabigatran. Andexanet alfa is a modified recombinant factor Xa molecule that reverses oral direct (e.g., apixaban, edoxaban, rivaroxaban) and injectable indirect (e.g., enoxaparin, fondaparinux) factor Xa inhibitors. Aripazine is a small, synthetic molecule with potentially universal anticoagulant reversal activity.

- Clinical evidence to support the use of individual antidotes is currently limited to phase 1 and phase 2 trials in healthy volunteers. All three antidotes were well tolerated during these studies and no pro-coagulant activity was observed. Phase 3 trials are underway for idarucizumab and andexanet alfa.

- Preliminary data shows promising results but assessment of long-term safety and efficacy requires more research. Additional research is also needed to determine impact on clinical practice. Clear guidance should be available at the time these reversal drugs are commercialized to promote their appropriate use.

The Technology

In the past decade, the use of direct oral anticoagulants (DOACs; apixaban, dabigatran, edoxaban, rivaroxaban) has been approved for a number of conditions such as the prevention of stroke in patients with non-valvular atrial fibrillation (AF); the prevention of venous thromboembolism (VTE) after hip or knee replacement surgery; and the treatment of VTE, as well as the prevention of VTE recurrence. [Note: apixaban, dabigatran, and rivaroxaban are currently available in Canada.] Unlike warfarin and other vitamin K antagonists, there are no specific antidotes available to reverse the anticoagulant effect of DOACs. Although the latter have short half-lives, which suggests reversal drugs may not be needed in non-urgent situations, the lack of such antidotes is a concern in emergency situations such as life-threatening major bleeding or non-elective major surgery. Currently, there are three specific reversal drugs for DOACs under clinical development (see Table 1).

Idarucizumab (aDabi-Fab/BI 655075/Boehringer Ingelheim, Germany) is a humanized, monoclonal antibody fragment that specifically binds with high affinity to dabigatran, an oral direct thrombin inhibitor (DTI), also developed by Boehringer Ingelheim. It acts by competitively displacing dabigatran from thrombin to reverse anticoagulation and restore fibrin formation. Dabigatran has an affinity for idarucizumab that is 350 times greater than its affinity for thrombin. The dose currently studied in the phase 3 trial is 5 g. Based on pre-marketing information obtained from the manufacturer, idarucizumab will be available as a single package consisting of two 50 mL vials (2 x 2.5 g); no reconstitution will be required. The complete dose of 5 g will be administered intravenously as two consecutive infusions over 5 to 10 minutes each, or as bolus injections (Ernie Hampel, Executive Director, Market Access and Healthcare Affairs, Boehringer Ingelheim Canada Ltd., Burlington, ON: personal communication, 2015 Mar 9).

Andexanet alfa (PRT064445 or PRT4445*/Portola Pharmaceuticals Inc., US) is a modified recombinant factor Xa (FXa) molecule intended for intravenous (IV) administration. It was developed as an antidote to reverse anticoagulant activity of oral direct (e.g., apixaban, edoxaban, and rivaroxaban) and injectable indirect (e.g., enoxaparin and fondaparinux) FXa inhibitors. Andexanet alfa acts as a decoy to target and sequester with high specificity both oral and injectable FXa inhibitors in the blood. It lacks a membrane-binding gamma-carboxyglutamic acid domain, rendering it catalytically inactive, but it retains a high binding affinity to FXa inhibitors. Two doses are currently being studied in phase 3 trials: 400 mg IV bolus followed by continuous infusion at 4 mg per minute for 120 minutes (reversal of apixaban) and 800 mg IV bolus followed by continuous infusion at 8 mg per minute for 120 minutes (reversal of rivaroxaban).

Aripazine (PER977/ciraparantag/Perosphere Inc., US) is a small, synthetic molecule designed with broad reversal activity and administered as a single IV bolus...
dose. It binds to oral FXa inhibitors and DTIs, as well as to injectable unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) via non-covalent bonding and charge-charge interactions to neutralize anticoagulation and bleeding. As the clinical development program for aripazine is currently at the phase 2 stage, it is not possible to comment on the dose that will be studied in the phase 3 trial and which is therefore more likely to be approved for clinical use.

**TABLE 1: ANTIDOTES UNDER DEVELOPMENT FOR DIRECT ORAL ANTICOAGULANTS**

<table>
<thead>
<tr>
<th>Antidote</th>
<th>Target</th>
<th>Structure</th>
<th>Route</th>
<th>Storage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idarucizumab (BI 655075)</td>
<td>Oral DTI</td>
<td>Humanized monoclonal antibody fragment</td>
<td>IV</td>
<td>Refrigerated</td>
</tr>
<tr>
<td>Andexanet alfa (PRT064445 or PRT4445*)</td>
<td>Oral FXa inhibitors; injectable LMWH and fondaparinux</td>
<td>Modified recombinant FXa protein</td>
<td>IV</td>
<td>Refrigerated</td>
</tr>
<tr>
<td>Aripazine (PER977)</td>
<td>Oral FXa inhibitors and DTI; injectable UFH, LMWH, and fondaparinux</td>
<td>Synthetic small molecule</td>
<td>IV</td>
<td>Room temperature</td>
</tr>
</tbody>
</table>

DTI = direct thrombin inhibitor; FXa = factor Xa; IV = intravenous; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

**Regulatory Status**

Currently, idarucizumab, andexanet alfa, and aripazine are not approved for use in Canada, the US, the United Kingdom, or European Union (EU) countries. Andexanet alfa and idarucizumab were granted breakthrough therapy designation by the US Food and Drug Administration (FDA) in November 2013 and June 2014, respectively. On February 26, 2015, the FDA also granted orphan drug designation to andexanet alfa for reversing the anticoagulant effect of direct or indirect FXa inhibitors in patients experiencing a serious, uncontrolled bleeding event or who require urgent or emergency surgery. On March 3, 2015, Boehringer Ingelheim, the manufacturer of idarucizumab, announced that submission for approval was filed in the US, the EU, and Canada for use in patients requiring an antidote to dabigatran. On April 24, 2015, the FDA granted priority review/accelerated approval status to idarucizumab. Of note, final results from phase 3 clinical studies for both idarucizumab and andexanet alfa are pending. Aripazine was granted fast-track status in the US on April 15, 2015; phase 3 trials are planned.

**Patient Group**

Pending confirmation of their efficacy and safety, these antidote treatments will fulfill an unmet need in patients using a DOAC and who need immediate reversal of the anticoagulant effect. At this time, it is anticipated that the targeted population for these drugs will be patients in emergency situations such as those with major bleeding or who require non-elective major surgery. Although the definition for major bleeding may vary across clinical trials, the International Society on Thrombosis and Haemostasis (ISTH) developed a classification commonly used in research and that provides a good description of these serious adverse events (AEs). Overall, major bleeds are those that result in death, are life-threatening, cause chronic sequelae, or consume major health care resources. Types of major bleeding events defined by ISTH’s classification include fatal bleedings and bleedings occurring in critical anatomical sites such as the brain, spine, eyes, abdominal cavity, joints, or pericardium, or in muscle if compartment syndrome is present. Other types of major bleeding events under ISTH’s definition include a fall in hemoglobin levels of at least 2 g/dL or the need for transfusing at least two red cell packs. Of interest, other potential conditions where reversal of DOACs may be considered have been identified in a recent review. These include clinical conditions at high risk of bleeding such as major head injury in patients treated with DOACs, DOAC overdose in patients with coagulation or platelet disorders or in patients also taking antithrombotic drugs at the same time. Of note, these conditions are not specifically included in currently ongoing phase 3 clinical trials.
Current Practice

In patients experiencing a DOAC-induced major bleeding event, current consensus-based guidelines recommend withdrawing the anticoagulant and administering oral charcoal (if within two hours of DOAC ingestion). The use of prothrombin complex concentrate (PCC, Octaplex) at a dose of 25 U/kg (which may be repeated once or twice), activated prothrombin complex concentrate (aPCC, FEIBA) at a dose of 50 IE/kg (max 200 IE/kg/day) or recombinant factor VIIa (rFVIIa, NiaStase) may be considered.

Overall, there appears to be relatively limited available data supporting the efficacy of these non-specific drugs in the reversal of DOAC-induced bleeding events.

Also, given that thrombosis is a potential AE from anticoagulant reversal therapy, these pro-coagulant drugs must be administered with caution.

Hemodialysis may also be considered to reverse the anticoagulant effect but only in the case of dabigatran-associated bleeding. Despite edoxaban being relatively low-protein-bound and slightly cleared by hemodialysis (6% to 20%), a small open-label pharmacokinetic study of 10 patients with end-stage renal disease indicates that hemodialysis is not effective at removing edoxaban from the bloodstream.

The Evidence

Current evidence for the reversal of a DOAC anticoagulant effect with antidote treatments is mostly limited to in vitro studies, animal models, and trials with healthy volunteers.

Idarucizumab

In an early phase trial, Van Ryn et al. evaluated the reversal of dabigatran’s anticoagulant effect with idarucizumab in 35 healthy volunteers. They each received 1 g, 2 g, or 4 g of idarucizumab or placebo. The treatment was administered as a five-minute IV infusion after four days of dabigatran 220 mg twice daily orally. Blood was collected from an incision wound to explore restoration of wound site fibrin formation by measuring fibrinopeptide A (FPA). There was a significant, dose-dependent return of fibrin formation with increasing doses of idarucizumab; reversal allowed participants to reach 24%, 45%, and 63% of control FPA values 30 minutes after 1 g, 2 g, and 4 g of idarucizumab was administered, respectively ($P < 0.05$).

A global phase 3 case series study known as RE-VERSE AD is currently enrolling patients treated with dabigatran who have uncontrolled bleeding or require emergency surgery or procedures (see Table 2). A dose of 5 g idarucizumab will be administered intravenously to reverse the effect of dabigatran. The trial will measure plasma-diluted thrombin time and ecarin clotting time as primary outcome measures.

Time to cessation of bleeding will be a secondary outcome. Results from the trial are anticipated in July 2017.

Andexanet alfa

Two phase 2 trials evaluated the safety and efficacy of andexanet alfa in healthy volunteers receiving apixaban or rivaroxaban, which are two DOACs available in Canada. Patients in one study by Crowther et al. received apixaban 5 mg twice daily orally for six days before 420 mg of andexanet alfa was administered as an IV bolus dose. This treatment was followed by a continuous IV infusion of andexanet alfa for either 45 minutes or two hours, at a rate of 4 mg per minute. At two minutes following the IV bolus dose, plasma concentrations of unbound apixaban decreased and the mean anti-FXa activity was reduced by more than 90%, with the level of reversal sustained throughout the infusion periods for both regimens ($P < 0.0001$). Thrombin generation remained within the normal range for two hours following cessation of infusion.

In the other placebo-controlled study, healthy patients were given rivaroxaban 20 mg per day orally for six days and were then randomly assigned to four different dosing cohorts of andexanet alfa (210 mg IV bolus, 420 mg IV bolus, 600 mg IV bolus, or 720 mg IV bolus followed by a one-hour IV infusion administered at a rate of 4 mg per minute). Results showed a dose-dependent reduction in anti-FXa activity by 20%, 53%, 70%, and 81%, respectively; anti-FXa activity returned to levels seen with placebo approximately two hours after treatment cessation. Similarly, the plasma concentration of unbound rivaroxaban decreased by 32%, 51%, 75%, and 70%, respectively, relative to pre-andexanet alfa values. Findings from the two first-dose cohorts of another small phase 2 trial were recently reported in abstract form; in this study patients received edoxaban, a DOAC not currently available in Canada. This study evaluated andexanet alfa for the reversal of the anticoagulant effect of edoxaban, administered at a dose of 60 mg daily for six days prior to andexanet alfa. Both dose cohorts (andexanet alfa 600 mg bolus [n = 9] and 800 mg bolus followed by 8 mg per minute infusion for one hour [n = 9]) resulted in an immediate decrease in anti-FXa activity of 52% and 73%, respectively, compared with the pre-andexanet alfa administration level. This decrease remained constant during the infusion and returned to placebo levels approximately two hours following cessation of...
andexanet alfa. The antidote was well tolerated and there were no serious or severe AEs and no thrombotic events.\textsuperscript{37} Part 1 of two phase 3 clinical trials — ANNEXA-A and ANNEXA-R — was recently completed. They evaluated reversal of apixaban and rivaroxaban with andexanet alfa in older healthy volunteers (ages 50 to 75 years).\textsuperscript{12,20,24} Final results of these trials are pending (see Table 2). Primary outcomes were measured by anti-FXa activity. Secondary outcomes include unbound FXa inhibitor plasma levels and thrombin generation.\textsuperscript{38,39} Of note, preliminary results from part 1 of the ANNEXA-R trial — which compared the administration of an 800 mg IV bolus of andexanet alfa to placebo in 39 patients pretreated with rivaroxaban 20 mg for four days — were presented at the 2015 American College of Cardiology (ACC) Scientific Sessions on March 16, 2015.\textsuperscript{40} Andexanet alfa produced a statistically significant and rapid reduction in anti-FXa activity from baseline (primary outcome); mean percent change anti-FXa from baseline to nadir was 92\% (P < 0.0001 versus placebo). Normalization of coagulation parameters was achieved within two minutes of completing the IV bolus infusion; the effect lasted one to two hours with the IV bolus dose.\textsuperscript{11} Part 2 is ongoing and will investigate IV bolus followed by a two-hour continuous infusion to demonstrate sustained reversal.\textsuperscript{11,40}

**Aripazine**

In a double-blind, placebo-controlled, phase 1/2 trial involving 80 healthy volunteers, single IV doses (administered over the course of two to five minutes) of aripazine (5 mg to 300 mg) or placebo were administered three hours after a 60 mg dose of edoxaban was given orally.\textsuperscript{7,16,41} The degree of reversal in anticoagulation was measured by whole-blood clotting time. At doses of 100 mg to 300 mg, aripazine reduced whole-blood clotting time to within 10\% above baseline value in 10 minutes; this effect was sustained for 24 hours. In comparison, the time to reach that level in patients receiving placebo was approximately 12 to 15 hours. Aripazine restored normal clot formation and fibrin integrity within the clot, as shown by scanning electron micrographs. There was also no evidence of pro-coagulant activity.\textsuperscript{7,16,41} A phase 2 clinical trial that evaluates re-anticoagulation in patients with edoxaban following reversal of anticoagulant effect by aripazine is near completion. This study aims to identify a dose regimen for aripazine that reverses the effects of edoxaban for up to 21 hours (see Table 2).\textsuperscript{42}

### Table 2: Ongoing Phase 2 and 3 Clinical Trials With Antidotes for Direct Oral Anticoagulants\textsuperscript{9,12,24,38,39,42}

<table>
<thead>
<tr>
<th>Key Study Descriptors</th>
<th>Title</th>
<th>Study Design and Intervention</th>
<th>Primary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Idarucizumab</strong></td>
<td>A phase 3 case series clinical study of the reversal of the anticoagulant effects of dabigatran by IV administration of 5 g idarucizumab in patients treated with dabigatran etexilate who have uncontrolled bleeding, or require emergency surgery or procedures. (RE-VERSE AD; A Study of the RE-VERSAl Effects of Idarucizumab on Active Dabigatran)</td>
<td>Phase 3, single-group, open-label, case series study</td>
<td>Maximum reversal of anticoagulant effect of dabigatran based on central laboratory determination of DTI or ECT, at any time point from the end of the first infusion up to 4 hours after the last infusion</td>
</tr>
<tr>
<td>NCT02104947</td>
<td>Idarucizumab 5 g IV</td>
<td></td>
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<tr>
<td>N = 300</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Andexanet alfa</strong></td>
<td>A study in older patients to evaluate the safety and ability of andexanet alfa to reverse the anticoagulation effect of apixaban. (ANNEXA-A; Andexanet alfa: A Novel Antidote to the Anticoagulant Effects of FXa Inhibitors — Apixaban)</td>
<td>Phase 3, randomized, double-blind, placebo-controlled study</td>
<td>Reversal of apixaban anticoagulation effect as measured by anti-factor Xa activity</td>
</tr>
<tr>
<td>NCT02207725</td>
<td>Andexanet alfa 400 mg IV bolus followed by continuous infusion at 4 mg/minute for 120 minutes</td>
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<td>Key Study Descriptors</td>
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<tr>
<td>Andexanet alfa</td>
<td>A study in older patients to evaluate the safety and ability of andexanet alfa to reverse the anticoagulation effect of rivaroxaban. (ANNEXA-R; Andexanet alfa: A Novel Antidote to the Anticoagulant Effects of FXa Inhibitors — Rivaroxaban)</td>
<td>Phase 3, randomized, double-blind, placebo-controlled study. Andexanet alfa 800 mg IV bolus followed by continuous infusion at 8 mg/minute for 120 minutes</td>
<td>Reversal of rivaroxaban anticoagulation effect as measured by anti-factor Xa activity</td>
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<tr>
<td>NCT02220725</td>
<td>N = 79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripazine</td>
<td>A phase 2, randomized, sequential group evaluation of ascending reversal doses of PER977 administered to patients with steady state edoxaban dosing and re-anticoagulation with edoxaban following PER977 reversal.</td>
<td>Phase 2, randomized, sequential group, single-blind study. Aripazine 25 mg, 50 mg, 100 mg, 300 mg, and 600 mg IV</td>
<td>Whole-blood clotting time as a measure of edoxaban anticoagulation reversal by aripazine</td>
</tr>
<tr>
<td>NCT02207257</td>
<td>N = 50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( \text{dTT} = \text{diluted thrombin time}; \text{ECT} = \text{ecarin clotting time}; \text{FXa} = \text{factor Xa}; \text{g} = \text{gram}; \text{IV} = \text{intravenous}; \text{mg} = \text{milligram}; \text{mg/minute} = \text{milligram per minute}; \text{N} = \text{estimated enrolment.} \)

### Harms

Idarucizumab was well tolerated during a phase 1 trial with 145 healthy volunteers receiving dabigatran. Only minor drug-related AEs were reported including headache, migraine, warmth, and flushing.\(^3^\) Similarly, in patients who received andexanet alfa and rivaroxaban in a phase 2 randomized controlled trial (\(n = 18\)), the investigational antidote was well tolerated with no serious or severe AEs observed. Reported AEs included mild infusion-related reactions (\(n = 3; 33\%\)), post-procedural hematoma (\(n = 2; 22\%\)), headache (\(n = 2; 22\%\)), and postural dizziness (\(n = 2; 22\%\)).\(^3^5\) Preliminary findings from part 1 of the phase 3 ANNEXA-R trial included no serious or severe AEs with andexanet alfa in any patient, including thrombotic events. No antibodies to FX or FXa were reported.\(^1^1\) Lastly, in a phase 1/2 clinical trial of 80 healthy volunteers, the use of aripazine in reversing edoxaban-induced anticoagulation was well tolerated, with no evidence of clinically significant or dose-limiting AEs. Reported AEs with aripazine were transient, mild, perioral, and facial flushing; dysgeusia; and moderate headache. One patient developed moderate muscle cramping with elevation in creatinine phosphokinase levels; these AEs were considered to be unrelated to aripazine.\(^7\)

All three antidotes have yet to exhibit thrombotic and/or pro-coagulant properties in clinical studies. This is critical considering that numerous patients requiring these antidotes will be using DOACs for stroke prevention or VTE treatment. Rebound anticoagulation may also be a concern, especially for antidotes with a short half-life and a single IV bolus administration. Although no antibodies toward the antidotes have been detected in the studies conducted, another safety concern relates to immunogenicity, given that idarucizumab is a monoclonal antibody and andexanet alfa is an endogenous FXa variant. More research is needed to elucidate their long-term safety.

### Administration and Cost

The manufacturers’ prices for idarucizumab, andexanet alfa, and aripazine are currently unavailable, as these drugs have not yet been approved for sale in Canada. Given that these antidotes are biologics in nature, with the exception of aripazine, they are expected to be relatively costly. As the antidotes will most likely be administered intravenously in a hospital setting, additional costs could potentially be encountered for their administration and subsequent monitoring of coagulation status.

### Concurrent Developments

There are ongoing studies evaluating the use of andexanet alfa and aripazine to reverse supratherapeutic anticoagulation states induced by non-oral anticoagulants including UFH and LMWH. Current recommendations to reverse UFH involve administering protamine sulfate but no drug is effective for the...
complete reversal of LMWH. Protamine sulfate can only partially reverse 60% to 75% of enoxaparin.28 Early results from phase 2 trials demonstrate that andexanet alfa is able to safely and rapidly reverse the anticoagulant effects of enoxaparin in healthy volunteers by reducing anti-FXa activity and restoring thrombin generation.13,45 Given andexanet alfa’s design and mechanism of action, reversal of pentasaccharide antithrombin III-dependent inhibitors such as fondaparinux is possible, as well.11 More research is required to determine the safety and efficacy of andexanet alfa when used in that context.

Aripazine is designed with broad reversal activity. Based on dynamic light-scattering data, it is a potentially universal antidote for parenteral heparin anticoagulants including UFH, LMWH, fondaparinux, as well as all DOACs.46 Results are pending from a phase 1/2 clinical trial completed in healthy volunteers evaluating the safety and pharmacodynamic effects of aripazine following a single dose of enoxaparin.47 Another trial evaluating aripazine following administration of UFH is anticipated to be completed in March 2016.48

Rate of Technology Diffusion

Considering the anticipated growth in the use of DOACs, the advent of these antidotes is of profound interest. Thus far, virtually all phase 2 or phase 3 studies are limited by small sample size, with healthy volunteers enrolled as patients in several of these studies and for short study duration. Portola Pharmaceuticals Inc. recently announced the initiation of an open-label, single-group, phase 4 (ANNEXA-4) clinical trial evaluating andexanet alfa’s ability to decrease anti-FXa activity and restore hemostasis. It will be conducted in over 50 sites located in North America and Europe. Participants will be patients receiving apixaban, rivaroxaban, or enoxaparin, who present with a major bleeding event.11,17,49 There are also plans to add edoxaban to the study by mid-2015.11

In the future, additional data will be necessary to compare the pharmacoeconomics and cost-effectiveness of the antidotes for DOACs, especially for those with potential overlapping indications. For example, both andexanet alfa and aripazine can reverse the effects of apixaban, but andexanet alfa may require a continuous IV infusion whereas aripazine is administered as a single IV bolus.7,34 The broad activity of both andexanet alfa and aripazine also creates a potential for off-label use in the reversal of non-oral anticoagulants including UFH, LMWH, and fondaparinux, unless manufacturers intend to also pursue regulatory approval for the reversal of these drugs. Off-label use for reversal of DOACs may also be possible as the studied populations are narrowly defined. Once these antidotes become available, it is possible that they will contribute to a larger adoption of DOACs, though clinical experience with the latter remains limited and their comparative cost-effectiveness versus vitamin K antagonists is unclear.

Implementation Issues

Availability and timely administration may be a barrier to the optimal usage of these antidotes. Given that idarucizumab and andexanet alfa are injectable biologics that require refrigeration, they will likely be used exclusively in hospital settings because of storage and distribution issues.50 Unlike the biologics, aripazine is a small molecule that is stable at room temperature with the current formulation; this feature may result in the potential for out-of-hospital use.51

It is anticipated that these antidotes will be more costly than the antidote traditionally used for warfarin-induced bleeding, i.e., vitamin K. However, compared with the cost of current non-specific reversal drugs for DOACs (i.e., PCC, aPCC, and rFVIIa), the use of these antidotes may be more favourable from a budget impact perspective.

Despite the promising results from existing clinical data, currently available evidence to establish the safety and efficacy of these antidotes remains limited. For example, whether the measurements of various surrogate markers (i.e., PT, aPTT, ecarin clotting time, diluted thrombin time, or anti-FXa) can be extrapolated to mortality or morbidity benefits remains to be demonstrated.4 Also, all ongoing phase 2 (aripazine) and phase 3 trials (andexanet alfa and idarucizumab) enrolled a small number of patients. In the case of idarucizumab, the phase 3 trial is the study with the largest sample size (N = 300) and is recruiting patients who have either bleeding or require emergency surgery. However, it is an open-label case series — a design in which findings are typically not as robust as those from randomized controlled trials. In the case of andexanet alfa, data on patients who are bleeding will have to await the release of the findings from the ANNEXA-4 study.

It is essential that clear guidance be provided to practitioners at the time these reversal drugs are commercialized in Canada to promote their optimal use. Areas of uncertainty for which guidance will be
needed for antidotes for DOACs include but are not limited to:

- Indications: type of bleeding, type of emergency procedures, overdose without bleeding.
- Dosing: standard dose for all patients, or situational dosing (e.g., based on type of procedure); duration of effect; risk of rebound anticoagulation; IV bolus versus continuous infusion.
- Appropriate use: optimal use (based on clinical and economic factors), off-label use, use of laboratory tests.

Given that the use of these reversal drugs is directly linked to the use of DOACs, clear guidance on the use of the latter may also reduce the need to reverse their anticoagulant effect. Development of such guidance is of interest to a number of organizations including Canadian health technology assessment agencies that recently produced guidance for some of the approved indications of DOACs.52,53 Also, ongoing clinical trials and future research on reversal drugs will help determine which patients are the most appropriate candidates to benefit from these antidotes and how to use these antidotes optimally.

References


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