Anticoagulation reversal in the era of the non-vitamin K oral anticoagulants

Andres Enriquez1*, Gregory Y.H. Lip2,3, and Adrian Baranchuk1

1Division of Cardiology, Queen’s University, Kingston, ON, Canada; 2University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK; and 3Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

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In recent years, non-vitamin K oral anticoagulants (NOACs) have emerged as an alternative to warfarin for the prevention and treatment of thrombo-embolic disease. Large randomized trials have demonstrated that these agents, which act by directly targeting thrombin (dabigatran) and factor Xa (rivaroxaban, apixaban, and edoxaban), are at least as effective as warfarin, with lower rates of bleeding and fewer interactions with food and drugs. In addition, NOACs have a more predictable anticoagulant effect, allowing a fixed dose regimen and obviating the need for routine anticoagulation monitoring. Since the introduction of NOACs, one of the major concerns for clinicians has been the lack of specific agents to reverse their anticoagulant effect in case of life-threatening haemorrhagic complications or emergency surgery, which have limited their use in patients deemed at a higher risk of bleeding. New specific antidotes (e.g. idarucizumab, andexanet alfa, and ciraparantag) show promising data, and may soon become available for clinical use. In this article, we review the pharmacology of these agents, the incidence and outcomes of haemorrhagic complications, the available strategies for anticoagulation reversal, and the more recent advances for the development of specific antidotes.

Keywords: Anticoagulation • Bleeding • Reversal • Antidote • Non-vitamin K oral anticoagulants • Warfarin • Dabigatran • Rivaroxaban • Apixaban • Edoxaban • Andexanet alfa • Idarucizumab • Ciraparantag

Introduction

For more than five decades, warfarin, a vitamin K antagonist, was the only oral anticoagulant available for prevention and treatment of thrombo-embolic disease. However, despite its efficacy, warfarin has several limitations, including a narrow therapeutic window, slow onset and offset of action, need for strict anticoagulation monitoring, and numerous food and drug interactions. A major advance in the prevention of stroke has been the introduction in recent years of non-vitamin K oral anticoagulants (previously referred to as new or novel oral anticoagulants or NOACs1), which act by targeting specific components of the coagulation cascade such as thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, and edoxaban).2 The first agent receiving approval by the Food and Drug Administration (FDA) was dabigatran (Pradaxa®, Boehringer Ingelheim) in 2010, followed by rivaroxaban (Xarelto®, Bayer) in 2011, and apixaban (Eliquis®, Pfizer and Bristol-Myers Squibb) in 2012. Edoxaban (Lixiana®, Daiichi Sankyo) is approved in Japan since April 2011 and is currently under review by the US FDA.

Non-vitamin K oral anticoagulants are at least as effective as warfarin with similar or lower rates of bleeding and fewer interactions with food and drugs. In addition, they have a more predictable anticoagulant effect, allowing a fixed dose regimen and obviating the need for routine anticoagulation monitoring. One of the potential drawbacks of NOACs since their introduction has been the absence of an antidote to reverse anticoagulation in case of life-threatening bleeding or emergency surgery. However, this will soon change as specific agents that counteract the effects of NOACs are under development and promising results of Phase 2 trials have been recently announced (Figures 1 and 2).

In this review article, we provide an overview the pharmacology of these agents, the incidence and outcomes of haemorrhagic complications, the available strategies for anticoagulation reversal in case of bleed, and the more recent advances for the development of specific antidotes.

Overview of warfarin-related bleeding

Warfarin acts by inhibiting the synthesis of vitamin K-dependent clotting factors II, VII, IX, and X. These factors are synthesized in the liver as precursor forms and are activated by carboxylation of specific glutamic acid residues which require vitamin K as a cofactor. Since factor

* Corresponding author. Tel: +1 613 549 6666; fax: +1 613 548 1387. E-mail address: andresaep@gmail.com

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II (prothrombin) has a half-life of 60–72 h, the onset of action of warfarin is slow and the maximum anticoagulant effect may not be achieved before 4–5 days.3 It has high bioavailability, is rapidly absorbed from the gastrointestinal (GI) tract, and reaches maximal blood concentrations about 90 min after oral administration.3 Warfarin circulates bound to plasma proteins and is mainly metabolized by cytochrome P450 2C9, which explains part of its multiple drug-to-drug interactions.4 Pooled data from randomized trials estimate the annual risk of major bleeding associated with warfarin at around 1–2%, 5 but the rates may be higher (≏3–4%) in community-based studies, which typically include older patients with more comorbidities and often poor dose management.6,7 The most devastating complication of warfarin is intracranial haemorrhage (ICH), which presents with larger haematoma volumes and worse clinical outcomes than spontaneous ICH.8,9 It has been estimated that and up to 10% of patients with warfarin-related major bleeding will die within 30 days and mortality associated with ICH approaches 50%.10 The main determinant of bleeding is the intensity of anticoagulant effect and the risk of ICH doubles for every increase of 1 point in the INR.11

In case of life-threatening bleeding, efforts should be directed towards the rapid reversal of anticoagulation. Vitamin K is necessary to permit the de novo synthesis of coagulation factors; and a dose of 5–10 mg IV is able to normalize the INR in most patients; however, the effect is slow (≏24 h).12 In consequence, vitamin K is not sufficient as a sole measure and should be associated with aggressive replacement of coagulation factors. Available options include: fresh frozen plasma (FFP), prothrombin complex concentrates (PCCs), and recombinant-activated factor VII (rFVIIa; Novoseven®). Fresh frozen plasma has been the most widely used product for coagulation factor replacement, but large volumes are required to achieve normalization of the INR added to the risk of allergic reactions and transmission of infections.13 In contrast, PCC contains much higher amounts of coagulation factors and three different products are commercially available: 3-factor PCC (contains factors II, IX, and X; Profilnine SD® and Bebulin VH®), 4-factor PCC (factors II, VII, IX, and X; Octaplex®, Beriplex®, and Cofact®), and activated PCC (APCC, coagulation factors in activated form; FEIBA®). Prothrombin complex concentrates achieve a more rapid reversal of the INR than FFP14–16 and one prospective observational study also found improved outcomes, given by less major haemorrhage, haematoma expansion, and better 3-month functional outcomes.17 A risk of thrombosis of 1.8% for 4-factor PCC and 0.7% for 3-factor PCC has been reported.18 The evidence for rFVIIa is less clear. Data from small case series show reductions in the INR to variable degrees19–21 but the use of rFVIIa failed to reduce blood loss in a human experimental model of punch biopsy-induced bleeding. Based on the available evidence, current guidelines recommend 4-factor PCC associated with vitamin K 5–10 mg IV for patients with warfarin-associated major bleeding.13 It is of note, however, that despite a rapid INR correction the prognosis of warfarin-associated ICH remains poor, with a high risk of haematoma expansion and in-hospital mortality.22,23

**Dabigatran**

**Pharmacology**

Dabigatran etexilate is a potent, direct, competitive inhibitor of thrombin, both free and bound to fibrin. It is a pro-drug with a bioavailability of 6% that after oral administration is rapidly converted to dabigatran by serum esterases. Dabigatran has a serum half-life of 12–17 h, with plasma levels peak around 2 h after ingestion, and 80% of the drug is excreted by the kidneys24 (Table 1).
The RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy) trial showed that dabigatran at a dose of 150 mg BID was superior to warfarin in preventing stroke and systemic embolism with a similar risk of major bleedings. The benefit of dabigatran has also been demonstrated for prevention of thromboembolism after knee or hip arthroplasty and for treatment of acute venous thrombo-embolic events. Its use is not recommended in patients with mechanic heart valves based on the RE-ALIGN (Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement) trial, which was terminated prematurely because of an excess of thromboembolic and bleeding events among patients in the dabigatran group.

**Figure 2** Mechanism of NOACs and their antidotes. (A) The prothrombinase complex, consisting of FXa and FIIa, catalyses the conversion of prothrombin (II) to thrombin (IIa), leading to fibrin generation and platelet aggregation. Dabigatran and FXa inhibitors (a-Xa) directly inhibit thrombin and FXa, respectively. (B) Andexanet alfa (And-α) is a modified inactive recombinant FXa that binds circulating FXa inhibitors, allowing native FXa to convert prothrombin to thrombin and restart the coagulation cascade. (C) Idarucizumab (aDabi-Fab) is a humanized antibody fragment that binds to dabigatran, preventing it from binding to thrombin and neutralizing its anticoagulant effect. (D) Small synthetic molecule ciraparantag competitively binds the NOACs, restoring activity of blocked coagulation factors.

**Risk of bleeding**

In the RE-LY study, the rate of major bleeding was 3.36% in the warfarin group, when compared with 2.71% per year in the group that received 110 mg of dabigatran (P = 0.003) and 3.11% per year in the group that received 150 mg of dabigatran (P = 0.31). There was a significantly higher rate of major GI bleeding with dabigatran at the 150 mg dose, but life-threatening and intracranial bleeding were more frequent with warfarin than with either dose of dabigatran. The outcome of ICH was also better in the dabigatran group, with lower rates of fatal bleeds, and among patients requiring urgent surgery, dabigatran was associated with similar rates of perioperative bleeding compared with warfarin. Data
from meta-analysis confirm a reduction of major bleeding [relative risk (RR) 0.88, 95% confidence interval (CI) 0.78–0.98] and ICH with dabigatran compared with vitamin K inhibitors.

After dabigatran was first approved in the US in 2010, the FDA received an unusually high number of reports of bleeds associated with the use of the drug. The Mini-Sentinel database was examined to compare intracranial and GI haemorrhage in new users of dabigatran and warfarin from October 2010 to December 2011. Results showed that bleeding rates associated with dabigatran use during that period did not appear to be higher than those associated with warfarin and concluded that the large number of reported cases of bleeding associated with dabigatran probably was explained by the biased tendency to report adverse effects with newly released drugs, the so-called Weber effect.

Other post-market studies have also addressed the safety of dabigatran. Hernandez et al. using the same dataset came to a different conclusion. This was based on a much smaller cohort (631 patient-years of dabigatran data) with a selected sample of 5% random Medicare beneficiaries with newly diagnosed AF initiating dabigatran or warfarin, and had a shorter study period (11 months, between October 2010 and October 2011). Dabigatran was associated with a higher incidence of major bleeding [Hazard ratio (HR) 1.30; 95% CI 1.20–1.41], a higher risk of GI bleeding (HR 1.58; 95% CI 1.36–1.83), but a lower risk of ICH (HR 1.85; 95% CI 1.64–2.07).

More post-marketing data may be needed to better understand the risks associated with real-world use, especially among high-risk patients.

### Measurement of anticoagulation effect

Although routine monitoring is not required for dose adjustment of NOACs, in specific situations some laboratory tests may help to assess for the presence of anticoagulation effect (overdose, acute bleeding, or in the event of an urgent surgery). For dabigatran, the most sensitive test is thrombin time (TT) that measures the direct activity of thrombin. The ecarin clotting time (ECT) and TT determine the correlation is not linear, especially at supratherapeutic levels. None of the previous tests can accurately assess the intensity of anticoagulation per se.

### Management

#### General measures

Until an antidote becomes available for clinical use, supportive care remains the mainstay of treatment in the event of haemorrhagic complications. The drug must be temporarily discontinued, the source of

| Table 1 Pharmacokinetic characteristics of new oral anticoagulants |
|---------------------------------|-----------------|-----------------|-----------------|
| **Dosing**                      | **Dabigatran**  | **Rivaroxaban** | **Apixaban**    |
| Non-valvular AF                 | 150 mg BID      | 20 mg QD        | 5 mg BID        |
| DVT prophylaxis                 | 220 mg QD       | 10 mg QD        | 2.5 mg BID      |
| DVT/PE treatment                | 150 mg BID      | 15 mg BID for 21 days, then 20 mg QD | 10 mg BID for 7 days, then 5 mg BID |
| Molecular weight (Da)           | 628             | 436             | 460             |
| Target                          | II              | Xa              | Xa              |
| Bioavailability (%)             | 6               | 63–79           | 66              |
| $T_{max}$ (h)                   | 2–3             | 2–4             | 1–3             |
| $T_{1/2}$ (h)                   | 12–17           | 7–13            | 8–15            |
| Protein binding (%)             | 35              | 95              | 87              |
| Metabolism                      | 80% renal       | 1/3 renal       | 25% renal       |
| Interactions                    | P-gp inhibitors | CYP3A4 inhibitors | CYP3A4 inhibitors |
| Approved indications            | Prevention of stroke and systemic embolism in non-valvular AF | Prevention of stroke and systemic embolism in non-valvular AF | Prevention of stroke and systemic embolism in non-valvular AF |
| VTE prophylaxis after hip and knee replacement | VTE prophylaxis after hip and knee replacement | VTE prophylaxis after hip and knee replacement |
| Molecular weight (Da)           | 436             | 66              | 1–3             |
| Target                          | Xa              | 87              | 9–11            |
| Bioavailability (%)             | 6               | 87              | 54              |
| $T_{max}$ (h)                   | 2–3             | 95              | 35% renal       |
| $T_{1/2}$ (h)                   | 12–17           | 95              | 63% liver       |
| Protein binding (%)             | 35              | 95              | 54              |
| Metabolism                      | 80% renal       | 1/3 renal       | 25% renal       |
| Interactions                    | P-gp inhibitors | CYP3A4 inhibitors | CYP3A4 inhibitors |
| Approved indications            | Prevention of stroke and systemic embolism in non-valvular AF | Prevention of stroke and systemic embolism in non-valvular AF | Prevention of stroke and systemic embolism in non-valvular AF |
| VTE prophylaxis after hip and knee replacement | VTE prophylaxis after hip and knee replacement | VTE prophylaxis after hip and knee replacement |

AF, atrial fibrillation; DVT, deep venous thrombosis; PE, pulmonary embolism; $T_{max}$, time to maximal concentration; $T_{1/2}$, half-life; VTE, venous thromboembolism.
bleeding investigated and general supportive measures should be adopted, including mechanical compression, surgical or endoscopic haemostasis, and replacement of fluids and blood products.\(^{40-43}\) Activated charcoal can be used if recent overdose of the medication is suspected (<2 h).\(^ {44}\) Haemodialysis can also be considered for removal of the drug, especially, in patients with renal impairment. In a study of six patients with end-stage renal disease on haemodialysis that received a 50 mg dose of dabigatran, 62% of circulating drug was removed after 2 h and 68% after 4 h.\(^ {45}\)

**Haemostatic agents**

In a rat-tail model of template bleeding, APCC at a dose of 50 or 100 U/kg significantly reduced prolongation of bleeding time (BT) associated with high-dose dabigatran (1 \(\mu\)mol/kg bolus + 0.5 \(\mu\)mol/kg/h infusion for 25 min).\(^ {46}\) Similarly, in a murine ICH model 4-factor PCC 100 U/kg prevented haematoma expansion associated with dabigatran.\(^ {47}\) Studies in humans have reported dissimilar results. Using thrombin generation (TG) tests, Marlu et al.\(^ {48}\) showed in vitro reversal of the anticoagulant effect of dabigatran with 4-factor PCC and especially FEIBA when added to blood samples of healthy volunteers. Prothrombin complex concentrate corrected the endogenous thrombin potential, whereas FEIBA also corrected the thrombin peak, lag-time and time to peak. The first in vivo study in humans was conducted by Eerenberg et al.\(^ {49}\) who investigated the effect of 4-factor PCC to revert the anticoagulant effect of dabigatran and rivaroxaban. In this randomized, placebo-controlled study, 12 healthy male volunteers received dabigatran 150 mg BID or rivaroxaban 20 mg daily for 2.5 days, followed by either a bolus of 50 IU/kg PCC or a similar volume of saline. After a washout period, the groups were crossed over and received the other anticoagulant following the same protocol. Dabigatran increased the aPTT, ECT, and TT, but PCCs failed to reverse these anticoagulant effects.

Recombinant FVIIa (0.1 or 0.5 mg/kg) has shown to reduce BT and prolongation of aPTT associated with dabigatran (1 \(\mu\)mol/kg bolus + 0.5 \(\mu\)mol/kg/h infusion for 25 min) in a rat-tail model of bleeding.\(^ {46}\) In contrast with PCC, however, rFVIIa failed to reduce haematoma expansion or mortality in a murine ICH model.\(^ {50}\) Its use has been reported to manage dabigatran-associated post-cardiac surgery bleeding,\(^ {50}\) but the evidence for this recommendation is weak.

Antifibrinolytic medications such as tranexamic acid or aprotinin have proved ineffective in reducing BTs with other direct thrombin inhibitors and are not recommended in patients taking dabigatran.\(^ {51}\)

**Antidotes**

Although supportive measures and replacement of coagulation factors with PCC or rFVIIa may be life-saving and remain today the keystone of management, the optimal strategy in case of anticoagulant-related bleeding is the use of antidotes to specifically target and inactivate the antithrombotic agent.

A specific antidote for dabigatran, idarucizumab, has been developed by Boehringer Ingelheim. The molecule is a humanized antibody fragment that binds to dabigatran with an affinity \(\sim 350\) times greater than thrombin, preventing it from binding to thrombin and neutralizing its anticoagulant effect.\(^ {52,53}\) In vivo studies in rats have shown that dabigatran levels of \(~ 200\) ng/mL are neutralized within 1 min of the injection of an intravenous bolus of idarucizumab.\(^ {52}\) In humans, the results from the first Phase 1 study were presented at the 2013 American Heart Association Scientific Sessions.\(^ {53}\) In this randomized, double-blind, placebo-controlled study of 145 healthy male volunteers, investigators evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of the antibody fragment. In a first step, the tolerability of the antibody fragment was tested as an intravenous infusion of rising doses of up to \(8\) g. In a second step, the potential for reversal of dabigatran-induced anticoagulation was evaluated, with 5-min infusions using three different doses (1, 2, and \(4\) g) following pre-treatment with dabigatran (\(220\) mg BID for 3 days). The anticoagulant effect of dabigatran and its reversal were assessed using diluted TT (Hemoclot\(^ {46}\) DTI assay), TT, aPTT, ECT, and activated clotting time (ACT). Dabigatran prolonged clotting times of all coagulation markers and there was a dose-dependent reversal with increasing doses of the antidote. Thrombin time was reversed from a ratio of up to 14-fold over baseline to \(<2\)-fold. Reversal was complete and sustained in seven of nine subjects administered \(2\) g and in all subjects administered \(4\) g. A Phase 3 study, the RE-VERSE AD (A Study of the Reversal Effects of Idarucizumab on Active Dabigatran) is already under way in patients with dabigatran-induced bleeding or requiring emergency surgery.

Another reversal agent is ciraparantag (PER977), a small, synthetic, water-soluble, cationic molecule developed by Perosphere Inc. that binds to unfractionated heparin, low-molecular-weight heparin, fondaparinux, dabigatran and to the new factor Xa inhibitors through hydrogen bonding and charge–charge interactions.\(^ {54}\) In tromboelasto-
tographic assays (ex vivo) and in a rat-tail-transaction bleeding model, ciraparantag has demonstrated to completely reverse the effect of dabigatran, rivaroxaban, apixaban, edoxaban, fondaparinux, and heparin.\(^ {55}\) Studies in humans treated with dabigatran are not yet available.

**Direct factor Xa inhibitors: rivaroxaban, apixaban, and edoxaban**

**Pharmacology**

Rivaroxaban and apixaban are the two direct inhibitors of factor Xa currently approved in North America and Europe, whereas Edoxaban is approved in Japan since April 2011. These agents reversibly inhibit free and clot-bound factor Xa, thus preventing the conversion of prothrombin to thrombin and subsequent fibrin clot formation. They have a high bioavailability, ranging from around 50% in apixaban, 62% in edoxaban, to 100% in rivaroxaban when taken with food.\(^ {56}\) The main difference is the once-daily dosing for rivaroxaban and edoxaban, compared with the twice-daily dosing for apixaban (Table 1).

Rivaroxaban, apixaban, and edoxaban are equally or more effective than enoxaparin for the prevention of thrombo-embolic events after orthopaedic surgery.\(^ {56-62}\) Rivaroxaban is non-inferior to enoxaparin followed by warfarin in patients with established venous thrombosis, with similar occurrence of major or relevant bleedings.\(^ {63}\) Apixaban and edoxaban were also non-inferior to enoxaparin with significantly less bleeding.\(^ {64,65}\)
In non-valvular AF, both rivaroxaban in the ROCKET AF (Rivaroxaban Once Daily Oral Direct factor Xa Inhibitor Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) and edoxaban in the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation—Thrombolysis in Myocardial Infarction 48) showed non-inferiority compared with warfarin in the prevention of stroke or systemic embolism. 66,67 On the other hand, using the same primary endpoint, the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial showed that apixaban was superior to warfarin. 68 All three factor Xa inhibitors exhibited a similar or better safety profile compared with warfarin, with equivalent or lower rates of major and intracranial bleeding. Apixaban and low-dose edoxaban (30 mg) were also associated with reduced all-cause mortality. 67,68

Risk of bleeding
When used for thromboprophylaxis after hip or knee replacement, the risk of major bleeding associated with rivaroxaban fluctuates between 0.3 and 0.6% if the drug is administered at a dose of 10 mg daily for a period of 2–6 weeks. 56,57 In the ROCKET AF study, the annual rates of major bleeding were similar in the rivaroxaban and warfarin groups (3.6 and 3.4%, respectively; HR 0.97, 95% CI 0.78–1.20). 58 Interestingly, the rates of ICH were significantly lower in the rivaroxaban vs. the warfarin group (0.5 vs. 0.7% per year; P = 0.02), whereas GI bleeding was more common in the rivaroxaban group (3.2 vs. 2.2, P < 0.001), a fact attributed to the presence of active drug in the GI lumen, which may induce or exacerbate bleeding from local lesions. Meta-analysis of major clinical trials comparing rivaroxaban with warfarin have confirmed a similar rate of major bleeding with both drugs (RR 1.01, 95% CI 0.91–1.10) 32 and reduced risk of ICH with rivaroxaban. 32,33

With apixaban, the annual rate of major bleeding was lower than with warfarin in the ARISTOTLE trial (2.13 vs. 3.09% per year; HR 0.69; 95% CI 0.60–0.80; P < 0.001), with less ICH (0.33 vs. 0.80% per year; HR 0.42, 95% CI 0.30–0.58), but similar rate of GI bleeds (0.76 vs. 0.85% per year, respectively; HR 0.86, 95% CI 0.70–1.15). 69 In addition, the outcomes of ICH were better with apixaban, leading less often to hospitalization, medical or surgical intervention, transfusion, or change in antithrombotic therapy.

In the ENGAGE AF-TIMI 48, the high and low doses of edoxaban were associated with lower rates of major bleeding compared with warfarin (2.75 and 1.61% per year vs. 3.73% per year). 67

Measurement of anticoagulation effect
All factor Xa inhibitors prolong the PT and usually a normal value excludes a residual anticoagulation effect due to these drugs, but the sensitivity depends on the reagents used. 70 A more specific indicator of the anticoagulant effect is the measurement of anti-factor Xa activity by chromogenic assays, but these are not available in most care facilities and there are no data on a cut-off to clearly define a safety margin. 41,71

Management
General measures
Same as with dabigatran, discontinuation of the drug and general support measures are the most important steps in case of major or life-threatening bleeding associated with direct factor Xa inhibitors. 40–42,72 Activated charcoal may reduce apixaban exposure by 50 and 28%, respectively, when administered at 2 and 6 h post dose. 73 Because of high plasma protein binding, rivaroxaban and apixaban are not dialyzable (Tables 2 and 3).

Haemostatic agents
In vitro, PCC, APCC, and rFVIIa resulted partially effective in reversing rivaroxaban-induced anticoagulation. Perzborn et al. 74 showed that APCC and rFVIIa were more effective than PCC in reversing prolongation of PT, CT, and TG lag time, but reversal was not complete, reaching a plateau with maximal effect of ~50%.

In animal models, PCC, APCC, and rFVIIa have also shown potential to improve laboratory parameters of coagulation, but the effects on BT are variable. 75,76 In a murine model of ICH associated with rivaroxaban FFP, PCC, and rFVIIa prevented excess haematoma expansion. 77

In the previously cited study by Eerenberg et al., 49 rivaroxaban induced a prolongation of the activated PT (15.8 ± 1.3 vs. 12.3 ± 0.7 s at baseline; P < 0.001) that was immediately and completely

![Table 2 Strategies for anticoagulation reversal in bleeding associated with warfarin and new oral anticoagulants](https://example.com/table2.png)

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<th>Dabigatran</th>
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<td>Drug discontinuation, mechanical compression, surgical haemostasis, transfusional support</td>
</tr>
<tr>
<td>Activated charcoal</td>
<td>Consider if last dose &lt;2 h</td>
<td>Consider if last dose &lt;2 h</td>
</tr>
<tr>
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<td>Removes 62–68% of circulating drug</td>
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<tr>
<td>Coagulation factors</td>
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<td>PCC (25 U/kg, repeat if necessary) rFVIIa (90 ug/kg)</td>
</tr>
<tr>
<td>Specific inhibitors</td>
<td>Vitamin K (5–10 mg IV)</td>
<td>Idarucizumab (Phase 1)</td>
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PCC, prothrombin complex concentrates; rFVIIa, recombinant-activated factor VII.
Reversal strategies of new oral anticoagulants

Table 3 Comparison of specific antidotes for NOACs

<table>
<thead>
<tr>
<th>Agent</th>
<th>Idarucizumab (Boehringer Ingelheim)</th>
<th>Andexanet alfa (Portola Pharmaceuticals)</th>
<th>Ciraparantag (Perosphere)</th>
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<tr>
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<td>Dabigatran, FXa inhibitors (Rivaroxaban, Apixaban, Edoxaban, Betrixaban), Fondaparinux, heparin</td>
</tr>
<tr>
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<td>Animal models</td>
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<td>Reduced blood loss induced by Rivaroxaban in mouse (tail transection) and rabbit (liver laceration) models</td>
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<td>Phase 1: Dose-dependent reversal of Rivaroxaban in healthy volunteers</td>
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<td>Phase 3: Rapid reversal of Apixaban (ANNEXA-A). Ongoing trial with Rivaroxaban (ANNEXA-R) and planned trial with Edoxaban (ANNEXA-E)</td>
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Antidotes

Andexanet alfa, an injectable antidote for factor Xa inhibitors, has been recently developed by Portola Pharmaceuticals. This recombinant protein is a modified form of factor Xa that is catalytically inactive but retains high-affinity binding to factor Xa inhibitors. Andexanet alfa reverses immediately and in a dose-dependent manner, the anticoagulant effect of rivaroxaban, apixaban, and edoxaban, and in two animal models the antidote reduced bleeding by >85%.80,81

In a Phase 1 study, 32 healthy volunteers were randomized to 4 intravenous doses of andexanet alfa or placebo, and rivaroxaban was added to plasma samples ex vivo.82 The antidote reversed anti-factor Xa in a dose-dependent manner and no thrombotic events were reported. In December of 2013, the results of a Phase 2, double-blind, placebo-controlled trial were presented at the American Society of Hematology meeting.83 In this study, 18 healthy volunteers were treated with rivaroxaban at an oral dose of 20 mg daily for 6 days and then given either an intravenous bolus of andexanet alfa or placebo on day 6. The doses of 210 and 420 mg reversed the anti-factor Xa activity by 32 and 51%, respectively. In addition, rivaroxaban-induced inhibition of thrombin generation and prolongation of both PT and ACT were also partially reversed by andexanet alfa in a dose-dependent manner. The drug was well tolerated and there were no thrombotic events or severe adverse effects. The results of andexanet alfa for apixaban were announced at the 2013 International Society on Thrombosis and Hemostasis congress.84 In this randomized, placebo-controlled, double-blind, Phase 2 study, 27 healthy volunteers were treated on days 1–6 with apixaban 5 mg BID and then randomized in a 6:3 ratio to intravenous andexanet alfa (in three different doses: 90, 210, or 420 mg) or saline on day 6, 3 h after receiving the last apixaban dose. Results demonstrated a dose-dependent reversal of the anticoagulant activity of apixaban. Two minutes after administration of 420 mg of andexanet alfa (n = 6), the anticoagulant activity of apixaban decreased by >95% as measured by anti-factor Xa activity. Similarly, the 210 mg dose reduced anti-factor Xa activity by 80% compared with saline (n = 9). An observation from the aforementioned studies was the fact that anticoagulation returns to pre-treatment levels within few hours after a bolus infusion of the antidote and therefore a constant infusion of the drug may be needed to reverse anticoagulation for longer periods.

More recently, the results of a Phase 3 study, the ANNEXA-A (Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of FXA Inhibitors-Apixaban) trial was presented at the American Heart Association 2014 Scientific Sessions.85 In the first part, 33 patients on apixaban were randomized to andexanet alfa bolus...
400 mg IV vs. placebo. The antidote administration resulted in rapid normalization of anti-factor Xa and thrombin levels, with peak effect observed a couple of minutes after completion of the bolus. In the absence of a maintenance infusion, anti-factor Xa levels gradually increased by 25% by 1 h and were similar to placebo by 2 h. There were no serious adverse events reported, including thrombotic events. The second part of the study, in which the intravenous bolus will be followed by a 2-h infusion or placebo, is under way and results are soon expected. Another Phase 3 study, known as ANNEXA-R (Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of FXA Inhibitors-Rivaroxaban), is also ongoing and a third one, the ANNEXA-E (Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of FXA Inhibitors-Edoxaban), is planned.

Finally, the preliminary data obtained with the universal antidote ciraparantag are promising. The molecule effectively reverses bleeding associated with factor Xa inhibitors in animal models of external and internal bleeding. In addition, the results of the first human, Phase I study has been recently published. In this study, a single intravenous dose of ciraparantag (100 and 300 mg) 3 h after the administration of edoxaban restored the whole-blood clotting time to baseline levels in 10 min or less and the effect was sustained for 24 h. Unlike andexanet alfa, ciraparantag showed no evidence of procoagulant activity, as assessed by measurement of d-dimer, prothrombin fragment 1.2, and tissue factor pathway inhibitor and by whole-blood clotting time. This, in addition to its broad spectrum, may represent a potential advantage over andexanet alfa. Possible related adverse effects were dysgeusia and transient perioral and facial flushing.

Conclusion

Non-vitamin K oral anticoagulants represent the new drug generation for prevention and treatment of thromboembolic disease. Owing to their proven efficacy and predictable anticoagulant effect, without need for routine monitoring, these agents have gradually started to replace warfarin for several indications. One of the major concerns for clinicians has been the lack of specific reversal agents for the management of severe haemorrhagic complications. However, a new line of antidotes specific for these drugs is at different stages of development and their release in the near future seems to be imminent. It is expected that the availability of such antidotes will dissipate the still existing concerns about NOACs in the medical community and lead to their full incorporation and into clinical practice.

Conflict of interest: G.Y.H.L. is consultant for Bayer, Astellas, Merck, Astra-Zeneca, Sanofi Aventis, Biotronik, BMS/Pfizer, Portola, and Boehringer Ingelheim; and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi Aventis.

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