Antidotes for Novel Oral Anticoagulants  
Current Status and Future Potential

Mark Crowther, Mark A. Crowther

Abstract—The direct thrombin inhibitor dabigatran and the anti-Xa agents rivaroxaban, edoxaban, and apixaban are a new generation of oral anticoagulants. Their advantage over the vitamin K antagonists is the lack of the need for monitoring and dose adjustment. Their main disadvantage is currently the absence of a specific reversal agent. Dabigatran’s, unlike the anti-Xa agents, absorption can be reduced by activated charcoal if administered shortly after ingestion and it can be removed from the blood with hemodialysis. Prothrombin complex concentrate, activated prothrombin complex concentrate, and recombinant factor VIIa all show some activity in reversing the anticoagulant effect of these drugs but this is based on ex vivo, animal, and volunteer studies. It is unclear, which, if any, of these drugs is the most suitable for emergency reversal. Three novel molecules (idarucizumab, andexanet, and PER977) may provide the most effective and safest way of reversal. These agents are currently in premarketing studies. (Arterioscler Thromb Vasc Biol. 2015;35:1736-1745. DOI: 10.1161/ATVBAHA.114.303402.)

Key Words: anticoagulants • apixaban • dabigatran • factor VIIa • hemorrhage • prothrombin complex concentrate • rivaroxaban

The desired effect of an anticoagulant is to reduce the chances of a pathological thrombosis; they achieve this by altering the normal coagulation. Thus, it is unlikely that there will ever be an anticoagulant where bleeding is not a side effect, this is the most likely reason to reverse the effects of anticoagulants, reversal may also be required to allow surgical procedures and in cases of accidental or deliberate overdose. The old anticoagulants (heparin and the vitamin K antagonists) have reversal agents but the advent of new anticoagulants currently leaves clinicians with the problem of lack of a highly effective, universally available reversal strategies.

Possible Drug Reversal Mechanisms
Possible reversal strategies are dependent on the absorption, metabolism, mechanism of action, and excretion of the drug. Examples of drug reversal can be found in Table 1.

Is Reversal Needed? An Approach to the Bleeding Patient
Often when a patient on anticoagulants attends with bleeding the emphasis is put on the management of the anticoagulant rather than the bleeding. Minor bleeding, for example, epistaxis, may just require local measures rather than interruption or reversal of the anticoagulant. For major bleeding other basic measures including resuscitation and optimization of temperature and pH may be just as important as reversal of the anticoagulant. Figure 1 discusses some general measures when presented with the bleeding patient.

Because of the short half-life of the new anticoagulants waiting for the effect of the drug to wear off may be a suitable strategy, weathering the storm. This watch and wait strategy avoids the hazards of both the reversal agents and the risk of thrombosis inherent in normalizing coagulation acutely in a patient with an underlying predisposition to thrombosis and is usually the preferred strategy in cases of minor bleeding. A similar strategy for the management of emergency surgery should be considered, that is, waiting for as long as possible after the last dose of the anticoagulant before operating, because few emergency operations or procedures cannot be delayed by several hours.

Reversal of the Vitamin K Antagonists
The vitamin K antagonists can be reversed although in practice clinicians rarely provide truly effective reversal as a result of their choosing the incorrect type, dose, and route of administration of the reversal agents.

Vitamin K antagonists block vitamin K epoxide reductase preventing the recycling of vitamin K which in turn is involved in the γ-carboxylation of clotting factors II, VII, IX, and X and
the natural anticoagulant proteins C and S. γ-Carboxylation of the clotting factors is required for their interaction with phospholipids which is in turn required for their action as enzymes. Immediate reversal of the anticoagulant effect is achieved by the administration of the deficient clotting factors. Options include fresh frozen plasma or prothrombin complex concentrate (PCC), these replace the deficient clotting factors normalizing coagulation in the time it takes to infuse the product. PCC is a plasma-derived mixture of the vitamin K–dependent clotting factors. PCC seems superior to fresh frozen plasma because of speed of infusion, routine viral inactivation, lack of need for crossmatching, the small volume to be infused, and the effectiveness of reversal. Fresh frozen plasma requires storage in a freezer and requires thawing before use; this is not the case for PCC. PCC may be either 3 factors (II, IX, and X) or 4 factors (II, VII, IX, and X), but it is unclear what is the superior product. Recombinant factor VIIa rapidly normalizes the international normalized ratio (INR) but it is unclear whether it reduces bleeding in patients with hemorrhage. The administration of vitamin K overcomes the blockage caused by the vitamin K antagonists and allows the production of normal vitamin K clotting factors. Intravenous administration provides more rapid increase in coagulation factors than oral but both methods usually provide normalization of coagulation within 24 hours.

### New Anticoagulants

Apart from low-molecular-weight heparin the old anticoagulants had the problems of variable pharmacokinetics and multiple drug interactions requiring monitoring and dose adjustments. With the better understanding of the molecular structure of the clotting factors researchers were able to design molecules which bound to specific clotting factors reducing their effect. These molecules could then be chosen for dependable pharmacokinetics and minimal drug–drug interactions allowing for standard dosing and oral administration. Licensed drugs include the direct thrombin inhibitor dabigatran and the anti-Xa agents apixaban and rivaroxaban. Edoxaban, an anti-Xa agent, is licensed in Japan and North America and is likely to receive its license in Europe in the near future. These drugs are summarized in Table 2.

Unlike unfractionated heparin and the vitamin K antagonists, the new oral anticoagulant (NOAC) drugs have no obvious mechanism of reversal, this is not dissimilar to low-molecular-weight heparin whose effect can only be partially reversed by protamine. Since their introduction, there are several problems with researching reversal strategies, these include

1. Randomized controlled trials, although the gold standard, are difficult to perform in emergency situations. The usual procedure of enrolment, consent, randomization, and drug administration is infeasible in many acutely ill patients.

2. Nonrandomized studies, reversal strategies, can be compared either between hospitals where they use different regimens or with historical controls (asking how did patients fair when there was no reversal). These have the problem of confounding factors, when compared with randomized trials, and where novel treatments are used ethically there still needs to be consent. They tend to be easier to perform and can usually enrol more patients and get results quicker. Patients can be used as their own control looking at bleeding before reversal and bleeding after, but blood loss in many situations is difficult to measure, for example, intracerebral hemorrhage.

3. Human volunteers may agree to take the drug and have reversal strategies tried, but the end point cannot be bleeding or survival. Thus the end point, frequently ex vivo measurement of residual anticoagulant effect, is a surrogate end point. Clotting assays may demonstrate correction of the anticoagulant effect of the drug, but as discussed later, measured reversal of the drug may not equate to reduction in bleeding.

4. Animal models can be designed so the drug is administered, bleeding is induced, and the reversal strategy is tried. Unfortunately because of differences between

<table>
<thead>
<tr>
<th>Table 1. Methods for Drug Reversal</th>
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<tr>
<td>Mechanism</td>
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<tr>
<td>Reducing absorption</td>
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<td>Reducing metabolism</td>
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<tr>
<td>Increasing metabolism/excretion</td>
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<tr>
<td>Blockage of site of action</td>
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<tr>
<td>Increasing the drug’s target or increasing the substance that the drugs action reduces</td>
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<tr>
<td>Bypassing the effect of the drug</td>
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</table>

Nonstandard Abbreviations and Acronyms

- aPCC: activated prothrombin complex concentrate
- APTT: activated partial thromboplastin time
- NOAC: new oral anticoagulant
- PCC: prothrombin complex concentrate
- PT: prothrombin time
- rFVIIa: recombinant factor VIIa
- TT: thrombin time

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Mechanism Example

- Reducing absorption: Drugs that have been recently ingested can be removed by administering emetics or giving activated charcoal that binds drugs and prevents it from being absorbed
- Reducing metabolism: Reducing the metabolism of prodrugs before their conversion into the active form
- Increasing metabolism/excretion: Enhancing the normal excretion of a drug or dialyzing the patient which removes drugs will reduce the level of the drug in the body
- Blockage of site of action: Drugs may be blocked either by the antidote binding to the drug or the site of action
- Increasing the drug’s target or increasing the substance that the drugs action reduces: The effects of drugs that reduce certain compounds in the body may be reversed by increasing the levels of these compounds, either by the administration of these compounds or reducing their metabolism/excretion
- Bypassing the effect of the drug: Drugs which block enzymic pathways effect can be reversed by administering the downstream products

New Anticoagulants

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4. Animal models can be designed so the drug is administered, bleeding is induced, and the reversal strategy is tried. Unfortunately because of differences between
species, animal models may not be representative of what happens in humans. For example, in many animal models, bleeding can only be induced through the administration of doses of anticoagulant far larger than those required to induce anticoagulation in humans, on a per kilogram basis.

Therefore, the quality of the current evidence for reversal of the new anticoagulants is weak and comes from animal models, healthy volunteer studies, and case series/case reports. A summary of the reversal strategies can be found in Figure 2.

Measurement of the Effect of the NOACs
Because the NOACs have, in most patients, dependable pharmacokinetics, routine measurement of effect is not required. Measurement of effect is useful when there is

1. bleeding to determine whether reversal is required, and if reversal is successful,
2. overdosage, and
3. Before surgery to determine when it is safe to operate or to provide neuroaxial anesthesia.

The NOACs can be measured using various methods including direct drug levels using chromatography, chromogenic assays (that reflect the degree of inhibition of coagulation enzymes by the agent), and their effects on the traditional coagulation assays. Whether an individual laboratory can provide an assay in a timely manner will depend on several factors including staffing, skill mix, and resources. A summary of the measurement of the new anticoagulants can be found in Table 3.

For many laboratories and clinicians this is a major problem as the only reliable coagulation test available 24 hours a day is the prothrombin time (PT) and activated partial thromboplastin time (APTT), but the effect of the NOACs on the PT and APTT varies significantly between the various reagents used. For the management of bleeding or in preparation for emergency surgery, every hospital/laboratory should have an immediate method of determining whether the drug is present in clinically significant quantities. Timing of dose is useful, for the first 12 hours after ingestion (24 hours for rivaroxaban), as long as the drug is absorbed, it is likely to be present in therapeutic levels and measurement of the level is unnecessary. After this time if the PT and APTT are normal, dabigatran, rivaroxaban, or edoxaban are unlikely to be present in significant quantities; however, this approach may misidentify some patients as being free of anticoagulant effect when, in actuality, they are anticoagulated.

The UK NEQAS (National External Quality Assessment Service) external quality assurance scheme performed a survey of its 700 participants on whom had an assay available for measuring the NOACs, with 614 responding: the percentage who had an assay was 7%, 12%, 20%, and <1% for apixaban, dabigatran, rivaroxaban, and edoxaban, respectively.14

With the NOACs becoming more widespread hopefully, manufacturers of coagulation analyzers will produce tests that can be performed on the majority of automated analyzers with little training and in a timely manner.
Dabigatran

The direct thrombin inhibitor dabigatran is rapidly but poorly absorbed from the gut, its concentration peaks at between 30 minutes and 2 hours and half-life is 12 to 14 hours but extends with renal impairment. Various reversal strategies have been described:

1. Reduction of absorption: the lipophilic nature of dabigatran should mean it will bind to the surface of activated charcoal and reduce the amount of the drug absorbed. Ex vivo experiments have confirmed this process but it has yet to be demonstrated in humans.15 Dabigatran is rapidly absorbed therefore this approach will only work within the first 2 to 3 hours of administration.

2. Removal of the circulating drug: the majority of circulating dabigatran is free in the plasma with little being protein bound, this along with its lipophilic properties results in its removal by hemodialysis/hemofiltration, ideally with a charcoal filter. This has been demonstrated in the controlled setting of chronic hemodialysis patients given single doses of dabigatran16 and in patients presenting with life-threatening hemorrhage.17 The main problem with dialysis is obtaining prompt vascular access in a patient with a hemorrhagic diathesis, access to the dialysis machine, the time taken to start dialysis, and the requirement that the patient is hemodynamically stable. It would be useful in overdosage.

3. Increased excretion: as the majority of the drug is excreted through the kidneys, ensuring good renal function is important, this can be achieved by optimizing renal blood flow with fluid administration and avoiding hypotension. Aggressive hemodynamic support, to mitigate renal injury because of hypoperfusion, will reduce the risk of delayed clearance of dabigatran.

4. Inactivating the drug: a specific antidote for dabigatran, idarucizumab (aDabi-Fab), has been synthesized by the manufacturers of dabigatran Boehringer Ingelheim. This antibody fragment binds to the thrombin binding site of the dabigatran hence inactivating the dabigatran molecule.18 It is given intravenously as a one-off dose. The idarucizumab molecule has a much greater affinity for dabigatran than thrombin. In vitro studies suggests that this molecule reverses the effect of dabigatran.18,19 Three studies in healthy volunteers have been reported in abstract form at conferences. One hundred forty-five men20 received 1, 2, or 4 g of idarucizumab after dabigatran for 4 days. Measurement of dabigatran levels and coagulation assays were performed (dilute thrombin time (TT), TT, APTT, ecarin clotting time, and activated clotting time. Reversal for 30 minutes was seen with 1 g, whereas complete reversal was achieved in 7 of the 9 who

Table 3. Measurement of the New Oral Anticoagulants

<table>
<thead>
<tr>
<th>Drug/Assay</th>
<th>PT</th>
<th>APTT</th>
<th>Chromogenic Assays</th>
<th>ECT*</th>
<th>dTT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran1–9</td>
<td>Insensitive</td>
<td>Demonstrates a curvilinear response. Peak level 1.4–1.8× normal, higher suggests overanticoagulation</td>
<td>Specific commercial assays available. Level &lt;30 ng/mL thought to be suitable for operations</td>
<td>Calibrated ECT demonstrates linear response to concentrations &lt;300 ng/mL therefore can be used to determine level</td>
<td>Calibrated dTT demonstrates linear response but sensitive</td>
</tr>
<tr>
<td>Apixaban10</td>
<td>Causes prolongation but great variability between assays, should not be used</td>
<td>Causes prolongation but great variability between assays, should not be used</td>
<td>Specific commercial assays available. Unclear what level is suitable for surgery</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Rivaroxaban11,12</td>
<td>Demonstrates a linear relationship</td>
<td>Variable response therefore should not be used</td>
<td>Specific commercial anti-Xa assays available. Level &lt;30 ng/mL thought to be suitable for operations</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Edoxaban13</td>
<td>Demonstrates linear relationship but variability between reagents</td>
<td>Demonstrates linear relationship with little variation between reagents</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

APTT indicates activated partial thromboplastin time; dTT, dilute thromboplastin time; ECT, ecarin clotting time; and PT, prothrombin time.

*Only appropriately calibrated assays should be used.
received 2 g and all the subjects who received 4 g doses. The second study21 in healthy volunteers administered dabigatran for 4 days and then 1, 2, and 4 g of idarucizumab or placebo. The effect of any reversal was measured using fibrinopeptide A generation after small skin cuts and ecarin clotting time, dilute TT, and dabigatran levels. Fibrinopeptide A generation returned to 24%, 45%, and 63% of normal after the addition of 1, 2, and 4 g, respectively. The clotting tests returned to normal after 2 and 4 g administration. The third study22 investigated the effect of idarucizumab in older volunteers, some with renal dysfunction. Four days of dabigatran was given and then dose of 1, 2.5, 5, or 2×2.5 g (1-hour apart) of idarucizumab. Coagulation was assessed using the dilute TT, ecarin clotting time, and the APTT. The 1-g dose reversed the effect for 2 to 4 hours, whereas the other doses led to complete reversal. The subjects were rechallenged with dabigatran the following day without problems and there were no side effects of readministering idarucizumab 2 months later.

Currently, there is a phase-III multinational study (RE-VERSE AD [A Study of the RE-VERSal Effects of Idarucizumab on Active Dabigatran]) where patients taking dabigatran and presenting with bleeding or requiring emergency surgery are given 5 g of idarucizumab and then information collected on bleeding, coagulation assays (APTT, TT, dilute TT, and ecarin clotting time), and dabigatran levels. The aim is to recruit 250 patients between May 2014 and March 2017. As dabigatran is lipophilic intravenous lipid emulsion was given to rats to determine whether this would sequester the drug hence reducing its activity, this was not successful.21

5. Increasing the target: dabigatran binds to thrombin, in theory administering thrombin would provide more thrombin than dabigatran could inactivate normalizing coagulation. At present there is no thrombin concentrate (either recombinant or plasma derived) that could be used. PCC and activated PCC (aPCC) are both plasma-derived products that contain prothrombin. PCC contains either 3 (factors II, IX, and X) or 4 (factors II, VII, IX, and X) factors and is routinely used in the reversal of the vitamin K antagonists. aPCC contains factors II, VII, IX, and X, but compared with PCC some of the coagulation factors are activated during the purification process making the aPCCs more thrombogenic than the PCCs. aPCC’s main role is in the treatment of hemophilic patients with antibodies against factor VIII. Both PCC and aPCC come as dry powder which can be rapidly reconstituted and administered. Their main side effect is unwanted thrombosis. They are costly and are human plasma derived, although virally inactivated. The evidence for their use in dabigatran patients who are bleeding is contradictory and is summarized in Table 4. Guidelines suggest that their use is limited to life-threatening bleeding and do not specify a preferred agent or dose.1,7 Case reports have reported possible favorable outcomes.41,42

6. Enhancing coagulation: recombinant factor VIIa (rFVIIa) was originally developed, like aPCC, to treat bleeding in hemophiliacs with inhibitors having the advantage that it is a recombinant product. Studies demonstrated its benefit in massive hemorrhage33 and vitamin K antagonist reversal. Its use for the reversal of dabigatran has been reported, and as with PCC and aPCC the evidence is both indirect and contradictory. This is summarized in Table 4.

**Rivaroxaban**

Rivaroxaban is an oral anti-Xa agent which is rapidly and almost completely absorbed from the gut. It is highly protein bound in the plasma. Because of this removal strategies are limited

1. Reduced absorption: rivaroxaban does not bind to activated charcoal and because of its rapid absorption gastric lavage is unlikely to be helpful unless used almost immediately after ingestion.

2. Removal of the circulating drug: because rivaroxaban is highly protein bound it will not be dialyzable.

3. Increased excretion: with one third of the drug excreted through the kidneys unchanged ensuring good renal function is important; this can be achieved by optimizing renal blood flow with fluid administration and avoiding hypotension.

4. Inactivating the drug: a recombinant protein (Andexanet alfa [Annexa/PRT064445]) has been developed by Portola Pharmaceuticals, which is similar in structure to factor Xa but is not active. It lacks the γ-carboxyglutamic acid terminal preventing it from interacting with cell surface phospholipids, and a serine to alanine mutation at the active site means it cannot convert prothrombin to thrombin. This protein binds both the factor Xa inhibitors and heparin-activated antithrombin, with an affinity greater than natural factor Xa, leading to inactivation of the anticoagulant. This suggests that it can be used as reversal agent for the anti-Xa NOACs, heparin, and fondaparinux. It seems to have a short half-life as after an hour infusion when andexanet is stopped the anti-Xa activity of the anticoagulant returns; therefore, in the treatment of bleeding, it may require a continuous infusion until the drug is cleared from the circulation.44 Animal models45 demonstrate reduced bleeding after the administration of andexanet. Phase I/II human volunteer studies46 show correction of laboratory parameters in humans. Phase III studies in healthy volunteers are ongoing. In the animal studies there may be interaction with tissue factor pathway inhibitor decreasing levels, but despite this in the same animals there was no evidence of increased thrombosis.46

A phase III study of andexanet in patients who have received any therapeutic anti-Xa agent and are bleeding is in set up and expected to start recruitment in 2015 with the aim of recruiting 270 patients by 2022.

5. Increasing the target: there is no commercially available factor X concentrates. Similar to dabigatran, several studies (summarized in Table 4) have reported improvements in coagulation assays and thrombin generation in vitro and in human studies with the addition of either PCC or aPCC. There is no evidence from clinical studies to support the use of these products. Guidelines suggest that their use is limited to life-threatening bleeding and do not specify a preferred agent or dose.1,7

6. Enhancing coagulation: the evidence for rFVIIa for the reversal of rivaroxaban is similar to dabigatran in being contradictory and limited. This is summarized in Table 4.
Apixaban is an oral anti-Xa agent. It is partially absorbed from the gut, is protein bound, and only a small proportion of its excretion (27%) is renal. Although it is a similar class to rivaroxaban, there are a few subtle differences to its reversal.

1. Reduced absorption: it is unclear whether activated charcoal binds apixaban, but the slower uptake from the gut may make charcoal or gastric lavage an option.

2. Removal of the circulating drug: the majority of apixaban is bound to protein but it is unclear whether dialysis would be useful.

3. Increased excretion: with one third of the drug excreted through the kidneys it may be less important to ensure good renal function. Bioaccumulation should be considered in patients with hepatic insufficiency who present with bleeding.

4. Inactivating the drug: the recombinant protein (Andexanet alfa) discussed above has above the potential to reverse apixaban. Phase III studies in healthy volunteers have demonstrated reversal of the effects of apixaban by andexanet.

5. Increasing the target: there are less data on the use of PCC and aPCC in apixaban when compared with that in rivaroxaban and dabigatran. In vitro studies have demonstrated improvements in coagulation parameters, but animal studies failed to demonstrate reduction in bleeding.

6. Enhancing coagulation: the evidence for rFVIIa for the reversal of apixaban is similar to that for PCC. This is summarized in Table 4.

### Table 4. Comparison of Reversal Strategies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Ex Vivo Model</th>
<th>Animal Model</th>
<th>Human Volunteers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>No evidence</td>
<td>Reduced bleeding in rabbits with renal injury,24 In high doses of dabigatran improvement in laboratory parameters but no reduction in bleeding25</td>
<td>One study which infused PCC into volunteers demonstrated no benefit,26 whereas 2 studies demonstrated improvement in exogenous thrombin potential when PCC was added in vitro27,28</td>
</tr>
<tr>
<td>aPCC</td>
<td>Improvement in thrombin generation.</td>
<td>Reduced tail bleeding time but not blood loss25,29</td>
<td>Improvement in exogenous thrombin potential and lag time27,29</td>
</tr>
<tr>
<td>rFVIIa</td>
<td>Failed to correct abnormal thrombin generation40</td>
<td>Reduced tail bleeding time but not blood loss25,29</td>
<td>Improvement in exogenous thrombin potential and lag time27,29</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Improved thrombin generation31</td>
<td>Improved laboratory parameters but no effect on blood loss32</td>
<td>No evidence</td>
</tr>
<tr>
<td>aPCC</td>
<td>Improved thrombin generation, clotting time, and clot formation time31</td>
<td>No evidence</td>
<td>No evidence</td>
</tr>
<tr>
<td>rFVIIa</td>
<td>Improved thrombin generation, clotting time, clot formation time, and platelet deposition31</td>
<td>Reduced bleeding time but no effect on blood loss in rabbits32</td>
<td>No evidence</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Demonstrated some improvement in PT, clotting time, and thrombin potential but not as effective as aPCC or rFVIIa.33 Different studies demonstrated no change34 or only improvement in thrombin generation33</td>
<td>Reduced PT and bleeding time in rats and baboons35</td>
<td>Improvement in laboratory parameters including PT and thrombin potential33,37 Four factor concentrate reduces the PT &gt;3 factor but 3 factor improves thrombin generation more37</td>
</tr>
<tr>
<td>aPCC</td>
<td>Demonstrated the most effective reversal of PT, clotting time, and thrombin potential compared with aPCC and rFVIIa33</td>
<td>Reduced PT and bleeding time in rats and baboons35</td>
<td>Improvement in laboratory parameters including PT and thrombin potential33,37</td>
</tr>
<tr>
<td>rFVIIa</td>
<td>Some correction of thrombin generation33,40 and clotting time</td>
<td>Reduced PT and bleeding time in rats and baboons35</td>
<td>Improvement in laboratory parameters including PT and thrombin potential33,37</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>…</td>
<td>…</td>
<td>Demonstrated reduction in punch biopsy bleeding time and thrombin generation, with partial improvement in PT at 50 IU/kg. Lesser effects with lower doses36</td>
</tr>
<tr>
<td>aPCC</td>
<td>Demonstrated improvement in PT, APTT, and anti-Xa assay37</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>rFVIIa</td>
<td>Demonstrated improvement in PT, APTT, and anti-Xa assay37</td>
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APTT indicates activated partial thromboplastin time; aPCC, activated prothrombin complex concentrate; PCC, prothrombin complex concentrate; PT, prothrombin time; and rFVIIa, recombinant factor VIIa.
Edoxaban
Edoxaban is an oral anti-Xa agent. It is a similar class to rivaroxaban and apixaban, being a newer drug there are less data on reversal strategies:

1. Reduced absorption: it is unclear whether activated charcoal binds edoxaban.
2. Removal of the circulating drug: it is unclear whether edoxaban can be dialyzed.
3. Inactivating the drug: Andexanet alfa, discussed above, has the potential to reverse apixaban but no studies have reported.
4. Increasing the target: a small study has presented data on the efficacy of PCC to mitigate bleeding in a punch biopsy model of health patients receiving a single 60 mg dose of edoxaban. This study demonstrated reduced shed blood and overcorrection of the endogenous thrombin potential, with less evident correction of the PT/INR, after 50 IU/kg of a 4-factor PCC. Lower doses were ineffective for correction of the outcomes measured. Ex vivo studies demonstrated reversal of edoxaban by aPCC.
5. Enhancing coagulation: the effects of edoxaban when measured by PT, APTT, and anti-Xa levels were reversed ex vivo by rFVIIa.

PER977 (Araptopazine/Ciraparantag)
An interesting development in the reversal of all the anticoagulants is PER977 from Perosphere. It is a small, synthetic, water-soluble, catatonic molecule that binds to the drug inactivating it, originally developed as a reversal agent for heparin and fondaparinux but also potentially seems to have activity against the oral anti-Xa agents and dabigatran. It does not seem to bind to plasma proteins or several common cardiovascular, antiepileptic, and anesthetic drugs.

Initial studies were in human plasma spiked with apixaban, rivaroxaban, or dabigatran or rats given overdosage of anticoagulants and then subjected to tail bleeding. These demonstrated a reversal of the anti-Xa effect in the plasma or reduction in bleeding to baseline. Further animal studies again demonstrated reduced bleeding and improvements in coagulation assays and thromboelastography with PER977, but no changes to these measures were observed in rats not given anticoagulants, suggesting that the molecule is not procoagulant. The first in vivo human study has been published; this was a placebo controlled study in healthy volunteers, which demonstrated that after a single dose of edoxaban the whole blood clotting time improved with the addition of 25 mg of PER977, with 100 and 300 mg almost completely reversed the effect. Electron microscopy of fibrin fibers demonstrated larger fibers with the higher doses. There was no evidence of coagulation activation with no increase in D-dimers, prothrombin fragment 1.2, and tissue pathway inhibitor. Further similar studies with unfractionated heparin and enoxaparin are taking place.

Two abstracts (produced by the manufactures of Andexanet) have questioned whether PER977 truly reverses

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**Figure 3.** Flowchart for the management of novel oral anticoagulant (NOAC) bleeding. aPCC indicates activated prothrombin complex concentrate; APTT, activated partial thromboplastin time; PCC, prothrombin complex concentrate; PT, prothrombin time; and rFVIIa, recombinant factor VIIa.
investigating further.

anti-Xa agents but reduces bleeding, then it is still worthwhile
of procoagulant activity with increased thrombin generation
and platelet activation. Even if PER977 does not reverse the
of anti-Xa agents by PER977, but there was the suggestion
abstracts which have not been thoroughly peer reviewed.
are readily recognized as anticoagulants by all healthcare
patients and healthcare professionals do not continue to
administer the drug in the event of bleeding or symptoms
require emergency surgery and that these new drugs
are readily recognized as anticoagulants by all healthcare
professionals.

Where bleeding is potentially life-threatening, then addi-
tional treatments may be considered, including PCC, aPCC,
and rFVIIa. Although none of these agents have been demon-
strated to be effective in clinical trials involving patients with
hemorrhage, the evidence comes from volunteer studies, ani-
mal studies, and in vitro experiments. There is no consensus,
because of conflicting data, on which of these agents is supe-
rior and their optimum dose. PCC is likely to be cheaper and
because of its indication for warfarin, reversal is more readily
available than aPCC or rFVIIa. Because aPCC contains ac-
vated clotting factors, it could be theorized that it would be
more effective in stopping bleeding than PCC, but it is known
that it is more thrombogenic increasing the risk of unwanted
thrombosis.

The new anticoagulants were designed with the knowl-
edge of the structure of their target molecule, the same prin-
ciples have been applied to specific antidotes which mimic
either thrombin or factor Xa (idarucizumab and andexanet,
respectively) or bind to the drug inactivating it (PER977).
The all information on these new agents are from conference
abstracts which have not been thoroughly peer reviewed.
These antidotes are not functional as a clotting factor but bind
the drug with high affinity making it inactive. These novel
antidotes may provide the most effective method of reversal;
however, they are yet to be proven in clinical trials with bleed-
ing patients. Given they are inert they would probably be safer
than recombinant thrombin or factor Xa, which may lead to
unwanted thrombosis; to date, none of the studies have dem-
onstrated coagulation activation or unwanted effects. PER977
seems to have the advantage of reversing all the NOACs along
with heparin but its exact mechanism is still unclear.

When compared with the majority of drugs, these anti-
dotes will be used relatively infrequently, the worry is that
the development costs, which will be passed on, will lead to
the drugs being prohibitively expensive, even when compared
with the cost of bleeds or alternative therapies.

In both bleeding and the work-up for emergency surgery,
time is critical. It is important that healthcare institutions have
readily accessible guidelines and procedures for managing
patients on the NOACs to ensure that they are assessed appro-
priately and if necessary specific management implemented.
A suggested algorithm is found in Figure 3.

Discussion
The NOACs offer the ability to anticoagulate patients with-
out the need for routine monitoring and dose adjustment,
hopefully enhancing quality of life. Within randomized con-
trolled trials they seem to be as or more effective and possi-
ble safer than their comparator agents, but it is unclear in
everyday clinical practice whether these benefits are present,
real-world registry data are awaited. Long-term side-effects,
if any, are still to be determined. The new anticoagulants still
cause bleeding and patients may require emergency surgery,
but unlike the vitamin K antagonists they replace there is no
specific reversal agent currently in widespread clinical use.
For the majority of episodes where reversal is required, the
short half-life of the drugs means the patient can be stabi-
lized and supported until the effect of the drug effect is lost.
Routinely available coagulation tests, if elevated, suggest
that the patient has significant amounts of drug present.
If normal, they do not indicate the patient is free of clinically
important levels of drug. Education is important to ensure
patients and healthcare professionals do not continue to
administer the drug in the event of bleeding or symptoms
that require emergency surgery and that these new drugs
are readily recognized as anticoagulants by all healthcare
professionals.

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References
1. Makris M, Van Veen JJ, Tait CR, Munford AD, Laffan M; British Committee for Standards in Haematology. Guideline on the manage-
of fresh frozen plasma and clotting factor concentrate on correction of the
4. Rosovsky RP, Crowther MA. What is the evidence for the off-label use of recombinant factor VIIa (rFVIIa) in the acute reversal of warfarin? ASH
5. Watson HG, Baglin T, Laidlaw SL, Makris M, Preston FE. A compari-
on of the efficacy and rate of response to oral and intravenous Vitamin
Haemostasis. Management of major bleeding complications and emer-
gency surgery in patients on long-term treatment with direct oral antico-
agulants, thrombin or factor-Xa inhibitors: proposals of the working group
laboratory assays in the measurement of dabigatran in patients receiv-
ing therapeutic doses: a prospective study based on peak and trough
9. Lindahl TL, Baghani F, Blixtar IF; Gustafsson KM, Stigendal L, Sten-
linder M, Strandberg K, Hillarp A; Expert Group on Coagulation of
the External Quality Assurance in Laboratory Medicine in Sweden.
Effects of the oral, direct thrombin inhibitor dabigatran on five common
TH10-06-0342.
10. Douxfils J, Chatelain C, Chatelain B, Dogné JM, Mullier F. Impact of
apixaban on routine and specific coagulation assays: a practical
TH12-12-0898.


Apixaban-Induced Anticoagulation in Older Subjects by Andexanet alpha (PRT064445), a Universal Antidote for Factor Xa (fXa) Inhibitors. *Circulation*. 2014;130:2116–2117.


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