Overview of direct oral anticoagulant therapy reversal

Purpose. Strategies for the management of bleeding complications and facilitation of an invasive procedure in patients receiving direct oral anticoagulants (DOACs) are reviewed.

Summary. The DOACs provide clinical advantages versus vitamin K antagonists, including fixed dosing with no routine coagulation monitoring and evidence of a lower risk of bleeding. However, as with all anticoagulants, there is a risk of bleeding complications in patients receiving DOACs, so urgent reversal of their anticoagulant activity may be required for spontaneous or traumatic bleeding events and in patients undergoing emergency invasive procedures. Reversal strategies are dependent on the anticoagulant involved, the location and severity of the bleeding, and/or the urgency of the invasive procedure. The recently approved specific reversal agent for dabigatran, idarucizumab, together with other reversal agents in development will hopefully allow for the emergent reversal of DOACs, without increasing the underlying risk of thrombosis. However, research is required to determine the optimal use of these reversal agents, in terms of choice of agent, dosing, and concomitant management. A systematic approach to their implementation in hospitals is also required to ensure that physicians, nurses, and pharmacists receive appropriate education and have the necessary protocols and guidelines to manage these clinical situations.

Conclusion. Reversal strategies in patients receiving a DOAC need to be tailored to the anticoagulant involved as well as the urgency and severity of the clinical situation. Reversal agents should help facilitate the urgent reversal of anticoagulation in patients with emergency bleeding or who require urgent surgery, though research and education are required to ensure the optimal use of these agents.

Am J Health-Syst Pharm. 2016; 73(suppl 2):S5-13

Direct oral anticoagulants (DOACs) provide an alternative therapeutic strategy to that of the vitamin K antagonists, such as warfarin, for stroke and systemic embolism risk reduction in patients with nonvalvular atrial fibrillation (NVAF), and for the prophylaxis and treatment of venous thromboembolism (VTE) (Table 1).1-4 The pharmacology of DOACs differs from that of warfarin. Warfarin prevents the production of functional vitamin K-dependent clotting factors by the liver, whereas DOACs directly inhibit activated factor X (FXa) (rivaroxaban, apixaban, and edoxaban) or activated factor II (FiHa) (dabigatran etexilate) (Figure 1). DOACs have a rapid and predictable onset and offset of anticoagulation, predictable pharmacokinetics without the need for routine monitoring of coagulation values, and few drug-food interactions.1-5 Due to their short half-lives (Table 2),6-13 the anticoagulant effect of DOACs diminish within one to two days after administration of the most recent dose in patients with normal renal function, but could be extended in patients with diminished renal function, particularly when dabigatran is used.14,15 Although DOACs appear to decrease the risk of intracranial hemorrhage (ICH) in patients with
NVAF when compared with warfarin, they are still associated with a risk of bleeding complications.\textsuperscript{16,20} Thus, the anticoagulant effect of DOACs must be reversed in patients experiencing spontaneous or traumatic bleeding and in patients undergoing emergency surgery or other urgent invasive procedures.

This article provides a brief introduction to DOACs, describing how the management of bleeding or facilitation of an invasive procedure in the setting of DOAC therapy varies greatly from that with warfarin. A brief overview of the strategies for managing bleeding complications in patients taking DOACs is also provided. The article concludes with a discussion of the clinical need for reversal agents for DOACs, as well as an introduction of the reversal agents in development.

Differences in anticoagulation reversal pharmacology

Due to warfarin’s mechanism of action, any product, including fresh frozen plasma (FFP) and prothrombin complex concentrate (PCC), which provides active, mature clotting factors, will immediately reverse warfarin’s effects. However, as the half-life of warfarin is long (1.5–2 days), phytonadione should also be given to ensure hepatic production of vitamin K clotting factors to replace those consumed from administered clotting supplements and to prevent rebound increases in the International Normalized Ratio (INR) values (Figure 2).\textsuperscript{14,21}

In contrast, pharmacologic reversal of DOACs requires a different strategy from that used with warfarin. The circulating DOAC will continue to inhibit exogenously administered clotting factors, such as those found in FFP, making this product of limited use when given to reverse DOACs.\textsuperscript{14,22} PCC has been used to reverse DOACs in an effort to overwhelm the inhibitory effect of the DOACs by providing additional quantities of coagulation factors, mainly FIIa for thrombin inhibitors and FXa for FXa inhibitors.\textsuperscript{23,24} However, this cannot be considered a true neutralization of the pharmacologic activity; this is partly why improved and potentially safer reversal strategies are being sought, as will be discussed later.

General approach to management of DOAC-related bleeding

As with any bleeding patient, the bleeding site, bleeding severity (i.e., volume of blood loss), and accessibility of the bleeding site should be assessed.\textsuperscript{25} The anticoagulant should be stopped, and the timing of the last dose determined. Supportive care measures should also be undertaken, such as volume replacement, blood transfusion, and bleeding site control if possible (e.g., suturing, pressure, cautery).\textsuperscript{14,22} The use of dialysis to remove remaining anticoagulant from the circulation should be considered for significant bleeding events involving dabigatran.

To determine the best course of action, the physician should conduct a thorough physical examination to determine the patient’s clinical status and to provide information on the location and severity of any internal or external bleeding. This is likely to include imaging and other diagnostic tests (e.g., endoscopy, computerized tomography, magnetic resonance imaging). Laboratory tests (including complete blood count and various coagulation tests, depending on the anticoagulant involved) should also be considered when evaluating and managing bleeding. The use of coagulation testing for this purpose is discussed in detail by Dager and Hellwig\textsuperscript{26} in this supplement. For severe, life-threatening bleeding, the source of bleeding should be identified and treated by invasive measures if possible.\textsuperscript{27}

Management of patients taking DOACs who require an invasive procedure

Patients receiving DOACs may at some point require invasive procedures. Management of patients undergoing elective invasive procedures who have a high risk of bleeding simply requires withholding the DOAC for an adequate length of time for the anticoagulant effect to dissipate. In contrast, management of patients taking DOACs who must undergo an emergent procedure is more challenging and depends on the patient’s indi-
Figure 1. Pharmacology of warfarin compared with direct oral anticoagulants (DOACs) in the setting of anticoagulation reversal. FFP = fresh frozen plasma, PCC = prothrombin complex concentrate.

Table 1. FDA-Approved Indications for Direct Oral Anticoagulants

<table>
<thead>
<tr>
<th>Indication</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of acute DVT/PE</td>
<td>Dabigatran, rivaroxaban, apixaban, edoxaban</td>
</tr>
<tr>
<td>Secondary prevention of DVT/PE</td>
<td>Dabigatran, rivaroxaban, apixaban</td>
</tr>
<tr>
<td>VTE prevention in total hip and total knee replacement surgeries</td>
<td>Dabigatran (total hip replacement), rivaroxaban, apixaban</td>
</tr>
<tr>
<td>Risk reduction of stroke and systemic embolism in nonvalvular atrial fibrillation</td>
<td>Dabigatran, rivaroxaban, apixaban, edoxaban (not recommended if creatinine clearance is &gt; 95 mL/min)</td>
</tr>
</tbody>
</table>

*FDA = Food and Drug Administration, DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venous thromboembolism.
*After parenteral anticoagulant (5–10 days).

Reversal of DOACs for bleeding or invasive procedures

Nutescu et al. recently proposed a strategy for bleeding management or emergent procedures for patients taking DOACs based on the urgency of the situation (Figure 3). The European Heart Rhythm Association has also provided similar guidance for managing bleeding complications and urgent surgery in DOAC-treated patients with NVAF, as have other authors.

Level of urgency: no rush (acceptable if reversal takes more than 24 hours). This encompasses most minor bleeding events (e.g., epistaxis, ecchymosis, and menorrhagia) and nonemergency surgeries where an intervention is needed (e.g., hip fracture, biopsies). These patients can generally be managed by withholding the anticoagulant, observing the patient, and providing supportive care. Blood products and fluids should be used if clinically necessary.
indicated, and local measures for controlling the bleeding should be implemented. The anticoagulation effect will dissipate over time, depending on the agent and renal function of the patient, with clearance times being similar to the timing of interruption of therapy before major surgery (Table 3).25

**Level of urgency: expedited (acceptable if reversal occurs in 1–24 hours).** This category comprises more serious bleeding events that are not in a closed space and where the patient remains hemodynamically stable with supportive care. Many, but not all, gastrointestinal bleeding events would fall into this category. Also included in this category are surgical situations where an emergency procedure is not required, but the patient optimally needs an intervention within the next 24 hours. Typical management, as with low-urgency situations, is based on temporary removal of the DOAC and supportive care.30,36 As a consequence of the relatively short half-lives of DOACs, a brief interval of support is required while coagulation returns to normal10,11; clearance times are likely to be similar to the lapse times before major surgery, shown in Table 3. Appropriate mechanical compression, volume replacement, and blood products should be used, as needed, to support the patient and keep them hemodynamically stable.33 This will facilitate clearance of

---

**Figure 2.** Onset and duration of effect on International Normalized Ratio (INR) of various warfarin reversal therapies. FFP = fresh frozen plasma, PCC = prothrombin complex concentrate, rFVIIa = recombinant factor VIIa. Reprinted from reference 14, with permission.

**Table 2. Pharmacokinetics of Direct Oral Anticoagulants***

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dabigatran6,7</th>
<th>Rivaroxaban8,9</th>
<th>Apixaban10,11</th>
<th>Edoxaban12,13</th>
</tr>
</thead>
<tbody>
<tr>
<td>( t_{\text{max}} ) (hr)</td>
<td>1.25–1.5c</td>
<td>2–3d</td>
<td>3–4c</td>
<td>2–3.5d</td>
</tr>
<tr>
<td>( t_{1/2} ) (hr)</td>
<td>14–17c</td>
<td>6–9d</td>
<td>8–15c</td>
<td>9–10d</td>
</tr>
<tr>
<td>Renal elimination (%)</td>
<td>80</td>
<td>36d</td>
<td>25–29</td>
<td>35</td>
</tr>
</tbody>
</table>

*\( t_{\text{max}} \) = time of maximum observed plasma concentration, \( t_{1/2} \) = apparent plasma terminal elimination half-life.
*After multiple doses were administered to healthy volunteers.
*Median.
*Geometric mean.
*Mean.
*Unchanged rivaroxaban.
Figure 3. Management of patients with bleeding or needing an urgent invasive procedure. Adapted from reference 25, with permission. NVAF = nonvalvular atrial fibrillation, VTE = venous thromboembolism, PCC4 = four-factor prothrombin complex concentrate, aPCC = activated prothrombin complex concentrate, DOACs = direct oral anticoagulants.
When deciding how to construct a DOAC reversal plan in these emergency situations, it is important to consider individual thrombotic risk, the bleeding site, and how the patient is responding to supportive care before treatment with clotting factors. Patients with a history of vascular or trauma and thus could be considered as adjuvant therapy in cases of bleeding. However, there is a lack of data on the role of this agent in managing serious bleeding in patients receiving oral anticoagulants. Further, idarucizumab can be considered for dabigatran-related bleeding as discussed in the article by Smythe et al.40 in this supplement. Prolonged dialysis for patients taking dabigatran should be considered to avoid redistribution of the medication from the tissue compartment.14 Patients should be in an intensive care setting with access to life-supporting therapies as required (e.g., volume replacement, vasopressors, mechanical ventilation). ICH is particularly devastating, and even with optimal care, mortality and morbidity are likely to be high.41

When deciding how to construct a DOAC reversal plan in these emergency situations, it is important to consider individual thrombotic risk, the bleeding site, and how the patient is responding to supportive care before treatment with clotting factors. Patients with a history of vascular or trauma and thus could be considered as adjuvant therapy in cases of bleeding. However, there is a lack of data on the role of this agent in managing serious bleeding in patients receiving oral anticoagulants. Further, idarucizumab can be considered for dabigatran-related bleeding as discussed in the article by Smythe et al.40 in this supplement. Prolonged dialysis for patients taking dabigatran should be considered to avoid redistribution of the medication from the tissue compartment.14 Patients should be in an intensive care setting with access to life-supporting therapies as required (e.g., volume replacement, vasopressors, mechanical ventilation). ICH is particularly devastating, and even with optimal care, mortality and morbidity are likely to be high.41

When deciding how to construct a DOAC reversal plan in these emergency situations, it is important to consider individual thrombotic risk, the bleeding site, and how the patient is responding to supportive care before treatment with clotting factors. Patients with a history of vascular or trauma and thus could be considered as adjuvant therapy in cases of bleeding. However, there is a lack of data on the role of this agent in managing serious bleeding in patients receiving oral anticoagulants. Further, idarucizumab can be considered for dabigatran-related bleeding as discussed in the article by Smythe et al.40 in this supplement. Prolonged dialysis for patients taking dabigatran should be considered to avoid redistribution of the medication from the tissue compartment.14 Patients should be in an intensive care setting with access to life-supporting therapies as required (e.g., volume replacement, vasopressors, mechanical ventilation). ICH is particularly devastating, and even with optimal care, mortality and morbidity are likely to be high.41

When deciding how to construct a DOAC reversal plan in these emergency situations, it is important to consider individual thrombotic risk, the bleeding site, and how the patient is responding to supportive care before treatment with clotting factors. Patients with a history of vascular or trauma and thus could be considered as adjuvant therapy in cases of bleeding. However, there is a lack of data on the role of this agent in managing serious bleeding in patients receiving oral anticoagulants. Further, idarucizumab can be considered for dabigatran-related bleeding as discussed in the article by Smythe et al.40 in this supplement. Prolonged dialysis for patients taking dabigatran should be considered to avoid redistribution of the medication from the tissue compartment.14 Patients should be in an intensive care setting with access to life-supporting therapies as required (e.g., volume replacement, vasopressors, mechanical ventilation). ICH is particularly devastating, and even with optimal care, mortality and morbidity are likely to be high.41
Table 4. Reversal Agents for Direct Oral Anticoagulants (DOACs)a

<table>
<thead>
<tr>
<th>Variable</th>
<th>Idarucizumab46-48</th>
<th>Andexanet alfa44,49</th>
<th>Ciraparantag44,50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulation reversal</td>
<td>Dabigatran</td>
<td>Direct and indirect factor Xa inhibitors</td>
<td>DOACs (edoxaban, rivaroxaban, apixaban, dabigatran), UFH, LMWH, and fondaparinux</td>
</tr>
<tr>
<td>Mode of action</td>
<td>Humanized monoclonal antibody fragment with 350-fold higher binding affinity for dabigatran vs. dabigatran for thrombin</td>
<td>Modified recombinant protein, truncated form of enzymatically inactive factor Xa</td>
<td>Small, synthetic, water-soluble, cationic molecule designed to bind to DOACs, UFH, and LMWH through noncovalent hydrogen bonding and charge–charge interactions</td>
</tr>
<tr>
<td></td>
<td>Specifically binds and neutralizes free and thrombin-bound dabigatran</td>
<td>Lacks ability to convert prothrombin to thrombin but retains ability to bind with direct factor Xa inhibitors, LMWH, and activated antithrombin III</td>
<td>Modified to prevent interaction with phospholipids to avoid competition with native factor Xa, which could impair coagulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Partial reversal agent for LMWHs (i.e., does not block their activity against factor IIa)</td>
<td>Partial reversal agent for LMWHs</td>
</tr>
<tr>
<td>Development trial phase</td>
<td>III/approved</td>
<td>III</td>
<td>II</td>
</tr>
<tr>
<td>Clinical findings</td>
<td>Demonstrated rapid and complete reversal activity against dabigatran in patients</td>
<td>Demonstrated reversal activity with apixaban, rivaroxaban, and edoxaban in healthy volunteers but appears to require different doses for apixaban and rivaroxaban</td>
<td>Demonstrated reversal activity against edoxaban in healthy volunteers within 10–30 min, with effect sustained for 24 hr</td>
</tr>
</tbody>
</table>

aUFH = unfractionated heparin, LMWH = low-molecular-weight heparin.

alpha and ciraparantag, depending on the agent to be reversed and the clinical situation? If different dosing strategies are required, then determining the appropriate dose of these agents in an emergency situation could be challenging and will need to be systematized.44 As andexanet alfa is only a partial reversal agent for low-molecular-weight heparins (LMWHs), trials are required to determine whether the addition of protamine is necessary to block LMWH inhibition against FIIa.44 Clinicians will also need to know if idarucizumab administration should be repeated as the dabigatran redistributes out of the tissues or if a better approach would be to combine idarucizumab with dialysis.46 The reversal agent that is selected will also affect the choice and timing of anticoagulation for patients who need to be emergently reanticoagulated (e.g., extracorporeal life support).44 Furthermore, research is required to determine how laboratory tests will guide reversal strategies after these agents are released.

Systems of care perspective

It is critical that pharmacists, in partnership with their clinical laboratories and medical staff, address DOAC reversal in a systematic way. Considering the complexity and risk involved, as well as the demanding emergency situations when these agents are needed, systematizing the care as much as is feasible is critical. All hospitals, no matter the size, must consider adopting protocols, guidelines, and order sets to ensure that emergency reversal is conducted correctly according to the best scientific literature available. These will need to evolve and include the appropriate reversal agent, dosing, and management strategy to optimize both the efficacy and safety of DOAC reversal for the patient. Pharmacy and therapeutics committees, regardless of the size of the hospital, must decide which agents they will stock based on efficacy, patient safety, and cost. Healthcare professionals need to be educated about reversal agents and their appropriate use so that they know how to respond in emergency situations in which the agents are required. Proactive steps should be taken to ensure that the correct agents are used at the correct dose and in the appropriate patients.

Conclusion

DOACs provide a number of clinical advantages over warfarin, such as fixed dosing without the need for routine laboratory monitoring of coagulation. However, as with all anticoagulants, they may still place
patients at risk of bleeding complications. Thus, there is a need to reverse their anticoagulant activity in certain clinical situations, including cases of life-threatening spontaneous or traumatic bleeding and in patients undergoing emergency invasive procedures. As the pharmacology of DOACs differs from that of warfarin, DOAC reversal also differs from that of warfarin. As DOACs inhibit administered clotting factors, clotting factor supplements are intended to overcome the pharmacologic effect and may pose a thrombotic risk to the patient. Management of bleeding and facilitation of surgical procedures are therefore dependent on the agent involved, the location and severity of the bleeding, and the urgency of the invasive procedure. The recently approved dabigatran-specific reversal agent idarucizumab, together with reversal agents in development, will hopefully allow for the emergent reversal of DOACs in emergency bleeding and surgical situations without increasing the underlying risk of thrombosis. However, research is required to understand how these reversal agents can best be used, in terms of choice of agent, dosing, and concomitant management. Hospitals should also adopt a systematic approach to the use of DOAC reversal agents, ensuring that healthcare professionals receive appropriate education and have the necessary protocols and guidelines to optimize the emergency reversal of DOACs.

Acknowledgments

Editorial support was provided by Joanne Vaughan, B.Sc., of Envision Scientific Solutions, which was contracted and funded by Boehringer Ingelheim Pharmaceuticals. Boehringer Ingelheim Pharmaceuticals was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations.

Disclosures

Dr. Gulseth received nonfinancial support from Boehringer Ingelheim during the development of this manuscript. Outside this submitted work, he has received personal fees from Bristol-Myers Squibb, Daiichi Sankyo, Portola Pharmaceuticals, Pfizer, and Janssen Pharmaceuticals, as well as personal fees and nonfinancial support from Boehringer Ingelheim.

References

23. Eerenberg ES, Kamphuisen PW, Sijpkins MK et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized,