ICU
MANAGEMENT & PRACTICE

Reversal of Direct Oral Anticoagulants

Direct oral anticoagulants (DOACs) like apixaban, edoxaban, rivaroxaban (all FXa inhibitors), and dabigatran (a thrombin inhibitor) have been used for many years, with their generic versions becoming increasingly available. Though DOACs have a lower risk of serious bleeding, such as intracranial haemorrhage, compared to vitamin K antagonists, bleeding is still their most common side effect.

A new review compares the mechanism of action of specific and non-specific reversal agents, reviews the clinical data supporting their use, and provides guidance on when reversal is indicated. It also discusses the reversal of oral FXIa inhibitors, a new class of DOACs currently under clinical development.

Specific Reversal Agents

- Idarucizumab: A monoclonal antibody fragment that reverses dabigatran's effects rapidly. It has a half-life of about 45 minutes, prolonged in renal dysfunction. The REVERSE-AD study confirmed its efficacy, showing a median haemostasis time of 2.5 hours for life-threatening bleeding cases and a 93% normal haemostasis rate in urgent surgeries.

- Andexanet alfa: A recombinant FXa variant shown to reduce anti-FXa activity and increase thrombin generation. The ANNEXA-4 study demonstrated a 93% reduction in anti-FXa activity and good haemostatic efficacy in 80% of patients. ANNEXA-I further showed improved outcomes compared to usual care, though thromboembolic events were more frequent.

Non-Specific Reversal Agents

- Prothrombin Complex Concentrates (PCCs): Contain multiple coagulation factors and are used off-label for DOAC-related bleeding. Four-factor PCCs are most commonly used, with an 80% efficacy rate and a low risk of thromboembolic events.

- Activated PCC (aPCC) and Recombinant FVIIa (rFVIIa): Also used but less commonly, with limited evidence supporting their effectiveness in DOAC-related bleeding.

Observational studies suggest andexanet may have a higher efficacy and a higher rate of thromboembolic events than PCCs. Various ongoing trials are investigating the optimal use of PCCs and other new reversal agents like ciraparantag and VMX-C001.

Haemadsorption using a styrene copolymer column with sorbent beads can remove oral FXa inhibitors (FXaI) like apixaban and rivaroxaban, achieving a 99% removal rate in an in vitro model. This method could potentially be integrated into cardiopulmonary bypass circuits during cardiac surgery. However, for patients without existing vascular access, placing a dialysis catheter might increase bleeding risks.

Reversal agents for DOACs carry a 4%-10% risk of thromboembolic complications. However, these risks vary depending on the patient population and specific agents used. While no complications were reported in healthy volunteers, clinical studies show a baseline thrombotic risk in patients. Thrombotic events, primarily before the resumption of therapeutic anticoagulation, highlight the importance of timely anticoagulation after bleeding control. Thromboembolic events are more common with andexanet, potentially due to its interactions with the tissue factor pathway inhibitor.

Oral FXIa inhibitors, like asundexian and milvexian, are newer anticoagulants under development. They offer a safer profile, particularly in reducing bleeding risks. Currently, no specific reversal agents exist for these drugs. In urgent cases, tranexamic acid and low-dose rFVIIa can be considered, though more evidence is needed.

Indications for reversal include major bleeding, urgent surgery, or invasive procedures with a high bleeding risk. While idarucizumab is licensed for dabigatran reversal, andexanet is approved for reversing rivaroxaban or apixaban in major bleeding. Despite the availability of these agents, 4F-PCCs are often used as they are more accessible. Further studies are needed to refine the use of andexanet and PCCs, especially given the unclear role of fresh frozen plasma and tranexamic acid in DOAC reversal.

For nonbleeding DOAC-treated patients requiring urgent surgery, risk management involves evaluating the urgency, the last DOAC dose, and the need for reversal. Depending on the DOAC level, surgery timing can be adjusted, or reversal can be considered. Preoperative and postoperative anticoagulation management are essential to mitigate bleeding and thromboembolism risks.

Hospitals should develop care pathways for managing bleeding in DOAC patients, considering costs, availability, and timing. Policies for specific provider access and approval pathways are crucial.

Despite progress in DOAC reversal, many questions remain, particularly regarding the efficacy and safety of available agents like andexanet. Further research and well-designed trials are needed to establish clear guidelines and compare various strategies, including the potential use of emerging agents and technologies like thrombin generation assays and viscoelastic testing.

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