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FIVE THINGS TO KNOW ABOUT ...

# Direct oral anticoagulants and the bleeding patient

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**Direct oral anticoagulant agents are now routinely used for the prevention of stroke in nonvalvular atrial fibrillation**

1

Rivaroxaban, apixaban and dabigatran are now commonly used as alternatives to vitamin K antagonist therapy (e.g., warfarin) for patients with atrial fibrillation, and for the treatment and prevention of venous thromboembolism. Dabigatran is a direct thrombin inhibitor, whereas apixaban and rivaroxaban are direct inhibitors of factor Xa.[1]

**Risk of bleeding with direct oral anticoagulants is lower than with vitamin K antagonists, but varies by site**

2

In a meta-analysis, fewer incidents of major bleeding were reported with direct oral anticoagulants than with vitamin K antagonists. Specifically, fewer intracranial bleeds occurred, but the incidence of gastrointestinal bleeding was higher.[1]

**Direct oral anticoagulants are characterized by rapid onset of action and short half-lives[2]**

3

Depending on the anticoagulant, the onset of action varies from 1.5 to 4 hours, with a half-life between 5 and 17 hours (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.150604/-/DC1). Dabigatran tends to have a shorter onset of action and longer half-life, compared with rivaroxaban and apixaban. Drug interactions can occur with all three drugs.

**Direct oral anticoagulants variably affect standard clot-based assays**

4

All three drugs cause variable test results. This may depend on the instrument and reagents used. The results may not have linear correlation to plasma concentrations of the drugs. The activated partial thromboplastin time is more sensitive to dabigatran, but a normal result does not preclude the ongoing presence of drug and concordant bleeding risk. A normal thrombin time, however, rules out the presence of dabigatran. The prothrombin time (PT) is more sensitive to factor Xa inhibitors. Depending on the reagent used, PT may be normal even with therapeutic concentrations of factor Xa inhibitors. In general, the international normalized ratio is not helpful.[3]

**There are no specific antidotes available to reverse the activity of these agents, and current strategies are extrapolated from bleeding in other settings**

5

Direct antidotes for the direct oral anticoagulants are currently in phase 3 clinical trials. Idarucizumab is a humanized monoclonal antibody against dabigatran, and andexanet is a recombinant factor Xa derivative designed to competitively counteract apixaban and rivaroxaban (Box 1).[4]

**Box 1: Potential management strategies for bleeding caused by direct oral anticoagulants and warfarin**

| Agent | Strategy |
|---|---|
| Warfarin | Vitamin K, PCC, FP, TXA |
| Dabigatran | Activated charcoal, hemodialysis, aPCC, TXA |
| Rivaroxaban | PCC, TXA |
| Apixaban | PCC, TXA |

Note: FP = frozen plasma, PCC = prothrombin complex concentrates, aPCC = activated prothrombin concentrates, TXA = tranexamic acid.

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