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# Direct oral anticoagulants

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## Introduction

Direct oral anticoagulants (DOACs) have become the standard of care for a wide range of prophylactic and therapeutic anticoagulation indications. They offer major advantages:

1. Compared with heparin, low molecular weight heparins (LMWH), and pentasaccharides, DOACs have an enteral route (increased suitability for long-term use) and increased predictability of response across a range of patient pathophysiological states.
2. Compared with oral vitamin K antagonists (e.g. warfarin) DOACs have a more rapid onset and offset of action (allowing early surgery after discontinuation), a predictable dose-response relationship obviating the need for monitoring, a wider therapeutic window, reduced bleeding risk (especially intracerebral), and relatively few food and drug interactions.

DOACs bind directly to the active site of their enzyme target and inhibit its further participation in the coagulation cascade. Both free and clot-bound thrombin and/or factor Xa are targeted. They are comprised of drugs from two pharmacological categories:

1. Direct thrombin (factor II) inhibitors (unlike heparins, LMWH, and pentasaccharides that inhibit factor II via an amplification process involving antithrombin). In South Africa, the sole available agent from this category is dabigatran etexilate.
2. Factor Xa inhibitors. This group is represented by rivaroxaban and apixaban. The release of edoxaban and betrixaban is anticipated.

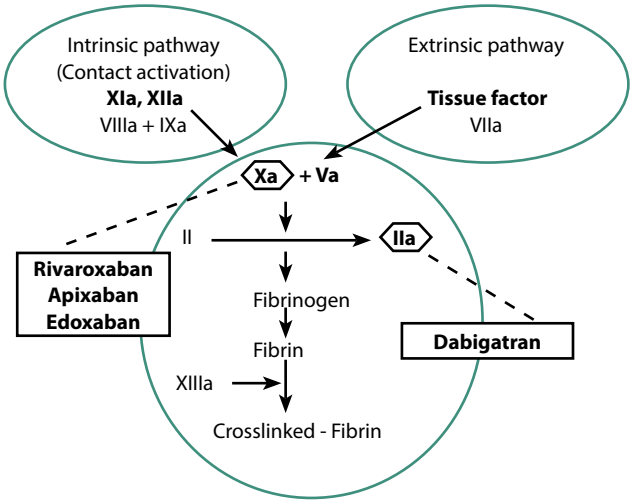


Figure 1: Schematic view of location of action of DOACs[1]

## Therapeutic indications

Table I: DOACs on-label therapeutic indications

| Indication | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|
| Stroke prevention in AF – non-valvular | Yes – intermediate-risk cases | Yes – including high-risk patients | Yes | Yes |
| DVT prophylaxis in major surgery/major medical disease | Yes – ortho | Yes – ortho/malignancy surgery | Yes – ortho | No |
| Long-term prophylaxis after recurrent VTE/ thrombophilia/malignancy | Yes<br>Not for malignancy | Yes | Yes | No |
| Treatment of acute VTE | Yes – after the initial LMWH treatment | Yes | Yes | Yes |
| Prophylaxis with mechanical heart valves | Only bioprosthetic valves | Only bioprosthetic valves | Only bioprosthetic valves | Only bioprosthetic valves |
| Anticoagulation with ACS/coronary stents/ chronic CAD (part of DAPT with aspirin or P2Y12 inhibitor)/PVD | No | Yes | No | No |

Notes on Table I:
- The on-label indications are expanding as phase 3 trials are concluded for the newer agents. All factor Xa antagonists will likely, in time, share the indications that apply to rivaroxaban. You will already encounter agents used off-label for the full spectrum of indications. DOACs were used extensively during the COVID-19 pandemic.
- In general, prophylactic doses are 50–66% of therapeutic doses and are applied after major surgery and to medically ill inpatients.
- Prophylaxis in stroke prevention in atrial fibrillation (SPAF) and cardiac bioprosthetic valves is at 66–100% of treatment doses.
- Rivaroxaban doses for coronary artery disease are half of prophylactic doses, provided it is used in combination with an anti-platelet agent.
- Dabigatran and (less so) apixaban require downward dose adjustment in the presence of renal dysfunction and dabigatran should not be used in patients with creatinine clearance < 30 ml/min.

## Pharmacokinetics

**Table II:** Pharmacokinetics (PK) of DOACs

| | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|
| Doses | SPAF 220–300 mg/day<br>Prophylaxis 150–220 mg/day<br>VTE treatment 300 mg/day | SPAF 20 mg daily<br>Prophylaxis 10 mg/day<br>VTE treatment 15 mg *bid* followed by 20 mg daily after 21 days | SPAF 5 mg *bid*<br>Prophylaxis 2.5 mg *bid*<br>VTE treatment 10 mg *bid* for 7 days then 5 mg *bid* | SPAF 60 mg daily<br>Treatment of VTE 60 mg daily |
| $T_{max}$ | 1.5 hours | 2–4 | 1–4 | 1–2 |
| $T_{1/2}$ | 9–17 hours (average 12) | 5–13 (average 9) | 12 | 10–14 |
| Elimination | 80–85% renal | 33% renal | 25–27% renal | 35–50% renal |
| Other PK features | Absorption inhibited by PPI<br>Prodrug | Safe in mild liver disease | Reduced dose in mild liver disease; mass < 60 kg and age > 80 years | Safe in mild liver disease |
| Dose adjustment | Halve dose if creatinine clearance < 50 ml/min.<br>Contra-indicated < 30 | Halve dose at creatinine clearance < 30 ml/min; contra-indicated in ESRD | Same as for rivaroxaban | Same as for rivaroxaban |

Notes on Table II:
- All agents are subject to increased metabolism and decreased efficacy from P-glycoprotein inducers (e.g. rifampicin) and increased efficacy from P-glycoprotein inhibitors (e.g. ketoconazole).
- All Xa inhibitors show similar changes with CYP3A4 inducers (e.g. carbamazepine and phenytoin) and inhibitors (e.g. HIV protease inhibitors). Antiarrhythmics may also interact to reduce metabolism and increase bleeding risk.
- Increasing drug doses increases antithrombotic efficacy but at the expense of an increased risk of bleeding. Bleeding risk is, in general, lower than that of warfarin at equi-effective doses (< 2% per annum risk of major bleeding).

## Contraindications

1. Conditions with a high bleeding risk (e.g. gastrointestinal [GI], varices, recent/acute intracerebral bleeding, or major neuro or ophthalmic surgery).
2. Concurrent use of other anticoagulants; however, may be used concurrently with anti-platelet drugs.
3. Severe or end-stage liver or kidney disease. Dabigatran is specifically contraindicated in kidney disease with functional impairment that is moderate or worse (glomerular filtration rate < 50 ml/min). All other DOACs require dose reduction in moderate kidney impairment and only rivaroxaban can be used with severe impairment (creatinine clearance 15–30 ml/min with a 50% dose reduction).
4. Old age and body mass < 60 kg also mandate a dose reduction.

## Bleeding

As stated previously, major bleeding rates are lower than those of warfarin and comparable to LMWH (< 2% per annum). Bleeding is frequently lower GI in nature and at surgical sites (at a similar rate to warfarin). Intracerebral bleeding is less frequent than with warfarin because DOACs do not inhibit factor VII, which is the dominant mediator of haemostasis in the cerebral circulation.

Because of the relatively short half-lives of DOACs, time and supportive measures (including infusion of clotting factors and prothrombin complex concentrate) are usually sufficient to deal with major drug-related coagulopathic bleeding, which should settle within 12–24 hours except in the presence of renal dysfunction. The four-factor prothrombin complex concentrates (PCC) are substantially more effective than FFP if urgent restoration of haemostasis is required. Should surgical urgency not permit a delay until drug activity has diminished, these agents should be available in theatre for early use if coagulopathic bleeding starts. Prophylactic use of PCC or specific reversal modalities should only be considered for procedures with prohibitive bleeding risk (e.g. neurosurgery in patients at high risk of bleeding or renal dysfunction and with clinical and laboratory evidence of critically high levels of anticoagulant). PCC, at doses > 25 IU/kg achieve a 66% moderate-to-good response rate in bleeding patients on Xa inhibitors; largely due to factor II in PCC bypassing the drug target site. The response rate with dabigatran is poorer since the target site of the drug is thrombin itself. Specific reversal (discussed below) is therefore recommended as a first-line intervention for severe dabigatran-related bleeding. The role of fibrinogen concentrates in the cessation of bleeding from all DOACs is still under investigation.

## Antidotes for uncontrollable DOAC-related bleeding

Early oral activated charcoal and haemodialysis may be of use in known cases of recent dabigatran ingestion. Specific antidotes have now been registered for the rare instance of otherwise uncontrollable DOAC-related bleeding:

1. Idarucizumab (Praxbind) for dabigatran is available in South Africa. This is a humanised monoclonal antibody fragment that binds and removes dabigatran from its site of action, eliminating its plasma presence within minutes and its anticoagulant effect within 2.5 hours. A dose of 5 g intravenous over 5–10 minutes will abort the majority of dabigatran-related bleeds. A repeat dose may be given if needed. It has no

intrinsic prothrombotic effect. This treatment is very costly at around R50 000 per treatment course.

2. Andexanet alfa (Ondexxya) is an inactive recombinant factor Xa analogue that acts as a surrogate target and binds and sequesters Xa antagonists (proven effect for rivaroxaban and apixaban thus far), rapidly reducing their activity in healthy volunteers. Trials in patient populations suggest an 89% successful reversal rate. Bolus doses of 400–800 mg are given at 30 mg/min, followed by ongoing infusions of 400–800 mg over the next two hours. Hypersensitivity-type infusion reactions are common. There is a prothrombotic signal in 30 days after its use. The cost per utilisation is that of a new, medium size car. This agent is still unavailable in South Africa.
3. Ciraparantag is a small synthetic cationic molecule, shown to bind to and reverse the effect of heparins and DOACs. It remains in phase 2 trials.

Irrespective of the management strategy employed to prevent or control bleeding, it is essential to understand that the initial indication for a DOAC persists and that anticoagulation must be resumed at the earliest opportunity to curtail intrinsic and reversal-related prothrombotic influences. In the non-emergent surgical setting, drug discontinuation for three half-lives should ensure that the drug effect is inconsequential. It is important to factor in patient risk factors, particularly renal function when making this calculation.

## Monitoring of DOACs

**Table III:** Available laboratory assays for DOACs

| | Dabigatran | Anti-Xa |
|---|---|---|
| INR | No | Suggestive but may yield false negatives with rivaroxaban<br>More predictable concentration-response derangement with other Xa antagonists |
| aPTT | Suggestive at peak drug levels, aPTT prolonged 1.5–1.8 times | Weakly suggestive |
| Thrombin time | Sensitive concentration-response relationship | Relatively to entirely insensitive |
| Ecarin clotting time | Sensitive | No |
| Specific anti-Xa assay | No | Available internationally<br>Quantitative |
| Fibrinogen | Levels affected but not quantitative | No |

Notes on Table III:

- Other than specific anti-Xa analysis, tests are relatively unpredictable in terms of the drug concentrations but helpful in identifying the drug group.
- A combination of tests yields greater accuracy.
- Viscoelastic tests may indicate the extent of coagulopathy in severe intoxication but will not identify the drug responsible. Since they are provoked tests, they may underestimate the extent of the coagulopathy. Despite this, the tests may reveal other coagulation abnormalities (e.g. fibrinolysis, which can be used to guide the administration of specific procoagulants, such as tranexamic acid).


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## References


1. Intagliata NM, Maitland H, Caldwell SH. Direct oral anticoagulants in cirrhosis. Curr Treat Options Gastroenterol. 2016;14(2):247-56. https://doi.org/10.1007/s11938-016-0092-0.
2. Joubert I, Beeton A. Chapter 21. In: Milner A, Welch E, editors. Applied pharmacology in anaesthesiology and critical care. 2nd ed.
3. Hurst K, Lee R, Handa A. Quick reference guide to the new oral anticoagulants. J Vasc Surg. 2016;63(6):1653-7. https://doi.org/10.1016/j.jvs.2016.02.054.
4. Laslo CL, Bacalbasa N, Stanescu AMA, et al. New oral anticoagulants - possible extension to other indications (review). Exp Ther Med. 2020;20(3):2401-5. https://doi.org/10.3892/etm.2020.8713.
5. Spahn DR, Beer J-H, Borgeat A, et al. NOACs in anesthesiology. Transfus Med Hemother. 2019;46(4):282-93. https://doi.org/10.1159/000491400.
6. Dubois V, Dincq A-S, Douxfils J, et al. Perioperative management of patients on direct oral anticoagulants. Thromb J. 2017;15(14). https://doi.org/10.1186/s12959-017-0137-1.
7. Shah SB, Pahade A, Chawla R. Novel reversal agents and laboratory evaluation for direct-acting oral anticoagulants (DOAC): an update. Indian J Anaesth. 2019;63(3):169-81. https://doi.org/10.4103/ija.IJA_734_18
8. Chen A, Stecker E, Warden BA. Direct oral anticoagulant use: a practical guide to common clinical challenges. J Am Heart Assoc. 2020;9(13):e017559. https://doi.org/10.1161/JAHA.120.017559.
9. Grottke O, Schulman S. Four-factor prothrombin concentrate for the management of patients receiving direct oral activated factor X inhibitors. Anesthesiology. 2019;131(5):1153-65. https://doi.org/10.1097/ALN.0000000000002910.
10. Cuker A, Burnett A, Triller D, et al. Reversal of direct oral anticoagulants: guidance from the anticoagulation forum. Am J Hematol. 2019;94(6):697-709. https://doi.org/10.1002/ajh.25475.
11. Eikelboom JW, Kozek-Langenecker S, Exadaktylos A, et al. Emergency care of patients receiving non-vitamin K antagonist oral anticoagulants. Br J Anaesth. 2018;120(4):645-56. https://doi.org/10.1016/j.bja.2017.11.082.
12. Kim K-S, Song JW, Soh S, Kwak Y-L, Shim J-K. Perioperative management of patients receiving non-vitamin K antagonist oral anticoagulants: up-to-date recommendations. Anesth Pain Med (Seoul). 2020;15(2):133-42. https://doi.org/10.17085/apm.2020.15.2.133.