

**Addendum to the guideline on the peri-operative management of
anticoagulation and antiplatelet therapy
(British Journal of Haematology. 2016;175:602-613)**

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Direct Oral Anticoagulants

So far, the peri-operative/peri-procedural management of the direct oral anticoagulants (DOACs) has largely been guided by pharmacokinetic data, with recommended periods of drug interruption based on drug-specific half-lives, an individual's renal function, and the assessment of operative or procedural bleeding risk.

The Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) study prospectively enrolled 3007 patients with atrial fibrillation receiving anticoagulation with a DOAC (apixaban 41.8%, rivaroxaban 36%, dabigatran 22.2%), who were planned to have an elective procedure/surgery that required anticoagulation interruption¹. The study used a simplified and standardised management protocol (see figure below). Patients undergoing a low bleeding risk procedure omitted the DOAC for one day prior to the procedure (i.e. last dose to be taken at least 36 hours prior to procedure), and those undergoing a high bleeding risk procedure omitted the DOAC for 2 days (i.e. last dose to be taken at least 60 hours prior to procedure). Due to its almost exclusive renal elimination, patients on dabigatran who had a creatinine clearance (CrCl) of < 50mL/min had double the period of pre-procedural interruption (i.e. 2 days and 4 days for low and high bleeding risk procedures respectively). DOACs were resumed one day after a low bleeding risk procedure and 2-3 days after a high bleeding risk procedure. Bridging with heparin was not employed prior to the procedure, although post-procedural use of prophylactic heparin was permitted in patients at high risk of venous thromboembolism until DOAC resumption.

DOAC	Procedural bleeding risk	Perioperative DOAC management									
		Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day +1	Day +2	Day +3	Day +4
Direct Xa Inhibitors and Dabigatran (CrCl ≥ 50mL/min)	Low	✓	✓	✓	✓	OMIT	Day of procedure Do not administer any DOAC	✓	✓	✓	✓
	High	✓	✓	✓	OMIT	OMIT		OMIT	Resume day +2 or day +3		✓
Dabigatran (CrCl < 50mL/min)	Low	✓	✓	✓	OMIT	OMIT		✓	✓	✓	✓
	High	✓	OMIT	OMIT	OMIT	OMIT		OMIT	Resume day +2 or day +3		✓

✓ - DOAC may be taken or administered

Adapted from Douketis et al, JAMA Intern Med. 2019;179(11):1469-78

Procedures classified as high risk included 230 patients (7.6%) who had neuraxial anaesthesia. Both 30-day rates of major bleeding (apixaban 1.35%, dabigatran 0.90%, rivaroxaban 1.85%) and arterial thromboembolic events (apixaban 0.16%, dabigatran 0.60%, rivaroxaban 0.37%) were low. Pre-operative residual DOAC drug levels were measured in 2541 patients (84.5%). Almost 99% of patients undergoing a high bleeding risk procedure had drug levels below 50ng/mL, and over 85% had levels below 30ng/mL.

Recommendations:

- **For direct Xa inhibitors, omit the anticoagulant for one day prior to low bleeding risk procedures and for 2 days prior to high bleeding risk procedures (1C).**
- **In patients with CrCl of ≥ 50 mL/min, omit dabigatran for one day prior to low bleeding risk procedures and 2 days prior to high bleeding risk procedures (1C).**
- **In patients with CrCl < 50 mL/min, omit dabigatran for 2 days prior to low bleeding risk procedures and for 4 days prior to high bleeding risk procedures (1C).**
- **Resume the DOAC one day after a low bleeding risk procedure and 2-3 days after a high bleeding risk procedure. Consider daily prophylactic heparin for patients at high risk of venous thrombosis prior to DOAC recommencement (2C).**

Peri-operative Reversal of Direct Xa Inhibitors with Andexanet Alfa

Currently, there is no evidence to support the use of andexanet alfa for the reversal of these anticoagulants in the setting of elective or emergency surgery². The recommendation in the guideline that andexanet alfa should be used for anticoagulation reversal in the peri-operative setting is withdrawn.

Disclaimer

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References:

1. Douketis JD, Spyropoulos AC, Duncan J, Carrier M, Le Gal G, Tafur AJ, et al. Perioperative Management of Patients With Atrial Fibrillation Receiving a Direct Oral Anticoagulant. *JAMA Intern Med.* 2019;179(11):1469-78.
2. Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, et al; ANNEXA-4 Investigators. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. *N Engl J Med.* 2019 Apr 4;380(14):1326-35.