# Making up for Lost Time: Perioperative Direct Oral Anticoagulant Assay Measurements

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#### Abstract

Current evidence and guidelines suggest a time-based approach to the perioperative administration of direct oral anticoagulants (DOAC). Quantifying haematological concentrations of DOACs is possible however, the evidence suggests a large inter-individual variation and unlike INR is to warfarin, it does no correlation with anticoagulant effect. There are multiple confounding factors that affect DOAC metabolism and may result in a cohort of patients who satisfy one guideline (time based) but are ruled out using an objective, serum quantity-based guideline. The unsubstantiated use of DOAC level testing to inform surgical triage and use of reversal agents preoperatively may increase harm to patients.

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Perioperative thromboembolic prophylaxis and treatment was primarily achieved with warfarin or in some cases heparin. Recently, DOACs have been commonly used as alternatives to Warfarin due to efficacy with fixed-dose regimens which abrogates the need for laboratory monitoring.<sup>1</sup> Consequently, physicians and surgeons commonly encounter perioperative patients who are being anticoagulated with DOACs. However, there is limited evidence on the efficacy and safety of DOACs in the perioperative period and best practice remains uncertain. Surgeons must consider the balance between avoiding bleeding complications of surgery versus the prevention of thromboembolic events. The anticoagulation effects of Warfarin can be monitored with the International Normalised Ratio (INR). However, there does not exist a similarly reliable marker to guide surgeons in assessing the peri- and intra-operative anticoagulant effect, triaging time to surgery and administration of reversal agents.

Quantifying haematological concentrations of DOACs is possible, however, the primary variable utilised to assess the safety of DOACs peri-operatively is time since cessation. The PAUSE trial is one such example, where DOACs were omitted for 1 or 2 days pre-operatively depending on preoperative bleeding risk, with no analysis of DOAC serum titre effect on surgical outcome.<sup>2,3</sup> Most other studies investigating perioperative DOAC implications are post hoc sub analyses of prior RCTs or retrospective assessment of registries that similarly assess outcomes according to preoperative cessation time rather than serum concentrations.<sup>4</sup> Consequently, guidelines for anticoagulated surgical patients generally advise proceeding to surgery in accordance with the time since last dose, rather than an anticoagulant or pharmacokinetic marker.

Currently, unlike INR and warfarin, there is no clear link between DOAC serum titres and efficacy or safety. There is a paucity of data describing the relationship between DOAC assay concentrations and clinical outcomes beyond an 'on therapy' range.<sup>5</sup> There is however some emerging evidence to suggest a correlation between plasma concentrations and clinical outcomes. Lower trough levels of DOACs are associated with an increased risk of ischaemic events<sup>6</sup> whilst more modest serum titres are associated with and increased risk of bleeding<sup>7,8</sup>. Whilst this evidence is growing and requires synthesis to better inform the possibility of changes in clinical practice according to serum titres, none of outcomes however were demonstrated in perioperative patients. Notably, the only strong evidence for DOAC levels in surgery demonstrate a majority of pre-surgery assays of <30-50 ng/ml<sup>2,9</sup> Accordingly, current expert consensus recommends that DOAC concentrations of <50 ng/ml are likely to be safe for surgery.<sup>10</sup> However, the validation of this cut-off level is limited, and surgeons may be cautious when using this in clinical practice. It is possible that the safe threshold varies significantly according to the surgical procedure that is being performed.

The lack of evidence regarding safe perioperative DOAC levels raises concern given the many confounding factors that influence DOAC metabolism. It is known that at least gender, weight, renal function and age are associated with higher than expected preoperative serum assays however, many other studies fail to consider the numerous confounding factors.<sup>3</sup> In patients with renal impairment, the renally-excreted DOACs (dabigatran and rivaroxaban) confer a prolonged elimination time. The pharmacodynamic implications of increased adiposity raises uncertainty in the safety of DOACs in patients >120kg or BMI >40 due to lack of supporting evidence. Surgical advances have also allowed for the provision of bariatric procedures and in general, safely performing operations on increasingly comorbid patients with significant polypharmacy, which both, may affect the pharmacokinetics and pharmacodynamics of DOACS, possibly reducing the reliability of dosing interruption guidelines.(Table 1) Further, the validity of using of the last dose time in emergency scenarios, situations where a reliable history is not possible and using DOAC assays as a surrogate is unclear.

Pre-operative testing of anticoagulant levels to identify patients with serum concentrations within a validated surgical reference range could help guide surgery timing and DOAC reversal. Despite the observation in 2017 that an assessment of individual anticoagulant effect is required,<sup>9</sup> a therapeutic reference range for DOACs continues to remain nebulous and there is still minimal research that describes a relationship between DOAC assay levels and operative outcomes, particularly in patients undergoing emergency operations. The unsubstantiated use of DOAC level testing to inform surgical triage and use of reversal agents preoperatively may

increase harm to patients by either inappropriately delaying or proceeding with the operation. Performing assays on comorbid individuals may introduce a cohort of patients who satisfy one guideline (time since last dose) but are contraindicated according to another (DOAC assay titre). Or, vice-versa, there may be a cohort of patients who 'washout' a DOAC quicker, satisfying the DOAC assay titre guideline without sufficient time since last dose. There is potential for significant changes to practice when utilising validated surgical DOAC concentration reference ranges and acknowledging their consequent perioperative implications on bleeding and thrombosis. Therefore, research in this area is urgently required so that perioperative practice can rely on measurements that are scientifically validated and globally applicable.

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Table 1: Common medications and their effect on DOAC metabolism

Class of drug	Inhibitor (increase time of elimination)	Inducer (decrease time of elimination)
Cardiovascular	Amiodarone, Carvedilol, Verapamil, Ticagrelor	Digoxin
Antibiotic	Erythryomycin, Azithromycin, Clarithromycin	Rifampicin
Anti-epileptic		Carbamazepine, Phenytoin
Antifungal	Ketoconazole, Fluconazole	
Retroviral	Ritonavir	
Analgesia	NSAIDs	Colchicine

Class of drug	Inhibitor (increase time of elimination)	Inducer (decrease time of elimination)
Other	Cannabidiol, Tamoxifen	St. John's Wort, Dexamethasone, Tacrolimus