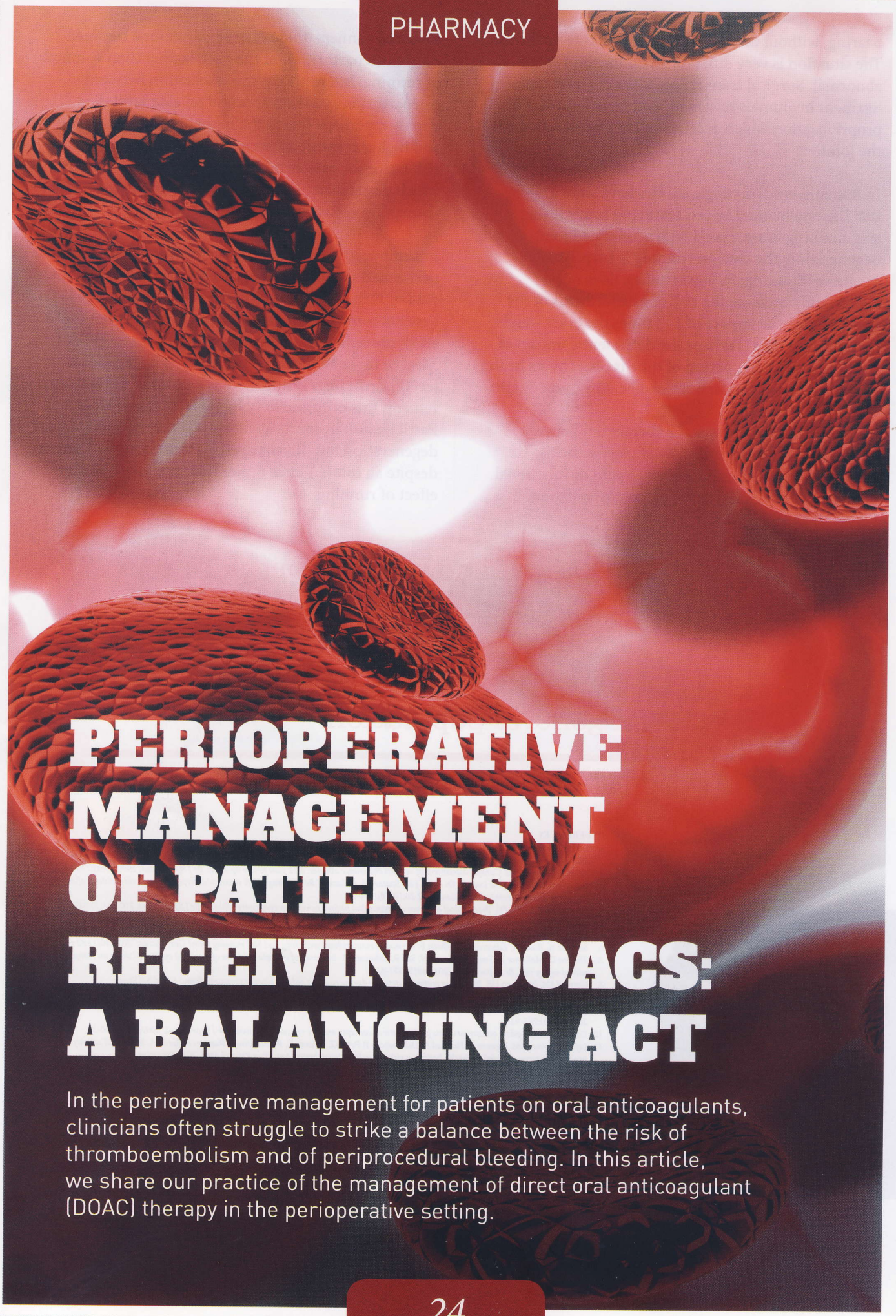


PERIOPERATIVE MANAGEMENT OF PATIENTS RECEIVING DOACS: A BALANCING ACT

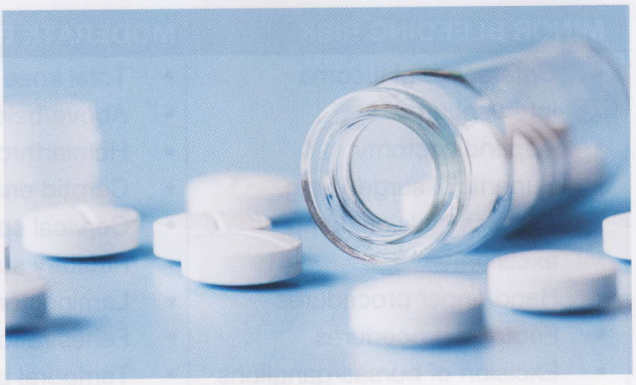
In the perioperative management for patients on oral anticoagulants, clinicians often struggle to strike a balance between the risk of thromboembolism and of periprocedural bleeding. In this article, we share our practice of the management of direct oral anticoagulant (DOAC) therapy in the perioperative setting.

Overview of DOACs

Oral anticoagulants are indicated for prophylaxis and treatment of thromboembolism and stroke prevention in patients with nonvalvular atrial fibrillation. Vitamin K antagonists like warfarin were the mainstay for conditions requiring oral anticoagulantion.[1] However, warfarin use is complicated by the need for frequent monitoring and numerous interactions with foods, herbs and drugs.[2]

DOACs were developed to overcome the shortcomings of warfarin. Since their regulatory approval in 2010, they have been popular with physicians and patients largely due to the simplified monitoring requirement and minimal drug-food and drug-herb interactions.

DOACs are classified according to their mechanism of action. Direct thrombin inhibitors (such as dabigatran) target the enzymatic activity of thrombin while factor Xa inhibitors (e.g. rivaroxaban, apixaban, edoxaban and betrixaban) block the activity of activated clotting factor Xa. Currently, only dabigatran (Pradaxa®, Boehringer Ingelheim Singapore Pte Ltd), rivaroxaban [Xarelto®, Bayer (South East Asia) Pte Ltd] and apixaban (Eliquis®, Pfizer Pte Ltd) are available in Singapore.



Factors to consider in perioperative management of elective procedures

Factors to consider in the perioperative management of patients treated with DOACs are thromboembolic risk of the individual, bleeding risk of the procedure and duration of DOAC interruption required before the procedure.

Thromboembolic risk

For patients with a high risk of repeat thrombotic events (e.g. stroke or deep vein thrombosis within the recent month), postponement of the surgery should be considered.[4]

Bleeding risk of the procedure

Based on Tan Tock Seng Hospital (TTSH)'s Pre-Admission Counselling and Evaluation (PACE)

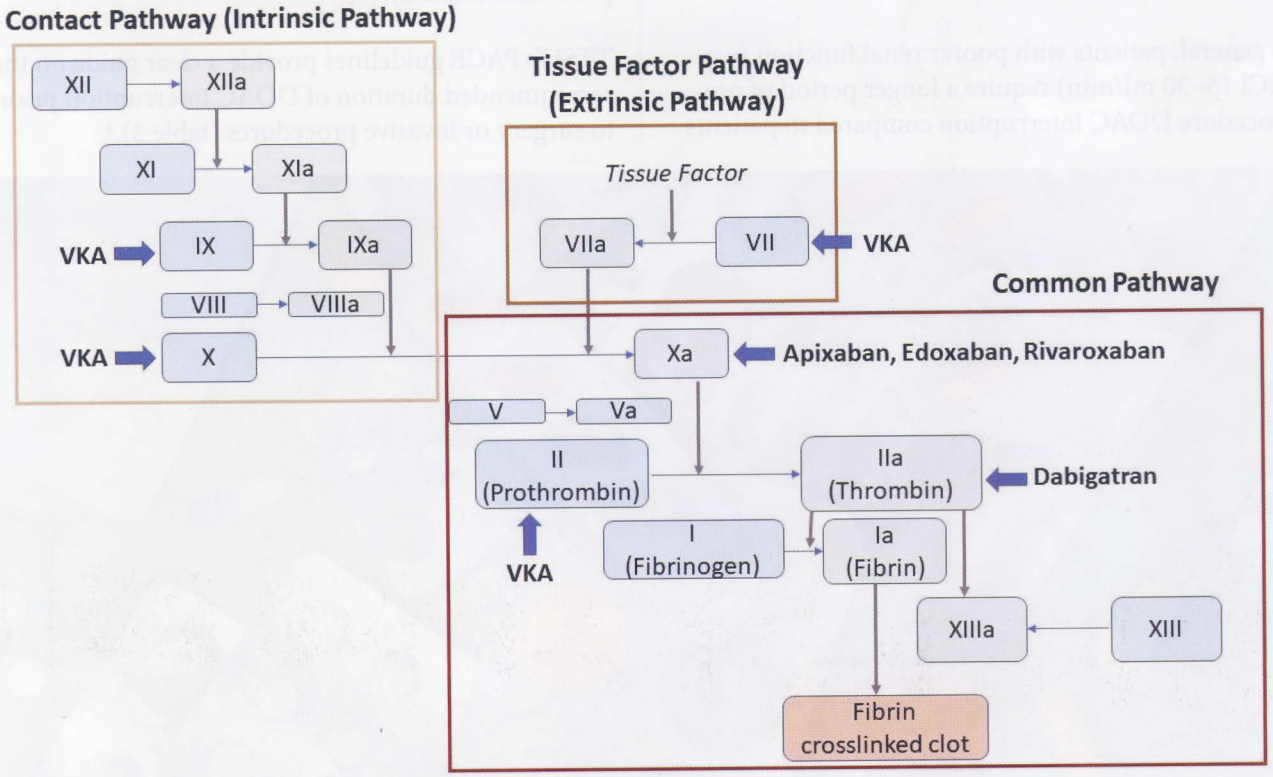


Figure 1. Mechanism of action of DOACs on the clotting cascade.
Diagram modified from Raval AN, et al.[3]

MINOR BLEEDING RISK	MODERATE BLEEDING RISK	HIGH BLEEDING RISK
• Cataract or glaucoma intervention • Appendicectomy • Superficial surgery (e.g. abscess incision, lump excision) • Hand/finger procedures • Foot/toe procedures • Excision of bursas/ganglions • Tendon repairs • Rigid cystoscopy or double J-stent insertion • Mastoidectomy • External ventricular drain / ventriculoperitoneal shunt	• Total knee arthroplasty • Above/below knee amputation • Hemiarthroplasty • Carotid endarterectomy • Cervical spine surgery • Pituitary surgery • Laminectomy 1–2 levels • Fenestration and discectomy • Temporal bone resection • Thyroidectomy • Urethroplasty • Orchidectomy • Arteriovenous fistula – creation, revision	• Craniotomy • Open reduction internal fixation of pelvic bones • Revision of spinal instrumentation • Spinal decompression >2 levels • Revision hip/knee arthroplasty • Total hip arthroplasty • Nasopharyngectomy • Major head and neck surgery • Prostatectomy • Total gastrectomy • Biliary bypass, Whipple's • Aortic procedures

Table 1. Bleeding risk of elective surgical procedures[4]

Guidelines,[4] bleeding risk of surgical procedures can be stratified into minor, moderate or high. Examples of procedures and the corresponding bleeding risk are shown in table 1.

When to stop administrating DOAC prior to procedure

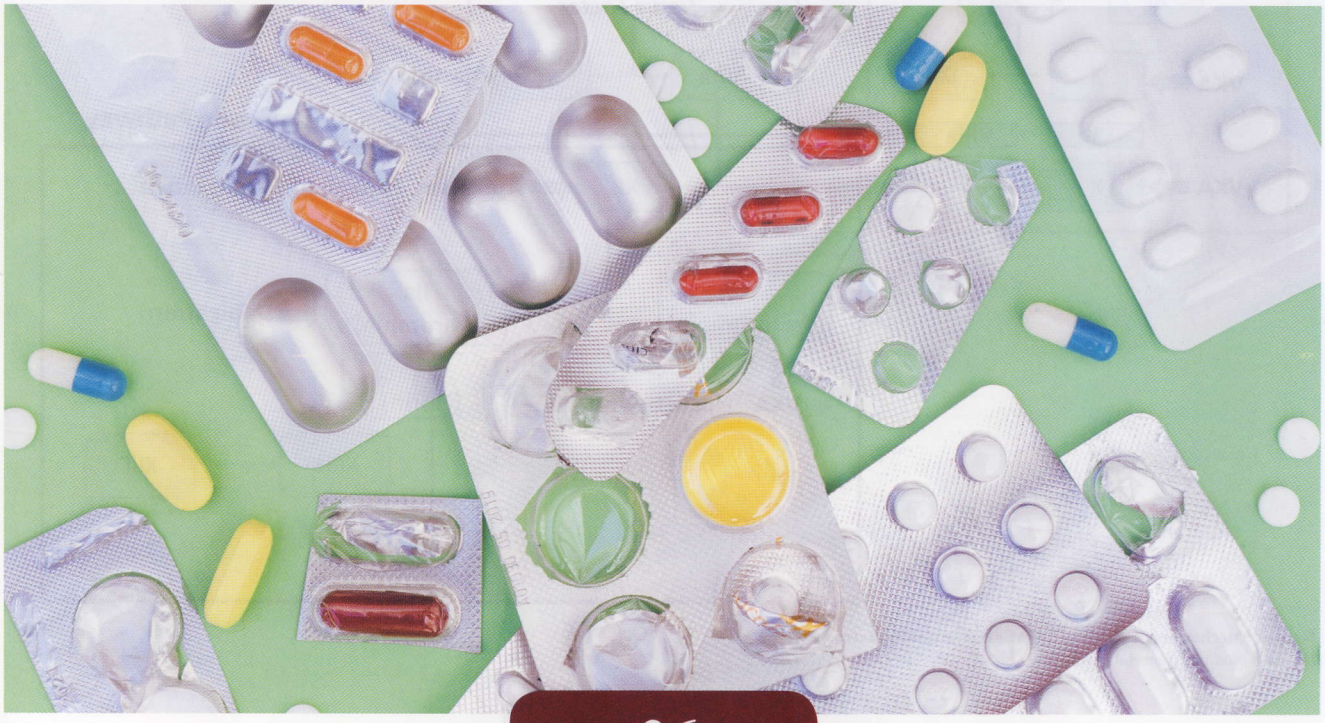
The time period to withhold DOAC therapy prior to a procedure depends on the patient's renal function (represented by the creatinine clearance), the half-life of the DOAC and the bleeding risk of the procedure.

In general, patients with poorer renal function (e.g. CrCl 15–30 ml/min) require a longer period of pre-procedure DOAC interruption compared to patients with good renal function (e.g. CrCl >50 ml/min) to allow most of the drug to be eliminated prior to the procedure (table 2).

DOAC	$t_{1/2}$
Dabigatran	12–17 hours
Rivaroxaban	5–9 hours (young) 11–13 hours (elderly)
Apixaban	12 hours

Table 2. Elimination half-life ($t_{1/2}$) of DOACs

TTSH's PACE guidelines provide a clear guide on the recommended duration of DOAC interruption prior to surgery or invasive procedures (table 3).[4]



	Procedures with Low Bleeding Risk		Procedures with Moderate/ High Bleeding Risk*	
Creatinine Clearance (CrCl)	Dabigatran	Apixaban/ Rivaroxaban	Dabigatran	Apixaban/ Rivaroxaban
CrCl >50 ml/min	1 day	1 day	2 days	2 days
CrCl 30–50 ml/min	2 days	1 day	4 days	2 days
CrCl <30 ml/min	4 days**	2 days	6 days**	4 days

DOAC, direct oral anticoagulant; PACE, Pre-Admission Counselling and Evaluation
*Patients are required to undergo a pre-operative prothrombin time and activate partial thromboplastin time check at the Day Surgery Centre 1 hour prior to the procedure
**Dabigatran is not indicated for patients with CrCl <30 ml/min

Table 3. Recommendations for DOAC interruption prior to surgical procedures according to TTSH PACE Guidelines

For procedures with very high bleeding risk (e.g. spinal anaesthesia, epidural anaesthesia or lumbar puncture), some guidelines suggest a longer interruption period of 5 days for dabigatran and 3 days for rivaroxaban and apixaban.[5]

Bridging therapy with parenteral anticoagulants

Given the predictable response of DOACs and their short half-lives, preoperative bridging with parenteral anticoagulants like low molecular weight heparin or heparin is generally not recommended as they increase the risk of bleeding without providing much clinical benefit.[5,6]

Post-operative resumption of DOACs

After the procedure, DOACs should be recommenced when haemostasis is secured to reduce the risk of thromboembolism. The recommended time period for post-operative resumption of DOACs is 24 hours for procedures with low bleeding risk. For procedures with high bleeding risk, DOACs can be resumed 48 to 72 hours post-procedure.[4] DOACs should be resumed at their usual dose as there is limited evidence on the safety and efficacy of using reduced dose for post-operative patients.[5]

Management of DOACs in emergencies

When emergency surgery is required, the DOAC should be discontinued immediately. Urgent blood investigations should be ordered to guide subsequent management: full blood count, renal panel, liver panel, prothrombin time (PT), activate partial thromboplastin time (aPTT), fibrinogen level, thrombin time (TT, for patients receiving dabigatran), and anti-Factor Xa levels (for patients receiving rivaroxaban or apixaban).[7]

Reversal strategies include administration of antidotes, reduction of intestinal absorption, increasing DOAC clearance and administration of coagulation factors (table 4).[5]

DOACs were developed to overcome the shortcomings of warfarin. Since their regulatory approval in 2010, they have been popular with physicians and patients largely due to the simplified monitoring requirement and minimal drug-food and drug-herb interactions.

MILD BLEEDING	MODERATE-SEVERE BLEEDING	LIFE-THREATENING BLEEDING
• Local measures (e.g. anti-fibrinolytics for gum bleeds) • Delay next dose or withhold one dose of DOAC	• Symptomatic treatment • Mechanical compression of bleeding site • Surgical or radiological intervention • Fluid replacement and haemodynamic support • Blood product transfusion (for blood loss or thrombocytopenia or coagulopathy) • Consider IV tranexamic acid • Oral activated charcoal (if last ingestion was within 3 hours) • Dialysis for dabigatran in cases of severe renal failure	• Use of reversal agents (e.g. idarucizumab, andexanet alfa) • Blood product transfusion • Coagulation factors products [e.g. prothrombin complex concentrate (PCC), activated PCC (aPCC, FEIBA), rFVIIa)]

Table 4. Management of bleed in patients receiving DOACs

Antidotes for DOACs

Idarucizumab

Idarucizumab (Praxbind®) is a fully humanised monoclonal antibody fragment that specifically binds to dabigatran and its metabolites with a 350-time higher affinity than that of thrombin to dabigatran.[8] It was approved by the United States Food and Drug Administration (FDA) in October 2015 for reversal of dabigatran's anticoagulant effect in emergency surgery, urgent procedures, or in cases of life-threatening or uncontrolled bleeding. It received approval by the Health Sciences Authority in Singapore in 2016.

The drug is available in 2.5 g/50 ml vials and the recommended dose is 5 g (two vials) administered intravenously, either as continuous infusions or as a single bolus dose. Its effect can be observed within minutes; in the RE-VERSE AD trial, the median time to bleeding cessation was approximately 9.8 hours.[8]

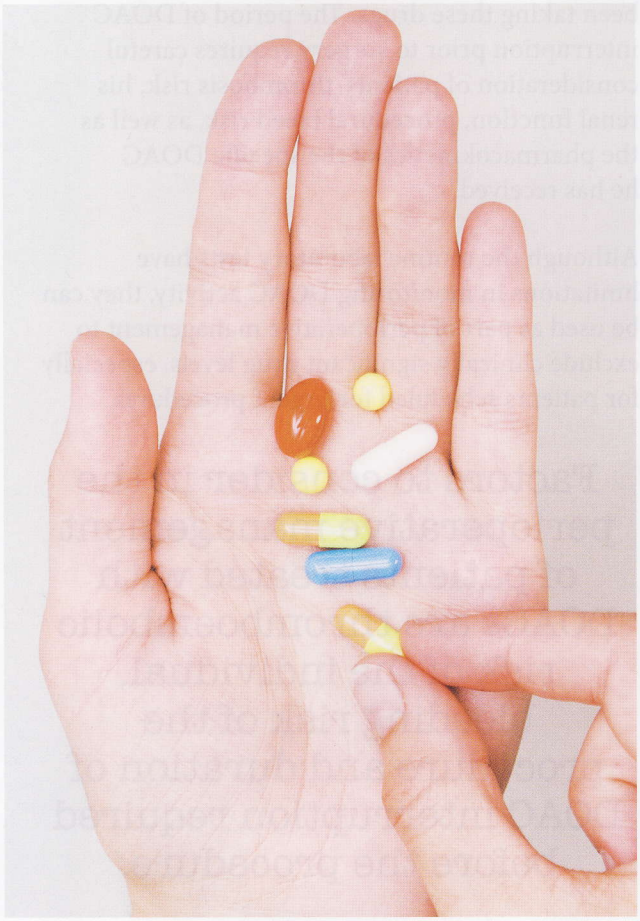
Andexanet alfa

More recently, in May 2018, Andexanet alfa (Andexxa®) received FDA approval for reversal of life-threatening or uncontrolled bleeding in patients receiving rivaroxaban and apixaban. This is a recombinant modified human factor Xa protein that acts as a decoy and binds to rivaroxaban and apixaban to inhibit their action. It has a rapid action onset of 2 to 5 minutes, and has been shown to successfully reverse factor Xa inhibition in healthy volunteers.[9]

The drug is given as a bolus followed by an infusion, with its dose determined by the type of factor Xa inhibitor used and timing of last ingestion (for rivaroxaban). Unfortunately, the antidote is not available in Singapore currently.

Ciraparantag (PER 977)

Ciraparantag is a small synthetic molecule that is designed as a broad spectrum antidote for oral



In general, routine tests are not specific to DOACs. While clotting times may detect the presence of clinically significant levels of DOACs, they cannot accurately reflect drug levels and their corresponding anticoagulant effect. It should be noted that the tests can also be prolonged in many other situations (e.g. bleeding states or disseminated intravascular coagulation) apart from DOAC ingestion.

factor Xa inhibitors, thrombin inhibitors and low molecular weight heparin.[10] Unlike other antidotes, it binds to anticoagulants through ionic charge interaction. The drug is currently still in its developmental phase.

Limitations of laboratory tests

Although routine coagulation monitoring is not required for DOACs, there are some scenarios whereby laboratory monitoring may be useful. For example, routine coagulation tests can be used to exclude clinically significant levels of DOACs in bleeding patients or those who require urgent surgical interventions. When interpreting the coagulation test results, it is important to note the difference between the time of the last DOAC intake and time of blood sampling.

Prothrombin time

Dabigatran has negligible effect on PT, while factor Xa inhibitors like rivaroxaban and apixaban can prolong PT. However, the result is dependent on the type of reagents used. In addition, certain PT reagents are less sensitive to apixaban compared to rivaroxaban. As such, a normal PT result does not exclude residual anticoagulant effect of any DOAC.

Activated partial thromboplastin time

In contrast to PT, aPTT is prolonged in the presence of dabigatran, and may be used to detect clinically significant plasma levels of the drug. However, the result is dependent on the sensitivity of the assay reagent, and a normal aPTT result does not exclude the presence of low drug concentrations. The test is also unable to exclude the activity of rivaroxaban and apixaban.

Thrombin time

The presence of dabigatran in serum plasma can be detected by TT, which is highly sensitive to the drug; a normal TT indicates the absence of the drug in patients. Rivaroxaban and apixaban, however, have no effect on TT.

Anti-factor Xa (Anti-Xa)

Since rivaroxaban and apixaban directly inhibit factor Xa, their levels can be quantitatively measured using anti-Xa chromogenic assays. Anti-Xa activity correlates with the various factor Xa inhibitors in a linear fashion, and a normal anti-Xa level excludes clinically significant levels of the drugs.

Ideally, the assays should be calibrated to the respective factor Xa inhibitors. However, such

assays may not be readily available. In the absence of these drug-specific assays, anti-Xa assays that are calibrated to low molecular weight heparins may be used but the measured drug concentrations may vary among different assays and results can be affected by the presence of heparin. It should also be noted that dabigatran has no effect on anti-Xa activity.

In general, routine tests are not specific to DOACs. While clotting times may detect the presence of clinically significant levels of DOACs, they cannot accurately reflect drug levels and their corresponding anticoagulant effect. It should be noted that the tests can also be prolonged in many other situations (e.g. bleeding states or disseminated intravascular coagulation) apart from DOAC ingestion. Hence, the results should be interpreted with caution and routine monitoring of anticoagulant activity in stable patients is not recommended.[4]

Conclusion

In summary, with the increasing use of DOACs, it is important for clinicians to know the perioperative management of patients who have been taking these drugs. The period of DOAC interruption prior to surgery requires careful consideration of patients' thrombosis risk, his renal function, procedural bleed risk, as well as the pharmacokinetics of the specific DOAC he has received.

Although the routine laboratory tests have limitations in monitoring DOAC activity, they can be used as part of perioperative management to exclude clinically significant drug levels, especially for patients scheduled for urgent procedures.

Factors to consider in the perioperative management of patients treated with DOACs are thromboembolic risk of the individual, bleeding risk of the procedure and duration of DOAC interruption required before the procedure.

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