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Management of anticoagulant treatment in patients who need non-cardiac surgery

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Abstract

The periprocedural management of anticoagulation in patients who require non-cardiac surgery is a common clinical problem due to the aging of the population associated with both an increase in the use of anticoagulants and a higher need for surgery. If surgery is needed in a patient on anticoagulant therapy, regardless of the drug used, it is necessary to consider the urgency of the surgical procedure and the balance between the thromboembolic risk related to the discontinuation of therapy and the hemorrhagic risk related to the surgical procedure itself. Finally, a topic still much discussed that derives from the combined evaluation of these factors is the possible indication of a bridge therapy ("bridging anticoagulation") to limit the thromboembolic risk related to the discontinuation of treatment. The different strategies in patients under antivitamin K and direct oral anticoagulants are reviewed.

Keywords: Antivitamin K, direct oral anticoagulants, surgery, complications

INTRODUCTION

As the population ages, the already high number of patients taking oral anticoagulant therapy is inevitably expected to increase. At the same time, in subjects over 65 years of age, the probability of undergoing surgery is constantly growing. It has been calculated that in the first two years following the start of anticoagulant treatment, about a quarter of patients require discontinuation of therapy for a scheduled intervention[1,2].

Over the last decade, direct anticoagulants have largely replaced drugs with antivitamin K action, which nevertheless retain well-defined indications. The anticoagulant action of dicoumarols is linked to the ability to interfere with epoxide reductase, which allows the conversion of vitamin K into its 2.3 epoxide [Figure 1]. This prevents the gamma-carboxylation process of glutamate residues of factors II, VII, IX, and X[3,4]. Vitamin K is also essential in the synthesis of C and S proteins, endowed with anticoagulant action. The short half-life of protein C means that in the first phase of treatment with warfarin, a pro-coagulant effect may be observed, which is why treatment with heparin is necessary in the induction phase of treatment with vitamin K antagonists.

Numerous studies have shown a therapeutic efficacy of direct anticoagulants comparable to warfarin and, on average, a lower hemorrhagic risk[5,6]. They also have the considerable advantage of not requiring periodic monitoring [Table 1].

If surgery is needed in a patient on anticoagulant therapy, regardless of the drug used, it is necessary to consider the urgency of the surgical procedure to which the patient must be subjected and the balance between the thromboembolic risk related to the discontinuation of therapy and the hemorrhagic risk related to the surgical procedure itself. Finally, a topic still much discussed that derives from the combined evaluation of the factors mentioned is the possible indication of a bridge therapy ("bridging anticoagulation") to limit the thromboembolic risk related to the discontinuation of treatment, but which is inevitably associated with an increased hemorrhagic risk related to the surgical procedure.

Stratification of thromboembolic risk

Risk stratification is reported for the three main indications for anticoagulant therapy [Table 2]. In patients at high thromboembolic risk at the time of discontinuation of anticoagulant therapy, treatment with heparin, unfractionated or low molecular weight, as a bridge therapy may be indicated to limit the risks of thrombotic complications.

The introduction of a more accurate thromboembolic risk scheme, for example, CHA_2DS_2VASc, does not seem to offer substantial additional elements. It is therefore still unresolved, for patients with NVAF, whether the indication for a bridge therapy is useful to consider an absolute cut-off value or, alternatively, to consider at high risk of thrombotic events, essentially those patients who have had a previous cerebral or systemic embolic event.

Estimation of bleeding risk

In the assessment of bleeding risk, individual factors (age, renal function, recent ischemic or hemorrhagic events, concomitant treatment with antiplatelet agents, thrombocytopenia, and liver disease) and factors related to the procedure (type of procedure, possibility to obtain adequate hemostasis, and the district involved by surgery) should be considered [Table 3]. The different patterns reported by the guidelines or consensus conferences provide a distinction in procedures with negligible, low-moderate, and high risk of bleeding[7].

Non-complex dental surgery, most ophthalmology and dermatological surgery, and endoscopic procedures that do not require biopsy can be performed without any interruption of anticoagulant therapy. In patients with indications for surgery, in whom the hemorrhagic risk of the procedure is incompatible with the maintenance of anticoagulation, this should be discontinued. The time of discontinuation is related to the half-life of the anticoagulant drug.

Table 1. Main difference between direct anticoagulants and antivitamin K

	Antivitamin K	Direct anticoagulants
Onset of action	Long (days)	Short (2-3 h)
Duration of action	Long	Brief
Food interference	Yes	Limited (rivaroxaban should be taken after a meal)
Drug interactions	Yes	Limited
Antidote	Yes	Iduracizumab for dabigatran, Andexanet for Xa inhibitors §
Renal excretion	No	Yes, essentially for dabigatran
Need for monitoring	Yes	No

§ Not yet approved in Europe for reversal before surgery.

Table 2. Stratified risk of thromboembolism in different clinical settings (modified from[2])

	Valve prosthesis	Non valvular AF	Venous thromboembolism
High	Mitral valve mechanic prosthesis Ball or disk aortic prosthesis CVA/TIA in the previous 6 months	$CHADS_2$ score 5 or 6. CHA_2DS_2VASc? CVA/TIA in the previous 3 months Rheumatic valve disease	Episode in the previous 3 months Severe thrombophilia
Intermediate	Two-hemidisk aortic valve with additional risk factors	$CHADS_2$ score 3 or 4 CHA_2DS_2VASc? No CVA/TIA	Episode in the previous 4-12 months Not severe thrombophilia§ Recurring episodes Neoplasms Recurring episodes Neoplasms
Low	Two-hemidisk aortic valve with no additional risk factors	$CHADS_2$ score 2 or less CHA_2DS_2VASc? No CVA/TIA	Episode occurred > 12 months prior No additional risk factors

† Deficiency of protein C, protein S, or antithrombin, antiphospholipid antibodies, or multiple abnormalities. ‡ Risk factors include atrial fibrillation, previous CVA/TIA, hypertension, diabetes, heart failure, and age > 75 years. § Factor V Leiden heterozygous or mutation in the prothrombin gene. AF: atrial fibrillation; CHADS2: congestive heart failure, hypertension, age > 75 years, diabetes mellitus, and stroke; CVA: cerebrovascular accident; TIA: transient ischemic attack; CHA_2DS_2VASc: congestive heart failure, hypertension, age > 75 years, diabetes mellitus, stroke, vascular disease, age 65-74 years, and sex.

Surgical timing

In relation to the timing of surgery, different strategies should be considered in elective procedures, for which there are consolidated indications in comparison to emergency (need to intervene within minutes), urgency (need to intervene within hours), and time-dependent procedures (beyond 24 h). Time-dependent procedures may be considered those interventions for which the results are strictly influenced by the timing of the intervention. A typical example, very frequent considering the age group, is the surgery for hip fracture in which the outcome in terms of both survival and functional recovery is closely related to the precocity of the intervention (within 48 h of trauma).

WARFARIN

Elective surgery

Warfarin discontinuation should take place 5-7 days before surgery. Considering the pharmacokinetic characteristics of warfarin, on the fifth day after discontinuation, the residual pharmacological action is approximately 3%. Depending on the individual embolic risk, a "bridge therapy" through administration of short half-life anticoagulants, unfractionated heparin (UFH), or low molecular weight heparin (LMWH) may or may not be considered.

Table 3. Stratification of hemorrhagic risk (modified[7])

Negligible risk
Dental interventions (extraction of 1-3 teeth, periodontal surgery, incision of abscesses, or implantology) Ophthalmology (cataract surgery or glaucoma)
Non-interventional endoscopic procedures
Superficial surgery (e.g., incision of abscesses or removal of small skin lesions)
Low risk
Endoscopic procedures with biopsy
Bladder and prostatic biopsies
Non-coronary angiography
Electrophysiological study or transcatheter ablation in the right chambers
Pacemaker or defibrillator implant (if anatomy is not complex)
High risk
Transcatheter ablation in the left heart chambers
Spinal or epidural anesthesia or lumbar puncture
Thoracic, abdominal, or orthopedic major surgery
Hepatic or renal biopsy
Transurethral resection of the prostate
Lithotripsy with wave shock

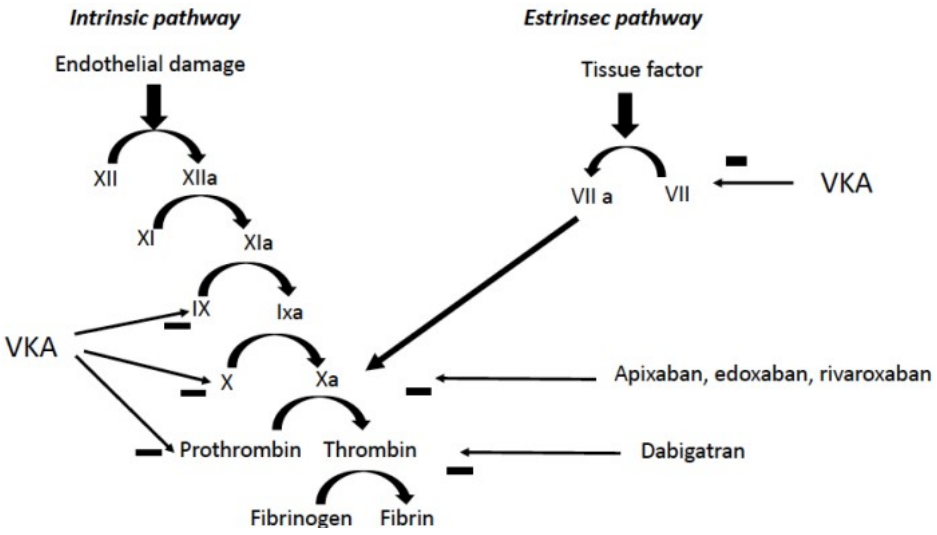

Figure 1. Site of action on "coagulation cascade" of anticoagulant drugs. DOACs rivaroxaban, apixapan, and edoxaban are direct inhibitors of factor Xa, while dabigatran is a thrombin inhibitor[5,6]. VKA: vitamin K antagonist; DOACs: direct oral anticoagulants.

In the past, intravenous infusion of UFH has been the most widely used solution for anticoagulation bridging; however, due to poor handling, it can currently be found due to its short half-life and the possibility of antagonism with the administration of protamine sulfate indication in surgical procedures characterized by high hemorrhagic risk, such as neurosurgical interventions, in the case of renal failure or recent or active bleeding. Currently, for "bridge therapy", the use of LWMH is preferred at a dose of about 70%-80% of the full anticoagulant dose[8]. Although it is advisable to start treatment when International Normalised Ratio (INR) values fall below the therapeutic range, as daily monitoring is not always possible, it is reasonable to start heparin treatment approximately two days after discontinuation of oral anticoagulant therapy. The last dose of LMWH should be 20-25 h away from the procedure, i.e., a period of time open to

about five times the elimination half-life of the drug, so that at the time of surgery, there is no residual anticoagulant effect[9,10].

The results of recent studies, however, clearly show that bridge therapy is accompanied by a significant increase in the risk of postoperative bleeding, while no significant protection is observed in the reduction of thromboembolic events, whose incidence is negligible[11]. "Bridge therapy" appears at the moment not indicated as a standard procedure in patients on anticoagulant treatment who must undergo surgery and must be limited to patients with a very high thromboembolic risk (mechanical valve prostheses in the mitral position or recent cerebrovascular or pulmonary thromboembolic event). LMWH at deep vein thrombosis prophylaxis dose should be considered, where necessary, for all other patients[11]. Resumption of warfarin therapy may be considered 24-48 h after the surgical procedure.

Emergency surgery-time-dependent

In patients who need to undergo emergency or strictly time-dependent surgery, such as the treatment of fractures of the proximal third of the femur, rapid restoration of hemostatic function is necessary. Discontinuation of warfarin and administration of vitamin K (1.0-2.5 mg intravenously or 5-10 mg orally) are sufficient to normalize INR within 24-48 h[12]. In patients who require emergency intervention, the administration of coagulation factor concentrates is indicated. For AVKs, the four-factor prothrombin complex concentrates (PCC) dose [administration of four-factor non-activated PCC (CONFIDEX®) may be considered in the case of very high INR values above 4.0] depending on the INR values and the patient's weight [Table 4][13].

The administration of vitamin K is especially useful in the case of time-dependent intervention, such as in patients with hip fractures[14]. Several treatment regimens have been proposed both by route of administration, per os or i.v., and by dosage (2.5 or 10 mg)[15]. Oral administration may be preferable, leading in 100% of cases to INR values before surgery < 1.7, in patients with INR values < 3.0, without ongoing bleeding, and in which surgery can be deferred by 24-36 h.

DIRECT ANTICOAGULANTS

Elective surgery

The patient who needs an elective surgical procedure should discontinue treatment with direct anticoagulants. For discontinuation of therapy, several factors should be considered: renal function (creatinine clearance, according to Cockcroft-Gault, although with several limits, is the most frequently used method to evaluate kidney function), the type of drug taken, the interval from the last administration, single or bi-administration, the hemorrhagic risk related to the surgical procedure, and the thromboembolic risk of each patient.

In the case of surgical interventions characterized by a negligible bleeding risk, such as dental interventions or superficial surgery procedures, the last dose of the drug should be taken approximately 18-24 h before surgery for apixaban, rivaroxaban, and edoxaban[16], while the time of withdrawal varies in relation to renal function for dabigatran [Table 5]. If the bleeding risk of the procedure is not negligible but is still low, as in the case of bladder and prostate biopsies or non-coronary angiography, discontinuation of therapy 24 h before is recommended if renal function is normal[17]. If the surgery is characterized by a high bleeding risk, e.g., thoracic, abdominal, or major orthopedic surgery procedures, anticoagulant therapy with apixaban, rivaroxaban, and edoxaban should be discontinued 48 h before surgery. Dabigatran discontinuation times still need to be evaluated on renal function.

Table 4. Median dosage of PCC in relation to baseline INR and weight

INR	PCC dose (Kedcom®)	PCC (Confidex®)§
< 2.0	20 UI/kg	
2-3	30 UI/kg	
3-4	40 UI/kg	
> 4	50 UI/kg	
2-3.9		25UI f IX/kg-1 mL/kg
4-6		35UI f IX/kg-1.4 mL/kg
> 6		50UI f IX/kg-2 mL/kg

§ After dilution of one vial of product in 20 mL of water for injection. INR: International Normalised Ratio. PCC: Prothrombin complex concentrates.

Table 5. Timing of DOACs withdrawal in relation to kidney function and procedural risk of bleeding

Creatinine clearance	Intervention at low risk of bleeding (< 2% risk within 48 h)	Intervention at high risk of bleeding (2-4% risk within 48 h)
Dabigatran		
> 80 mL/min	24 h	48 h
50-80 mL/min	36 h	72 h
30-50 mL/min	48 h	96 h
Apixaban, edoxaban, rivaroxaban		
> 80 mL/min	24 h	48 h
50-80 mL/min	24 h	48 h
30-50 mL/min	24 h	48 h
15-30 mL/min	36 h	48 h

DOACs: direct oral anticoagulants.

Recent data show that in about 20% of patients, a concentration of drugs in the plasma still able to exert an anticoagulant action may be detected more than 48 h after the last intake of a direct anticoagulant, an effect more frequently observed with apixaban. This finding has called into question the safety of the adoption of rigid suspension schemes when neuraxial anesthesia is hypothesized[18].

After surgery in which complete hemostasis could be achieved, direct anticoagulants can generally be resumed 6-8 h after surgery. However, resuming the full anticoagulation dose within the first 48-72 h after most of the thoracic or abdominal procedures may carry a risk of bleeding that outweighs the risk of AF-related embolism. In these cases, postoperative thromboprophylaxis with LMWH in prophylaxis dose 6-8 h after surgery and delay of therapeutic anticoagulation, postponing the restart of direct oral anticoagulants (DOACs) by ≥ 48-72 h, can be considered.

Emergency surgery-time-dependent

Given their short half-life, in a patient with preserved renal function, reduction of the anticoagulant effect occurs relatively quickly from the last intake; for this reason, a waiting strategy accompanied by supportive therapy is considered sufficient if the intervention can be postponed by at least 12-24 h from the last administration. The reversal of anticoagulant activity should instead be considered in conditions of emergency (minutes) or urgency (hours). Before any treatment, the coagulation status of the patient (PT, aPTT, anti-FXa dosage, dTT/ECA, *etc.*) should be evaluated. Although in an emergency situation, the indication for the use of specific antidotes and/or pro-hemostatic factors is regulated by the clinical presentation of the patient, the results of these initial tests may have important implications for further

treatment during the following hours since an excessive prothrombotic state as well as an insufficient reversal may be observed, both needing correction. Recently, it has also been shown that the evaluation of plasma levels of DOAC may be useful in interpreting the anticoagulation state and the residual effects of DOACs[18].

The recent EHRA (European Heart Rhythm Association) guidelines provide an algorithm [Figure 2] for the management of anticoagulant treatment in surgical emergencies[19].

When the last dose was taken within 2 h prior to arrival in the emergency room, the administration of activated charcoal by oral route has been shown to be effective in reducing absorption by 99.9% for dabigatran, while there is no evidence for factor Xa inhibitors[20].

PCCs represent a heterogeneous combination of coagulation factors and inhibitory components. PCCs typically contain three (II, IX, and X) or four (II, VII, IX, and X) coagulation factors. The overall concentrations of coagulation factor in these preparations are 25 times higher than plasma concentrations. Three- or four-factor concentrates of the PCC demonstrated a discordant effect based on the type of DOAC used: in healthy volunteers, 50 U/kg of four-factor PCC was shown to be effective in reducing PT elongation due to rivaroxaban, while they did not have the same effect for dabigatran-supported aPTT prolongation[21].

The activated prothrombin complex concentrate (aPCC-FEIBA), containing factors II, VII, IX, and X, seems to correct the anticoagulant effect of high doses of rivaroxaban: at high doses (75-80 U/kg), aPCC corrects and promotes the generation of thrombin *in vitro* on the plasma of healthy volunteers who have taken a single dose of rivaroxaban or dabigatran, and in the blood of healthy volunteers after administration of apixaban[22]. Administration of activated factor VII has not been effective in counteracting bleeding complications in DOAC patients and should be considered as adjuvant therapy during severe bleeding refractory to other treatments.

To date, the only DOAC antagonist drug approved in Europe is idarucizumab, a dabigatran-specific inactivator. It is a humanized monoclonal antibody fragment, which binds to dabigatran with an affinity about 300 times more powerful than dabigatran's binding affinity with thrombin. As a result of its predominantly renal excretion, the clearance of idarucizumab is reduced in patients with impaired renal function[23]. In total, 202 patients requiring urgent procedure/surgery (Group B) were included in the RE-VERSE AD study. The median age was 78 years, and creatinine clearance averaged 52.6 mL/min[24]. Most patients achieved complete inactivation of dabigatran anticoagulant effect, measured by dilute thrombin time and ecarin clotting time, in the first 4 h after administration of 5 g of idarucizumab. Restoration of hemostasis was achieved in 80.3% of evaluable patients with severe bleeding, while, in patients for whom an emergency procedure was required, normalization of hemostasis was observed in 93.4%[23].

Andexanet, an enzymatically inactive truncated form of factor Xa, has recently been approved by the US Food and Drug Administration (but not yet in Europe) and is capable of binding to direct inhibitors of factor Xa, preventing their anticoagulant action. Although it is still being studied, PER977 (ciraparantag), a small synthetic molecule, seems to be able to bind all new oral anticoagulants. In the study "Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors 4" (ANNEXA-4), andexanet alfa was successfully used in major or life-threatening bleeding[25]; unlike RE-VERSE-AD, the study did not include patients undergoing emergency surgery.

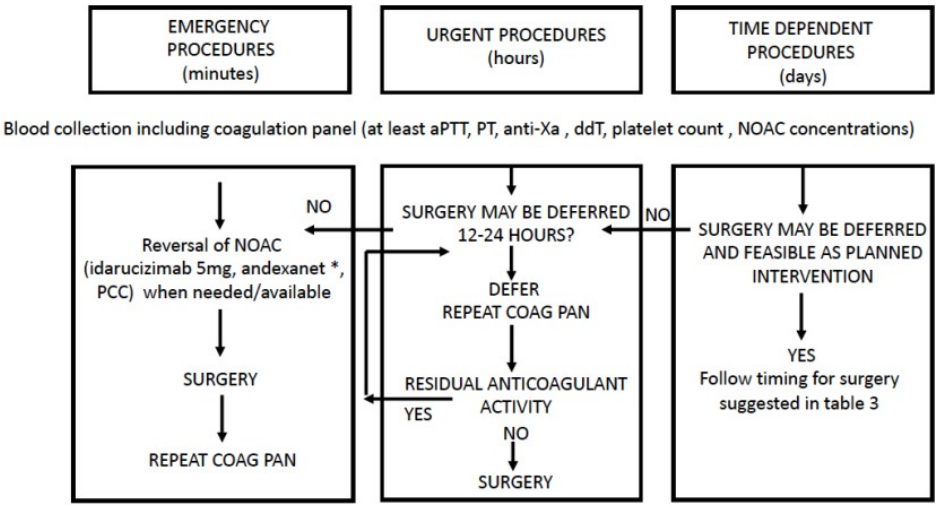

Figure 2. Management of DOACs in relation to surgery timing (modified from[19]). *Andexanet alfa must be administered as a bolus of 30 mg/min in 15 min (low dose) or 30 min (high dose), followed by i.v. infusion of 4 mg (low dose) or 8 mg (high dose) per min for 120 min. DOACs: direct oral anticoagulants.

CONCLUSION

Restoring coagulative activity is mandatory before surgery. In elective-planned surgery, discontinuation of anticoagulation according to guidelines allows for limiting hemorrhagic complications with a low rate of thromboembolic events. No bridge therapy is needed for DOACs, and DVT LMWH prophylactic dose is appropriate for most patients in antivitamin K therapy. Identification of patients at very high risk suitable for bridge therapy is essential in preoperative evaluation. In emergency surgery, rapid reversal of anticoagulation may be obtained by administering specific antidotes or prothrombin complex concentrates, although few studies have been published yet. Finally, for time-dependent surgery, vitamin K allows obtaining INR < 1.5 in most patients within 12 h after administration. Determination of plasma concentration of DOACs after 40-48 h after the last intake may be helpful, particularly in patients who have high bleeding risk surgery or when neuraxial anesthesia is considered.

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The author contributed solely to the article.

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Conflicts of interest

The author declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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