



Management of DOAC in Patients Undergoing Planned Surgery or Invasive Procedure: Italian Federation of Centers for the Diagnosis of Thrombotic Disorders and the Surveillance of the Antithrombotic Therapies (FCSA) Position Paper

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Abstract

Patients on anticoagulant treatment are constantly increasing, with an estimated prevalence in Italy of 2% of the total population. About a quarter of the anticoagulated patients require temporary cessation of direct oral anticoagulants (DOACs) or vitamin K antagonists for a planned intervention within 2 years from anticoagulation inception. Several clinical issues about DOAC interruption remain unanswered: many questions are tentatively addressed daily by thousands of physicians worldwide through an experience-based balancing of thrombotic and bleeding risks. Among possible valuable answers, the Italian Federation of Centers for the diagnosis of thrombotic disorders and the Surveillance of the Antithrombotic therapies (FCSA) proposes some experience-based suggestions and expert opinions. In particular, FCSA provides practical guidance on the following issues: (1) multiparametric assessment of thrombotic and bleeding risks based on patients' individual and surgical risk factor, (2) testing of prothrombin time, activated partial thromboplastin time, and DOAC plasma

Keywords

- ▶ direct oral anticoagulant
- ▶ surgery
- ▶ FCSA

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levels before surgery or invasive procedure, (3) use of heparin, (4) restarting of full-dose DOAC after high risk bleeding surgery, (5) practical nonpharmacological suggestions to manage patients perioperatively. Finally, FCSA suggests creating a multidisciplinary “anticoagulation team” with the aim to define the optimal perioperative management of anticoagulation.

Introduction

About a quarter of the anticoagulated patients require temporary cessation of direct oral anticoagulant (DOAC) or vitamin K antagonist (VKA) for a planned intervention within 2 years from anticoagulation inception.¹ Many interventions carry a trivial bleeding risk and do not necessarily require discontinuation of anticoagulant therapy,^{1,2} in particular for those procedures where bleeding is easily manageable when it occurs, such as bleeding after a single and simple dental extraction.

Many other interventions are at higher risk of bleeding and include those procedures classified by the EHRA (European Heart Rhythm Association) at low and at high risk of bleeding according to the epidemiology of frequency and clinical impact of postprocedure/surgery hemorrhage.¹ The International Society of Thrombosis and Haemostasis (ISTH) provided some recommendations based only on bleeding risk: a strategy of DOAC interruption of 2 to 3 half-lives preprocedure and resumption within 1 day postprocedure for surgeries/procedures classified in the low/moderate bleed-risk category, and a strategy of DOAC interruption of 4 to 5 half-lives preprocedure and resumption 2 to 3 days postprocedure for procedures/surgeries in the high bleed-risk category have been proposed.²

In patients undergoing an invasive procedure or surgery at higher bleeding risk, however, also patient characteristics (including age, history of bleeding complications, concomitant medication, and kidney function) in addition to surgical factors^{1,2} need to be taken into account in the decision of when to discontinue and when to restart DOAC. Conversely to VKA discontinuation, patients' thrombotic risk assessment is less relevant than bleeding risk assessment: DOAC is contraindicated in several high-thrombotic risk conditions, such as atrial fibrillation (AF) with prosthetic mechanical heart valves or moderate-to-severe mitral stenosis, mechanical heart valves, and antiphospholipid syndrome. Therefore, bleeding risk is necessarily the primary determinant of the DOAC discontinuation strategy for invasive procedures or surgery.

Perioperative bridging with full-dose heparin has been used and suggested in DOAC-treated patients, but this practice seems unnecessary and too complex as the DOAC half-life is 8 to 15 hours. Moreover, the use of heparin is associated with an increased bleeding risk if not correctly “bridged,” and it may have questionable efficacy, as indirectly suggested by the BRIDGE trial.^{3,4} In this study, 1,884 patients with AF who had warfarin discontinuation for an elective—mainly at low risk of bleeding—operation or other

elective invasive procedure were randomly assigned to receive no bridging therapy or to receive full-dose heparin bridging.³ The incidence of arterial thromboembolism was 0.4% in the no-bridging group and 0.3% in the bridging group (risk difference: 0.1 percentage points; 95% CI: -0.6 to 0.8). The incidence of major bleeding was 1.3% in the no-bridging group and 3.2% in the bridging group (relative risk: 0.41; 95% CI: 0.20–0.78).³

Available Evidence

A simple, standardized perioperative DOAC therapy interruption and resumption strategy based on DOAC pharmacokinetic properties, procedure-associated bleeding risk, and creatinine clearance (CrCl) levels has been recently investigated in 3,007 patients with AF.⁴ No patients received full-dose heparin bridging. Preoperative DOAC plasma levels were measured but the treating physicians were unaware of the results. The DOAC regimens (apixaban, rivaroxaban, and dabigatran with a CrCl \geq 50 mL/min) were suggested to be omitted for 1 day (i.e., 36–42-hour interval corresponding to approximately 3 DOAC half-lives) before a low risk of bleeding procedure and 2 days (i.e., 60–68-hour interval corresponding to approximately 5 DOAC half-lives) before a high risk of bleeding procedure (2 and 4 days before for dabigatran administration with a CrCl < 50 mL/min).⁴ The DOAC regimens were suggested to be resumed 1 day after a low risk of bleeding procedure and 2 to 3 days after a high risk of bleeding procedure.⁴ In summary, the 30-day postoperative rate of major bleeding was 1.35% (95% confidence interval [CI]: 0–2.00%) in the apixaban cohort, 0.90% (95% CI: 0–1.73%) in the dabigatran cohort, and 1.85% (95% CI: 0–2.65%) in the rivaroxaban cohort. The rate of arterial thromboembolism was 0.16% (95% CI: 0–0.48%) in the apixaban cohort, 0.60% (95% CI: 0–1.33%) in the dabigatran cohort, and 0.37% (95% CI: 0–0.82%) in the rivaroxaban cohort. In patients undergoing a procedure at high bleeding risk, the rates of major bleeding were 2.96% (95% CI: 0–4.68%) in the apixaban cohort, 0.88 (95% CI: 0–2.62%) in the dabigatran cohort, and 2.95% (95% CI: 0–4.76%) in the rivaroxaban cohort.⁴ All 43 major bleeding events occurred postoperatively at a median (interquartile range) of 2 (0–6) days; 9 of 10 arterial thromboembolic events occurred postoperatively at a median of 2 (0–6) days.⁴

The proportion of patients with a preoperative DOAC level below 50 ng/mL was 90.5% in the apixaban cohort, 95.1% in the dabigatran cohort, and 96.8% in the rivaroxaban cohort. Indeed, the PAUSE study was not powered to determine if a residual anticoagulant effect was a determinant of bleeding.^{4–6}

Unmet Clinical Needs

Several clinical issues remain unanswered. Many questions are tentatively addressed daily by thousands of physicians worldwide through an experience-based balancing of thrombotic and bleeding risk: which patients' individual and surgical risk factors pose patients at higher/lower risk of bleeding than "routinely" defined by the current type-of-surgery-based bleeding risk classification? When is the patient thromboembolic risk high enough to be taken into account together with bleeding risk? May testing for prothrombin time (PT) and activated partial thromboplastin time (aPTT) and for DOAC plasma levels before surgery or invasive procedure reduce bleeding events in selected patients? Should heparin be used only as prophylaxis of venous thromboembolism (VTE) postoperatively? Is it safe to restart full-dose of DOAC 48 to 72 hours after surgery in all patients at high risk of bleeding?

Among possible valuable answers, the Italian Federazione dei Centri per la diagnosi della trombosi e la Sorveglianza delle terapie Antitrombotiche (Federation of Centers for the diagnosis of thrombotic disorders and the Surveillance of the Antithrombotic therapies [FCSA]) proposes some experience-based suggestions and expert opinions.

Perioperative bleeding and thrombotic risk evaluation should always be based on a multiparametric assessment. Age, familial and personal history of acquired (in particular surgery-associated) or inherited bleeding disorders, thrombotic risks, comorbidities, concomitant drugs, and laboratory tests such as platelet count, PT, aPTT, kidney, and liver function should be always assessed. In addition, site of surgery and type of anesthesia are certainly main determi-

nants of bleeding risk: bleeding in the central nervous system (neurosurgery or epidural anesthesia) may cause an irreversible and severe damage. Conversely, patients on DOAC at high thromboembolic risk are AF patients with a recent stroke (1–3 months), AF with CHA₂DS₂-VASc >6, recent VTE (1–3 months), VTE in patients with severe inherited thrombophilia, or active cancer.²

In the preoperative/invasive procedure assessment, usually performed by the anesthesiologists, it should be kept in mind that DOAC may prolong PT and/or aPTT, and therefore masking a mild bleeding disorder. A persistently prolonged PT and/or aPTT after DOAC discontinuation may suggest both an underlying mild bleeding disorder and a persistent DOAC activity. On the other hand, PT and/or aPTT within normal ranges after DOAC discontinuation does not exclude an increased bleeding risk due to residual activity. DOAC plasma concentrations poorly correlate with PT and/or aPTT clotting times, and a normal screening test is not always associated with the absence of or minimal residual concentration of drugs.

FCSA considers the measurement of DOAC plasma levels clinically useful in patients at high risk of bleeding, in patients at high risk of elevated DOAC plasma level, or at risk of severe complication from bleeding. A detailed list is reported in **Table 1**. When testing for DOAC, plasma level is necessary; DOAC interruption should be anticipated of 12 to 24 hours, to measure DOAC optimally at trough and to timely reschedule the list of interventions in the operating room. It is useful to remind the 5th percentiles of expected plasma trough levels of anti-Xa DOAC in patients treated for AF: apixaban 34 ng/mL, edoxaban 12 ng/mL, rivaroxaban 12 ng/mL, and the 10th percentiles of trough level of dabigatran, 28 ng/mL.¹

Table 1 Patients who may benefit from direct oral anticoagulant (DOAC) blood level testing

| Higher risk of bleeding | Higher risk of elevated DOAC blood level | Risk of severe complications from bleeding |
|---|--|---|
| Advanced age (>75 y) | Renal failure (eGFR less than 30 mL/min) | Procedure at risk of permanent organ/tissue damage from bleeding (e.g., neurosurgery) |
| Procedure at high risk of bleeding (>2% major bleeding) | Liver failure (Child–Pugh B and C) | Spinal/epidural anesthesia |
| History of previous bleeding after surgery | Low body weight (<50 kg) | |
| History of unexplained bleeding suggesting a bleeding diathesis | Polytherapy and concomitant interferent drugs (e.g., amiodarone) | |
| Concomitant antiplatelet agents or other antithrombotic drugs | | |
| Platelet count < 70,000/mm ³ | | |
| Prolonged prothrombin time (PT) and/or activated partial thromboplastin time (aPTT) and/or thrombin time (TT), hypofibrinogenemia | | |
| Known bleeding disorders | | |

Abbreviation: eGFR, estimated glomerular filtration rate.

Table 2 Risk stratification for procedural bleed risk as suggested by the International Society of Thrombosis and Haemostasis Guidance Statement

| High bleeding risk procedure (30-day risk of major bleed >2%) | Low/moderate bleeding risk procedure (30-day risk of major bleed 0–2%) |
|---|---|
| <ul style="list-style-type: none"> • Major surgery with extensive tissue injury • Cancer surgery, especially solid tumor resection • Major orthopaedic surgery, including shoulder replacement surgery • Reconstructive plastic surgery • Urologic or gastrointestinal surgery, especially anastomosis surgery • Transurethral prostate resection, bladder resection, or tumor ablation • Nephrectomy, kidney biopsy • Colonic polyp resection • Bowel resection • Percutaneous endoscopic gastrotomy (PEG) placement, endoscopic retrograde cholangiopancreatography (ERCP) • Surgery in highly vascular organs (kidneys, liver, spleen) • Cardiac, intracranial, or spinal surgery • Any major operation (procedure duration >45 minutes) • Neuraxial anesthesia | <ul style="list-style-type: none"> • Arthroscopy • Cutaneous/lymph node biopsies • Foot/hand surgery • Coronary angiography • Gastrointestinal endoscopy ± biopsy • Colonoscopy ± biopsy • Abdominal hysterectomy • Laparoscopic cholecystectomy • Abdominal hernia repair • Hemorrhoidal surgery • Bronchoscopy ± biopsy • Epidural injections |

Source: Modified from Spyropoulos et al.²

FCSA suggests against heparin use when stopping DOAC before invasive procedure/surgery if invasive procedure/surgery is not delayed; if invasive procedure/surgery is delayed, heparin at a prophylactic or subtherapeutic/intermediate dose should be started. FCSA recommends the use of prophylactic doses of heparins for VTE prevention as in nonanticoagulated patients undergoing the same invasive procedure/surgery; it is advisable to daily evaluate a gradual increase of low-molecular-weight heparin (LMWH) dosage in case of delayed DOAC resumption in patients at high thromboembolic risk.

In patients at high risk of bleeding, FCSA considers it safer to restart full-dose DOAC at least 48 to 72 hours after surgery. A shared daily multiparametric risk/benefit assessment among anticoagulation experts and the treating physician/surgeon is advisable to eventually postpone the day of DOAC restarting.

FCSA Good Clinical Practice Guidelines' Suggestions

FCSA suggests to stratify patients into three risk categories:

- High bleeding risk and high thromboembolic risk.

- High bleeding risk and non-high thromboembolic risk.
- Low bleeding risk.

Bleeding risk stratification according to procedure/surgery is detailed in ►Table 2. In case of procedures of unknown bleeding risk, FCSA suggests to classify the bleeding risk as high.⁷

High thromboembolic risk is defined according to ISTH as a >10%/year risk of arterial or VTE, such as AF patients with a recent stroke (1–3 months), AF with CHA₂DS₂-VASc >6, recent VTE (1–3 months), VTE in patients with severe inherited thrombophilia (e.g., antithrombin deficiency), or active cancer.² The following therapeutic advices, in addition to some management tips reported in ►Table 3 and in ►Figs. 1, 2, and 3, may be suggested.

High Bleeding Risk and High Thromboembolic Risk

- Stop DOAC according to ►Table 4; when testing for DOAC, plasma level is necessary, DOAC interruption should be anticipated of 12 to 24 hours, to measure DOAC plasma levels at least 12 hours before surgery, and perform invasive procedure/surgery without any residual anticoagulant

Table 3 Practical suggestions

| Pre-surgery/-procedure | Post-surgery/-procedure |
|---|---|
| Discuss with surgeon/specialist risk of bleeding | Start prophylactic low-molecular-weight heparin 12 hours postprocedure if surgery/procedure at risk for venous thromboembolism |
| Plan with surgeon/specialist a definite date of the procedure: any delay will force to start heparin as “bridging” to procedure | Discuss with surgeon/specialist when local hemostasis may be judged to be achieved |
| It is suggested that in each institution a collaboration between the local laboratory and the surgery service should be organized to obtain DOAC blood level determination soon before surgery and minimize inconvenience | Use prophylactic or intermediate dose of low-molecular-weight heparin when starting a full dose of DOAC >48 hours is judged too risky by surgeon/specialist |

Abbreviation: DOAC, direct oral anticoagulant.

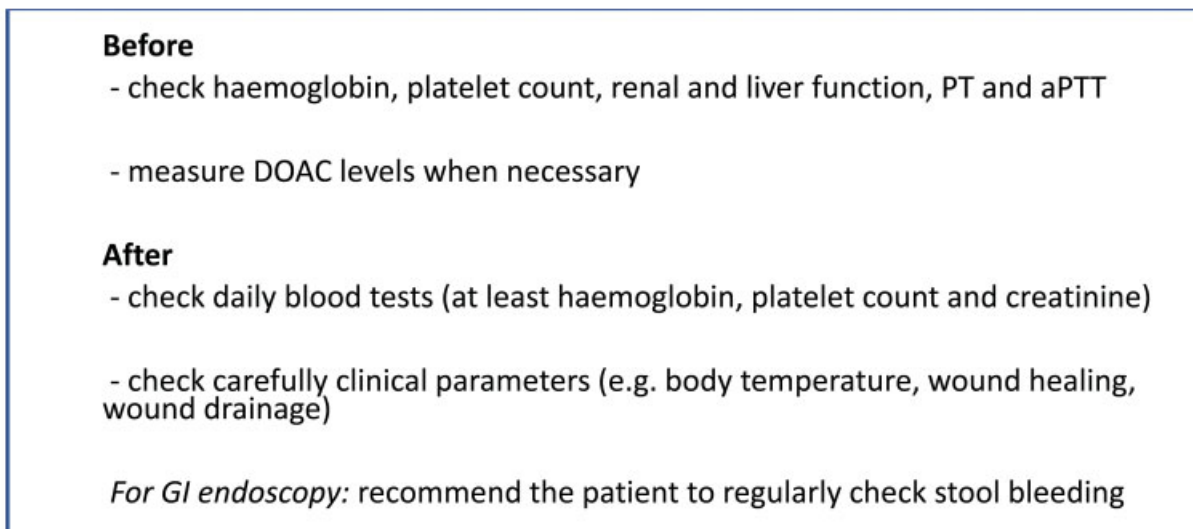


Fig. 1 Practical nonpharmacological suggestions for patients at high bleeding risk in the periprocedural phase.

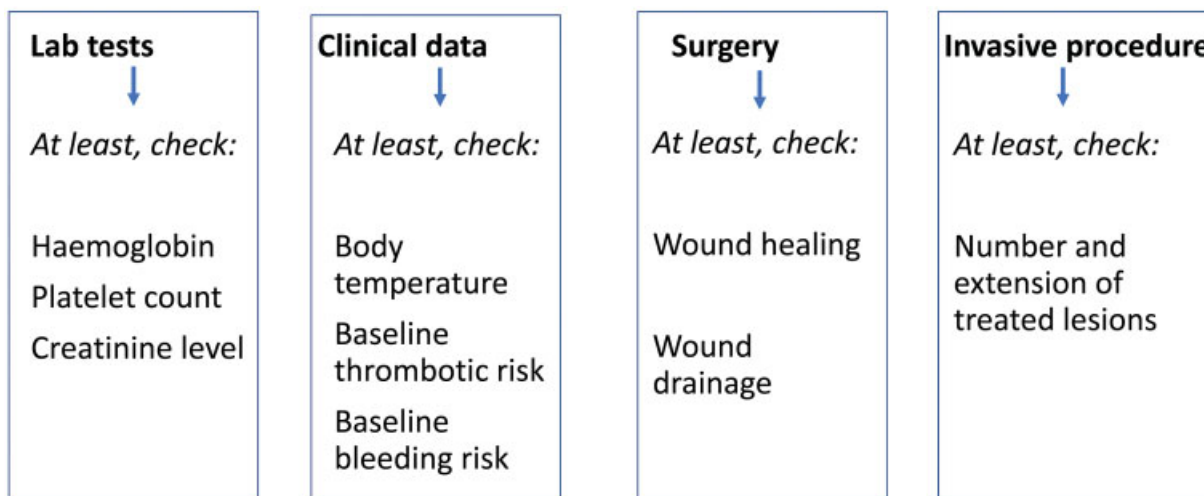


Fig. 2 Multiparametric daily assessment for patients at high bleeding risk after surgery/invasive procedure.

activity (i.e., lower than limit of detection, specific for each drug as indicated by the local laboratory).

- If invasive procedure/surgery is delayed 48/72 hours after stopping DOAC, start LMWH at a subtherapeutic/intermediate dose (i.e., 70 IU/kg twice daily) up to 24 hours before procedure/surgery. In case of early administration of LMWH, exclude persistent DOAC anticoagulant activity before administering LMWH.
- Start LMWH at prophylactic dose 12 hours after procedure/surgery until local hemostasis is safe; it is advisable to gradually increase at intermediate/subtherapeutic dosage, evaluating the risk/benefit daily.
- Restart DOAC at least 3 to 5 days after invasive procedure/surgery and stop LMWH concomitantly. The day of DOAC restarting may be postponed; in any case the risk/benefit should be daily evaluated by a multiparametric clinical and laboratory assessment in accordance with

the treating physician/surgeon: hemoglobin level, platelet count, and creatinine levels should be evaluated, along with routine postoperative clinical parameters (e.g., body temperature, wound healing, wound drainage); finally,

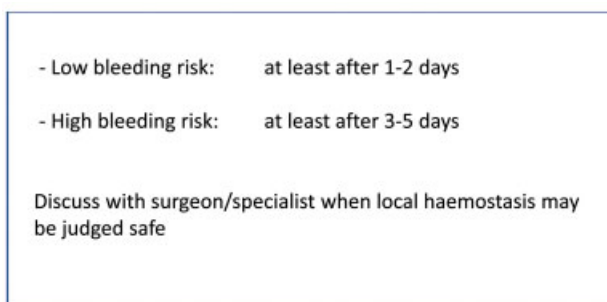


Fig. 3 Restarting DOAC after surgery/invasive procedure. DOAC, direct oral anticoagulant.

Table 4 Last day of DOAC intake before an elective intervention: day 0 is the day of surgery/procedure (modified from Steffel et al,¹ EHRA Practical Guide)

| | Dabigatran | | Apixaban–rivaroxaban–edoxaban | |
|-----------------------|-------------------|--------------------|-------------------------------|--------------------|
| | Low bleeding risk | High bleeding risk | Low bleeding risk | High bleeding risk |
| eGFR \geq 80 mL/min | Day 2 | Day 3 | Day 2 | Day 3 |
| eGFR = 50–80 mL/min | Day 2/3 (>36 h) | Day 4 | Day 2 | Day 3 |
| eGFR = 30–50 mL/min | Day 3 | Day 5 | Day 2 | Day 3 |
| eGFR = 15–30 mL/min | Contraindicated | Contraindicated | Day 2/3 (>36 h) | Day 3 |

Abbreviations: eGFR, estimated glomerular filtration rate; h, hour; min, minute.

the optimal timing of DOAC restarting should be carefully established in agreement with the operator/treating physicians to reduce the risk of delayed bleeding after mucosal (mainly endoscopic) procedures at the time of final wound healing.

In case of estimated glomerular filtration rate (eGFR) between 15 and 30 mL/min, dosage of LMWH should be modified according to the summary of product characteristics or use of unfractionated heparin might be considered.

High Bleeding Risk and Non-High Thromboembolic Risk

- Stop DOAC according to ► **Table 4**; when testing for DOAC, plasma level is necessary, DOAC interruption should be anticipated of 12 to 24 hours, to measure DOAC plasma levels at least 12 hours before surgery and perform invasive procedure/surgery without any residual anticoagulant activity (i.e., lower than the limit of analytical sensitivity specific for each drug as indicated by the local laboratory).
- If invasive procedure/surgery is delayed 48/72 hours after stopping DOAC, confirm the absence of any residual anticoagulant activity and start LMWH at a prophylactic dose up to 12 hours before procedure/surgery.
- Start LMWH at prophylactic dose, when indicated, 12 hours after procedure/surgery until local hemostasis is safe.
- Restart DOAC at least 3 to 5 days after invasive procedure/surgery and stop LMWH concomitantly. The day of DOAC restarting may be postponed: in any case the risk/benefit should be daily evaluated by a multiparametric clinical and laboratory assessment, in accordance with the treating physician/surgeon/operator: at least hemoglobin levels, platelet count, and creatinine levels should be considered, along with routine postoperative clinical parameters (e.g., body temperature, wound healing, wound drainage); finally, the optimal timing of DOAC restarting should be carefully established in agreement with the treating physician/surgeon/operator to reduce the risk of delayed bleeding after mucosal (mainly endoscopic) procedures at the time of final wound healing.

In case of eGFR between 15 and 30 mL/min, dosage of LMWH should be modified according to the summary of product

characteristics or use of unfractionated heparin might be considered.

Low Bleeding Risk

- Stop DOAC according to ► **Table 4**.
- If invasive procedure/surgery is delayed 24/48 hours after stopping DOAC, restart DOAC.
- Start LMWH at prophylactic dose, when indicated, 12 hours after procedure/surgery until local hemostasis is safe.
- Restart DOAC at least 1 to 2 days after invasive procedure/surgery and stop LMWH concomitantly. The day of DOAC restarting may be postponed with a possible start of LMWH or an increase at intermediate/subtherapeutic dosage according to thrombotic risk: it is, however, suggested to routinely evaluate the risk/benefit in agreement with the treating physician/surgeon.

In case of eGFR between 15 and 30 mL/min, dosage of LMWH should be modified accordingly to the summary of product characteristics or use of unfractionated heparin might be considered.

Finally, FCSA suggests creating a multidisciplinary “anti-coagulation team” with the aim to define the optimal perioperative management of anticoagulation. Medicine is moving to an integrated care approach to management: as it happened for other thrombotic disorders—such as AF and pulmonary embolism (PE) (i.e., PERT: PE Response Team)—our proposal may improve clinically relevant outcomes.^{8,9} Thrombosis and hemostasis experts, laboratory experts, anesthesiologists, intensivists, endoscopy experts, and surgeons of different specializations should work dynamically together. Every hospital should implement such an “anti-coagulation team” to optimize the management of bleeding patients, coordinated by the anticoagulation clinic’s physicians.

In conclusion, several clinical issues about periprocedural DOAC interruption remain unanswered. Among possible valuable answers and waiting for the results of ongoing and future studies, FCSA suggests a management strategy based on a pre- and postoperative multiparametric assessment, testing of DOAC plasma levels, and practical nonpharmacological suggestions to help thousands of physicians in their daily clinical practice.

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