The perioperative management of new direct oral anticoagulants: a question without answers

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Summary

New direct oral anticoagulant agents (DOAC) are currently licensed for thromboprophylaxis after hip and knee arthroplasty and for long-term prevention of thromboembolic events in non-valvular atrial fibrillation as well as treatment and secondary prophylaxis of venous thromboembolism. Some other medical indications are emerging. Thus, anaesthesiologists are increasingly likely to encounter patients on these drugs who need elective or emergency surgery. Due to the lack of experience and data, the management of DOAC in the perioperative period is controversial. In this article, we review available information and recommendations regarding the periprocedural management of the currently most clinically developed DOAC, apixaban, dabigatran, and rivaroxaban. We discuss two trends of managing patients on DOAC for elective surgery. The first is stopping the DOAC 1–5 days before surgery (depending on the drug, patient and bleeding risk) without bridging. The second is stopping the DOAC 5 days preoperatively and bridging with low-molecular-weight heparin. The management of patients on DOAC needing emergency surgery is also reviewed. As no data exist for the use of haemostatic products for the reversal of the anticoagulant effect in these cases, rescue treatment recommendations are proposed.

Keywords

Anticoagulants, thrombosis, haemorrhage, perioperative, dabigatran, apixaban, rivaroxaban

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Introduction

Traditional methods of anticoagulation and thromboprophylaxis include vitamin K antagonists (VKA) such as warfarin or acenocumarol, heparin (both low-molecular-weight, LMWH, and unfractionated, UFH), fondaparinux and antiplatelet agents. Despite their proven efficacy, they have significant limitations, for example the poor predictability of response to VKA and their high potential for drug-interactions and the need of parenteral administration of heparin. This has prompted the development of new agents with higher efficacy and a better safety profile, which are closer to the ideal anticoagulant (1). The new direct oral anticoagulant agents (DOAC) produce a direct, selective and reversible inhibition of factor Xa (apixaban, rivaroxaban, edoxaban) or factor IIa (dabigatran) (2, 3). Compared to VKA they have the following advantages: oral administration with stable bioavailability (not for dabigatran), predictable pharmacokinetics and predictable dose response, wide therapeutic window, shorter half-life, little interaction with other drugs or food, rapid onset of action and no need for routine laboratory monitoring (4-7).

Some of the new DOAC have been licensed for short-term thromboprophylaxis after hip and knee arthroplasty by the European Medicines Agency (EMA) (8). They have also been proposed as alternatives to VKA for long-term treatment after venous thromboembolism and the prevention of thromboembolic events in atrial fibrillation (8-10). Other medical and surgical indications are being investigated in several on-going trials. Moreover the indications approved may vary between countries. Due to the lack of experience with these drugs, their management in the perioperative period is controversial (5). In this article, we provide an update on the management of the already clinically used DOAC: apixaban, dabigatran and rivaroxaban. We discuss the different proposals, with application mainly in the European countries at the moment of the revised recommendations (until the end of 2012).

New direct oral anticoagulants: an update

New DOAC have common features but also important differences, which are summarised in ►Table 1 (11, 12).

Apixaban

Apixaban (Eliquis®, Bristol-Myers Squibb/Pfizzer EEIG, Uxbridge, UK) is an oral highly selective, reversible, and directly acting factor Xa inhibitor. It has more than 50% bioavailability and reaches peak plasma concentrations in 30 minutes (min) to 2 hours (h), with a terminal half-life of approximately 12 h. It is metabolised in the liver and eliminated through both the renal (30%) and faecal route (70%) (13). Apixaban is not recommended in patients with a creatinine clearance (CrCl) less than 15 ml/min, patients on dialysis, or with severe hepatic impairment. It should be used with caution in patients in severe renal (CrCl 15-29 ml/min) and mild to moderate hepatic impairment (Child Plugh class A or B). No dose adjustment is required for body weight, gender or age. The use of apixaban is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-glycoprotein (P-gp) inducers, such as azole-antyfungals and HIV protease inhibitors (14).

The first trials of this drug were conducted in thromboprophylaxis after major orthopaedic surgery (ADVANCE-1, ADVANCE-2, ADVANCE-3) (15-17). Based on them, apixaban 2.5 mg twice daily, starting 12-24 h after surgery, has recently been approved by the EMA. In atrial fibrillation apixaban 5 mg twice daily has been compared to acetylsalicylic acid (AVERROES) (18) and warfarin (ARISTOTLE) (19). Also this indication has recently been adopted by the EMA. There have been other clinical trials with different regimens both for prevention (ADOPT) (20) and treatment (AMPLIFY) of venous thromboembolism (VTE) in medical patients.

Rivaroxaban

Rivaroxaban (Xarelto®, Bayer HealthCare AG, Leverkusen, Germany) is an oral direct FXa inhibitor. The peak level is reached 2–4 h after ingestion and is slightly enhanced by food. Its half-life is 5–9 h. Approximately 66% of the administered dose is metabolised with half then being eliminated by renal clearance and the other half through the faecal route. The other 33% of the administered dose is excreted unchanged in the urine (21, 22). It is not necessary to adjust the dose in mild or severe renal impairment. Rivaroxaban is contraindicated in hepatic disease with coagulopathy and bleeding risk and should be used with caution in moderate hepatic impairment (Child Pugh class B). It is not recommended in patients being treated with potent inhibitors of CYP3A4 and P-gp, such as azole antifungals or systemic HIV-protease inhibitors (23).

The first indication approved for rivaroxaban was thromboprophylaxis after hip and knee arthroplasty, after the four RECORD studies: RECORD 1 and 2 in total hip replacement (THR), RECORD 3 and 4 in total knee replacement (TKR) (24-27). The recommended dose is 10 mg daily, starting 6–8 h after wound closure.

EMA also approved rivaroxaban for two medical indications: prevention of stroke and systemic embolism in high-risk patients in atrial fibrillation (ROCKET-AF) (28) with 20 mg once daily, and treatment of deep-vein thrombosis (EINSTEIN-DVT) (29) with 15 mg rivaroxaban twice daily for three weeks, followed by 20 mg once daily. A recently published trial about treatment of pulmonary embolism (EINSTEIN-PE) (30) showed that rivaroxaban 15 mg twice daily for three weeks, followed by 20 mg once daily was not inferior to standard therapy.

Dabigatran

Dabigatran etexilate (Pradaxa®, Boehringer Ingelheim International GmbH, Ingelheim, Germany) is a direct thrombin inhibitor (31). It is a prodrug which undergoes biotransformation to the active molecule, dabigatran, by esterases. As its absorption requires an acidic environment, the oral capsule contains tartaric acid and must not be manipulated, it should be swallowed whole with water, with or without food. Its half-life extends to 12-17 h after multiple doses. As much as 80% of the drug is excreted unchanged by the kidneys and 20% by the biliary system after conjugation. Thus the drug is contraindicated in patients with a CrCl less than 30 ml/min, and the dose needs to be adjusted in patients

	Apixaban	Rivaroxaban	Dabigatran
Mechanism of action	Direct Xa inhibitor	Direct Xa inhibitor	Direct IIa inhibitor
Protein-binding (%)	35	40–59	> 90
Substrate of transporters (P-gp)	Yes	Yes	Yes
Half-life (h)	8–15	5–9	14–17
Substrate or CYP enzymes	Minor (CYP3A4)	Major (CYP3A4, CYP2J2)	No
Elimination	70% Unchanged 30% Inactive metabolites	50% Unchanged 50% Inactive metabolites	100% Unchanged drug+ active metabolites
Route of elimination	25% Urine 70% Faeces	70% Urine 30% Faeces	80% Urine 20% Faeces

Table 1: Pharmacokinetic properties of new anticoagulants.

with a CrCl 30-50 ml/min. It is not recommended in patients with elevated liver enzymes raised to more than twice the upper limit of normal (32, 33). As dabigatran is a substrate for the P-gp transport system close clinical surveillance is required when it is co-administered with strong P-gp inhibitors. Systemic ketoconazole, itraconazole, cyclosporine and tacrolimus are contraindicated. Dose reductions should be considered in patients who receive dabigatran together with amiodarone, quinidine or verapamil (34).

Dabigatran 220 mg once daily has been licensed for thromboprophylaxis after THR based on RE-NOVATE (35) and RENOVATE-II (36) as well as after TKR based on RE-MOBILIZE (37) and RE-MODEL (38). The dose has to be reduced to 150 mg daily in moderate renal impairment (CrCl 30 to 50 ml/min), patients older than 75 or on amiodarone. A first half dose (110 or 75 mg) should be given orally 1-4 h after the end of surgery (34).

Based on the RE-LY study (39), EMA has approved dabigatran 150 mg twice daily for stroke prevention in atrial fibrillation. Dabigatran has also been studied in patients with acute VTE (RECOVER-I and RECOVER-II) (40), and two trials have been conducted for secondary prevention of VTE comparing it to warfarin (RE-MEDY) (41) and with placebo (RE-SONATE) (42).

Proposals for perioperative management

Most patients on anticoagulant treatment require temporary interruption of this therapy in the perioperative period or prior to an invasive procedure. In this situation a careful balance between the risk of a thromboembolic event and of bleeding is needed. For patients on VKA it is current practice to bridge therapy with parenteral heparin. Although international guidelines recommend this practice (43) in order to outweigh the periprocedural thrombotic and bleeding risk, this is based on low-grade evidence. For patients on DOAC, there is even more uncertainty regarding perioperative management as there is no evidence base and little clinical experience. Thus it is necessary to highlight some points before giving any recommendation:

- There is no clinically validated antidote or reversal agent for these drugs (44). Some authors have suggested the use of fresh frozen plasma (45), prothrombin complex concentrate (PCC) (46, 47) or factor VIIa, (48, 49) for the reversal of their anticoagulant effect, based on experimental or laboratory studies. Nevertheless, whether these results can be related to reversing the bleeding tendency in patients on DOAC remains to be studied (50). More specific antidotes are being developed (51-53), although their clinical efficacy is yet to be demonstrated.
- The dose for chronic anticoagulation is significantly higher than for thromboprophylaxis. The proposed dose of these drugs for different diagnoses is shown in ▶Table 2.
- Residual drug levels of DOAC that can be considered safe for surgery are presently unknown, and no biological test has been correlated with bleeding risk. With these two things in mind, there is currently no known "threshold" at which the haemorrhagic risk of patients on DOAC would be comparable to non-treated ones.
- Although the administration of a DOAC reduces the thrombotic events compared with control groups on warfarin, it results in a non-negligible risk of bleeding. Some scores have been developed to assess this bleeding risk. The HAS-BLED score (uncontrolled hypertension, abnormal renal and/or liver function, previous stroke, bleeding history or predisposition, labile international normalised ratio [INR], elderly (>65 years), concomitant drugs or alcohol) is the most commonly used (54). It has good predictive accuracy for spontaneous bleeding in chronic anticoagulant treatment, allows making therapeutic decisions in patients with atrial fibrillation (55), and may predict bleeding events during bridging therapy with LMWH (56). However, the HAS-BLED score has not been evaluated for the prediction of bleeding during and after surgery in patients with chronic anticoagulation.

With all this in mind, before elective surgery we could split up the current recommendations in two options: to stop the DOAC before surgery with or without bridging therapy with LMWH (▶Figure 1).

Preoperative discontinuation of DOAC without bridging

Some publications and technical specifications propose stopping the drug without administration of LMWH, mainly based on the characteristics of DOAC (57).

Table 2:
Main proposal dosage of DOAC.

	Apixaban	Rivaroxaban	Dabigatran
Thromboprophylaxis in orthopaedics	2.5 mg /12 h (12–24 postop)	10 mg/24 h (6–10 h postop)	220 mg/24 h* (1–4 h postop)
Stroke prevention in atrial fibrillation	5 mg/12 h	20 mg/24 h	110–150 mg/12 h*
VTE treatment 1st week 6 months 6º-12º month	 10 mg/12 h 5 mg/12 h 2.5 – 5 mg/12h	 15 mg/12 h (3 w) 20 mg/24 h 20 mg/24 h	 150 mg/12 h

Only some of the indications and the dosage proposed in this table have already been approved by the EMA and also they can vary between countries (see text). *Dosage adjustments may be needed in some situations (see text). Postop: postoperative, h: hours, w: weeks: VTE: venous thromboembolism.

The technical specifications of rivaroxaban recommend to discontinue treatment at least 24 h before an operation (23). This interval covers around 3 half-lives of 5-9 h (22). This recommendation is adopted by the last consensus guidance about rivaroxaban (58).

For dabigatran, a recently published revision proposed stopping between 1 and >5 days pre-operatively depending on renal function and risk of bleeding (59). The manufacter's technical specifications for dabigatran recommend this too (34), as does a recently published Austrian expert guidance (60). The latter, however, proposes the use of bridging with LMWH when treatment with dabigatran is interrupted for more than one day in patients with atrial fibrillation and a $CHADS_2$ score above 2 or with a history of ischaemic cerebrovascular accident (60).

Another recent publication proposes a pre-procedural treatment discontinuation for 5-7 days with dabigatran and 3-5 days with rivaroxaban, depending on whether CrCl is above or below 50 ml/min (61).

The Spanish Forum on Anticoagulants and Anaesthesia proposes a pre-operative period withdrawal covering at least 3 half-lives of any of them as a common recommendations for the three currently available DOAC (62).Taking into account the upper limit of their elimination half-lives, this implies treatment withdrawal for 45 h for apixaban, 33 h for rivaroxaban and 51 h for dabigatran, respectively. Thus, the last administration of the DOAC should be about 48 h before procedures with low to moderate thrombotic or haemorrhagic risk in patients with normal renal function (CrCl > 50 ml/min) and without any other conditions that could increase the half-life of the DOAC.

In a similar approach, the French Working Group on Perioperative Haemostasis and the French Study Group on Thrombosis and Haemostasis (GIHP and GEHP) propose a short treatment interruption of 24 h before and after procedures with a low haemorrhagic risk (in terms of amount, location and control of a potential bleed) (63).

Preoperative discontinuation of DOAC bridging with LMWH

The Spanish Forum proposes this option as the safest one for the three currently available DOAC (62). The French experts working group (GIHP and GEHP) and the ANSM (French Agency for Drugs and Sanitary Products Safety) also favour this option (63). In this approach, the DOAC is discontinued 5 days before any invasive procedure. This implies that for all three DOAC the treatment is stopped for more than three times their respective half-life, so any remaining anticoagulant should be minimal (after 3 elimination half-lives plasma levels decrease to less than 15% of initial values). This prolonged discontinuation provides enough time for plasma levels of the DOAC to decrease to minimal levels even in the elderly, patients with renal impairment or with other conditions associated with decreased drug elimination. Hence this option is proposed for patients with high or moderate thrombotic and/or haemorrhagic risk (►Table 3 and ►Table 4) (64, 65). The Spanish Forum also recommends this for patients with CrCl less than 50 ml/min and/or over 75 years, due to their unpredictable and possibly prolonged elimination of DOAC.

Obviously, as these patients are at moderate to high thrombotic risk, it is necessary to administer a LMWH to bridge the anticoagulant effect, similar to patients on VKAs. The dose of the LMWH (prophylactic or anticoagulant) has to be based on the thrombotic risk of any given patient. There is some controversy as to when to start the LMWH. The French group proposes that heparin should be initiated 12 h after the last dose of DOAC, if it is to be administered twice a day or 24 h after the last dose of DOAC, if it is to be administered daily (63). This is in accordance the manu-

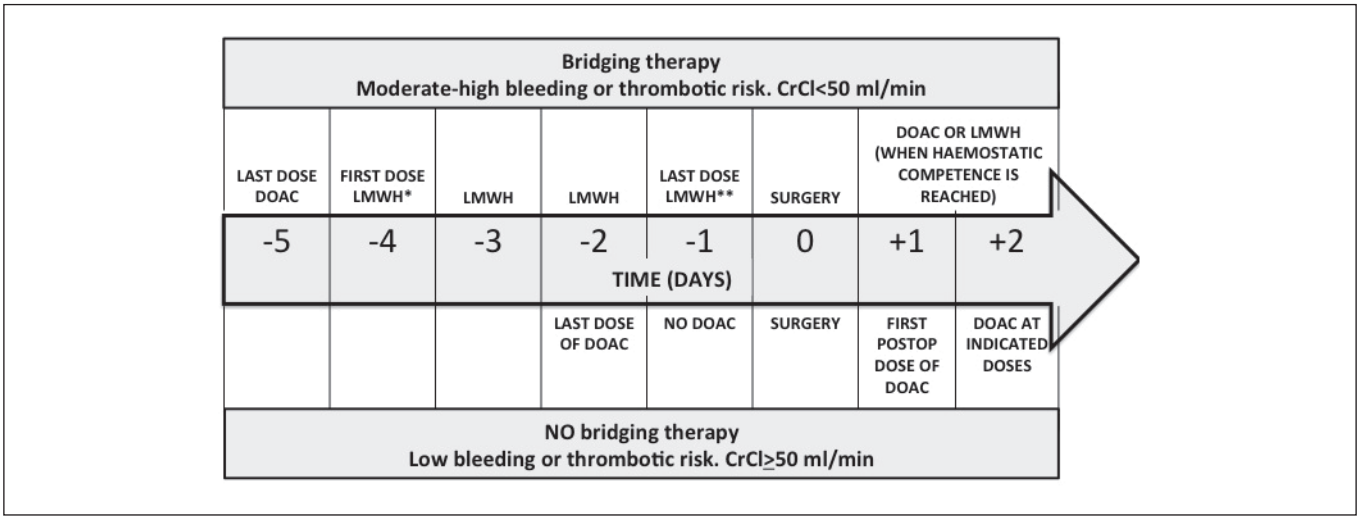

Figure 1: Scheme of the recommendations based and modified from the Spanish Forum on Anticoagulants and Anaesthesia for bridging therapy (57). *The optimal time to start LMWH in bridging therapy differs between authors and it is yet to be addressed in patients with renal function impairment (see text). **The last anticoagulant dose of LMWH will be 24 h before surgery (it will be half dose if given on a daily manner) (43), or 12-24 h if a thromboprophylaxis dosage is used (66). DOAC: direct oral anticoagulant; LMWH: low-molecular-weight heparin; POSTOP: postoperative.

facturers' recommendations regarding switching from oral to parenteral anticoagulation (23, 34). The Spanish group suggests giving the first dose of LMWH 24 hours after the last dose of DOAC to minimise the risk of bleeding (62). Whether this first dose of LMWH should be delayed in patients with impairment is yet to be addressed. Concerns about the risk of accumulation of DOAC in these latter patients have arisen, particularly for dabigatran. The last therapeutic anticoagulant dose of LMWH should be administered 24 h before surgery, and should be half dose if was given once daily (43). The last dose of thromoboprophylactic LMWH should be given 12-24 h pre-operatively (66).

Experience from the trials

The large DOAC trials did not provide much information regarding perioperative. An analysis of the RELY study focused on 3,033 patients who underwent surgery or invasive procedures (3,033 patients) (67). The mean time of preoperative dabigatran discontinuation was 49 h (range 35-85 h). Observed rates of periprocedural bleeding were similar to those of a group of patients receiving warfarin. Only 248 patients (8.2%) underwent emergency surgery, with an incidence of major bleeding of 17.7%. In elective major surgery, major bleeding was observed in 62/948 operations (6.5%), with no significant difference in patients receiving warfarin. No information was provided about any possible relationship between types of surgery and time of DOAC discontinuation to bleeding and the implications for management of major haemorrhages. For rivaroxaban, there are no data about patients undergoing an invasive procedure while there were included in the ROCKET-AF trial (28).

Data provided about spontaneous bleeding in trials of therapeutic use of DOAC show that the rates of spontaneous bleeding were not negligible. The incidence of major bleeding in this case ranges from 0.8 to 1.1 % for rivaroxaban in EINSTEIN studies (29, 30), and 1.6% for dabigatran (150 mg twice daily) in RECOVER study (40). In both cases the rate of bleeding associated with the administration of warfarin was higher or at least similar.

The information about bleeding in these trials has led to the publication of simple protocols for the routine clinical practice (58, 68, 69), although their usefulness has not been evaluated yet. Further prospective studies and observational data from clinical practice are necessary to assess safety and efficacy of the management of DOAC in theses scenarios.

Post-operative reintroduction of DOAC

The optimal time for the resumption of DOAC will mainly depend on the postoperative risk of bleeding. The first dose should be given in the early postoperative period "as soon as possible", when surgical bleeding risk is under control (58). At present there are no specific indications for post-operative use of DOACs at therapeutic dose. Most available recommendations agree that DOAC

Table 3: Proposal for haemorrhagic risk classification according to surgery of the Spanish Forum on Anticoagulants and Anaesthesia (57).

Low	- If necessary, appropiate haemostasis can be achieved. - A possible bleeding does not expose the patient to a vital risk nor put at risk the surgery outcome - No transfusion is usually needed. - Examples: minor surgery (plastic, minor orthopaedics, endoscopic ear, nose and throat surgery, eye anterior chamber surgery, dental procedures)
Moderate	- If necessary, surgical haemostasis can be difficult. - A possible bleeding increases the need of transfusion or it implies a need of reintervention. - Examples: major abdominal surgery, cardiovascular, major orthopaedics, ear, nose and throat, urology, reconstructive.
High	- A perioperative bleeding may put at risk the patient life or the surgery outcome. - Examples: intracranial neurosurgery, intervention in the spinal cord, eye posterior chamber surgery.

Table 4:
Proposal for thrombotic risk classification according to patient characteristics (based and modified from the Spanish Forum on Anticoagulants and Anaesthesia suggestions [57]).

Low	Moderate	High
Atrial fibrillation		
CHA_2DS_2-VASc 0–1 points No other risk factor	CHA_2DS_2-VASc 2–4 points	CHA_2DS_2-VASc >5 points Stroke within 3 months Rheumatic valvulopathy
Venous thromboembolism		
Thromboembolic disease more than 1 year previous to surgery	Thromboembolic disease within 3–12 months Recurrent DVT Active oncologic disease Mild thrombophilia	Thromboembolic disease within less than 3 months Serious thrombophilia
CHA_2DS_2-VASc: Congestive heart failure/left ventricular dysfunction, Hypertension, Age >75 (doubled), Diabetes mellitus, Stroke (doubled), Vascular disease, Age 65–74, Sex category (female).		

should be re-started from 24-48 h postoperatively. To minimise the risk of bleeding, some authors have proposed resuming DOAC with a half dose (75 mg for dabigatran and 10 mg for rivaroxaban) (5). Alternatively, prophylactic doses of a LMWH can be given early after surgery before restarting a DOAC at full doses (68). In this case, the DOAC should be reintroduced after the third or fourth postoperative day 24 h after the last dose of LMWH. Finally, if for any reason re-start of DOAC is not considered and thromboprophylaxis is needed postoperatively, LMWH should be used.

Emergency surgery

Depending on the bleeding risk of the surgery, and the half-life of the specific DOAC, a delay in restarting treatment with it of 24-36 h is recommended (62, 63). It is very important to know the exact time of the last dose of DOAC, as a delay of two elimination half-lives is desirable. If a sensitive laboratory assay is performed, a normal dilute thrombin time (for thrombin inhibitor) or the absence of detectable activity for factor Xa inhibitor could be assumed as there is no clinical effect of the DOAC. Nevertheless, an abnormal test cannot be used as a guide for the risk of bleeding, as there is no direct relationship with the clinical effect.

For emergency surgery, prophylactic administration of any haemostatic product as fresh frozen plasma, PCC (activated or not) factor VIIa is not routinely recommend Instead, they have been proposed for rescue in case of moderate or severe haemorrhage directly or indirectly related with the anticoagulant treatment, such a spontaneous or traumatic cerebral bleeding (60, 62, 70).

Conclusions

In summary, at present new DOAC are licensed for thromboprophylaxis after hip and knee replacement and have limited accepted medical indications. Many clinical studies are being conducted to extend their approved indications and it is foreseen that their their much wider use can be foreseen for the future. The last update of the European Society of Cardiology on atrial fibrillation, for example, includes DOAC as the best option for anticoagulation in many cases (71). There is a lack of experience in managing patients treated with DOAC who need to undergo elective or emergency surgery, and some recommendations are needed until more objective data are obtained on this area. Current perioperative recommendations are mainly based on the pharmacology of DOAC. Three half-lives of elimination is the recommended time of preoperative DOAC discontinuation in patients with normal renal function, no coagulopathy and less than 65 years of age. Impairment of renal and hepatic function and advanced age can prolong the elimination half-life of DOAC and may require longer withdrawal times. In these circumstances, bridging with LMWH at anticoagulant or prophylactic dose could be the most recommended regimen. In emergency surgery, routine prophylactic administration of clotting factors is not recommended. These recommendations should be considered with caution, due to the lack of information and experience, and applied with a strict recording of each individual case.

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Conflicts of interest

Raquel Ferrandis has received honoraria from Bayer, Boehringer and Rovi. Jorge Castillo has received honoraria from Bayer, BMS-Pfizer, Boehringer. Juan V. Llau has received honoraria from Bayer, BMS-Pfizer, Boehringer, Sanofi, Rovi. For the remaining authors none were declared.

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