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GUIDELINES

Clinical guideline on reversal of direct oral anticoagulants in patients with life threatening bleeding

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BACKGROUND Anticoagulation is essential for the treatment and prevention of thromboembolic events. Current guidelines recommend direct oral anticoagulants (DOACs) over vitamin K antagonists in DOAC-eligible patients. The major complication of anticoagulation is serious or life-threatening haemorrhage, which may necessitate prompt haemostatic intervention. Reversal of DOACs may also be required for patients in need of urgent invasive procedures. This guideline from the European Society of Anaesthesiology and Intensive Care (ESAIC) aims to provide evidence-based recommendations and suggestions on how to manage patients on DOACs undergoing urgent or emergency procedures including the treatment of DOAC-induced bleeding.

DESIGN A systematic literature search was performed, examining four drug comparators (dabigatran, rivaroxaban, apixaban, edoxaban) and clinical scenarios ranging from planned to emergency surgery with the outcomes of mortality, haematoma growth and thromboembolic complications. The GRADE (Grading of Recommendations, Assessment, Development and Evaluation) methodology was used to assess the methodological quality of the included studies. Consensus on the wording of the recommendations was achieved by a Delphi process.

RESULTS So far, no results from prospective randomised trials comparing two active comparators (e.g. a direct reversal agent and an unspecific haemostatic agent such as prothrombin complex concentrate: PCC) have been published yet and the majority of publications were uncontrolled and observational studies. Thus, the certainty of evidence was assessed to be either low or very low (GRADE C). Thirty-five recommendations and clinical practice statements were developed. During the Delphi process, strong consensus (>90% agreement) was achieved in 97.1% of recommendations and consensus (75 to 90% agreement) in 2.9%.

DISCUSSION DOAC-specific coagulation monitoring may help in patients at risk for elevated DOAC levels, whereas global coagulation tests are not recommended to exclude clinically relevant DOAC levels. In urgent clinical situations, haemostatic treatment using either the direct reversal or nonspecific haemostatic agents should be started without waiting for DOAC level monitoring. DOAC levels above 50 ng ml^{-1} may be considered clinically relevant necessitating haemostatic treatment before urgent or emergency procedures. Before cardiac surgery under activated factor Xa (FXa) inhibitors, the use of andexanet alfa is not recommended because of inhibition of unfractionated heparin, which is needed for extracorporeal circulation. In the situation of DOAC overdose without bleeding, no haemostatic intervention is suggested, instead measures to eliminate the DOACs should be taken. Due to the lack of published results from comparative prospective, randomised studies, the superiority of reversal treatment strategy vs. a nonspecific haemostatic treatment is unclear for most urgent and emergency procedures and bleeding. Due to the paucity of clinical data, no recommendations for the use of recombinant activated factor VII as a nonspecific haemostatic agent can be given.

CONCLUSION In the clinical scenarios of DOAC intake before urgent procedures and DOAC-induced bleeding, practitioners should evaluate the risk of bleeding of the procedure and the severity of the DOAC-induced bleeding before initiating treatment. Optimal reversal strategy remains to be determined in future trials for most clinical settings.

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Introduction

Anticoagulant therapy is fundamental for the prevention and treatment of thromboembolic diseases. With an aging population, the number of patients requiring long-term oral anticoagulation is increasing. Currently available options include vitamin K antagonists (VKAs) and the direct oral anticoagulants (DOACs; dabigatran, rivaroxaban, apixaban, edoxaban). A predictable pharmacology (Table 1), lower incidence of major bleeding and simplified peri-operative management are key advantages of DOACs compared with VKA. Although the overall bleeding risk in DOAC-anticoagulated patients (2.1 to 3.6% in phase III clinical trials) is lower than in VKA-treated patients,[1] patients under DOACs may develop serious bleeding or need for urgent surgery. Annually, approximately 10% of patients on DOACs require invasive procedures,[2] so that reversal of DOAC may also be needed for patients requiring urgent invasive procedures. DOAC-associated bleeding might impair the outcome and have detrimental or even fatal consequences. The clinical need to antagonise the anticoagulant effect depends on several factors including the anticipated bleeding risk of the procedure/operation, localisation of bleeding and the urgency for surgical intervention. Further, timing of the last intake of the anticoagulant and the renal function of the patient are the major factors influencing the elimination of the DOACs. A clinical evaluation must exclude that the invasive procedure/operation cannot be postponed to wait for the elimination of the DOAC.

In principle, DOAC reversal can be achieved by specific antidotes (idarucizumab or andexanet alfa) or unspecific haemostatic agents used to enhance the haemostatic function of the coagulation system, such as prothrombin complex concentrate (PCC), activated PCC (aPCC) or recombinant factor VIIa (rFVIIa). The purpose of this guideline is to provide clinical guidance for the management of DOAC-treated patients and DOAC-induced bleeding on specific predefined clinical questions. This includes a discussion about specific reversal using direct antidotes vs. a treatment with nonspecific haemostatic agents based on current evidence.

Overview of specific antidotes and unspecific reversal agents

Specific reversal: idarucizumab

Idarucizumab is a humanised, monoclonal antibody fragment against dabigatran.[3] Idarucizumab binds dabigatran with high affinity (approximately 350-fold that of thrombin) neutralising the anticoagulatory effects of dabigatran. Animal models and phase I to II clinical data show that idarucizumab achieves immediate, complete and sustained biochemical reversal of dabigatran.[4,5] The multicentre, prospective cohort REVERSE-AD study evaluated idarucizumab (5 g intravenously) in 503 dabigatran anticoagulated patients with major bleeding or urgent surgery. The study involved 301 patients with uncontrolled bleeding and 202 patients about to undergo an urgent procedure.[6] The majority of patients had gastrointestinal and intracranial bleeding. Haemostatic efficacy was measured by the correction of the diluted thrombin time (dTT), the ecarin clotting time (ECT) and the activated partial prothrombin time (aPTT) in more than 90% of patients. Thrombotic events were observed in 4.8 and 6.8% of all patients after 30 and 90 days, respectively. Median correction of anticoagulant effect was 100% (95% confidence interval (CI), 100 to 100) based on reduction of prolonged dTT and ECT. Sixty-eight percent of patients showed cessation of bleeding within 24 h, whereas the median time to haemostasis was 2.5 h. The 30 day-mortality was 13.5 and 12.6%, respectively. Half of thrombotic events occurred within 5 days after infusion and one-third occurred after resumption of anticoagulation. Several aspects should be considered when transferring the findings of REVERSE-AD to clinical practice: it was a noncontrolled and nonrandomised study and the efficacy in terms of percentage reversal was assessed using biological markers at 4 h after the second infusion of idarucizumab. Furthermore, the duration of the haemostatic effect is to be discussed as 23% of patients had detectable dabigatran plasma levels within 12 to 24 h after administration of the antidote, which was probably because of redistribution from the extravascular to the intravascular space. This may be particularly important in patients with high plasma levels, which may be due to renal dysfunction, which, in turn, also prolongs the elimination half-life of dabigatran.[7] A few case reports have reported the incomplete reversal of dabigatran following the standard dose of 5 g idarucizumab.[8,9]

Based on the data of the REVERSE-AD study, idarucizumab (total of 5 g iv) was approved by the European Medicines Agency (EMA) in 2016 for dabigatran reversal.

Specific reversal: andexanet alfa

Andexanet alfa is a modified, recombinant, inactive form of human FXa, with the ability to reversibly bind FXa-inhibitor molecules, thereby reducing its activity and restoring the amount of unbound endogenous FXa. Andexanet alfa therapy is administered as an intravenous (i.v.) bolus over a duration of 15 to 30 min, followed by a 2 h infusion. The ANNEXA-4 study evaluated the clinical utility of andexanet alfa as a single-group cohort study in patients who experienced acute major bleeding within 18 h after administration of apixaban (54%), rivaroxaban (40%) or enoxaparin (6%) and baseline anti-FXa activity of at least 75 ng ml^{-1}.[10] Sixty-four percent of patients suffered from ICH and 26% from gastrointestinal bleeding. Treatment with andexanet alfa resulted in a 92% reduction of anti-FXa activity. Despite a significant rebound of anti-FXa activity at 4 h after andexanet alfa infusion, in 85% of patients with gastrointestinal bleeding

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Table 1 Characteristics and indications of direct oral anticoagulants with therapeutic options for haemostasis

	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Drug Classification	Direct FXa inhibitor	Direct FXa inhibitor	Direct FXa inhibitor	Direct thrombin (FII) inhibitor
Half-life	5 to 9 h	12 h	10 to 14 h	12 to 14 h
Time to max effect	2 to 4 h	3 to 4 h	1 to 2 h	2 h
Renal contraindication	CrCl <15 ml min^{-1}	CrCl <15 ml min^{-1}	CrCl <15 ml min^{-1}	CrCl < 30 ml min
Direct antidote (dose)	Andexanet alfa Low-dose: 400 mg bolus infusion over 15 min followed by an 480 mg infusion over 2 h High dose: 800 mg bolus infusion over 30 min followed by an 960 mg infusion over 2 h	Andexanaet alfa Low dose: 400 mg bolus infusion over 15 min followed by an 480 mg infusion over 2 h High dose: 800 mg bolus infusion over 30 min followed by an 960 mg infusion over 2 h	Andexanet alfa not approved	Idarucizumab Idarucizumab: Infusions of 2 × 2.5 g over 5 to 10 min, infusions no more than 10 min apart.
Non-specific haemostatic treatment (dose)	Not approved: PCC or aPCC at a dose of 25 to 50 IU kg^{-1}; rFVIIa: no recommendation	Not approved: PCC or aPCC at a dose of 25 to 50 IU kg^{-1}; rFVIIa: no recommendation	Not approved: PCC or aPCC at a dose of 25 to 50 IU kg^{-1}; rFVIIa: no recommendation	Not approved: PCC or aPCC at a dose of 25 to 50 IU kg^{-1}; rFVIIa: no recommendation
Venous thromboembolism prophylaxis after major orthopaedic surgery (hip or knee replacement surgery)				
Dosage	10 mg OD	2.5 mg BID	NA	220 mg OD
Dosage adjustments	No	No		150 mg × 1 daily if: CrCl 30 to 50 ml min^{-1}; or age ≥75; or concomitant use of verapamil, amiodarone or quinidine
Stroke prevention in nonvalvular atrial fibrillation				
Dosage	20 mg OD	5 mg BID	60 mg OD	150 mg BID
Dosage adjustments	15 mg daily if CrCl 15 to 50 ml min^{-1}	-2.5 mg BID if 2 of 3 criteria met: age ≥80 years; body weight ≤60 kg; Creatinine ≥133 μmol l^{-} - CrCl 15 to 29 ml min^{-1}: 2.5 mg BID	30 mg daily if: CrCl 15 to 50 ml min^{-1}; or - body weight ≤ 60 kg; or concomitant use of ciclosporin, dronedarone, erythromycin or ketoconazole	- 110 mg BID if: age≥80 years or concomitant use of verapamil - 110 mg or 150 mg BID if CrCl 30 to 50 ml min^{-1} or age 75 to 80 years
Acute venous thromboembolism treatment				
Dosage	15 mg BID × 21 days, then 20 mg OD	10 mg BID x 7 days, then 5 mg BID	60 mg OD	150 mg BID
Dosage adjustments	15 mg BID × 21 days, then 15 mg daily if CrCl 15 to 50 ml min^{-1}	No dose adjustment	30 mg daily if: - CrCl 15 to 50 ml min^{-1}; or - body weight ≤60 kg; or concomitant use of - ciclosporin, - dronedarone, - erythromycin or - ketoconazole	- 110 mg BID if age ≥80 or concomitant use of verapamil - 110 or 150 mg BID if CrCl 30 to 50 ml min^{-1} or age 75 to 80 years.
Extended prevention of recurrent DVT and PE				
Dosage	10 mg OD or 20 mg OD	2.5 mg BID		
Dosage adjustments	consider 15 mg BID instead of 20 mg BID if CrCl 15 to 50 ml min^{-1} 10 mg: no adjustment	No		
Acute coronary syndrome				
Dosage	2.5 mg BID (plus aspirin 100 mg)	NA	NA	NA

Data from the respective SmPC; aPCC, activated prothrombin complex concentrate; BID, twice a day; CrCl, creatinine clearance (ml min^{-1}); NA, not approved; OD, once daily; PCC, prothrombin complex concentrate; rFVIIa, recombinant activated factor VII. References (5/11/2020), https://www.ema.europa.eu/en/documents/product-information/xarelto-epar-product-information_en.pdf; https://www.ema.europa.eu/en/documents/product-information/apixaban-accord-epar-product-information_en.pdf; https://www.ema.europa.eu/en/documents/product-information/lixiana-epar-product-information_en.pdf; https://www.ema.europa.eu/en/documents/product-information/pradaxa-epar-product-information_en.pdf; https://www.ema.europa.eu/en/medicines/human/EPAR/ondexxya; https://www.ema.europa.eu/en/medicines/human/EPAR/praxbind.

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and in 80% of patients with intracranial bleeding, 'excellent' or 'good' haemostatic efficacy was observed at 12 h, as adjudicated according to prespecified criteria. Fourteen percent of the patients died within 30 days after study inclusion. Thrombotic events occurred in 10% of patients, none of whom had yet restarted oral anticoagulation. However, andexanet alfa binds to tissue factor pathway inhibitors (TFPI) as well, which may lead to increased thrombin generation and may explain the higher rate of thromboembolic complications compared with similar studies.[11] Prior to the initiation of andexanet alfa, the dose is adjusted according to the timing of the last intake of the FXa inhibitor. Low dose consists of an intravenous bolus of 400 mg at 30 mg min^{-1}, followed by an infusion of 480 mg at 4 mg min^{-1}. High dose consists of a double bolus of 800 mg followed by an infusion of 960 mg at 8 mg min^{-1}. For clinical practice, it is important to consider that the use of andexanet alfa for mild, nonlife-threatening bleeding and for patients undergoing urgent or immediate high-risk surgery has not been investigated. Similarly, to the REVERSE-AD study, the ANNEXA-4 trial was a noncontrolled and nonrandomised study with biomarkers as the primary (Reverse-AD) or co-primary (ANNEXA-4) outcome variables. Based on the data of the ANNEXA-4 trial, the European Medical Agency (EMA) and the Food and Drug Administration (FDA)-approved andexanet alfa for adult patients treated with the direct FXa inhibitors apixaban or rivaroxaban when reversal of anticoagulation is needed because of life-threatening or uncontrolled bleeding.

Haemostatic interventions with prothrombin complex, activated prothrombin complex, and rFVIIa

PCC, aPCC, and rFVIIa have been investigated for their effectiveness to treat bleeding disorders associated with recent intake of DOACs.

PCCs are lyophilised, human plasma-derived vitamin K-dependent factors containing FII (prothrombin), FVII, FIX, and FX. Potentially, three-factor PCCs that lack FVII could also be used but they are rather uncommon in Europe. As PCCs were originally used for FIX replacement in patients with haemophilia B, their potency is standardised to FIX content (about 500 international units per vial). Some PCCs might also contain protein C and S as well as small amounts of heparin or antithrombin.[12]

aPCC are used for controlling bleeding in haemophilia patients with inhibitors. They are composed mostly of nonactivated FII, FIX, and FX and activated FVII as well as small amounts of proteins C and S. They have been used to manage peri-operative bleeding in both nonhaemophilic and haemophilic patients. Further, PCC and aPCC have been suggested as a factor replacement approach to manage DOAC-associated life-threatening bleeding.[13,14] The approach using PCC or aPCC for the management of indirect reversal strategy of DOAC-induced bleeding aims to raise the levels of vitamin K-dependent coagulation factors, notably FX for FXa inhibitors and prothrombin for dabigatran. Eventually, they will increase thrombin generation, although the exact mechanism for the treatment of DOAC-associated bleeding is not known.[15] Treatment with PCC, aPCC or rFVIIa unevenly increases the concentration of several coagulation factors, including prothrombin which has the longest half-life of approximately 60 h of all these coagulation factors.[16] Thrombin generation may, therefore, be enhanced for several days after the use of PCCs to treat or to prevent major bleeding in trauma or the peri-operative setting.[17] This may increase the risk thromboembolic complications after treatment with PCC or aPCC.[5]

Recombinant FVIIa induces thrombin generation and increases FXa activity[18,19] and has been associated with an increased rate of thromboembolic complications in nonhaemophilic patients with intracranial haemorrhage.[20]

Materials and methods

A panel of seven experts including three members of the Subcommittee 'Fluid, Transfusion and Haemostasis' from the European Society of Anaesthesia and Intensive Care (ESAIC) convened in 2019 to assess the latest available published evidence on the clinical management of life-threatening bleeding under DOACs. A proposal was submitted to the ESAIC guideline committee for approval of title and scope of this guideline while acknowledging the need for logistic and methodological support.

Following the 2019 Euroanaesthesia conference, scientific queries of interest were defined by the authors and formulated into 14 PICO's (population/intervention/comparison/outcome) by three authors (CvH, CFE, OG, Appendix, http://links.lww.com/EJA/A924, http://links.lww.com/EJA/A925). These PICOs were revised and merged during a discussion process among all authors resulting in a complete list of nine PICOs. These PICOs were subsequently approved by the task force in consultation with the methodologist (AA) (Table 2).

Criteria for considering studies for data analysis and search results

Data analysis was based on all randomised, parallel, quasi-randomised studies (including cross-over design) and observational studies that addressed the above queries. Systematic reviews and meta-analyses were considered on a case-by-case basis when meeting inclusion criteria. Data from quasi-randomised and observational and large retrospective studies were included as very few if any randomised controlled trials (RCTs) were anticipated. Case reports were removed from all databases. However, in case of a lack of evidence, case reports were

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Table 2 Summary of guidance

Summary of guidance	
Clinical scenario: Adults under DOAC therapy undergoing urgent surgery. Should laboratory monitoring be used in DOAC patients scheduled for urgent surgery? If yes, which laboratory monitoring should be applied?	
R 1.1	In patients without impaired kidney and/or liver function complying with the recommended stopping intervals (24 h for low bleeding risk, 48 to 72 h for high-bleeding risk surgery), DOAC-specific coagulation testing is not necessary. (2B)
R 1.1	Measurement of DOAC levels is suggested, when stopping intervals cannot be adhered to or in patients with risk factors for elevated DOAC levels. (2C)
R 1.3a	Global coagulation tests including prothrombin time (PT) and activated partial thromboplastin time (aPTT) are not recommended to exclude relevant DOAC concentrations. (2B)
R 1.3b	In patients on FXa inhibitors with a high bleeding risk, the use of anti-FXa activity is suggested. (2B)
R 1.3c	In patient on dabigatran with a high bleeding risk, the use of the diluted thrombin time (dTT) or the thrombin time (TT) is suggested. (2B)
Clinical scenario: Adults under DOAC therapy undergoing urgent surgery. Which test should be used: Point of care monitoring (POC) vs. non-POCT (standard laboratory) measurements and which assay (i.e. concentration/functional monitoring)?	
R 2.1	We do not suggest the use of nonspecific viscoelastic coagulation monitoring to reliably detect DOAC levels. (2B)
R 2.2	If available, we suggest considering the use of specific tests (Ecarin clotting time and the Russell's viper venom test) in viscoelastic coagulation monitoring to exclude DOAC plasma levels. (2C)
R 2.3	In the absence of specific coagulation testing, DOAC dipstick testing can be suggested to demonstrate the presence of DOACs. (2C)
Clinical scenario: Adults undergoing urgent surgery with DOAC therapy. Should the prevention and/or management of DOAC induced bleeding with antidotes and nonspecific haemostatic agents (PCC, aPCC) be based on DOAC level monitoring?	
R 3.1	In urgent surgery and when time permits, we suggest a 'wait and see strategy' to reduce anticoagulant activity. A predose lab sample should be taken. (3)
R 3.2a	In urgent surgery, we suggest using DOAC concentration measurement to guide the administration of antidotes or nonspecific haemostatic agents. (2C)
R 3.2b	If DOAC monitoring is not available, and surgery cannot be delayed, antidote and nonspecific haemostatic treatment should depend on the clinical severity of bleeding. (3)
R 3.3a	When urgent surgery with high risk of bleeding cannot be delayed, and if relevant residual concentration of dabigatran is suspected, specific antidote therapy with idarucizumab is recommended without waiting for DOAC level monitoring. However, a predose lab sample should be taken. (1C)
R 3.3b	If idarucizumab is not available, PCC or aPCC may be used for the urgent surgical setting in patients on dabigatran without waiting for DOAC level monitoring. A predose lab sample should be taken. (3)
R 3.4	When urgent surgery with high risk of bleeding cannot be delayed, and if relevant residual concentration of FXa inhibitors is suspected, andexanet alfa, PCC or aPCC is suggested without waiting for DOAC level monitoring. However, a predose lab sample should be taken. (3)
R 3.5	In urgent surgery with a high risk of bleeding, the plasma concentrations of DOACs above 50 ng ml^{-1} may be considered for haemostatic or antidote intervention. (3)
R 3.6	In cardiac surgery under FXa inhibitors, we recommend not to use andexanet alfa. The use of haemadsorption filters may be considered. (3)
Clinical scenario: Adults undergoing urgent surgery with DOACs therapy. Should laboratory measurements be performed after reversal (which time frame of measurements)?	
R 4.1	After specific reversal of dabigatran with idarucizumab, we suggest to assess dabigatran concentrations by the diluted thrombin time (dTT) test or the thrombin time (TT) regularly for at least 48 h because of potential drug rebound. (2B)
R 4.2	After specific reversal of direct FXa inhibitors with andexanet alfa, caution is advised in interpretation of the concentration measurements as anti-FXa activities are influenced by andexanet alfa. (3)
R 4.3	After administration of nonspecific haemostatic treatment in patients with elevated or suspected high levels of direct FXa inhibitors, it is unclear when and whether anti-FXa levels should be re-assessed. Conventional coagulation testing including PT or aPTT may indicate normalisation for several hours despite insufficient haemostasis. (3)
Clinical scenario: DOAC-treated adult patients with traumatic and nontraumatic intra cerebral haemorrhage without need for surgery. Are antidotes or nonspecific haemostatic agents indicated for DOAC-treated patients with traumatic and nontraumatic ICH without need for surgery?	
R 5.1	We recommend antidote reversal or nonspecific haemostatic agents to prevent increasing haematoma volume. (1C)
R 5.2a	We recommend the use of idarucizumab for the reversal of dabigatran-associated intracerebral bleeding. (1C)
R 5.2b	PCC or aPCC may be considered for patients taking dabigatran if idarucizumab is not available. (3)
R 5.3	We suggest the use of andexanet alfa or PCC to prevent increasing haematoma volume following apixaban and rivaroxaban-associated intracerebral bleeding. If andexanet alfa or PCC are not available, aPCC may be considered. (2C)
R 5.4	PCC may be considered for patients taking edoxaban. (3)
Clinical Scenario: Nonbleeding adults with overdose of DOACs not considered for urgent or elective surgery. Should reversal agents be used to manage nonbleeding patients with an overdose of DOAC?	
R 6.1	We suggest not to reverse dabigatran or FXa inhibitors in the absence of bleeding. (3).
R 6.2	We suggest general measures to eliminate FXa inhibitors, which may include stimulation of diuresis and/or haemadsorption. (2 C)
R 6.3	We suggest the stimulation of diuresis and the use of haemodialysis in the haemodynamically stable patient with dabigatran overdose. In early dabigatran overdose, activated charcoal may be considered. (2C)
Clinical scenario: Adult patients under FXa inhibitor therapy, who present with severe bleeding in urgent surgical or nonsurgical settings. Should andexanet alfa or PCC, aPCC or rFVIIa be used to manage FXa inhibitor-associated bleeding in urgent surgical or nonsurgical settings?	
R 7.1	We recommend that PCC or andexanet alfa should be considered in patients under FXa inhibitor therapy presenting with severe bleeding. However, the superiority of one agent over another has not been demonstrated. (1C)
R 7.2	In the absence of the availability of andexanet alfa and PCC, aPCC may be considered in patients under FXa inhibitor therapy presenting with severe bleeding. (2C)
R 7.3	Due to the paucity of clinical data, we are unable to provide any recommendation for the use of rFVIIa in patients under FXa inhibitor therapy presenting with severe bleeding. (3)
Clinical scenario: Adult patients under dabigatran therapy, who present with severe bleeding in urgent surgical or nonsurgical settings. Should idarucizumab or PCC, aPCC or rFVIIa be used to manage dabigatran associated bleeding in urgent surgical or nonsurgical settings?	
R 8.1	We recommend that idarucizumab should be considered in patients under dabigatran therapy presenting with severe bleeding or in urgent surgical or nonsurgical settings. (1 C)
R 8.2	In the absence of the availability of idarucizumab, we suggest the use of PCC or aPCC. However, the superiority of one agent over another has not been demonstrated. (2C)
R 8.3	Due to the paucity of clinical data, we are unable to provide any recommendation for the use of rFVIIa. (3)
Clinical scenario: Invasive nonsurgical procedures with a high risk of bleeding under DOAC therapy in adults. Should reversal agents be used before an urgent invasive procedure, including regional anaesthesia, aortic stent placement, and so forth?	
R 9.1	In patients on dabigatran who are undergoing urgent invasive procedures with a high risk of bleeding, idarucizumab is recommended to reduce levels of dabigatran in order to normalise coagulation. (1C)
R 9.2	Andexanet alfa has not been investigated before urgent invasive procedures. We are unable to provide any recommendation for the use of andexanet alfa nor for any haemostatic agents. (3)

aPCC, activated PCC; aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; PCC, prothrombin complex concentrate; PT, prothrombin time; rFVIIa, recombinant activated factor VII; TT, thrombin time.

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allowed to be added by the individual authors to answer the PICOs.

Types of interventions and comparators

Searches were based on DOAC (Population) and the intervention (Measurement of DOAC/anticoagulants or reversal/antidote).

Search methods for identification of studies

The electronic database search was run on 10 February 2021 by Cochrane Trial Search Specialist (JV) and included articles published since 2010 to increase clinical relevance. For more information on the search strategy and the search results, please see appendix, http://links.lww.com/EJA/A924, http://links.lww.com/EJA/A925. The panel members were also encouraged to add any missing papers of interest that they were aware of and to conduct related searches themselves. This was carried out by all authors subsequently.

Search results

Literature search bundles and corresponding structured search strategies were developed and conducted in Medline (3890), EMBASE (3830), Web of Science (2828), Epistemonikos (77) and Cochrane Central Register of Controlled Trials (CENTRAL, 769). After removing all duplicates, the titles resulting from the searches were screened by all authors. Relevant full-text articles were retrieved and assessed in detail. Furthermore, the authors were allowed to recommend inclusion of any landmark study or relevant articles published after the search date during the entire process of guideline creation. The decision to include any relevant study was undertaken subsequent to voting by the entire task force for each article of relevance. This decision was taken to compensate for the COVID-related delay in the guideline drafting process.

The authors aimed to include a restricted number of supporting references to support each recommendation as part of a brief accompanying rationale, with studies of the best available quality from any publication date given priority. A total number of 138 studies were included for this evidence synthesis.

Recommendations were formulated and graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (Table 3)[21] and in accordance with ESAIC methodology guidelines. Recommendations, grading and rationales were initially drafted and critically reviewed by the entire author group for review prior to the virtual consensus process and in between each round of virtual meetings. The quality of the literature cited to support each recommendation was reviewed separately by the methodologist (AA), who applied Cochrane risk-of-bias assessment criteria for RCTs. For non-RCT, the Scottish Intercollegiate Guideline Network (SIGN) checklists (https://www.sign.ac.uk/what-we-do/methodology/checklists/) was used to assess risk of bias of the included studies prior to grading and drafting recommendations, suggestions or clinical practice statements in accordance with GRADE for guidelines and ESAIC SOPs for guidelines.

Authors participated in a series of six virtual consensus conferences during 2022, and three virtual Delphi method rounds in 2023 during which the wording and grading of each recommendation was finalised and confirmed by voting members of the expert panel (Table 2). For the clinical scenarios of urgent surgery, life-threatening and non-life-threatening bleeding different flow charts comprising relevant recommendations and clinical practice statements have been developed that may help to inform clinicians to manage these scenarios successfully (Figs. 1–3).

Grading was confirmed and disagreements resolved in consultation with the methodologist (AA). During the virtual consensus conferences, it became apparent to the entire task force that there was a great degree of overlap between the various PICOs and the included references. This resulted initially in many similar recommendations and suggestions for various PICOs. To increase the clinical relevance, while avoiding repetition and with the aim of a higher degree of implementation in clinical practice, the task force decided after consultation with the methodologist to merge several overlapping PICOs into nine final PICOs prior to the Delphi method rounds:

1. Should laboratory monitoring be used in DOAC patients scheduled for urgent surgery? If yes, which laboratory monitoring should be applied?
2. Which test should be used: point of care monitoring vs. non-POCT (standard laboratory) measurements and which assay (i.e. concentration/functional monitoring)?
3. Should the prevention and/or management of DOAC-induced bleeding with antidotes and nonspecific haemostatic agents (PCC, aPCC) be based on DOAC level monitoring?
4. Should laboratory measurements be performed after reversal (which time frame of measurements)?
5. Are antidotes or nonspecific haemostatic agents indicated for DOAC-treated patients with traumatic and nontraumatic ICH without need for surgery?
6. Should reversal agents be used to manage nonbleeding patients with an overdose of DOAC?
7. Should PCC, andexanet alfa, aPCC or rFVIIa be used to manage factor Xa inhibitor-associated bleeding?
8. Adult patients under dabigatran therapy, who present with severe bleeding in urgent surgical or nonsurgical settings.
9. Invasive nonsurgical procedures with a high risk of bleeding under DOAC therapy in adults.

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Table 3 GRADE definitions

Grade of Recommendation	Clarity of risk/benefit	Quality of supporting evidence
1A Strong recommendation, high quality evidence	Benefits clearly outweigh risk and burdens, or vice versa.	Consistent evidence from well performed randomised, controlled trials or over-whelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.
1B Strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa.	Evidence from randomised, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate.
1C Strong recommendation, low quality evidence	Benefits appear to outweigh risk and burdens, or vice versa.	Evidence from observational studies, unsystematic clinical experience, or from randomised, controlled trials with serious flaws. Any estimate of effect is uncertain.
2A Weak recommendation = suggestion, high quality evidence	Benefits closely balanced with risks and burdens.	Consistent evidence from well performed randomised, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.
2B Weak recommendation = suggestion, moderate quality evidence	Benefits closely balanced with risks and burdens, some uncertainly in the estimates of benefits, risks and burdens.	Evidence from randomised, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate.
2C Weak recommendation = suggestion, low quality evidence	Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens.	Evidence from observational studies, unsystematic clinical experience, or from randomised, controlled trials with serious flaws. Any estimate of effect is uncertain.
3 Clinical practice statement	High uncertainty in the estimates of benefits, risks, and burdens; benefits may outweigh risks and burdens.	Evidence from observational studies, unsystematic clinical experience, case reports or extrapolated from other settings and populations from trials with serious flaws. Any estimate of effect is uncertain.

For more information on which PICOs were merged, please see Supplementary Appendix, http://links.lww.com/EJA/A924, http://links.lww.com/EJA/A925. Following final revisions, manuscript collation and approval by the author group, the manuscript was submitted to ESAIC guideline committee, ESAIC board and all ESAIC members for an open-peer review assessment in May 2023.

Discussion

The present guideline summarises available evidence on proper management of bleeding complications with or without the need of acute surgery among DOAC-treated patients. The original purpose of this project was to provide clinicians with a set of meaningful recommendations regarding monitoring, strategies for planning surgery and choice of antidote or haemostatic therapy.

In summary, our recommendations are clearly dependent on the specific clinical situation. As all DOAC have a relatively rapid effect offset, a 'wait-and-see strategy' is in general recommended awaiting natural elimination of the drug. However, in life-threatening bleeding, or if emergency surgery is needed, active treatment with antidote or haemostatic therapy may be needed. In all cases, laboratory monitoring is recommended, although in urgent situations, results should not be awaited.

The era of specific antidotes for DOAC has evolved within a short period of time, whereby the number and scientific quality of relevant studies are low, especially lacking published randomised controlled trials. This implies that only a few grade 1 recommendations could be given and hampers drawing definite conclusions about the efficacy of specific reversal and nonspecific haemostatic agents.

For life-threatening or nonlife threatening bleeding in which a 'wait and see strategy' is not clinically applicable, we recommend the antidote idarucizumab for dabigatran, PCC for edoxaban while the antidote andexanet alfa and PCC are equal treatment options for apixaban and rivaroxaban. This aligns with recent published guidelines from the European Society of Anaesthesiology and Intensive Care from April 2023,[22] with the exception that PCC rather than andexanet alpha in patients treated with anti-FXa agents (rivaroxaban and apixaban) is recommended (grade 2C) in bleeding patients and opposite to a European guideline on management of major bleeding and coagulopathy following trauma that recommends only PCC if andexanet alfa is unavailable in life-threatening bleeding and the presence of apixaban or rivaroxaban.[23]

During the reviewing process of this guideline preliminary results of the prospective, randomised ANNEXA-I study that investigated the efficacy of andexanet alfa vs. usual care therapy in patients with intracranial haemorrhage were published during an oral presentation at the World Stroke Congress in October 2023. The study was prematurely stopped after a planned interim analysis of 452 patients and the results indicate a significantly higher efficacy of andexanet alfa as compared with usual care that including 86% of patients having been treated with PCC. However, the treatment with andexanet alfa showed a significantly higher rate of thromboembolic events and the mortality between the groups was not different at 30 days. The majority of the guideline authors decided to not wait for the full publication of this study,

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Fig. 1 Treatment algorithm for the management of patients with confirmed intake of direct oral anticoagulants before urgent surgery.

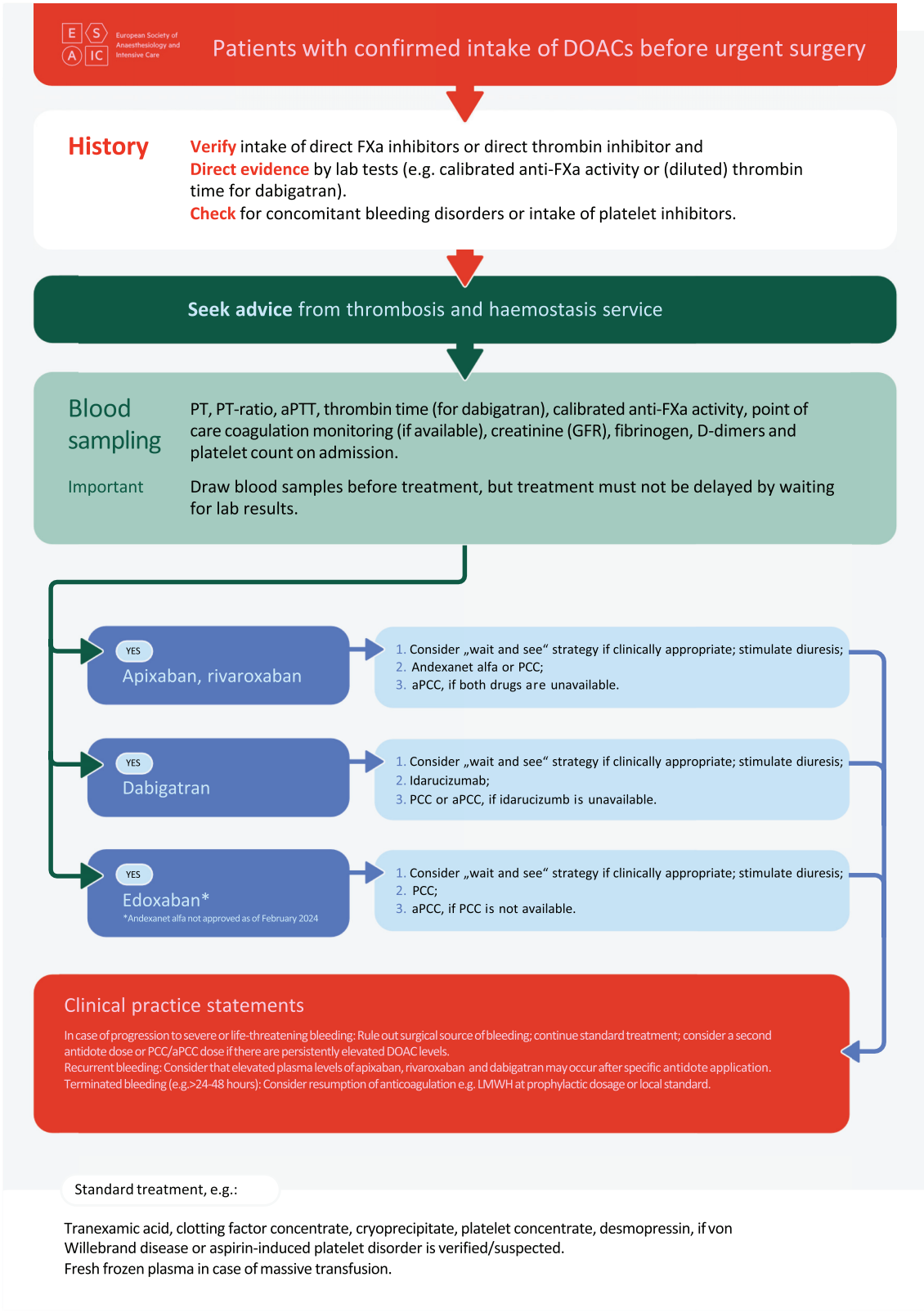

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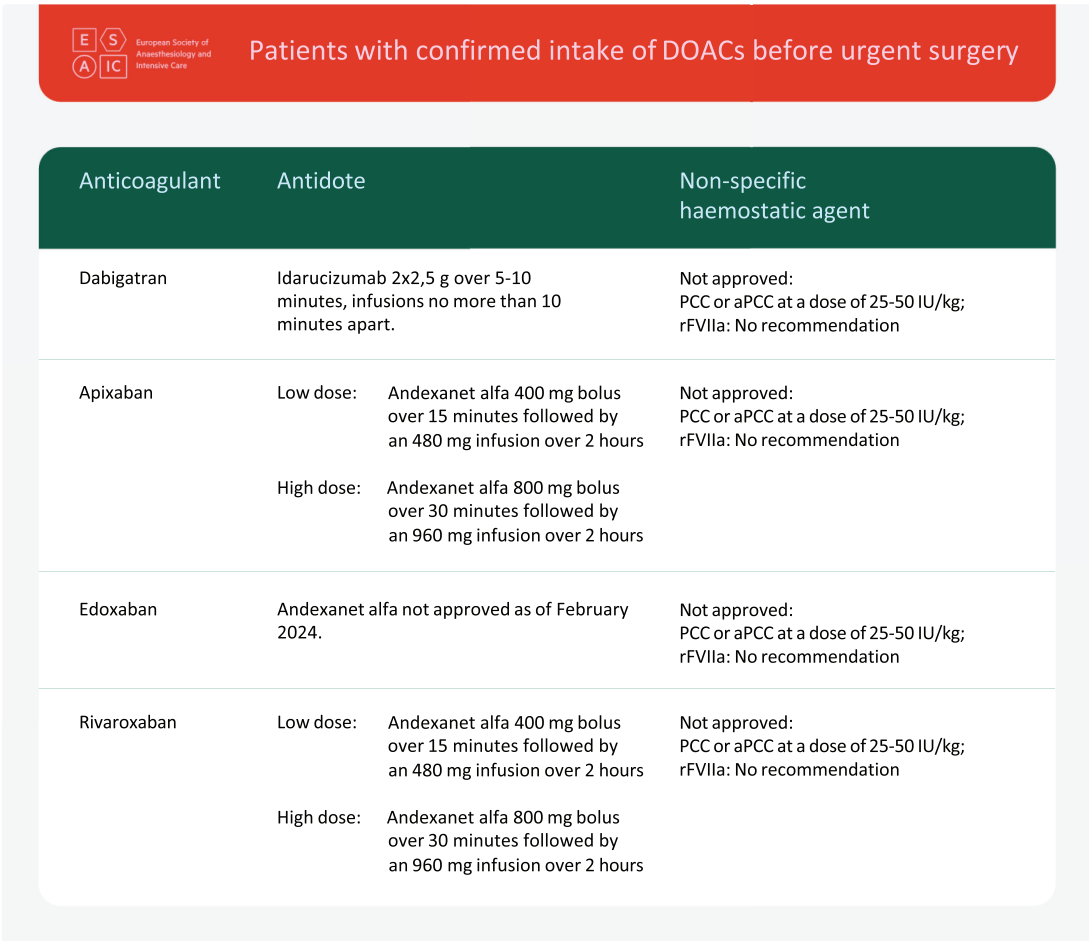
Fig. 1 Continued.



as this would unnecessarily postpone the publication of this guideline for months and leave the readers without evidence-based recommendations for the management of life-threatening bleeding associated with FXa-inhibitors. Furthermore, the guideline group felt that access to the full study data only would justify a potential revision of clinical recommendations regarding the use of andexanet alfa and nonhaemostatic therapies.

Apart from this study, for all published recommendations so far the level of evidence is low to very low whereby recommendations given are weak. This guideline is associated with several limitations. First, only a few of the recommendations are based on high-quality evidence, a fact that highlights the need for future research in this area. Second, to support a more general approach to the trauma patient, specific recommendations for special populations such as paediatric patients or patients with traumatic brain injury (TBI) have not been included. Third, these guidelines are limited to recommendations for which implementation is likely to be feasible within most European healthcare systems.

Finally, the present evaluation of medical therapeutic options for DOAC-related bleeding has focused on clinical outcomes, including side effects. However, it has to be noted that there are different costs associated with the suggested drugs that may influence decision-making in clinical routine. Despite the fact that this guideline concerns the evaluation of the published evidence, we cannot rule out that financial considerations may influence recommendations on the choice of drugs.

PICO 1

Clinical scenario: Adults under DOAC therapy undergoing urgent surgery.

Should laboratory monitoring be used in DOAC patients scheduled for urgent surgery? If yes, which laboratory monitoring should be applied?

Recommendation

R 1.1: In patients without impaired kidney and/or liver function complying with the recommended stopping intervals (24 h for low bleeding risk, 48 to 72 h for

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Fig. 2 Treatment algorithm for the management of patients with non-life threatening bleeding.

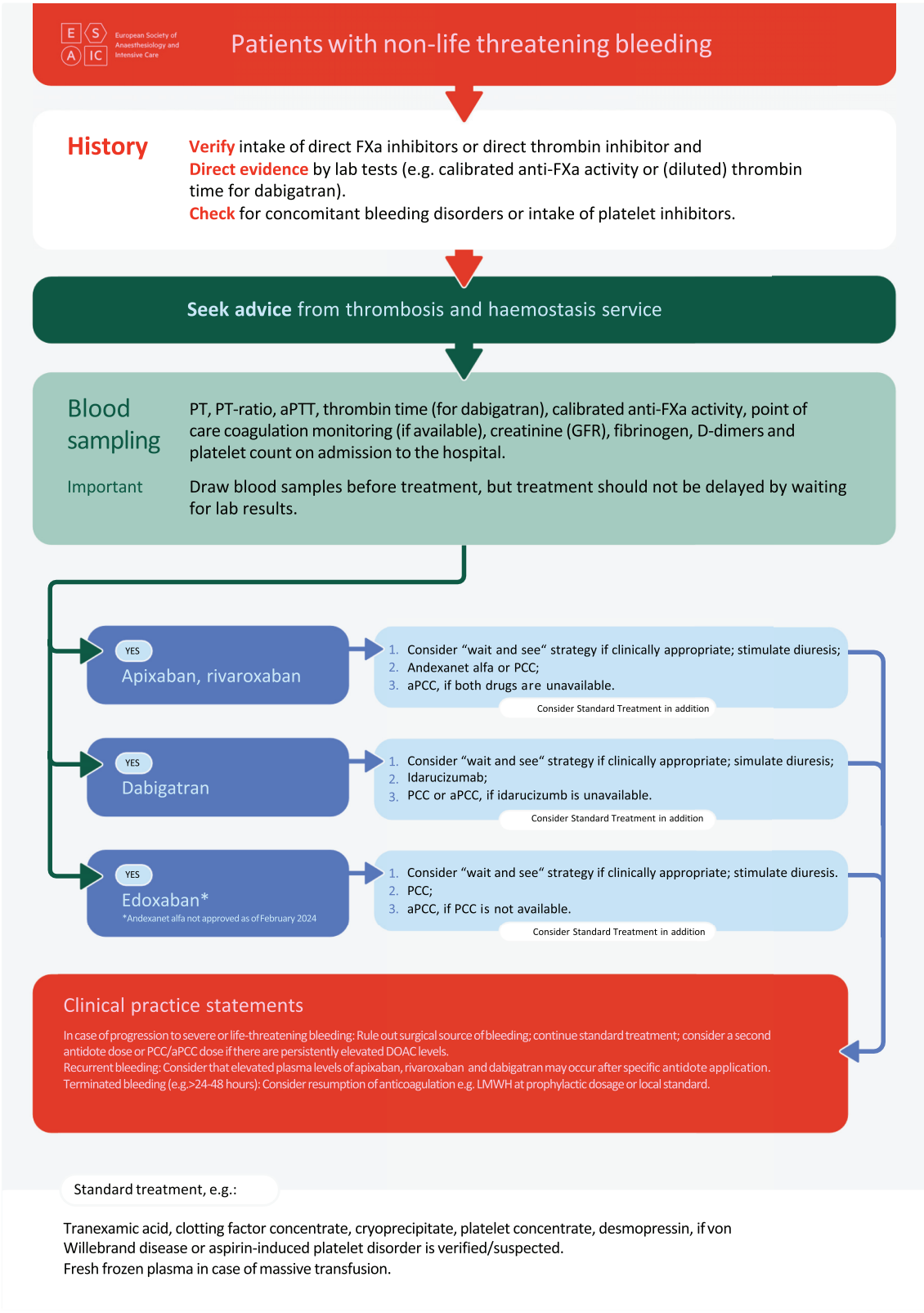

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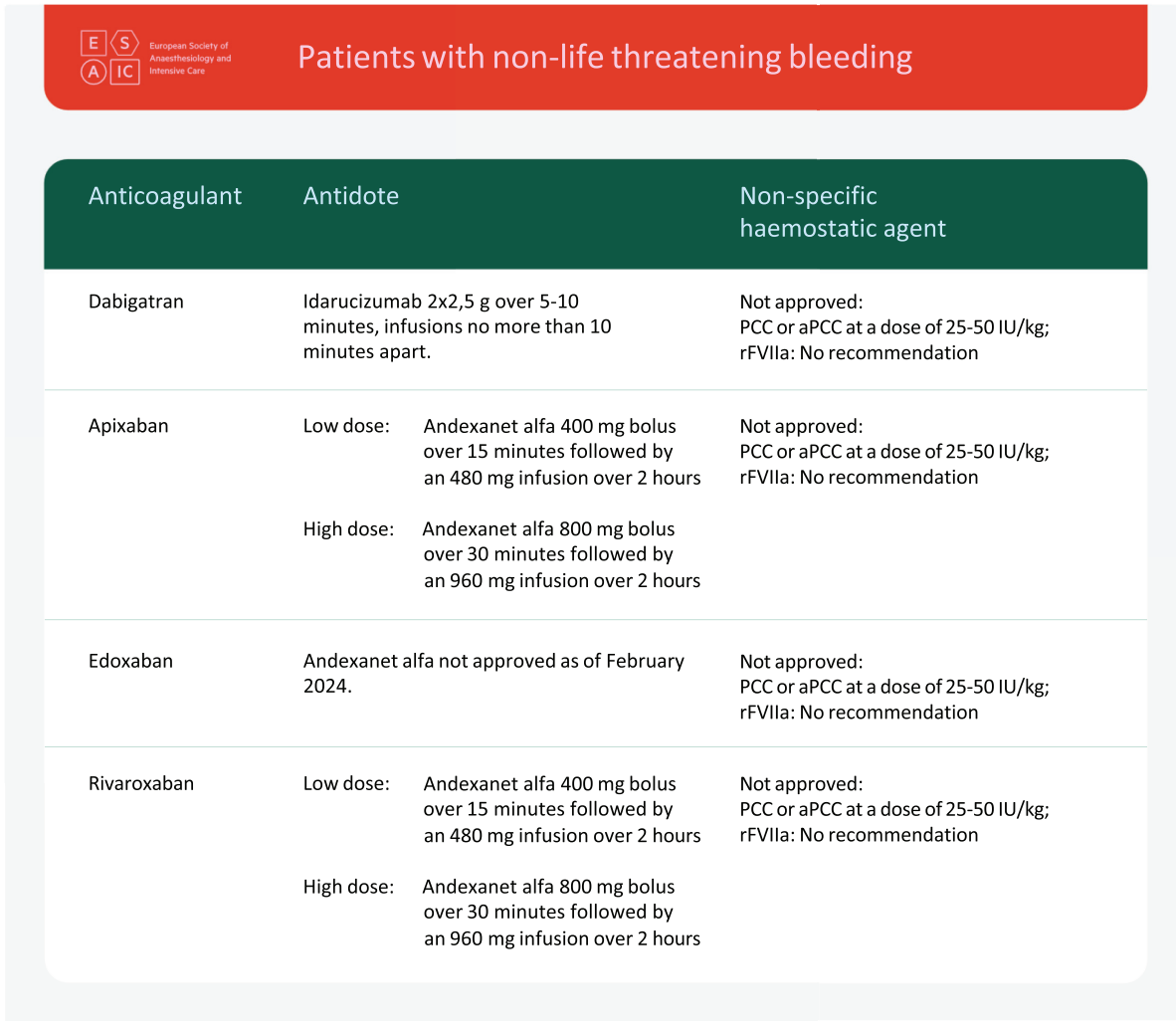
Fig. 2 Continued.



Anticoagulant	Antidote	Non-specific haemostatic agent
Dabigatran	Idarucizumab 2x2,5 g over 5-10 minutes, infusions no more than 10 minutes apart.	Not approved: PCC or aPCC at a dose of 25-50 IU/kg; rFVIIa: No recommendation
Apixaban	Low dose: Andexanet alfa 400 mg bolus over 15 minutes followed by an 480 mg infusion over 2 hours High dose: Andexanet alfa 800 mg bolus over 30 minutes followed by an 960 mg infusion over 2 hours	Not approved: PCC or aPCC at a dose of 25-50 IU/kg; rFVIIa: No recommendation
Edoxaban	Andexanet alfa not approved as of February 2024.	Not approved: PCC or aPCC at a dose of 25-50 IU/kg; rFVIIa: No recommendation
Rivaroxaban	Low dose: Andexanet alfa 400 mg bolus over 15 minutes followed by an 480 mg infusion over 2 hours High dose: Andexanet alfa 800 mg bolus over 30 minutes followed by an 960 mg infusion over 2 hours	Not approved: PCC or aPCC at a dose of 25-50 IU/kg; rFVIIa: No recommendation

high-bleeding risk surgery), DOAC-specific coagulation testing is not necessary. **(2B)**

R 1.2: Measurement of DOAC levels is suggested, when stopping intervals cannot be adhered to or in patients with risk factors for elevated DOAC levels. **(2C)**

R 1.3a: Global coagulation tests including prothrombin time (PT) and activated partial thromboplastin time (aPTT) are not recommended to exclude relevant DOAC concentrations. **(2B)**

R 1.3b: In patients on FXa inhibitors with a high bleeding risk, the use of anti-FXa activity is suggested. **(2B)**

R 1.3c: In patients on dabigatran with a high bleeding risk, the use of the diluted thrombin time (dTT) or the thrombin time (TT) is suggested. **(2B)**

Rationale: The recommended DOAC stopping intervals before elective surgery are 24 h for minor surgery with a low bleeding risk and at least 48 h for major surgery with a high bleeding risk. Longer interruption intervals of up to 96 h should be considered in patients with risk factors for elevated DOAC levels (e.g. renal and/or hepatic insufficiency), especially in patients with dabigatran intake.[24–27] This approach without additional laboratory coagulation testing has been proven to be safe and effective in elective noncardiac surgery.[28]

No RCT or large cohort studies on DOAC-specific testing including calibrated anti-FXa activity or dTT have been performed in urgent situations or emergency surgery when stopping intervals often cannot be precisely determined. Of note, DOAC-specific testing is infrequently requested and performed in emergency settings.[28–30] However, a cohort study in bleeding

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Fig. 3 Treatment algorithm for the management of severe (haemodynamically unstable) or life-threatening bleeding (intracerebral, epidural, intraspinal, gastrointestinal, traumatic or other refractory bleeds).

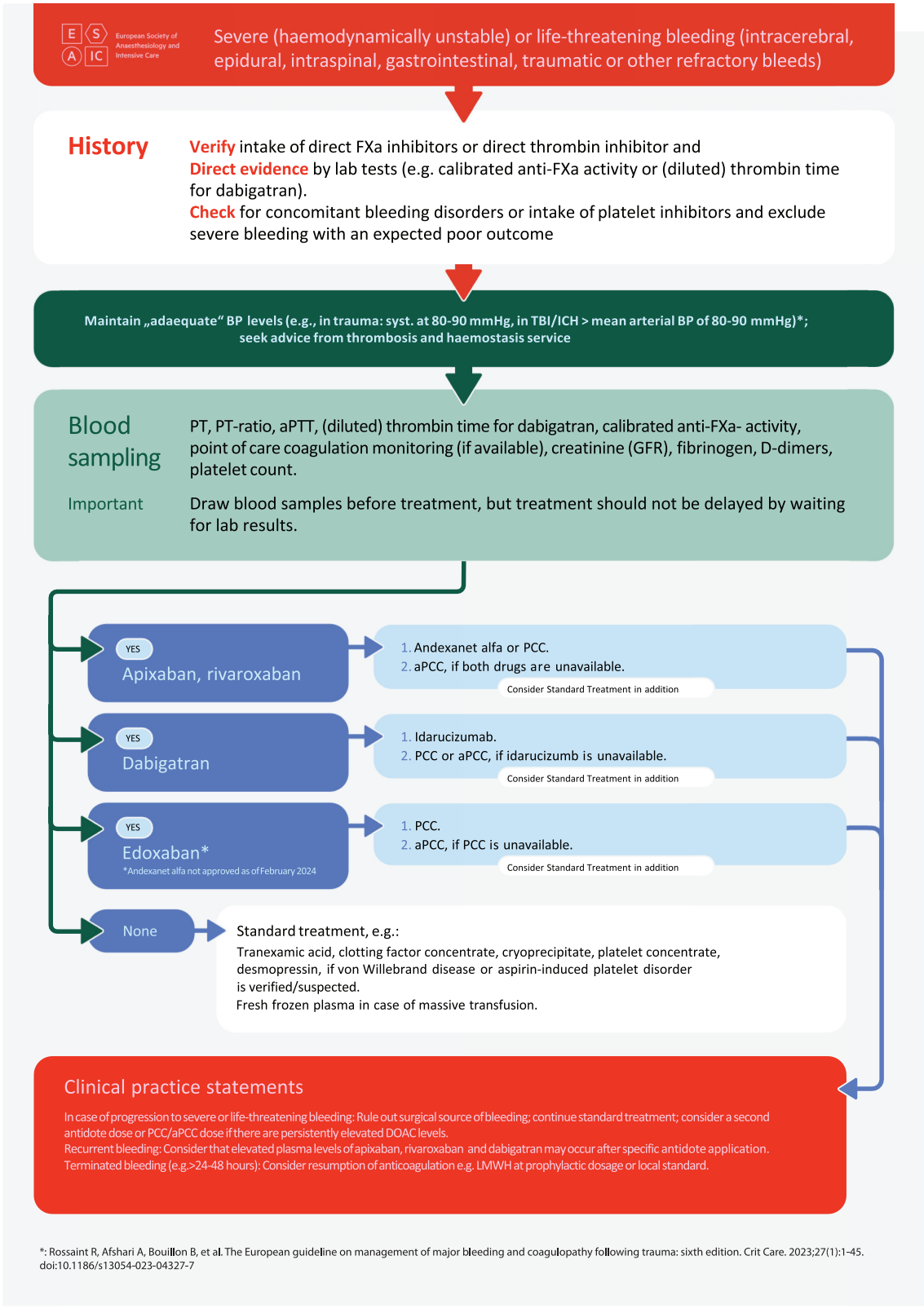

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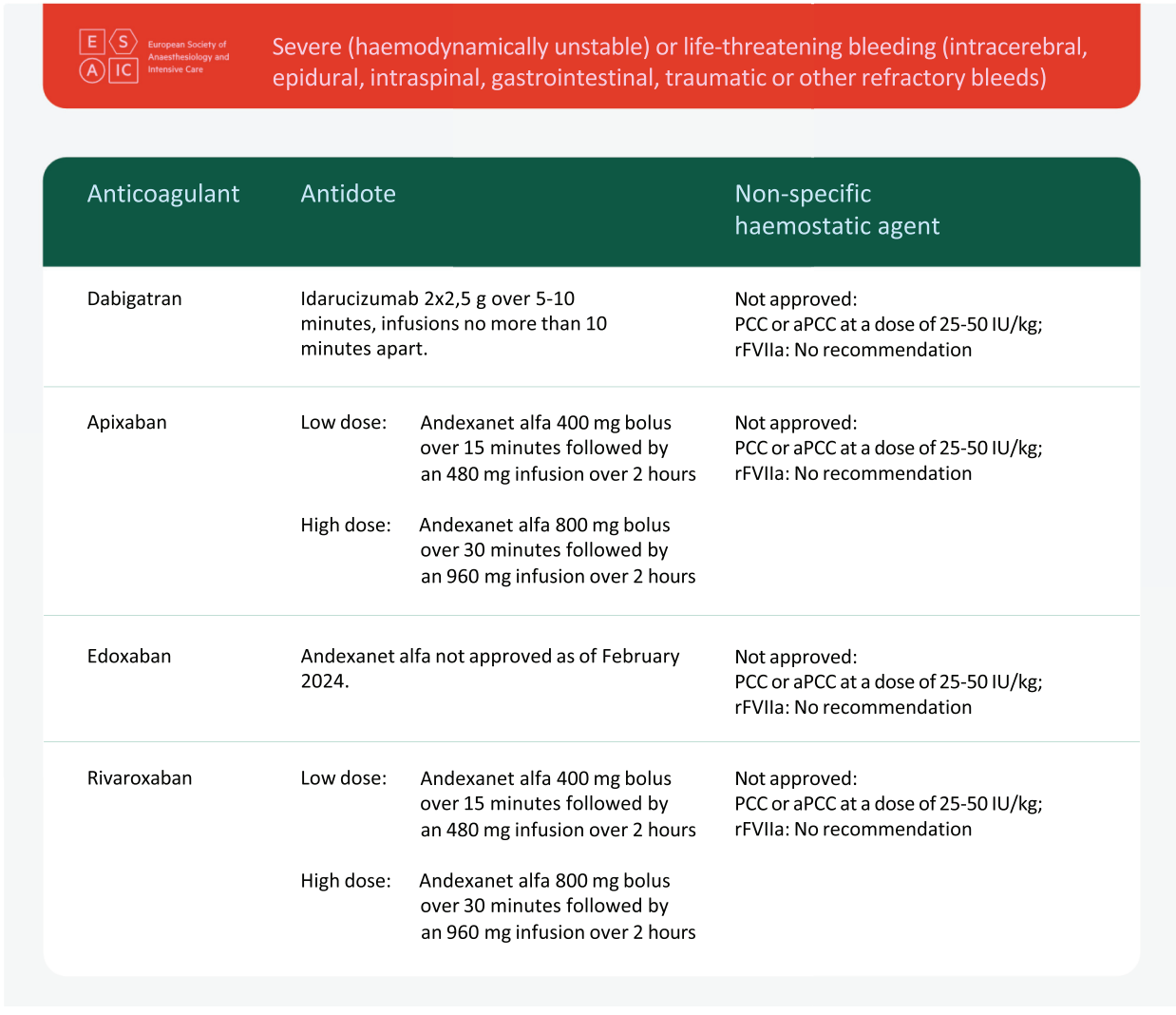
Fig. 3 Continued.



patients with recent intake of DOAC (median time since last intake: 12 h) reported DOAC plasma concentrations greater than 50 mg l^{-1} and greater than 400 mg l^{-1} in greater than 90 and 6.6% of patients, respectively.[31]

Different risk factors for higher than expected DOAC concentrations have been identified in a secondary analysis of the PAUSE study[32] and in a single-centre cohort study[33]: shorter interruption interval,[32] creatinine clearance 50 ml min^{-1} or less,[32,33] age at least 75 years,[32] female sex[32] and concomitant intake of amiodarone.[33] Thus, in patients scheduled for urgent or emergency surgery or in case of above-mentioned risk factors, specific coagulation testing might be considered to better estimate bleeding risk and discuss whether delay of surgery is potentially beneficial. However, if urgent surgery cannot be postponed, clinicians must not wait for laboratory results before treatment (Fig. 1).

The drug-specific, calibrated anti-FXa assays should be used for determination of concentrations of direct FXa inhibitors as a 'gold standard'. If not available, the chromogenic anti-FXa assays calibrated for unfractionated heparin, which are available in many institutions, can estimate the anti-FXa activity of rivaroxaban,[34–36] apixaban,[34–36] and edoxaban.[37] Strong to very strong correlations between DOAC levels and unfractionated heparin-calibrated anti-FXa assays over a broad range of drug concentrations (20 to 500 ng ml^{-1}) have been shown.[34,35] Anti-Xa tests calibrated for unfractionated heparin-also allow for the safe detection of relevant anticoagulant activity (>30/50 ng ml^{-1}) with a very good positive predictive value (PPV 0.96; 95% CI, 0.92 to 0.99).[35] Of note, the sensitivity of available anti-FXa assays may substantially differ depending on the manufacturer, the methodology, the calibrator and the specific FXa inhibitor, leading to different conversion factors to estimate anti-FXa activity.[35]

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For semi-quantitative assessment of dabigatran, dTT is recommended as the gold standard. Alternatively, the ECT or the thrombin time (TT) can be used to exclude relevant activity of dabigatran.[7]

Global coagulation tests including PT and aPTT the normal range are not suited to safely identifying DOAC concentrations below the suggested, safe treatment threshold of 30 ng ml^{-1},[38] and their use can, therefore, not be recommended.

PICO 2

Clinical scenario: Adults under DOAC therapy undergoing urgent surgery.

Which test should be used: Point of care monitoring (POC) vs. non-POCT (standard laboratory) measurements and which assay (i.e. concentration/functional monitoring)?

Recommendation

R 2.1: We do not suggest the use of nonspecific viscoelastic coagulation monitoring to reliably detect DOAC levels. (**2B**)

R 2.2: If available, we suggest the use of specific tests (Ecarin clotting time and the Russell's viper venom test) in viscoelastic coagulation monitoring to exclude DOAC plasma levels. (**2C**)

R 2.3 In the absence of specific coagulation testing, DOAC dipstick testing can be suggested to demonstrate the presence of DOACs. (**2C**)

Rationale: POC coagulation testing allow for rapid and timely bedside coagulation testing. Chromogenic DOAC-specific or heparin-calibrated anti-Xa assays are unavailable as POC tests at the moment. The viscoelastic POC coagulation tests (VET) such as thromboelastography/thromboelastometry (TEG, ROTEM, ClotPro) or devices based on sonic estimation of elasticity via resonance (SEER) (TEG6S, Quantra) might be potentially useful to rapidly determine elevated DOAC levels before surgery. Different studies using VETs showed dose-dependent increases in clotting time (CT) for rivaroxaban, edoxaban, apixaban and dabigatran and good to very good correlations between DOAC levels and CT values.[39–42] However, low doses had minimal effects on CT only, and normal CT ROTEM EXTEM values do not allow to exclude residual DOAC activity and impairment of blood coagulation.[41–44] The use of a modified ROTEM technique using low-dose tissue factor (TF) activation might provide better sensitivity (up to 90%) and specificity (up to 85%) to detect FXa inhibitor concentrations greater than 30 ng ml^{-1}.[45] However, such modified ROTEM assays are not commercially available. Increasing dabigatran concentrations prolonged reaction time in kaolin-activated TEG with moderate correlation and inconsistent effect.[46]

Recently, DOAC-specific tests in VET devices have become available. Using the automated TEG 6S, such specific assays allow for the detection of DOACs with good sensitivity (>92%) and specificity (>95%).[39,41] Similarly, the ClotPro devices provides an ECT and a RVV test. A recent single centre study showed strong to very strong linear correlations between CT in ECT test and plasma concentration of dabigatran ($r = 0.969$), and between CT in RVV test and plasma concentrations of apixaban ($r = 0.739$), edoxaban ($r = 0.925$) and rivaroxaban ($r = 0.879$) in a total of 203 measurements from 108 trauma patients.[47] A CT in ECT test greater than 188 s provided 100% sensitivity and 90% specificity for dabigatran levels at least 50 ng ml^{-1}. However, two other studies found moderate correlations between dabigatran levels with CT in the ClotPro ECT[48] and with a POC ECT assay.[49] Using the ClotPro RVV test, a clotting time greater than 135 s provided 80% sensitivity and 100% specificity to detect apixaban levels at least 50 ng ml^{-1}. For edoxaban and rivaroxaban levels at least 50 ng ml^{-1}, the corresponding CTs in RVV test were greater than 167 s (100% sensitivity and 100% specificity) and greater than 176 s (90% sensitivity and 100% specificity), respectively.[47]

Further, elevated DOAC concentrations regularly prolong the activated clotting time (ACT) but correlations are poor, and a normal ACT might not allow for exclusion of relevant DOAC concentrations.[50]

Finally, a urine dipstick test might be used to detect DOAC in emergency settings and before urgent surgery within a few minutes. Studies including a total of more than 1000 patients and a meta-analysis showed that sensitivity, specificity, accuracy and predictive values and agreement between determination of DOAC levels in urine using the DOAC dipsticks were noninferior or superior as compared with mass spectroscopy.[51,52] However, these tests require patient urine, which might not be available in urgent or emergency situations.

PICO 3

Clinical scenario: adults undergoing urgent surgery with DOAC therapy.

Should the prevention and/or management of DOAC-induced bleeding with antidotes and nonspecific haemostatic agents (PCC, aPCC) be based on DOAC level monitoring?

Recommendations

R3.1: In urgent surgery and when time permits, we suggest a 'wait and see strategy' to reduce anticoagulant activity. A predose lab sample should be taken. **(3)**

R3.2a: In urgent surgery, we suggest using DOAC concentration measurement to guide the administration of antidotes or nonspecific haemostatic agents. (**2C**)

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R3.2b: If DOAC monitoring is not available, and surgery can not be delayed, antidote and nonspecific haemostatic treatment should depend on the clinical severity of bleeding. **(3)**

R3.3a: When urgent surgery with high risk of bleeding cannot be delayed, and if relevant residual concentration of dabigatran is suspected, specific antidote therapy with idarucizumab is recommended without waiting for DOAC level monitoring. However, a predose lab sample should be taken. **(1C)**

R3.3b: If idarucizumab is not available, PCC or aPCC may be used for the urgent surgical setting in patients on dabigatran without waiting for DOAC level monitoring. A predose lab sample should be taken. **(3)**

R3.4: When urgent surgery with high risk of bleeding cannot be delayed, and if relevant residual concentration of FXa inhibitors is suspected, andexanet alfa, PCC or aPCC is suggested without waiting for DOAC level monitoring. However, a predose lab sample should be taken. **(3)**

R3.5: In urgent surgery with a high risk of bleeding, the plasma concentrations of DOACs above 50 ng ml^{-1} may be considered for haemostatic or antidote intervention. **(3)**

R3.6: In cardiac surgery under FXa inhibitors, we recommend not to use andexanet alfa. The use of haemadsorption filters may be considered. **(3)**

Rationale: There are no RCTs that investigated the value of plasma level measurements of DOACs to guide the use of antidotes against nonspecific haemostatic agents in DOAC-treated patients undergoing urgent surgery. For this reason, the benefit of reversing DOACs must be carefully weighed against the risk of thromboembolic events, especially in patients who need to undergo surgery that is not urgent or lifesaving (not required within the next 24 h). It seems that a pre-operative wait and see strategy could be reasonable to reduce anticoagulant activity and the consequent risk of bleeding in these patients (Fig. 1).

Previous guidelines and consensus statements recommend laboratory data to guide the administration of antidotes for adults on DOACs therapy undergoing urgent surgery.[53,54] In the case of emergency surgery for life-threatening conditions, such as a ruptured aortic aneurysm, literature suggests that the administration of an antidote should not be delayed while awaiting tests results[55,56] (Fig. 1). However, no RCTs exist that investigate the use of antidotes for reversal of DOACs based on laboratory values or POC tests against 'blind' DOAC reversal in adults undergoing urgent surgery.

As mentioned in the introduction, the REVERSE-AD study investigated the efficacy of idarucizumab for patients on dabigatran in the urgent surgical setting.[6] According to the study protocol, dabigatran concentrations were obtained from all patients. However, these did not drive the decision for idarucizumab administration. It seems that even if patients had little or no circulating dabigatran, the use of idarucizumab was shown to be safe.[6] Similarly, real-world data suggests that when urgent surgery cannot be delayed, reversal with idarucizumab without dabigatran level evaluation is an effective and safe approach.[57]

Evidence is even more limited for treating patients on direct FXa inhibitors with andexanet alfa who undergo urgent surgery. The ANNEXA-4 study investigated the use of andexanet alfa in the setting of uncontrolled bleeding but not in the urgent surgical setting and showed that patients who had received apixaban, the median anti-FXa activity decreased from 149.7 ng ml^{-1} at baseline to 11.1 ng ml^{-1} after the andexanet alfa bolus, while in patients who had received rivaroxaban, the median value decreased from 211.8 to 14.2 ng ml^{-1}.[10] Data from a sub-study of the ANNEXA 4-trial showed that the reduction in anti-FXa activity with andexanet alfa appears to be smaller in patients on edoxaban than in patients on rivaroxaban or apixaban (there was a median of 68.9 and 69.2% decrease in antifactor Xa activity with baseline anti-FXa activity >40 and >75 ng ml^{-1}, respectively).[58] Despite experts' recommendations, andexanet alfa for the reversal of FXa inhibitors in urgent or emergent surgery is off-label.[24,59]

Several guidelines and consensus statements recommended the off-label use of haemostatic agents as PCC or aPCC if a DOAC-specific reversal agent is not available.[24,59] Data with small number of patients showed that aPCC might contribute to haemostasis among patients needing urgent surgery.[60,61] Recently, a multicentre study supported the use of PCCs in patients treated with rivaroxaban or apixaban who need to undergo an urgent procedure.[62] Of note, PCC was given only prior to surgery that could not be delayed as judged by the treating surgeons, and when the interval from the last dose of anticoagulant did not exceed 24 h. In accordance, data with a small number of patients on apixaban, rivaroxaban or edoxaban, who underwent emergency high bleeding risk surgery, showed that pre-operative administration of PCCs without DOAC level monitoring supported haemostasis without clinical signs of thromboembolic events.[63] In the literature, plasma concentrations cut off point of 50 ng ml^{-1} for seriously bleeding patients and 30 ng ml^{-1} for urgent intervention with a high risk of bleeding are suggested for antidote or haemostatic intervention.[56] The PAUSE study used the 50 ng ml^{-1} cut off to define a clinically important residual pre-operative DOAC level.[28] Of note, in a prespecified analysis of the PAUSE database, there was no association between

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pre-operative residual DOAC levels greater than 50 or 30 to 49.9 ng ml^{-1} and the occurrence of peri-operative major bleeding or clinically relevant nonmajor bleeding.[64] However, according to authors, the study had insufficient power to assess the effect of different residual DOAC levels (<30 or 30 to 49 ng ml^{-1}) as determinants of bleeding compared with higher DOAC levels, for example, as compared with 50 to 75 or greater than 75 ng ml^{-1}. Of note, the PAUSE study investigated patients scheduled for elective surgery and did not include urgent or emergency surgeries. Nevertheless, studies in elective patients may help to inform clinicians on plasma level thresholds that are yet to be validated to ensure that reversal based on laboratory thresholds guarantees the optimal balance between the prevention of bleeding and thrombosis in urgent surgical settings.

Finally, special concerns arise over cardiac surgery patients on FXa inhibitors and the use of andexanet alfa. In the original article, describing the use of andexanet alfa for reversal of FXa inhibitors, it was also found to be a reversal agent for heparin.[65] An in-vitro study and several case reports suggested a relevant heparin resistance after the use of andexanet alfa.[66,67] Despite a recent recommendation in US guidelines,[68] andexanet alfa should be avoided or used with great caution only in patients undergoing cardiac and major vascular surgery requiring heparinisation to prevent intra-operative thromboembolism. Administration after heparin reversal with protamine should be feasible. In contrast, the administration of idarucizumab before cardiac or major vascular surgery to reverse relevant dabigatran levels is not a concern.[69]

Of note, DOAC activity might be, at least partially blunted by intra-operative haemodilution. If andexanet alfa has been administered prior to cardiac or vascular surgery, we suggest the use of an alternative intra-operative anticoagulation (e.g. intravenous direct thrombin inhibitor such as argatroban or bivalirudin) or the substitution with antithrombin concentrate to improve heparin activity and increase ACT as suggested in a case report.[66] The administration of PCC in emergency cardiac surgery or interventions requiring anticoagulation has also been suggested.[70] Alternatively, the use of a haemadsorption filter using a highly porous polymer filter integrated in the CPB circuit might help to reduce DOAC concentrations.[71,72]

PICO 4

Clinical scenario: Adults undergoing urgent surgery with DOAC therapy.

Should laboratory measurements be performed after reversal (which time frame of measurements)?

Recommendation

R 4.1: After specific reversal of dabigatran with idarucizumab, we suggest to assess dabigatran concentrations by the diluted thrombin time (dTT) test or the thrombin time (TT) regularly for at least 48 h because of potential drug rebound. (**2B**)

R 4.2: After specific reversal of direct FXa inhibitors with andexanet alfa caution is advised in interpretation of the concentration measurements as anti-FXa activities are influenced by andexanet alfa. **(3)**

R 4.3 After administration of nonspecific haemostatic treatment in patients with elevated or suspected high levels of direct FXa inhibitors, it is unclear when and whether anti-FXa levels should be re-assessed. Conventional coagulation testing including PT or aPTT may indicate normalisation for several hours despite insufficient haemostasis. **(3)**

Rationale: Rebound anticoagulant DOAC activity has been reported after administration of specific reversal agents.[7] The repeated measurement of DOAC concentrations might be necessary after reversal, but evidence is very limited.

A 2020 systematic review of 240 published cases receiving idarucizumab at a dose of 5 g reported dabigatran rebound in 33 (14%) cases within a median time of 22 h.[7] Specific risk factors for incomplete response to idarucizumab at 5 g and dabigatran rebound were high baseline dabigatran concentrations (>265 ng ml^{-1}) and impaired renal function (glomerular filtration rate <30 ml min^{-1}).[7,73,74] Based on these real-world data, it is suggested to measure dabigatran concentration every 6 h up to 48 h after idarucizumab administration using the dTT test.[7,73,74]

Real-world data after approval for andexanet alfa are scarce. Data from the ANNEXA-4 trial suggest that DOAC activity should be assessed every 4 h up to 36 to 48 h after andexanet alfa administration using the anti-FXa activity test.[10] However, in this study, there was no significant relationship between haemostatic efficacy of andexanet alfa and a reduction in anti-Xa activity, so that the clinical impact of anti-FXa activity testing after andexanet alfa administration remains unclear. Furthermore, the validity of anti-FXa activity measurements after application of andexanet alfa were questioned as andexanet alfa may dissociate from the FXa inhibitor binding, so that the levels of the FXa inhibitor may be falsely high.[75] Of note, the ANNEXA-4 trial did not include patients scheduled for emergency or urgent surgery, and therefore, the findings from this study cannot directly be extrapolated to this population. Furthermore, the effectiveness of andexanet alfa and coagulation testing might also be affected by administration of heparin, for example, in cardiac surgery as is the effectiveness of heparin anticoagulation if andexanet alfa has been administered before start of cardiopulmonary bypass.[76]

After administration of PCC, aPCC or rFVIIa in bleeding patients following recent DOAC intake or at risk of bleeding, it is unclear whether laboratory coagulation

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testing should be performed. In addition, if coagulation testing is performed, it is unclear which laboratory test should be used to evaluate the effectiveness of unspecific haemostatic treatment and at which time interval such testing should be performed.

PICO 5

Clinical scenario: DOAC-treated adult patients with traumatic and nontraumatic intracerebral haemorrhage without need for surgery.

Are antidotes or nonspecific haemostatic agents indicated for DOAC-treated patients with traumatic and nontraumatic ICH without need for surgery?

Recommendations:

R 5.1: We recommend antidote reversal or nonspecific haemostatic agents to prevent increasing haematoma volume. (**1C**)

R 5.2a: We recommend the use of idarucizumab for the reversal of dabigatran-associated intracerebral bleeding. (**1C**)

R 5.2b: PCC or aPCC may be considered for patients taking dabigatran if idarucizumab is not available. **(3)**

R 5.3: We suggest the use of andexanet alfa or PCC to prevent increasing haematoma volume following apixaban and rivaroxaban associated intracerebral bleeding. If andexanet alfa or PCC are not available, aPCC may be considered. (**2C**)

R 5.4: PCC may be considered for patients taking edoxaban. **(3)**

Rationale: Because intracranial haemorrhage takes place in the cranium, which has a restricted volume capacity, if a bleed takes place the risk for haematoma enlargement causing pressure effects on cerebral tissue is high (compare flow charts of life-threatening and nonlife-threatening bleeding). While awaiting the publication of the full results of the ANNEXA-I study, up to now, the superiority of andexanet alfa over nonspecific haemostatic agents has not been demonstrated by a prospective, randomised, head-to-head comparison against PCC or aPCC in the clinical setting of FXa inhibitor-related ICH. However, the results from retrospective studies and meta-analyses were heterogenous in terms of efficacy and safety outcomes.[58,77–81]

In the absence of oral anticoagulation, antiplatelet therapy modestly reduced stroke, but there was a corresponding signal for harm when used on top of an oral anticoagulant.[58] Nederpelt considered 21 studies in their meta-analysis of PCC vs. andexanet alfa for FXa reversal and concluded that neither reversal agent was significantly associated with increased effectiveness or a higher rate of venous thromboembolic events and the evidence does not unequivocally support the clinical effectiveness of andexanet alfa or PCC to reverse factor Xa inhibitor-associated acute major bleeding nor does it permit conventional meta-analysis of potential superiority.[81] In 182 patients who were in part recruited from the ANNEXA-4 trial, Huttner *et al.*[78] found that compared with usual care, andexanet alfa was associated with a lower rate of haematoma expansion in atraumatic factor-Xa inhibitor-related ICH; however, without translating into significantly improved clinical outcomes. In 36 studies, Chaudhary *et al.*[77] found the overall anticoagulation reversal, mortality and thromboembolic event rates in their systematic review and meta-analysis appeared similar among available DOAC reversal and nonspecific haemostatic agents for managing ICH.

A single-centre retrospective observational study found that the use of 4-factor PCC in a dose of 35 U kg^{-1} produced haemostasis [assessed by computed tomography (CT) for radiographic imaging to evaluate bleeding progression] in patients with a traumatic brain injury who were taking DOACs.[82] Thirty-three patients were included in the study, and 31 patients that had traumatic and nontraumatic ICH, 83.8% achieved haemostasis with 4-factor PCC.

A retrospective case series found that of the 25 patients evaluated, 13 received andexanet alfa for ICH.[83] Eleven of the 13 had follow-up imaging available and no enlargement of the haematoma was observed in 90.9%. Three patients received andexanet alfa for reversal prior to neurosurgical procedures, and 100% haemostatic effectiveness was achieved. Nine patients received andexanet alfa for reversal of extracranial bleeding, including gastrointestinal bleed ($n = 4$). There were no thrombotic events in the cohort, and 30-day mortality was 24%. Sixty-four percentage of patients would have met exclusion criteria for the ANNEXA-4 trial. Their series showed haemostatic efficacy in 90.9% of patients with ICH, and 100% in patients undergoing surgical procedures.

The use of 4-factor-PCC has been investigated in a retrospective cohort study that concluded that 4-factor-PCC appears to be an effective and safe option for factor Xa-inhibitor (FXaI)-associated ICH with outcomes comparable to andexanet alfa.[84] A formal prospective evaluation of this strategy vs. andexanet alfa including cost analysis was warranted in view of its cost. Intracerebral haemorrhage related to DOAC use is associated with a high mortality and an unfavourable outcome, and haematoma expansion is frequent. Larger scale prospective studies are needed to determine whether the early administration of specific antidotes can improve the poor prognosis of DOAC-associated ICH.[85]

Exploring the use of aPCC,[86] a prospective study of patients with spontaneous ICH was conducted. Hospital complications including haemorrhage (gastrointestinal bleeding, anaemia requiring transfusion and surgical site

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bleeding) and thrombosis (pulmonary embolus, deep vein thrombosis, ischaemic stroke and myocardial infarction) were recorded. All ICH patients underwent baseline head CT and a follow-up stability scan in 6 h. DOAC taken within 48 h of presentation as per protocol. Of 127 ICH patients enrolled, 6 (5%) had DOAC-related ICH including: oral factor Xa inhibitor $n = 5$ (4%; $n = 4$ rivaroxaban, $n = 1$ apixaban] and direct thrombin inhibitor $n = 1$ (0.8%; dabigatran). The indication for DOAC was atrial fibrillation in all patients and the median [range] CHADS2-VASC score was 4 [2 to 5]. The median admission NIHSS was 2 [0 to 14] and the median ICH volume was 8 ml [1 to 20]. Five patients (3 rivaroxaban, 1 apixaban, 1 dabigatran) presented within 48 h and received aPCC within a median of 13 h [10 to 29 h] from their last DOAC dose and 8 h [4.5 to 20] from the time last known well. None of the patients had ICH expansion, haemorrhagic or thrombotic complications. The authors concluded that aPCC appears to be a reasonable reversal agent for patients with DOAC related ICH.

PICO 6

Clinical Scenario: Nonbleeding adults with overdose of DOACs not considered for urgent or elective surgery.

Should reversal agents be used to manage nonbleeding patients with an overdose of DOAC?

Recommendations

R 6.1: We suggest not to reverse dabigatran or FXa inhibitors in the absence of bleeding. **(3)**

R 6.2: We suggest general measures to eliminate FXa inhibitors, which may include stimulation of diuresis and/or haemadsorption. **(2 C)**

R 6.3: We suggest the stimulation of diuresis and the use of haemodialysis in the haemodynamically stable patient with dabigatran overdose. In early dabigatran overdose, activated charcoal may be considered. **(2C)**

Rationale: Accidental or deliberate ingestion of DOACs resulting in overdose is a known clinical problem. The elimination half-lives of DOACs are such that plasma concentrations decrease over a short period of time. However, after ingestion of DOAC patients are more likely to develop any bleeding than those ingesting antiplatelet agents (relative risk (RR) 6.68, 95% CI, 2.63 to 17.1) and major bleeding (RR 18.1 95% CI, 3.85 to 85.0).[87] Given the short half-lives of DOACs, it is suggested to not reverse the anticoagulant effect of DOACs in patients without bleeding in order not to increase the risk of systemic thromboembolism (compare the urgent surgery flow chart).

For DOACs, the important clinical issue is if their measured concentrations (or activity based on calibrated concentrations) reflect their biological effect.[88] For dabigatran, this has been shown in the RE-LY clinical RCT.[89] Although no therapeutic range has been identified for the DOACs, it has been demonstrated for dabigatran and edoxaban that their antithrombotic effect increases gradually with increasing concentrations and that the risk of major bleeding also gradually increases.[88] Multiple logistic regression (c-statistic 0.715, 95% CI: 0.69 to 0.74) showed major bleeding risk increased with dabigatran exposure ($P < 0.0001$), age ($P < 0.0001$), ASA use ($P < 0.0003$) and diabetes ($P = 0.018$) as significant covariates.[89] The ORBIT-AF registry showed that overdosing of DOACs resulted in a significantly higher rate of mortality but no significantly increased rate of major bleeding or stroke.[90]

Dabigatran and FXa inhibitors, such as apixaban or rivaroxaban, can be antagonised with specific reversal agents, idarucizumab and andexanet alfa if the patient is severely bleeding and haemodynamically unstable. For dabigatran overdose, the use of haemodialysis in the haemodynamically stable patient is an option to rapidly reduce plasma levels.[91] Similarly in early apixaban overdose, the administration of activated charcoal may be considered.[92] Furthermore, 4-factor-PCCs have been shown to be effective in doses of 35 to 50 U kg^{-1} for reversal of overdose of DOACs.[82]

PICO 7

Clinical scenario: Adult patients on FXa inhibitor therapy, who present with severe bleeding in urgent surgical or nonsurgical settings.

Should andexanet alfa or PCC, aPCC or rFVIIa be used to manage FXa inhibitor-associated bleeding in urgent surgical or nonsurgical settings?

R7.1: We recommend that PCC or andexanet alfa should be considered in patients under FXa inhibitor therapy presenting with severe bleeding. However, the superiority of one agent over another has not been demonstrated. (**1C**)

R7.2: In the absence of the availability of andexanet alfa and PCC, aPCC may be considered in patients on FXa inhibitor therapy presenting with severe bleeding. (**2C**)

R7.3: Due to the paucity of clinical data, we are unable to provide any recommendation for the use of rFVIIa in patients on FXa inhibitor therapy presenting with severe bleeding. **(3)**

Rationale: Therapy with PCC is supported by a number of cohorts, in-vitro and animal studies.[15] Two prospective cohort studies, investigated the effect of PCC for management of FXa-associated major bleeding. According to ISTH criteria of haemostasis, reversal was effective in both studies around 68% while major thromboembolic event occurred in 8 and 3%, respectively.[14,80] A larger, but retrospective study, included 663 patients with ICH and apixaban or rivaroxaban treatment. Evaluated by modified Sarode criteria, excellent/good haemostasis

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was reported in 82% of cases, with thrombotic events in 4%.[13] These data suggest that PCC may be an effective treatment option with low thromboembolic complication rate. However, mechanism of action in patients on FXa inhibitor is partly unknown and the drug is not licensed for this indication, hence is to be considered off-label use.

Despite that biochemical efficacy of andexanet alfa administration among apixaban/rivaroxaban-treated patients is high, data available on clinical outcome is conflicting and sparse. Among 21 patients with Xa inhibitor-associated extracranial bleeding, reversal with andexanet alfa was adjudicated with prespecified criteria and associated with excellent or moderate in 47.6% and poor efficacy in 52.4% of patients. Ischaemic complications or mortality occurred in 19 and 38% of patients, respectively.[93] Opposite conclusions were drawn from a substudy of the ANNEXA-4 trial, including 171 patients with spontaneous or traumatic ICH. Excellent/good haemostasis was reported in 80% of patients, based on predefined criteria for haematoma expansion.[94] Similarly, Giovino *et al.* reported an excellent/good haemostatic effect in 83% of patients with intracranial bleeding who were treated with andexanet alfa, whereas 10% of patients died and 5% had thrombotic complications.[95]

In three retrospective studies, including a total of 273 patients, with both FXa and thrombin inhibitor-related bleeding, aPCC treatment was not associated with bleeding expansion nor any complications, and with a high degree of haemostasis. However, several case series demonstrated high rates of thrombotic events at 10%.[86,96,97] A safety study by Whitaker *et al.* investigated thromboembolic events after aPCC administration (20 to 50 U kg^{-1}) as treatment of apixaban and rivaroxaban-associated bleeding in 288 patients. The majority of patients had an ICH (71%) or gastrointestinal (11%) bleeding. Bleeding complication rate, defined as continued bleeding, surgical site bleeding or haematoma expansion on CT was 7%. Primary outcome, thrombotic events, occurred in 6% of cases, which was slightly higher than for PCC administration.[98] Another study showed that nonspecific haemostatic treatment with aPCC vs. PCC to prevent haematoma expansion in patients on rivaroxaban or apixaban-associated ICH had a similar excellent (87%) or good haemostatic efficacy (89%), respectively. No differences in thromboembolic events, mortality or transfusion requirements within 30 days were observed.[99]

No clinical studies investigating the efficacy and safety of recombinant activated FVII (rFVIIa) as a nonspecific haemostatic agent to reverse FXa-inhibitor-associated bleeding have been published. The use of rFVIIa has been investigated to reverse the anticoagulant effects of FXa inhibitors both in animal and healthy volunteer studies. These studies showed a correction of coagulation parameters following rFVIIa administration in the setting of FXa inhibition. However, the impact on coagulation parameters including thrombin generation, plasma-based coagulation tests and viscoelastic haemostatic measurements were variable and not consistent throughout the available studies.[60,100] Thus, if rFVIIa is used for the reversal of FXa inhibitors, the improvement of coagulation parameters may not necessarily reflect the in-vivo capacity to normalise FXa inhibitor-associated coagulopathy.

At present, the results of the ANNEXA-I study comparing PCC, aPCC or rFVIIa with andexanet alfa have not been published. A systematic review investigated the use of PCC vs. andexanet alfa for reversal of FXa inhibitor-related bleeding in 21 studies with 1716 patients. Haemostatic efficacy as evaluated by prespecified criteria was 88% for PCC and 82% for andexanet alfa.[81] Thromboembolic event rates and mortality for andexanet alfa were 10.7 and 23%, and for PCC 3.1 and 16%, respectively. However, a retrospective, multicentre study evaluated 3030 patients hospitalised with FXa inhibitor-related bleeding and reported lower mortality rates for those treated with andexanet alfa (4%) compared with patients who received PCC (10%).[101] In 396 andexanet alfa-treated patients, mortality rate ranged from 14 to 24%,[79] and from 15 to 30% in the two cohorts from the UPRATE studies[14,80] investigating the use of PCC in patients with apixaban or rivaroxaban-associated bleeding. In both treatment groups, the majority of bleedings were intracranial.

In patients with ICH, a systematic review including 1832 patients reported similar efficacy between andexanet alfa and PCC ranging from 75 to 82%. Thromboembolic events occurred in 14% (andexanet alfa), 8% (PCC) and 5% (idarucizumab).[77] A newer indirect comparison study of apixaban and rivaroxaban-associated ICH bleedings, andexanet alfa compared with PCC was associated with better haemostatic effectiveness (85.8 vs. 68.1%) and improved survival (7.9 vs. 19.6%), but more thromboembolic complications (2 vs. 0).[102]

In conclusion, no head-to-head clinical studies have investigated the effectiveness and safety of andexanet alfa vs. nonspecific haemostatic treatment using PCC, aPCC or rFVIIa in patients on FXa inhibitors with bleeding complications. The strongest evidence for the use of nonspecific haemostatic reversal is based on prospective, uncontrolled observational data investigating PCC. The results of several meta-analyses show a similar efficacy and mortality rates of PCC and andexanet alfa while thromboembolic events appeared numerically higher in andexanet-alfa studies.[79]

This evidence suggests that either andexanet alfa or PCC may be given as first-line treatment for severe bleeding associated with the use of FXa inhibitors. In the absence of the availability of andexanet alfa or PCC, aPCC may be considered, whereas no firm recommendations can be

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made on rFVIIa because of lack of clinical evidence (compare flow charts life-threatening and nonlife-threatening bleeding).

PICO 8

Clinical scenario: Adult patients on dabigatran therapy, who present with severe bleeding in urgent surgical or nonsurgical settings.

Should idarucizumab or PCC, aPCC or rFVIIa be used to manage dabigatran associated bleeding in urgent surgical or nonsurgical settings?

Recommendation

R8.1: We recommend that idarucizumab should be considered in patients under dabigatran therapy presenting with severe bleeding or in urgent surgical or nonsurgical settings. **(1C)**

R 8.2: In the absence of the availability of idarucizumab, we suggest the use of PCC or aPCC. However, the superiority of one agent over another has not been demonstrated. **(2C)**

R 8.3: Due to the paucity of clinical data, we are unable to provide any recommendation for the use of rFVIIa. **(3)**

Rationale: Various guidelines have been published that recommend the use of idarucizumab in the setting of dabigatran-associated bleeding or urgent surgery.[27,53,103–106] Data on the clinical use of idarucizumab support the efficacy in dabigatran-associated bleeding in various clinical settings[107–111] (compare flow charts urgent surgery, life threatening and nonlife-threatening bleeding).

Several case reports have shown the efficacy of PCCs for treatment of bleeding associated with dabigatran-induced anticoagulation.[112,113] Similarly, animal studies investigating the use of PCC for dabigatran reversal showed a significant dose-dependent effect of PCCs on reducing blood loss and haematoma growth.[114–118] However, no prospective and comparative clinical data investigating PCC against an active comparator for the reversal of dabigatran is available.

aPCC as an unspecific reversal agent has been investigated in a small prospective cohort study (median dose of 44 IU kg^{-1} [24 to 98]) in 14 patients with dabigatran-associated bleeding. The efficacy of aPCC on haemostasis was evaluated by the treating physician. In 64% of patients, haemostasis was rated as 'good' and 'moderate' in 36% of patients. No thromboembolic events occurred during the 30-day follow-up. One death occurred 3 days after administration of aPCC in a patient with a large intracranial haemorrhage following the withdrawal of life support.[119] The successful use of aPCC has also been reported in several case reports and case series.[61,86,96,120–122]

There are no published data on use of idarucizumab vs. PCC or aPCC for the reversal of dabigatran-associated bleeding and because of the limited clinical evidence, PCC or aPCC are recommended to be only used in the absence of idarucizumab. Clinicians shall be informed that the lack of comparative studies on the efficacy and safety of idarucizumab in dabigatran-associated bleeding may represent a bias in favour of the use of this antidote.

Due to controversial results from an animal study[123] and case reports[123–125] and because of the lack of prospective randomised clinical trials for rFVIIa in dabigatran-induced bleeding and the availability of a direct reversal agent, an expert recommendation is made that rFVIIa should be used in life-threatening or organ-threatening bleeding only, when idarucizumab, PCC or aPCC are not readily available.

PICO 9

Clinical scenario: Invasive nonsurgical procedures with a high risk of bleeding under DOAC therapy in adults.

Should reversal agents be used before an urgent invasive procedure, including regional anaesthesia, aortic stent placement, and so forth?

Recommendation

R9.1: In patients on dabigatran who are undergoing urgent invasive procedures with a high risk of bleeding, idarucizumab is recommended to reduce levels of dabigatran in order to normalise coagulation. **(1C)**

R9.2: Andexanet alfa has not been investigated before urgent invasive procedures. We are unable to provide any recommendation for the use of andexanet alfa nor for any haemostatic agents. **(3)**

Rationale: So far, there are no results from prospective randomised controlled trials investigating the use of a reversal agent (idarucizumab, andexanet alfa) or nonspecific haemostatic agents such as PCC aPCC or rFVIIa against an active comparator in the setting of urgent invasive procedures have been published.

Study results that were submitted for approval of the direct antidotes result from uncontrolled trials[6,10], whereas only the study investigating idarucizumab evaluated its efficacy in the setting of urgent surgery or invasive procedures.

Two hundred and two patients treated with dabigatran undergoing urgent invasive procedures were included. The primary outcome of this study was the plasma level of unbound dabigatran that fell to 20 ng ml^{-1} or below after the application of idarucizumab in all but three patients of this group. These data suggest that idarucizumab infusion completely neutralises the effect of dabigatran to facilitate a surgical or interventional procedure.

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Previous guidelines assessed the existing evidence concerning the reversal of DOACs before invasive procedures: For the setting of regional anaesthesia with a high risk of bleeding, we refer to previous international guidelines that recommend idarucizumab for this indication,[26,53] but not andexanet alfa as it has not been investigated in the setting of neuraxial anaesthesia or other high bleeding risk interventional procedures. Furthermore, an earlier guideline had already stated that there are no data for the direct reversal agent andexanet alfa in patients on apixaban and rivaroxaban before urgent or invasive procedures.[27]

For the reversal of dabigatran anticoagulation in acute ischaemic stroke prior to the use of intravenous thrombolysis (IVT) idarucizumab was investigated in 13 patients (7 men, mean age 70 ± 9.1 years) with a median National Institutes of Health Stroke Scale (NIHSS) admission score of 7 points.[126] Idarucizumab was administered 427 ± 235 min after the last intake of dabigatran. Ten patients (76.9%) had a good 3-month clinical outcome, whereas three patients (23.1%) died. Recurrent ischaemic stroke occurred in two patients (15.4%). These data, although small, suggest that idarucizumab can be used to reverse dabigatran anticoagulation before intravenous thrombolysis.

This view is supported by the recent guideline of the European Stroke Organisation (ESO)[127] that published an expert consensus statement for patients with ischaemic stroke of less than 4.5 h duration, who used dabigatran during the last 48 h before stroke onset, the combination of idarucizumab and intravenous thrombolysis with alteplase is suggested over no intravenous thrombolysis.

However, for patients with ischaemic stroke of less than 4.5 h duration, the same guideline issued an expert consensus statement against the combination of andexanet alfa and intravenous thrombolysis in patients who used FXa inhibitors during the last 48 h before stroke onset, over no intravenous thrombolysis. The reason for this was that only anecdotal data are available and the risk of arterial or venous thromboembolic events that occurred in 10% of patients of the ANNEXA-4 trial.

To the best of our knowledge, the use of reversal agents for DOACs have not been investigated in controlled trials involving patients undergoing aortic stent placement or other invasive procedures. In these situations, expert opinion is the best option to answer whether the risk of bleeding in DOAC-anticoagulated patients will be reduced by the specific antidote.

In conclusion, only very limited data support the use of idarucizumab to reverse the anticoagulant effect of dabigatran before invasive procedures. The use of idarucizumab before intravenous thrombolysis for stroke may be an exception. For the use of andexanet alfa to reverse the effect of apixaban or rivaroxaban in this clinical setting, no recommendations can be given because of lack of sufficient published data.

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