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GUIDELINES

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

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Introduction

- Anticoagulation is essential for the treatment and prevention of thromboembolic events.

- Reversal of DOACs may also be required for patients in need of urgent invasive procedures.

- Approximately 10% of patients on DOACs require invasive procedures, so that reversal of DOAC may also be needed for patients requiring urgent invasive procedures.

Characteristics of direct oral anticoagulants

	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

Overview of specific antidotes and unspecific reversal agents

- ***Idarucizumab*** is a humanised, monoclonal antibody fragment against dabigatran

- ***Andexanet alfa*** is a modified, recombinant, inactive form of human FXa, with the ability to reversibly bind Fxainhibitor molecules, thereby reducing its activity and restoring the amount of unbound endogenous Fxa

- ***PCCs*** are lyophilised, human plasma-derived vitamin K-dependent factors containing FII (prothrombin), FVII, FIX, and FX

- ***Recombinant FVIIa*** induces thrombin generation and increases FXa activity and has been associated with an increased rate of thromboembolic complications in nonhaemophilic patients with intracranial haemorrhage

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 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

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

- The electronic database search was run on 10 February2021 by Cochrane Trial Search Specialist (JV) and included articles published since 2010 to increase clinical relevance

- A total number of 138 studies were included forthis evidence synthesis.

- Recommendations were formulated and graded according to the Grading of Recommendations Assessment,Development and Evaluation (GRADE) system and in accordance with ESAIC methodology guidelines.

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.

result

- 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

clinical scenarios ①

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

Patients with confirmed intake of DOACs before urgent surgery

History

Verify intake of direct FXa inhibitors or direct thrombin inhibitor and
Direct evidence by lab tests (e.g. calibrated anti-FXa activity or (diluted) thrombin time for dabigatran).
Check for concomitant bleeding disorders or intake of platelet inhibitors.

Seek advice from thrombosis and haemostasis service

Blood sampling

PT, PT-ratio, aPTT, thrombin time (for dabigatran), calibrated anti-FXa activity, point of care coagulation monitoring (if available), creatinine (GFR), fibrinogen, D-dimers and platelet count on admission.

Important

Draw blood samples before treatment, but treatment must not be delayed by waiting for lab results.

YES
Apixaban, rivaroxaban

1. Consider „wait and see" strategy if clinically appropriate; stimulate diuresis;
2. Andexanet alfa or PCC;
3. aPCC, if both drugs are unavailable.

YES
Dabigatran

1. Consider „wait and see" strategy if clinically appropriate; stimulate diuresis;
2. Idarucizumab;
3. PCC or aPCC, if idarucizumb is unavailable.

YES
Edoxaban*
*Andexanet alfa not approved as of February 2024

1. Consider „wait and see" strategy if clinically appropriate; stimulate diuresis;
2. PCC;
3. aPCC, if PCC is not available.

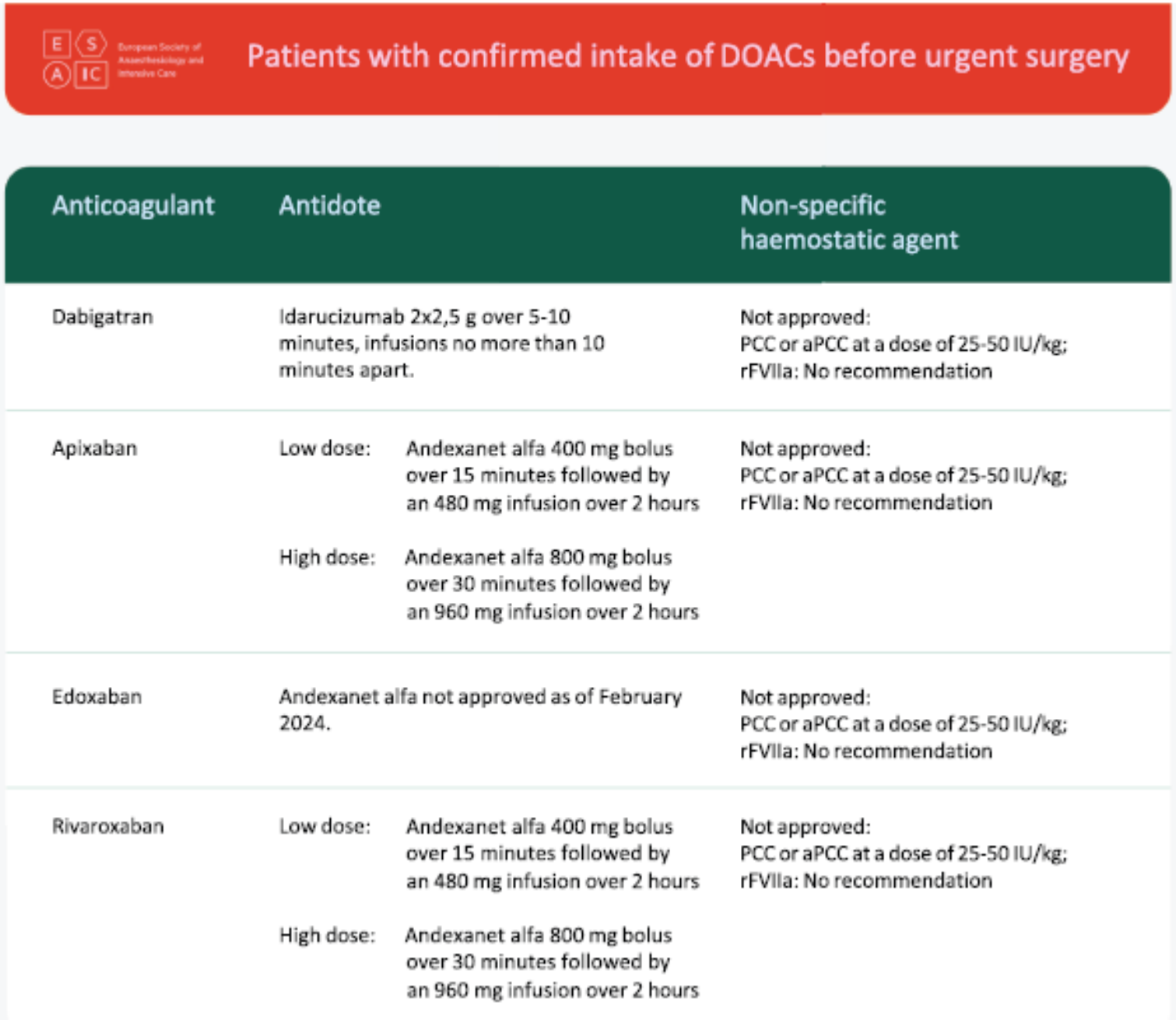
Clinical practice statements

In case of progression to severe or life-threatening bleeding: Rule out surgical source of bleeding; continue standard treatment; consider a second antidote dose or PCC/aPCC dose if there are persistently elevated DOAC levels.
Recurrent bleeding: Consider that elevated plasma levels of apixaban, rivaroxaban and dabigatran may occur after specific antidote application.
Terminated bleeding (e.g.>24–48 hours): Consider resumption of anticoagulation e.g. LMWH at prophylactic dosage or local standard.

Standard treatment, e.g.:

Tranexamic acid, clotting factor concentrate, cryoprecipitate, platelet concentrate, desmopressin, if von Willebrand disease or aspirin-induced platelet disorder is verified/suspected.
Fresh frozen plasma in case of massive transfusion.

Fig. 1 Continued.



clinical scenarios ②

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

Patients with non-life threatening bleeding

History

Verify intake of direct FXa inhibitors or direct thrombin inhibitor and
Direct evidence by lab tests (e.g. calibrated anti-FXa activity or (diluted) thrombin time for dabigatran).
Check for concomitant bleeding disorders or intake of platelet inhibitors.

Seek advice from thrombosis and haemostasis service

Blood sampling

PT, PT-ratio, aPTT, thrombin time (for dabigatran), calibrated anti-FXa activity, point of care coagulation monitoring (if available), creatinine (GFR), fibrinogen, D-dimers and platelet count on admission to the hospital.

Important

Draw blood samples before treatment, but treatment should not be delayed by waiting for lab results.

YES
Apixaban, rivaroxaban

1. Consider "wait and see" strategy if clinically appropriate; stimulate diuresis;
2. Andexanet alfa or PCC;
3. aPCC, if both drugs are unavailable.

Consider Standard Treatment in addition

YES
Dabigatran

1. Consider "wait and see" strategy if clinically appropriate; simulate diuresis;
2. Idarucizumab;
3. PCC or aPCC, if idarucizumb is unavailable.

Consider Standard Treatment in addition

YES
Edoxaban*
*Andexanet alfa not approved as of February 2024

1. Consider "wait and see" strategy if clinically appropriate; stimulate diuresis.
2. PCC;
3. aPCC, if PCC is not available.

Consider Standard Treatment in addition

Clinical practice statements

In case of progression to severe or life-threatening bleeding: Rule out surgical source of bleeding; continue standard treatment; consider a second antidote dose or PCC/aPCC dose if there are persistently elevated DOAC levels.
Recurrent bleeding: Consider that elevated plasma levels of apixaban, rivaroxaban and dabigatran may occur after specific antidote application.
Terminated bleeding (e.g.>24–48 hours): Consider resumption of anticoagulation e.g. LMWH at prophylactic dosage or local standard.

Fig. 2 Continued.

Patients with non-life threatening bleeding

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	Not approved: PCC or aPCC at a dose of 25-50 IU/kg; rFVIIa: No recommendation
	High dose:	Andexanet alfa 800 mg bolus over 30 minutes followed by an 960 mg infusion over 2 hours	
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	Not approved: PCC or aPCC at a dose of 25-50 IU/kg; rFVIIa: No recommendation
	High dose:	Andexanet alfa 800 mg bolus over 30 minutes followed by an 960 mg infusion over 2 hours	

clinical scenarios ③

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

European Society of Anaesthesiology and Intensive Care

Severe (haemodynamically unstable) or life-threatening bleeding (intracerebral, epidural, intraspinal, gastrointestinal, traumatic or other refractory bleeds)

History

Verify intake of direct FXa inhibitors or direct thrombin inhibitor and
Direct evidence by lab tests (e.g. calibrated anti-FXa activity or (diluted) thrombin time for dabigatran).
Check for concomitant bleeding disorders or intake of platelet inhibitors and exclude severe bleeding with an expected poor outcome

Maintain „adaequate" BP levels (e.g., in trauma: syst. at 80–90 mmHg, in TBI/ICH > mean arterial BP of 80–90 mmHg)*; seek advice from thrombosis and haemostasis service

Blood sampling

PT, PT-ratio, aPTT, (diluted) thrombin time for dabigatran, calibrated anti-FXa- activity, point of care coagulation monitoring (if available), creatinine (GFR), fibrinogen, D-dimers, platelet count.

Important

Draw blood samples before treatment, but treatment should not be delayed by waiting for lab results.

YES
Apixaban, rivaroxaban

1. Andexanet alfa or PCC.
2. aPCC, if both drugs are unavailable.

Consider Standard Treatment in addition

YES
Dabigatran

1. Idarucizumab.
2. PCC or aPCC, if idarucizumb is unavailable.

Consider Standard Treatment in addition

YES
Edoxaban*
*Andexanet alfa not approved as of February 2024

1. PCC.
2. aPCC, if PCC is unavailable.

Consider Standard Treatment in addition

None

Standard treatment, e.g.:
Tranexamic acid, clotting factor concentrate, cryoprecipitate, platelet concentrate, desmopressin, if von Willebrand disease or aspirin-induced platelet disorder is verified/suspected.
Fresh frozen plasma in case of massive transfusion.

Clinical practice statements

In case of progression to severe or life-threatening bleeding: Rule out surgical source of bleeding; continue standard treatment; consider a second antidote dose or PCC/aPCC dose if there are persistently elevated DOAC levels.
Recurrent bleeding: Consider that elevated plasma levels of apixaban, rivaroxaban and dabigatran may occur after specific antidote application.
Terminated bleeding (e.g.>24–48 hours): Consider resumption of anticoagulation e.g. LMWH at prophylactic dosage or local standard.

Fig. 3 Continued.

European Society of Anaesthesiology and Intensive Care

Severe (haemodynamically unstable) or life-threatening bleeding (intracerebral, epidural, intraspinal, gastrointestinal, traumatic or other refractory bleeds)

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	Not approved: PCC or aPCC at a dose of 25-50 IU/kg; rFVIIa: No recommendation
	High dose:	Andexanet alfa 800 mg bolus over 30 minutes followed by an 960 mg infusion over 2 hours	
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	Not approved: PCC or aPCC at a dose of 25-50 IU/kg; rFVIIa: No recommendation
	High dose:	Andexanet alfa 800 mg bolus over 30 minutes followed by an 960 mg infusion over 2 hours	

Discussion

- As all DOAC have a relatively rapid effect offset, a ‘wait-and-see strategy’ is in 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.

- 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.

limitation

- 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.

PICO

Clinical scenario 1

- 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 ntervals (24 h for low bleeding risk, 48 to 72 h for high-bleeding risk surgery), DOAC-specific coagulation testing is not necessary. (2B)
- R 1.2: 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)

Clinical scenario 2

- 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)

Clinical scenario 3

- 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?

Recommendation

- 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)
- 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 ml1 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)

Clinical scenario 4

- 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)

Clinical scenario 5

- 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

Recommendation

- R 5.1: We recommend antidote reversal or nonspecific haemostatic agents to prevent increasing haematom 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 6

- 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?

Recommendation

- 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 7

- 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?

Recommendation

- 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)

Clinical scenario 8

- 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 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)

Clinical scenario 9

- Invasive nonsurgical procedures with a high risk of bleeding under DOAC therapy in adults. Should reversal agents be used before an urgent invasive, 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)

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