Management of major bleeding for anticoagulated patients in the Emergency Department: an European experts consensus statement

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An increasing number of patients presenting to the emergency department (ED) with life-threatening bleeding are using oral anticoagulants, such as warfarin, Factor IIa and Factor Xa inhibitors. Achieving rapid and controlled haemostasis is critically important to save the patient's life. This multidisciplinary consensus paper provides a systematic and pragmatic approach to the management of anticoagulated patients with severe bleeding at the ED. Repletion and reversal management of the specific anticoagulants is described in detail. For patients on vitamin K antagonists, the administration of vitamin K and repletion of clotting factors with four-factor prothrombin complex concentrate provides real-time ability to stop the bleeding. For patients using a direct oral anticoagulant, specific antidotes are necessary to reverse the anticoagulative effect. For patients receiving the thrombin inhibitor dabigatran, treatment with idarucizamab has been demonstrated to reverse the hypocoagulable state. For patients receiving a factor Xa inhibitor (apixaban or rivaroxaban), andexanet alfa is the indicated antidote in patients with major bleeding. Lastly, specific treatment strategies are discussed in patients using anticoagulants with major traumatic bleeding, intracranial haemorrhage or gastrointestinal bleeding. ***European Journal of Emergency Medicine*** **30: 315–323** **Copyright © 2023 Wolters Kluwer Health, Inc. All rights reserved.**

European Journal of Emergency Medicine 2023, **30**:315–323

Keywords: algorithm, anticoagulants, direct oral anticoagulants, emergency department, gastrointestinal bleeding, intracranial haemorrhage, major bleeding, trauma, treatment, vitamin K antagonists

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Received 23 January 2023 **Accepted** 21 May 2023.

Introduction

With increasing age and vascular comorbidities, oral anticoagulants are increasingly prescribed to prevent clot formation in high-risk patients. Oral anticoagulation is a cornerstone of therapy for patients with atrial fibrillation, to prevent acute ischaemic stroke, and in the management of venous thromboembolism (VTE), including deep venous thrombosis and pulmonary embolism [1–4]. These drugs act by inhibiting the coagulation cascade at different levels, resulting in a decreased formation of fibrin.

Vitamin K antagonists (VKAs) such as warfarin, acenocoumarol, phenindione and phenprocoumon have been used for decades as anticoagulants. In recent years, direct oral anticoagulants (DOACs) including Factor Xa inhibitors such as rivaroxaban and apixaban as well as the Factor IIa inhibitor dabigatran have in many cases replaced VKAs as they often have an improved safety profile [5–8] (Table 1). Despite thorough risk assessments prior to anticoagulant administration, bleeding remains the most common and feared complication of oral anticoagulation.

Patients on oral anticoagulants may present to the emergency department (ED) with major anticoagulant-related intracranial haemorrhage, gastrointestinal or trauma-related bleeding which warrants immediate therapy to prevent serious complications including death. During resuscitation, targeted intervention includes surgical, interventional radiology or endoscopy, followed by reversal of the anticoagulants.

The aim of this review is to provide a multidisciplinary European expert consensus statement to define the optimal management of patients on anticoagulants presenting to the ED with major bleeding.

Initial emergency department management of major bleeding

In the ED, frequent and significant causes of major bleeding in the anticoagulated patient include traumatic

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DOI: 10.1097/MEJ.0000000000001049

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Table 1 Summary of the key findings of large noninferiority randomized controlled trials comparing direct oral anticoagulants to warfarin in patients with nonvalvular atrial fibrillation

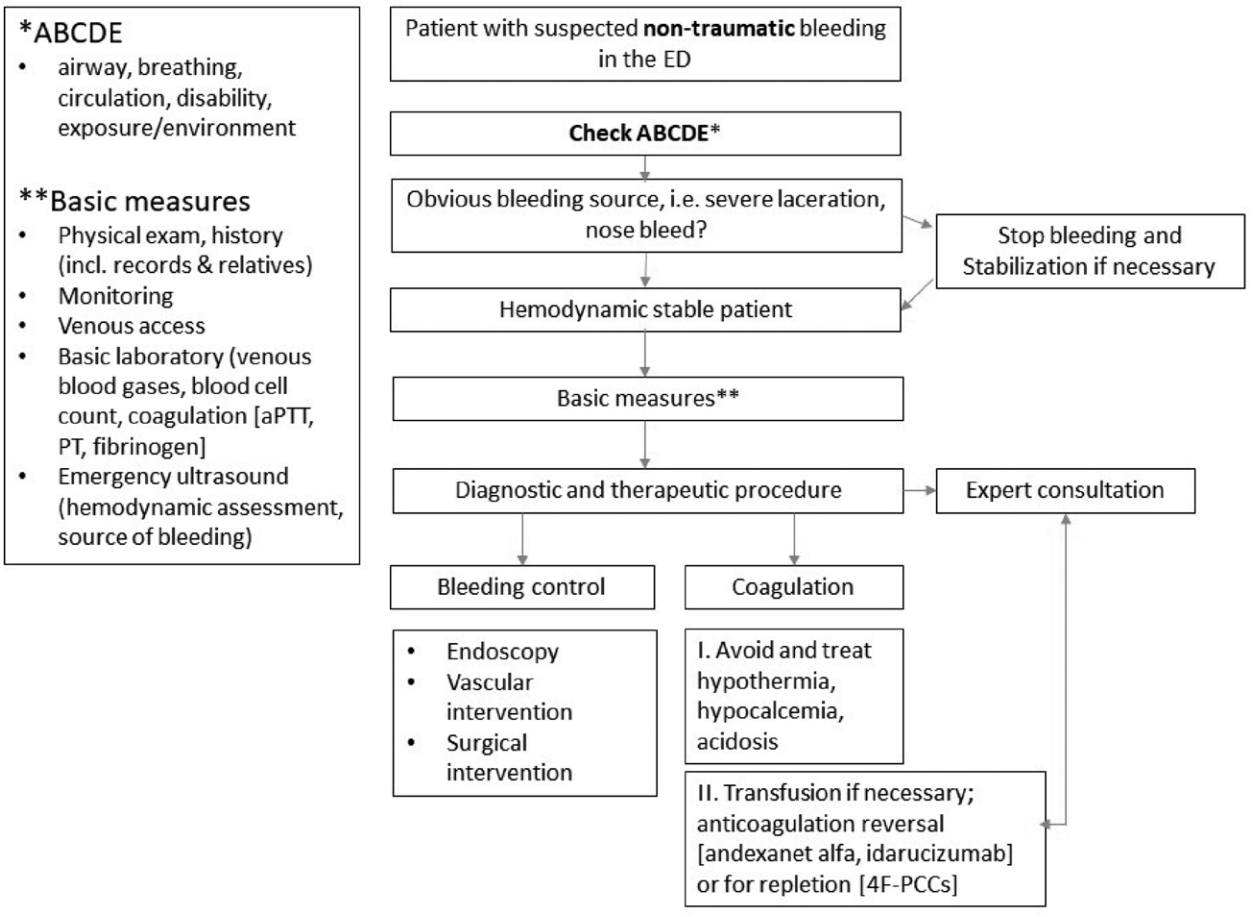
Agent and reference	Hazard ratio (HR) or relative risk (RR) for stroke or systemic embolism (95% CI) when compared to warfarin, relevant *P* value	Relative risk (RR) for bleeding (95% CI) when compared to warfarin, *P* value for superiority
Dabigatran [5] – two doses of 110 and 150 mg twice a day	RR 0.66 (0.53–0.82), $P < 0.001$ for superiority	0.80 (0.69–0.93), $P = 0.003$ [major bleeding]
Rivaroxaban [6]	HR 0.88 (0.75–1.03), $P < 0.001$ for noninferiority	HR 1.03 (0.96–1.11), $P = 0.44$ [major or clinically relevant nonmajor bleeding]
Apixaban [7]	HR 0.79 (0.66–0.95), $P < 0.001$ for noninferiority, $P = 0.01$ for superiority	HR 0.69 (0.60–0.80), $P < 0.001$ [major bleeding]
Edoxaban [8]	HR 0.79 (0.63–0.99), $P < 0.001$ for noninferiority	HR 0.80 (0.71–0.91), $P < 0.001$ [major bleeding]

CI, confidence interval.

bleeds, gastrointestinal bleeding, intracranial haemorrhage and epistaxis [9]. Direct visualization and control of the bleeding source are often very difficult, except in some trauma-associated bleeding and nasal bleeding where direct compression is effective. Therefore, the primary assessment after the standard 'ABCDE check' (Fig. 1) starts with the ascertainment of the diagnosis 'bleeding', which may not be obvious in many patients. In parallel, the patient needs a detailed clinical assessment with respect to cardiopulmonary stability. Supplementary Addendum 1, Supplemental digital content 1, *http://links.lww.com/EJEM/A387* shows a checklist for shock criteria [10]. Potentially, other medical conditions such as sepsis may be responsible for the patient's presentation.

(Checklist for primary shock assessment – see Supplementary Addendum 1, Supplemental digital content 1, *http://links.lww.com/EJEM/A387*).

Fig. 1



Flowchart of primary assessment of patients with suspected bleeding in the Emergency Department. aPTT, activated partial thromboplastin time; PT, prothrombin time.

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Patients with shock warrant immediate intensive care in the shock room [11]. To guide further management, the source and severity of bleeding and predisposing factors need to be established as soon as possible. This includes measurements of vital signs and a physical examination, which starts by examining the patient's airway, breathing, circulation, neurological functioning and core body functions following the ABCDE protocol. Physical examination is followed by a short history taking, including information from medical records and relatives considering oral anticoagulation use and last intake of drugs, supplemented with basic laboratory parameters, and primary diagnostic imaging with emergency sonography. Simultaneously, insertion of two safe large bore venous lines and cardiorespiratory monitoring is indicated.

Necessary laboratory parameters are venous blood gases, complete blood cell count, platelet count, renal function tests and coagulation tests including activated partial thromboplastin time, prothrombin time (PT)/international normalized ratio (INR) and fibrinogen [12]. Once the source and severity of bleeding are localized, specific treatment can be initiated. These approaches are described elsewhere in detail [9,12].

The following flow chart summarizes the primary assessment at the ED. In many cases, further treatment warrants collaboration with other medical and surgical specialists [12]. If indicated, follow appropriate guidelines for administering packed red blood cells, platelets and coagulation factors [13] which may include a 'massive transfusion protocol' (MTP) specific to the emergency physician's institution.

Initial emergency department management of major traumatic bleeding

Bleeding is the leading cause of death after trauma. Short transfer time to the next appropriate hospital remains crucial for survival [14,15]. In the prehospital setting, recognition and initial treatment of major traumatic bleeding are crucial and can be life-saving. Life-threatening external bleeding should be treated by local compression bandaging or tourniquet [16]. Local haemostatic agents can be applied additionally [16]. An unstable pelvis should be fixed with a pelvic binder [17]. An SBP of 80–90 mmHg should be the target if no brain injury is suspected ('permissive hypotension') with restricted volume therapy using isotonic crystalloids until the target blood pressure (BP) is achieved [18]. In some emergency medical systems, prehospital blood transfusion and the application of an endovascular balloon occlusion are available [19].

Apart from vital signs and clinical re-assessment, routine use of point-of-care (POC) diagnostic testing including a focused assessment with sonography in trauma exam and a blood gas analysis [haemoglobin (Hb), lactate and base excess] supports the detection of bleeding. A low initial Hb, elevated serum lactate and base deficit indicate severe bleeding associated with coagulopathy and shock [18]. Renal function testing should be performed. Repeated measurements should be performed as an initially normal Hb might conceal severe bleeding. Critical patients with an obvious bleeding source should undergo immediate life-saving procedures including surgery or angiographic embolization [20]). A whole-body computed tomography (CT) scan with contrast agent is the gold standard to detect bleeding and should be performed as early as possible during in-hospital trauma management. Administration of blood products should be defined in the MTP.

(General aspects of trauma care – see Supplementary Addendum 2, Supplemental digital content 2, *http:///links.lww.com/EJEM/A388*).

Preinjury use of anticoagulants is associated with a higher risk for major traumatic bleeding. Surgery rates are significantly higher in all patients with anticoagulants compared to controls. Patients on VKAs have higher total in-hospital mortality rates whereas patients taking antiplatelet drugs demonstrated significantly higher early mortality [21]. In case of ongoing life-threatening bleeding, the effect of antithrombotic agents should be reversed [18] and the need for reversal must be weighed against risks [22].

Following the ABCDE evaluation approach, once major bleeding is suspected, one gram of tranexamic acid (TXA) should be administered intravenously within 3 h, followed by another gram over the next 8 h. In trauma patients, TXA has been proven to reduce coagulopathy and improve survival without an increase in thromboembolic events [23].

For patients with intracranial hemorrhage the effectiveness of TXA is less convincing because, in the largest trial of >2300 patients, those on anticoagulants were excluded [24]. In patients with acute gastrointestinal bleeding (AGIB) TXA is not recommended. A recent randomized controlled trial of 12 000 patients (of which approximately 10% were taking oral anticoagulation) showed that TXA did not reduce bleeding mortality but doubled the risk for VTE [25].

Repletion and reversal of oral anticoagulants

In patients with major anticoagulant-related bleeding, the treating clinician must decide on repletion or targeted reversal therapy. The decision to reverse DOAC anticoagulation or replete clotting factors must be carefully weighed in each patient judging the benefit of reduction of the bleeding against the accompanying prothrombotic risk. To accomplish this goal, the extent to which an anticoagulant drug is still available in the patient's body and thus contributing to the bleeding should be evaluated by answering the following questions – which medication is

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the patient using, when was the last dosage of anticoagulant taken, what is the half-life and mode of elimination for the drug, and is there evidence of impaired renal function which increases the potency of oral anticoagulants?

If the timing of the last dosage and route of excretion and half-life of the anticoagulant suggest the drug has been cleared, there is no indication for targeted treatment, and discontinuation of the drug is sufficient. When time since the last dosage is short, the drug has a long half-life, or excretion is disturbed because of renal insufficiency, targeted treatment of the anticoagulant is indicated.

(Laboratory and POC assessments of anticoagulation intensity in emergency settings – see Supplementary Addendum 3, Supplemental digital content 3, *http://links.lww.com/EJEM/A389*).

Major bleeding during vitamin K antagonist therapy – repletion management

Reversal of the anticoagulative effect of VKAs is mainly based on the repletion with active clotting factors. This treatment in patients with major bleeding is challenging for several reasons. First, half-lives of VKAs are long and range between 2 days (warfarin) and 7 days (phenprocoumon), with considerable inter-individual variance (Table 2). The INR provides the best indicator of the anticoagulation level due to VKAs.

Instead of selective inhibition of a specific coagulation factor as with parenteral anticoagulants or DOACs, VKA exposure to the human liver leads to the production of noncarboxylated and therefore dysfunctional coagulation factors II, VII, IX and X leading to a multilevel dysfunction of the coagulation cascade. Therefore, for the individual bleeding patient, the duration of residual VKA activity beyond repletion treatment is unpredictable and rebound VKA activity is a common problem after sufficient initial reversal.

In case of major bleeding, reversal of the anticoagulative effect of VKAs warrants the following actions:

(1) Vitamin K 10 mg intravenously: Onset of action is slow, typically taking 2 h after intravenous administration, and further delayed by impaired liver function. Therefore, vitamin K supplementation is a supportive measure in VKA-related bleedings which reduces rebound effects of VKA after acute care [26].
(2) Four-factor prothrombin complex concentrate (4F-PCC), given intravenously, contain activated factor II, VII, IX and X, plus Protein C and Protein S [27,28], providing repletion of clotting factors. Effect begins within 30 min and lasts for 6–8 h. The 4F-PCCs act much faster than fresh frozen plasma (FFP) with fewer cardiovascular complications but at a higher cost [29]. Further limitations of 4F-PCC use include incomplete reversal [27], delayed application [30], wrong dosage [31], a lack of clinical hemostasis despite adequate PT correction [32] and a reduced effectiveness in obese patients [33]. Lastly, the high concentration of coagulation factors in 4F-PCC might induce severe thromboembolic complications [34]. Adequate dosing of 4F-PCC depends on body weight and pretreatment INR, starting with 25 IU/kg body weight. After administration of 4F-PCC, the INR should be measured again to monitor the coagulative effect. If the INR is still above 1.5, an additional dosage of 4F-PCC should be given to a maximum of 50 IU/kg body weight.
(3) FFP has a relatively slow onset of action and reversal of the anticoagulant is often incomplete [27]. FFP therapy may be complicated by volume overload. For these reasons, 4F-PCC is preferred for major bleeding in patients taking VKA.

Major bleeding during direct oral anticoagulant therapy – reversal management

For patients with major bleeding, the pharmacological profile of the DOACs provides advantages over VKAs (Table 3).

The half-life of a DOAC is considerably shorter (8–12 h) so patients with a last DOAC intake >12 h before admission often demonstrate subtherapeutic levels; however, the reported short half-lives of DOACs are derived from healthy volunteer studies, while data from the German RADOA (Reversal Agent use in patients treated with Direct Oral Anticoagulants or vitamine K antagonists) registry have demonstrated a prolongation of DOAC half-lives in emergency patients of up to 20 h [35].

Table 2 Vitamin K antagonist and properties

	Warfarin	Acenocoumarol	Phenindione	Phenprocoumon
Elimination half-life (pharmacokinetics)	40	8–11 h	5–6 h	6.5 days
Time to PT response	24 h	Unknown (wide variability)	8–12 h	2–3 days
Time to maximum PT response	3–4 days	Unknown (wide variability)	2 days	Unknown (wide variability)
Time to PT normalization after last dose	2–5 days	Unknown (wide variability)	>4 days	Unknown (wide variability; but >7 days)
Renal clearance, %	Negligible	Unknown (contraindicated in severe renal impairment)	Unknown	Negligible (but contraindicated in severe renal impairment

PT, prothrombin time.

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In contrast to VKA treatment, all coagulation factors are fully carboxylated and functional in a DOAC patient with only factor II or factor X being inhibited. Consequently, reversal of the anticoagulative effect in patients with DOAC-related bleeding follows a more targeted strategy. The shorter half-lives and more predictable dose-response relationship of DOACs result in less overdosing and drug accumulation with fewer rebound effects post-reversal.

In patients with severe DOAC-related bleeding, specific reversal agents are available. For dabigatran, the antibody idarucizumab is now approved for reversal of dabigatran in major haemorrhage and emergency surgery in many countries globally. It is a manufactured antibody fragment, similar to thrombin, which binds dabigatran with high affinity. In a dosage of 5 g intravenously, idarucizumab works rapidly and results in complete reversal of the anticoagulation effect [36]. Continued bleeding after initial therapy, warrants a second dose of 5 g.

For the factor Xa inhibitors apixaban and rivaroxaban andexanet alfa is effective. A modified human Xa protein, very similar to endogenous activated factor X, binds with high affinity to the factor Xa inhibitors and thus inactivates their effect. After intravenous administration, the drug reaches its maximum effect within 2 min after initial bolus. To prevent a return of the anticoagulation effect of the Factor Xa inhibitor, the bolus of andexanet alfa must be followed by a continuous infusion. Depending on timing of the last dose of the factor Xa inhibitor, andexanet alfa is given in a low dose (400 mg within 15 min, followed by a 2-h infusion of 4 mg/min) or a high dose (800 mg within 30 min, followed by a 2-h infusion of 8 mg/min) (Fig. 2) [37]. Andexanet alfa is approved for life-threatening bleeding, but not for emergency surgery [37]. Andexanet alfa is also effective in reversing edoxaban [38] but approval for this indication is still lacking.

In institutions where idarazucimab or andexanet alfa are not available, some clinicians may treat DOAC-related bleeding with 4F-PCC though this therapy is off-label and not approved for this purpose. When given at recommended dosages of 25–50 IU/kg body weight, supplementation of FII and FX (both contained in 4F-PCC) may override the DOAC effects [39,40] though data are quite limited. Direct comparisons of andexanet alfa with 4F-PCC are still lacking, therefore the randomized Andexanet alfa, a Novel aNtidote to the anticoagulation Effects of factor XA inhibitors (ANNEXA-I) study will compare andexanet alfa against 4F-PCC in intracranial hemorrhage (ICH) [41,42]. Figure 2 provides an algorithm for treatment of major bleeding in anticoagulated patients.

Evaluation and treatment of spontaneous intracranial haemorrhage

Spontaneous intracranial haemorrhage encompasses bleeding in the intracerebral, subarachnoid, subdural and intraventricular spaces. Unlike intracerebral haemorrhage, which is typically managed by stroke neurologists in Europe, subdural and subarachnoid haemorrhage are managed initially by emergency physicians and subsequently by neurosurgeons. In patients with subarachnoid haemorrhage identification and control of ruptured aneurysms through coiling or surgical clipping is a key focus, while in patients with life-threatening bleeding in the subdural, subarachnoid and intracerebral space haematoma evacuation may be performed. For all intracranial haemorrhages, the prevention of further bleeding after presentation is paramount because secondary haematoma expansion can be catastrophic for the patient's prognosis. Rapid BP control with an SBP target less than 140 mmHg is recommended.

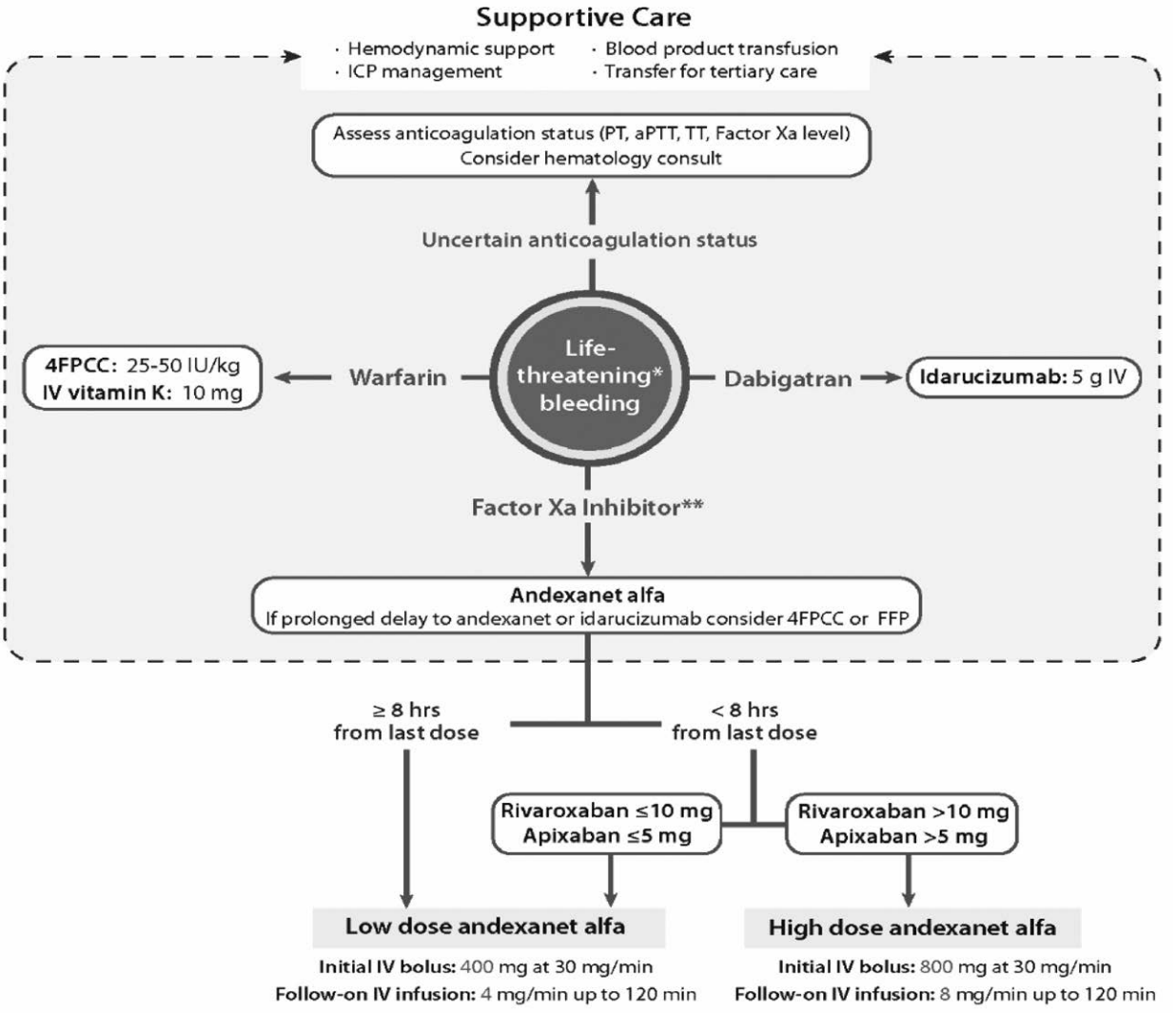
Pre-existing oral anticoagulation is a complicating factor for intracranial haemorrhage and is associated with a significantly increased risk of secondary haematoma expansion, in-hospital mortality and 3-month mortality [43]. Intracranial haemorrhage in patients with pre-existing DOAC treatment seems to result in smaller haematomas, however short- and long-term mortality rates are comparable to patients on VKA. A recent report however suggests lower mortality rates of DOAC-associated ICH compared to VKA although information on haematoma volumes was missing [44].

Time is critical in assessing and treating intracranial haemorrhage associated with anticoagulants, so actively inquiring about anticoagulant use is crucial. Prehospital recognition and advance notification of the hospital stroke team can save valuable time, ensuring prompt brain imaging to establish the diagnosis of intracranial haemorrhage [45,46]. Establishing the time of the last dose of anticoagulant can be challenging in patients with intracranial haemorrhage suffering reduced consciousness or communication difficulties. Laboratory tests assessing the persistent anticoagulant effect, combined with time from symptom onset, haematoma volume on

Table 3 Direct oral anticoagulants and properties

	Dabigatran	Apixaban	Betrixaban	Edoxaban	Rivaroxaban
Half-life, h	14–17	10–14	19–27	10–14	5–9
Peak onset of action, h	2	1–4	3–4	1–2	2–4
Renal clearance	80%	27%	10–20%	50%	35%

Fig. 2



Treatment algorithm for major or life-threatening bleeding in the anticoagulated patient. *Life-threatening bleeding including intracerebral haemorrhage and exsanguinating gastrointestinal bleeding. **FDA approved for rivaroxaban and apixaban only, but mechanism of action suggests it may be equally effective for edoxaban. ICP, intracranial pressure; 4F-PCC, four-factor prothrombin complex concentrate; aPTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time; Factor Xa level, anti-Factor Xa level. Algorithm available online at http://www.emcreg.org/algorithms. Reprinted with permission from Gibler WB, Racadio JM, editor(s). Management of severe bleeding in patients treated with oral anticoagulants. **Crit Path Cardiol** 18 (3):143–166, September 2019.

CT scan, untreated hypertension and concurrent use of antiplatelet agents, together establish the immediate risk of haematoma expansion [47]. The main treatment target for VKA-associated intracranial haemorrhage is to achieve INR < 1.3 to prevent secondary haematoma expansion [30].

For dabigatran-associated intracranial haemorrhage, the specific reversal agent idarucizumab has been tested in a single-arm open-label study (RE-VERSal Effects of Idarucizumab on Active Dabigatran, REVERSE-AD). Results are encouraging, showing rapid reversal of dabigatran activity in the blood; however because no comparison group was included, no firm conclusions about clinical efficacy can be drawn. With no other dabigatran-specific reversal agents, use of idarucizumab in dabigatran-associated intracranial haemorrhage seems indicated. For anti-Xa agents, in the past 4F-PCCs have been used to

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treat life-threatening bleeding, overriding the effect of the DOAC. More recently, andexanet alfa has been licensed by the Food and Drug Administration (FDA) and European Medicines Agency for use in this setting, which is not yet available in all European countries. Andexanet alfa has been tested in the single-arm ANNEXA-4 trial in which 128 patients with spontaneous anti-Xa-associated intracranial haemorrhage were included. Whilst there was no overall increase in haematoma volume from baseline to 12 h, the median baseline haematoma volume was low (9.4 ml) and there was no comparator arm, so firm conclusions regarding efficacy cannot be made [48]. The ongoing ANNEXA-I trial (andexanet alfa vs. standard care) will address this uncertainty.

Management of severe gastrointestinal bleeding

AGIB is a potentially life-threatening condition with a mortality of up to 15% [49]. Patients presenting with haematemesis, melaena and coffee-ground vomiting, in the absence of an alternative diagnosis (e.g. bowel obstruction) should trigger activation of local protocols for the management of AGIB. Immediate resuscitation at the ED follows the ABCDE approach. In order to prevent aspiration, prompt airway protection is important in patients with persistent haematemesis or patients with suspected variceal haemorrhage, preferably with a Sengstaken-Blakemore tube, which also serves to tamponade varices. In order to ensure adequate tissue perfusion, early correction of hypovolemia with intravenous crystalloid, following a 'restrictive' transfusion strategy is vital and significantly reduces mortality [50].

A target Hb of 7–9 g/dl is recommended; higher in those with cardiovascular comorbidities. The shock index (heart rate divided by SBP) can be used to identify unstable patients (<1 stable, >1 unstable) who require more prompt intervention [51]. Administration of blood products follows the MTP for the clinician's institution.

Unstable patients who can't be hemodynamically resuscitated should proceed directly to computed tomographic angiogram (CTA) followed by treatment of the bleeding source either endoscopically or via interventional radiology [52]. Because upper gastrointestinal (UGI) bleeding has a higher mortality than lower gastrointestinal bleeding it is generally recommended that an UGI endoscopy should be performed immediately in unstable patients if no bleeding source is identified on CTA. In stable patients, the Oakland score can be used to decide which patients require in-patient admission and endoscopy when available (score > 8) or can be discharged with urgent outpatient investigation (score < 8) [53].

(Risk stratification in gastrointestinal bleeding [54–62] – see Supplementary Addendum 4, Supplemental digital content 4, *http://links.lww.com/EJEM/A390*).

Treatment for patients with AGIB suspected of cirrhosis/variceal bleeding includes intravenous terlipressin and the prophylactic antibiotic ceftriaxone which are given to reduce mortality and infection, respectively [63]. These two medications, including dosing, should be given in collaboration with the gastroenterologist caring for the patient with gastrointestinal bleeding. Pre-endoscopy treatment with intravenous proton pump inhibitors significantly reduces the incidence of high-risk stigmata of haemorrhage. No benefit was seen, however, with respect to re-bleeding, need for surgery or mortality [64].

In terms of reversal of anticoagulants for patients on VKAs the protocol as mentioned above can be followed, including Vitamin K 10 mg intravenously, FFPs and 4F-PCC at a dose of 25–50 IU/kg body weight. For patients on DOACs, andexanet alpha has been shown to achieve excellent or good haemostasis in 85% of patients with AGIB who use a factor Xa inhibitor [37]. On the basis of these data, andexanet alfa is now recommended by the National Institute for Healthcare and Clinical Excellence in the UK in patients with life-threatening AGIB who are treated with either apixaban or rivaroxaban.

Conclusion

This consensus paper on the treatment of severe bleeding in the anticoagulated patient provides the emergency clinician with practical information which should improve the care of these critically ill and injured patients. Emphasis is placed on four important clinical presentations of anticoagulated patients – the initial management in the ED of the patient with nontraumatic and traumatic bleeding, intracranial haemorrhage and gastrointestinal bleeding along with a detailed discussion of approaches to repletion of VKA-induced clotting factor deficiencies and treatment using specific reversal agents for DOAC anticoagulation.

Acknowledgements

The authors wish to thank Judy M. Racadio, MD, for her helpful initial organization and comments, which improved the structure and content of the final manuscript.

The EMCREG-International Europe Multidisciplinary Consensus Panel on Management of Severe Bleeding in the Anticoagulated Patient, which met in Berlin in October 2022 before the EUSEM 2022 meeting, served as the basis for this manuscript. This meeting was supported by an unrestricted educational grant from AstraZeneca.

Conflicts of interest

There are no conflicts of interest.

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