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Management of bleeding in patients on direct oral anticoagulants in emergency department: where we are and where we are going

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Many patients who access in the emergency department for acute bleeding are on anticoagulants; before specific reversal agents were developed, bleeding on anticoagulants was burdened with a substantial increase in morbidity and mortality. Clinical trials demonstrated favourable risk-benefit profiles of direct-acting oral anticoagulants compared with vitamin K antagonists in patients with atrial fibrillation and compared with low molecular weight heparin in patients treated and prevented from venous thromboembolism. Even if they drastically reduced some types of bleeding, particularly intracranial haemorrhage, they have not completely eliminated this risk. The arrival of a patient with active bleeding in the emergency department is always a critical scenario that involves resources and costs. In critical setting, the diagnosis and treatment of bleeding should occurred simultaneously. Understanding the pathophysiological mechanisms that occur during bleeding is essential for establish the most appropriate therapies and improve the standard of care of the haemorrhagic patients.

General consideration

One of the most dramatic events that we face almost daily in emergency department (ED) is bleeding. Death from bleeding is a substantial global problem, with more than 60 000 deaths annually in the United States and approximately 1.9 million deaths annually worldwide, 1.5 million of which result from physical trauma.[1] Furthermore, who survive the initial bleeding insults have a high long-term mortality and poor functional outcomes.[2]

Understanding the pathophysiological mechanisms that occur during bleeding is essential for establish the most appropriate therapies and improve the standard of care of the haemorrhagic patient.

Anticoagulant therapy is one of the major risk factors for bleeding. It is estimated that over 6 million patients in the United States are treated with anticoagulants.[3] Most of the patients who come to the ED for acute bleeding are treated with anticoagulant therapy and this increases morbidity and mortality compared to those who do not.

Anticoagulants are the mainstay of treatment, primary and secondary prevention of stroke in patients with atrial fibrillation[4] (AF) and the main therapy of venous thromboembolism (VTE).[5] Conventional agents such as vitamin K antagonists (VKAs) and low molecular weight heparin, which have been the gold standard therapy for over 50 years, have been increasingly replaced by direct-acting oral anticoagulants (DOACs), which directly inhibit factor IIa (dabigatran) or factor Xa (i.e. apixaban, betrixaban, edoxaban, rivaroxaban). The ease of use of DOAC compared to VKA has decreed the beginning of a new era of anticoagulation. The underlying reasons for this change in clinical practice are clear: DOACs are generally simpler to dose, they do not require routine monitoring and they have a rapid onset of effect and a short half-life, absorption is not affected by food (except for rivaroxaban and betrixaban), and drug-drug interactions are limited.

However, their better handling in prescription and use, do not appear to come at the cost of safety and efficacy. Since the introduction of DOAC to the market, together

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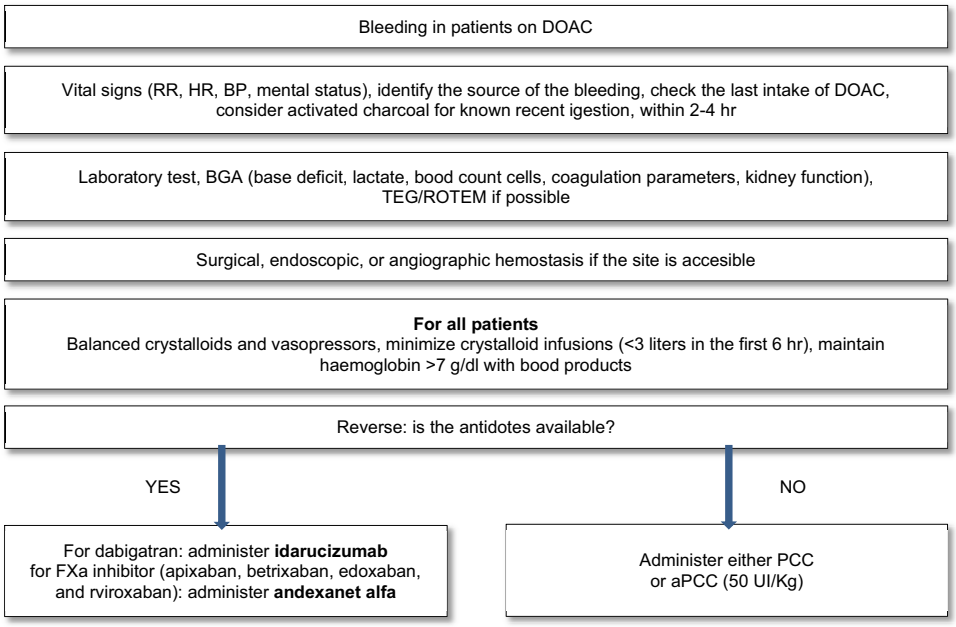

Figure 1 Management of bleeding in emergency department. aPCC, activated prothrombin complex concentrate; RR, respiratory rate; HR, heart rate; BP, blood pressure; BGA, blood gas analysis; TEG, thromboelastography; ROTEM, rotational thromboelastometry; PCC, prothrombin complex concentrate.

with the increased confidence of physicians on the safety and efficacy of DOAC, the rate of patients treated with vitamin K antagonists has been declining and DOAC are used preferentially. A determining factor was certainly the rate of developing intracranial haemorrage (ICH) which was almost halved with DOAC compared with VKA. The reduction in the risk of intracranial bleeding caused by DOAC is so evident that it can be said that the protective effect on haemorrhagic stroke is a true class effect. However, the risk is not completely eliminated and ICH is associated with a poor prognosis and a high in-hospital mortality rate.

Although several clinical trials have demonstrated favourable risk-benefit profiles of DOAC compared with VKA in patient with AF and compared with low molecular weight heparin in patients in treatment and prevention of VTE,[6,7] we must consider that anticoagulant therapy should be taken for life, therefore we cannot fail to consider the risk of future trauma or the development of other pathologies that increase the risk of bleeding (for example, the development of renal failure or dehydration in the elderly patient) under DOAC.

So is crucial for the emergency physician to reverse effect of DOAC in bleeding patients especially when bleeding is severe, if the patient requires urgent surgery or when bleeding is due to a trauma.

Indications for reversal of anticoagulant activity have evolved as evidences for specific antidotes have grown. However, even if every emergency physician should have knowledge about haemostasis and anticoagulant drug reversal, clinical stabilization remains the priority of every doctors, and assessment of haemodynamic stability and bleeding site control (such as mechanically compressing bleeding sites if accessible, see *Figure 1*) remain essential first interventions for improve survival of the bleeding patient.

The identikit of the bleeding patient

Several scores have been developed to assess the risk of bleeding in patients on anticoagulant therapy, and to try to identify those at risk. Examples of scores are HAS-BLED (estimates risk of major bleeding for patients on anticoagulation to assess risk-benefit in atrial fibrillation care),[8] ORBIT (bleeding risk score for atrial fibrillation),[9] and more recently the ABC (Age, Biomarkers, Clinical history) score[10] which also uses selected biomarkers such as troponin. The latest European Society of Cardiology (ESC) guidelines on the management of AF suggest that from a systematic review including 38 studies on bleeding risk prediction, the HAS-BLED score is the score that had the best evidence for predicting bleeding risk (moderate strength evidence), consistent with other systematic reviews and meta-analyses comparing bleeding risk prediction approaches.[11]

If we compare thromboembolic disease risk scores (see CHA_2DS_2-VASc [score for atrial fibrillation stroke risk] score) and bleeding scores, we notice that some items overlap. For example, advanced age is one of the most important predictors of both ischaemic stroke and bleeding in the patient with atrial fibrillation. Therefore a high score in bleeding risk scores should not be a contraindication to the use of oral anticoagulants but rather should lead to the identification and possibly modification of correctable risk factors (see for example the use of NSAIDs or concomitant antiplatelet therapy, hypertension, excessive alcohol consumption). Other potential risk factors are age, history of major bleeding, cancer, previous stroke, renal and hepatic impairment. In the elderly treated with DOAC the history of falls is not an independent predictor of bleeding and should not be a reason to not prescribe anticoagulants as well as cognitive impairment and frailty. Indeed, as reported in the ESC

guidelines, one modelling study has evaluated that a patient would need to fall 295 times per year for the benefits of ischaemic stroke reduction with DOAC to be counterbalanced by the possibility of severe bleeding.[11,12]

These assumptions should encourage emergency physicians to prescribe DOAC in patients who have the indications for them when the diagnosis of atrial fibrillation or VTE is made.

Management of bleeding patient

Anyone who works in an ED knows that managing of bleeding is a considerable expenditure of energy, time and costs. Several years ago when we talked about bleeding management in patients taking DOAC the recommendations of the literature suggested to stratify into minor and major or life-threatening bleeding. Emergency physicians know that there are no such sensitive indicators of severity and that the patient with bleeding is always a potentially critical patient.

For example, some authors suggest that if the bleeding occurs in a critical site such as the brain, or there are signs of haemodynamic instability or the patient requires transfusion because the blood loss is over than 2 g of haemoglobin, then it is a major bleeding.[13]

In the practice of the ED we know that the signs and symptoms of bleeding are subtle, especially if occult. In fact, in most patients there are so important compensatory mechanisms to make hypotension a no-sensitive indicator of shock until at least 30% of the circulating blood volume has been lost.[1] More sensitive signs of volume loss include anxiety, tachypnoea, cold extremities and a weak pulse.

When the patient arrives at the hospital, the priorities for management of bleeding include restoration of intravascular volume and rapid control of bleeding as part of the damage control resuscitation paradigm (see *Table 1*).

Severe blood loss leads to inadequate oxygen delivery at the cellular level, and haemorrhagic shock results when the oxygen demand is greater than oxygen delivery, leading to anaerobic metabolism. At the tissue level, hypovolemia and vasoconstriction lead to hypoperfusion and end-organ damage and in the most critical patients a multiorgan failure can occur. The hypoperfusion of the brain and myocardium, leading to cerebral anoxia and fatal arrhythmias, results often in death. Restoring the intravascular volume as quickly as possible is determinant to implement every possible action to avoid haemorrhagic shock, since the median time from onset of bleeding to death is 2 hours.[14,1] The restoration of intravascular volume has to be done with blood transfusion to compensate oxygen-carrying capacity before shock becomes irreversible. Imbalances in plasma, platelet, and red-cell transfusions should be minimized in order to optimize haemostasis.

During the initial assessment, efforts should be made to identify the source of the bleeding (e.g. intracranial, gastrointestinal) and mechanical haemostasis should be done if the site is accessible.

Although Focused Ultrasound Assessment for Trauma (FAST) was born to detect the source of bleeding in cavities such as peritoneum, intrathoracic, or pericardial in the trauma patient, it can also be used in non-trauma patients to locate the source of bleeding (e.g. rupture of aortic aneurysm).

Table 1 Damage control resuscitation (adapted from Cannon JW, NEJM, 2018)

Damage control resuscitation
Avoid hypothermia
Delay fluid administration until the time of definitive haemostasis in selected patients
Minimize crystalloid infusions (<3 L in the first 6 h)
Maintain haemoglobin >7 g/dL with blood products
Surgical, endoscopic, or angiographic haemostasis
Minimize imbalances in plasma, platelet, and red-cell transfusions in order to optimize haemostasis
Obtain functional laboratory measures of coagulation (e.g. by means of thromboelastography or rotational thromboelastometry) to guide the transition from empirical transfusions to targeted therapy
Selectively administer pharmacologic adjuncts to reverse any anticoagulant medications and to address persistent coagulopathy

Among the laboratory tests, the initial evaluation of the blood count is essential for evaluating both the haemoglobin and platelet values even in patients with concomitant therapy with antiplatelet drugs and the blood gas analysis should be performed to measure cellular hypoperfusion by assessing the base deficit and lactates. The same parameters can be used to evaluate whether the patient stabilizes or not (if there are no changes, the base deficit and lactate improve, if there are no further reductions in haemoglobin).

In the emergency room, coagulopathy should be identified especially in unconscious patients and when it is not known whether they are on anticoagulant therapy or when the last dose has been taken, using thromboelastography (TEG) or rotational thromboelastometry (ROTEM) which are promising tools for detection of anticoagulant drug activity and for guiding reverse therapy.[15,16]

The doctors who deal with bleeding management are well aware that often iatrogenic factors worsen coagulopathy. It is often routine to use massive fluid infusions that have no therapeutic effect other than transiently expanding circulating volume, but they dilute clotting factors and reduce the ability to carry oxygen. Additionally, cold fluids exacerbate heat loss related to blood loss and lead to impaired enzyme function in the coagulation cascade. In addition, administration of acidic crystalloid solutions worsens acidosis caused by hypoperfusion and further impairs clotting factor function, resulting in a 'vicious circle of coagulopathy, hypothermia, and acidosis'.[1] To avoid rebleeding it is reasonable to accept a lower than usual values of blood pressure; it is so called 'permissive hypotension'.

Anticoagulants and antiplatelet agents should be discontinued, and reversal of DOAC is recommended if an agent is available but obtaining and administering the reversal agent must not delay resuscitation and local haemostatic like specific diagnostic and treatment interventions

	Characteristcs	Dosage	Time of reverse
Idarucizumab	Idarucizumab is a humanized monoclonal antibody (Fab) fragment with a structure similar to thrombin. It binds dabigatran highly selectively and with high affinity (350-fold higher than observed between dabigatran and thrombin)	5 g i.v. divided in two 2.5g-doses, given within up to 15 minutes apart	Idarucizumab stopped bleeding in a few minutes with a median time of 2.5 h
Andexanet alfa	Andexanet alfa is an engineered variant of factor Xa whose similarity to the human form. It allows to bind factor Xa inhibitors with high affinity	Low-dose regimen: 400 mg IV bolus administered at a rate of 30 mg per minute. High dose: 800 mg IV bolus given at a rate of 30 mg per minute, followed by a two-hour IV infusion given at rate of 8 mg per minute. The recommended regimen for a particular patient is based on the factor Xa inhibitor used, the dose of factor Xa inhibitor, and the time since the last dose of factor Xa inhibitor	Efficacy occours within two minutes of giving the IV bolus dose. The reduced anti-cator Xa activity remains up to two hours after stopping the infusion

Figure 2 Characteristics and dosage of antidotes.

to identify and manage the cause of bleeding (e.g. gastroscopy) should be performed promptly.

If the last intake of DOAC was less than 2–4 h before bleeding assessment, charcoal administration and/or gastric lavage will reduce further exposure.

Severe or life-threatening bleeding requires immediate reversal of the antithrombotic effect.

Management of patients with active bleeding while on DOAC is shown in *Figure 1*.

Specific antidotes and prothrombin complex concentrate (PCC).

The availability of antidotes represents a useful tool to reverse anticoagulation.

Two antidotes are currently available (and another antidote, ciraparantag, is being tested) for DOAC: idarucizumab (for dabigatran) and andexanet alfa (for factor Xa inhibitors). Trials have shown that they actually have the ability to determine the reverse of anticoagulation and to restore normal haemostasis[17,18] even if it must be clear that restoring haemostasis is not a guarantee of a favourable prognosis, for the mechanisms that we have already illustrated, the prognosis could be poor despite the restoration of normal haemostasis, if no action is taken before the patient presents signs of organ hypoperfusion.

Dabigatran was the first DOAC to have an antidote available that could neutralize the activity of dabigatran within minutes. This has allowed emergency physicians to have extra help in patients on oral anticoagulant therapy who present with life-threatening bleeding or in patient that needs to be underwent surgery not procrastinable.

Idarucizumab is a humanized monoclonal antibody (Fab) fragment with a structure similar to thrombin. Idarucizumab binds dabigatran in a highly selective way and with high affinity (350-fold higher than that observed between dabigatran and thrombin). It has no prothrombotic effects because it has a high affinity only for dabigatran and it is able to bind both the drug that is free in the blood and the one that is fixed to thrombin, displacing the bond. It allows the anticoagulant activity to be neutralized within few minutes by dabigatran.

A specific reversal agent is also available for adult patients treated with a direct factor Xa inhibitor (apixaban or rivaroxaban), when reversal of anticoagulant therapy is required due to life-threatening or uncontrolled bleeding.

In the ANNEXA-4 trial, the number of patients enrolled receiving edoxaban was limited and for this reason, to date, its use is still off-label.

Reversal of betrixaban with andexanet alfa has only been evaluated in healthy volunteers.

Andexanet alfa is an engineered variant of factor Xa whose similarity to the human form allows it to bind factor Xa inhibitors with high affinity without promoting further anticoagulant activity.

Administration of an intravenous (IV) bolus dose of andexanet alfa followed by a 2-h continuous intravenous infusion results in a rapid onset of anti-factor Xa activity. Efficacy occurs within two minutes of giving the IV bolus dose. The reduced anti-factor Xa activity remains up to two hours after stopping the infusion. In addition, andexanet alfa has the ability to inhibit tissue factor pathway inhibitor, which is maintained for at least 22 h following andexanet alfa administration.

The antidote has two dosage regimens, a low dose and a high dose. The low-dose regimen consists of a 400 mg intravenous bolus administered at a rate of 30 mg per minute, followed by a two-hour intravenous infusion at a rate of 4 mg per minute. The high dose is an 800 mg intravenous

bolus given at a rate of 30 mg per minute, followed by a two-hour intravenous infusion given at a rate of 8 mg per minute. The recommended regimen for a particular patient is based on the factor Xa inhibitor used, the dose of factor Xa inhibitor, and the time since the last dose of factor Xa inhibitor.

Characteristics of the two antidotes are shown in *Figure 2*.

If andexanet alfa is not available, it is reasonable to use haemostatic agents such as prothrombin complex concentrate (PCC or activate-PCC).

Evidence supporting the use of PCC in FXa inhibitor-treated patients with major bleeding is limited and are mostly retrospective studies, currently there are no data from randomized trials.

An initial intravenous dose of 50 U/kg is suggested for patients with FXa inhibitor major bleeding who are known or likely to have clinically significant anticoagulant levels. However, when andexanet alfa is available, this should be preferred to the use of PCC for treatment of patients with major bleeding on oral direct FXa inhibitors.[19,20]

Conclusion

In the emergency department, the arrival of a patient with active bleeding is always a serious emergency that requires considerable expenditure of resources, costs and risks for the patient.

Emergency physicians should be familiar with the principles of haemostasis and anticoagulant reverse because bleeding in patients on anticoagulant therapy could benefit from use of antidotes, particularly to manage life-threatening bleeding, when the patient requires urgent surgery, or when bleeding is due to trauma. However, life-saving interventions should aim at managing the impaired oxygen delivery. Indeed, the priority of every emergency physician is to support haemodynamic status and restore blood volume by transfusion of blood products.

Indications for activity neutralization of DOAC are constantly evolving along with the recent development and commercialization of specific reversal agents.

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Data availability

No new data were generated or analysed in support of this research.

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