How we treat bleeding associated with direct oral anticoagulants

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Abstract

Direct oral anticoagulants are at least as effective as vitamin K antagonists for the prevention and treatment of thromboembolism. Unfortunately, differently from vitamin K antagonists, they have the great drawback of lacking specific antidotes in the case of bleeding or emergency situations such as trauma, stroke requiring thrombolysis, and urgent surgery. The progressive development of antidotes for these new drugs, which, it is hoped, will become available in the near future, will allow better and safer management of the rapid reversal of their anticoagulant effect.

Keywords: direct oral anticoagulants, bleeding, anticoagulation reversal, fresh-frozen plasma, prothrombin complex concentrates.

Introduction

Anticoagulant therapy is a fundamental approach for the prevention and treatment of thromboembolic diseases and the currently available therapeutic armamentarium includes unfractionated heparin, low-molecular-weight heparins and vitamin K antagonists (VKA)[1-3]. Moreover, a new class of direct oral anticoagulants (DOAC) has been developed in the last decade to overcome the main limitations of traditional anticoagulants, i.e. parenteral administration and onset of thrombocytopenia for heparins, and the need for routine International Normalised Ratio (INR) monitoring and susceptibility to a number of food and drug interactions for VKA[4-6]. Two types of DOAC are currently available: the factor Xa inhibitors apixaban, edoxaban, and rivaroxaban and the thrombin inhibitor dabigatran (see Figure 1 and Table I for the description of their mechanisms of action and main characteristics, respectively)[7]. Unlike VKA, which block the formation of multiple, active vitamin K-dependent coagulation factors, DOAC antagonise the activity of a single step in coagulation[7]. In addition to their above mentioned practical advantages, at the moment there is robust evidence from several phase 3 trials that DOAC are at least as effective as VKA for the prevention and treatment of thromboembolism[8-23]. However, as the most feared complication of VKA is the onset of severe haemorrhage, especially intracerebral[24],

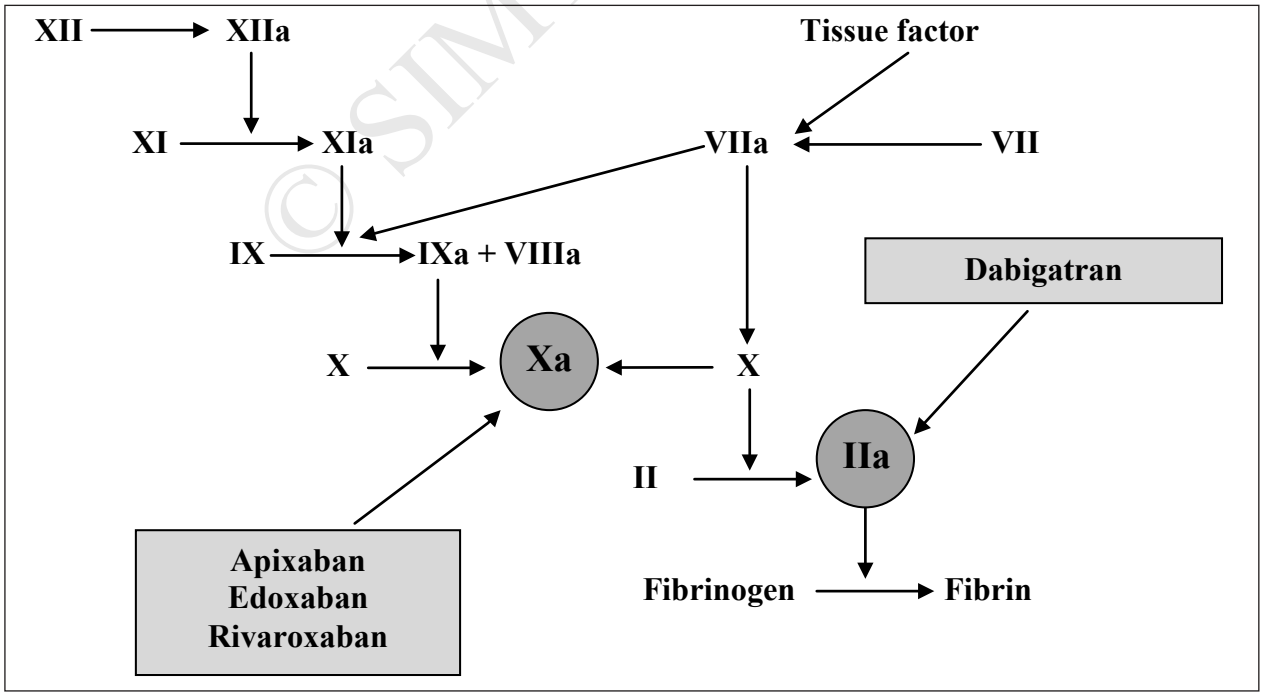

Figure 1 - Mechanisms of action of direct oral anticoagulants.

Table I - Characteristics of the new oral anticoagulants.

Characteristics	Direct thrombin inhibitor	Factor Xa inhibitors		
	Dabigatran	*Apixaban*	*Edoxaban*	*Rivaroxaban*
Prodrug	Yes	No	No	No
Bioavailability (%)	3-7	50	62	80
Time to peak concentration (hours)	1-3	1-3	1-3	2-4
Half-life (hours)	12-17	8-15	8-10	7-13
Renal clearance (%)	80	25	35	36
Elimination	Urine and faeces	Urine and faeces	Urine and faeces	Urine and faeces
Dosing regimen	110-150 mg twice daily	2.5-5 mg twice daily	15-30 mg once daily	10-30 mg once daily
Metabolism	P-glycoprotein	P-glycoprotein, CYP3A4	P-glycoprotein, CYP3A4	P-glycoprotein, CYP3A4
Antidotes under development	Idarucizumab, modified thrombin molecules	Andexanet alfa, Aripazine	Andexanet alfa, Aripazine	Andexanet alfa, Aripazine

the comparison between these two classes of drugs is based mainly on the ability of DOAC to reduce the incidence of life-threatening bleeding complications[25-28].

In this review, after a brief discussion of the safety of DOAC, we summarise the current knowledge on the management of bleeding complications associated with the use of DOAC. A section is also dedicated to the current status of development of specific antidotes. Finally we propose a treatment algorithm based on the literature and our personal experience.

Safety of direct oral anticoagulants

The results of large, randomised licensing trials have shown that bleeding rates with DOAC are generally the same or even lower than the bleeding rates with VKA and a number of meta-analyses pooling together the data from such trials have confirmed these findings[29-36]. Thanks to their efficacy and safety profile[37], DOAC are being increasingly used in clinical practice worldwide[38-40]. In parallel, to validate the data from phase 3 trials, a number of real-world studies have recently been completed and their results have been published. A nationwide Danish prospective cohort study, assessing the safety and efficacy of dabigatran *vs* warfarin for the treatment of patients with atrial fibrillation in everyday clinical practice, found that the rates of major bleeding and gastrointestinal bleeding were similar between the dabigatran and warfarin groups: for major bleeding the adjusted hazard ratio (aHR) with 95% confidence interval (95% CI) was 0.82 (0.59-1.12) in the dabigatran 110 mg group, and 0.77 (95% CI: 0.51-1.13) in the dabigatran 150 mg group, while for gastrointestinal bleeding the aHR was 0.60 (95% CI: 0.37-0.93) in the dabigatran 110 mg group, and 1.12 (95% CI: 0.67-1.83) in the dabigatran 150 mg group[41].

However, a study carried out in the USA in a large population of elderly Medicare patients, comparing the safety of dabigatran (75 or 150 mg twice daily) *vs* warfarin, showed that dabigatran was associated with a significantly reduced risk of ischaemic stroke (aHR: 0.80; 95% CI: 0.67-0.96), intracranial haemorrhage (aHR: 0.34; 95% CI: 0.26-0.46) and death (aHR: 0.86; 95% CI: 0.77-0.96), but with an increased risk of major gastrointestinal bleeding (aHR: 1.28; 95% CI: 1.14-1.44)[42]. A similar gastrointestinal bleeding risk between the DOAC dabigatran and rivaroxaban and warfarin was observed in two studies conducted in the USA on large populations of commercially insured adults[43,44], although particular caution was recommended when prescribing such novel oral anticoagulants to older people (>75 years) due to an increased gastrointestinal bleeding risk[44]. In the Dresden prospective registry, the observed 6.1% of rivaroxaban-related major bleeding was lower and the outcome (6.3% of bleeding-related case fatality rates at day 90) better than that reported for VKA[45]. An update from the same registry showed that only a small proportion (5.3%) of reported bleeding events observed with DOAC were major[46]. Overall, these post-marketing, real-life efficacy data document that a number of DOAC-associated bleeding events do occur. The management of such events can be a major concern among physicians because of the lack of specific antidotes (see below).

Recently, various reviews and the opinions of panels of experts on the treatment of DOAC-related bleeding have been published with the aim of filling the gap consequent to the lack of evidence based on clinical trials[26,27,47-49].

Management of bleeding associated with direct oral anticoagulants

Since their introduction, one of the potential downsides of DOAC administration has been the absence of specific antidotes to reverse their anticoagulant effects. Until an antidote becomes available for clinical use, supportive care remains the pillar of the treatment of haemorrhagic complications; however, based on experience with VKA-related bleeding[24,50-53], the use of

fresh-frozen plasma, prothrombin complex concentrates (PCC), or recombinant activated factor VIIa (rFVIIa) has been proposed[54,55]. In addition, although it is not usually necessary to monitor the anticoagulant effects of DOAC, an assessment of coagulation status is necessary in the case of major bleeding, trauma, urgent surgery or overdose (for the most appropriate tests for the quantitative measurement of the anticoagulant activity of DOAC, see reference 28).

In most cases of DOAC-associated mild bleeding, considering their short half-life, drug discontinuation, investigation of the source of bleeding, and general supportive measures can be adopted. The general management of major bleeding includes prompt control of the haemorrhage by mechanical compression, surgical or endoscopic haemostasis, radiological interventional procedures, transfusion of blood components and haemodynamic support with fluid replacement as well as the use of adjunctive haemostatic agents (i.e., antifibrinolytics or desmopressin)[28].

Other possible therapies exploited include haemodialysis and activated charcoal. Haemodialysis may reverse the anticoagulant effects of dabigatran overdose because of the low protein binding (35%) of this drug[56] and, in a single-centre study in patients with end-stage renal disease, it proved to be effective in removing approximately 70% of a single 50-mg dose of dabigatran at 4 hours[57]. However, it is not effective for rivaroxaban or apixaban because these drugs are highly protein bound (95% and 87%, respectively)[58,59]. Oral activated charcoal can be used if a recent (<2-3 hours) overdose of dabigatran is suspected, as shown by *in vitro* data[60], but no data are available on factor Xa inhibitors.

This review focuses on the use of non-specific procoagulant agents and specific antidotes (though currently still at various stages of clinical development) that can be used for the urgent reversal of anticoagulation with DOAC in severe acute haemorrhage[61]. Figure 2 presents a proposed treatment algorithm for patients with DOAC-associated bleeding patients or at high risk of bleeding.

Non-specific procoagulant agents

In the case of serious bleeding, in the absence of specific antidotes, non-specific procoagulant agents (PCC, activated prothrombin complex concentrates [aPCC)], and rFVIIa) have been used for their capacity to reverse the anticoagulant effects of DOAC.

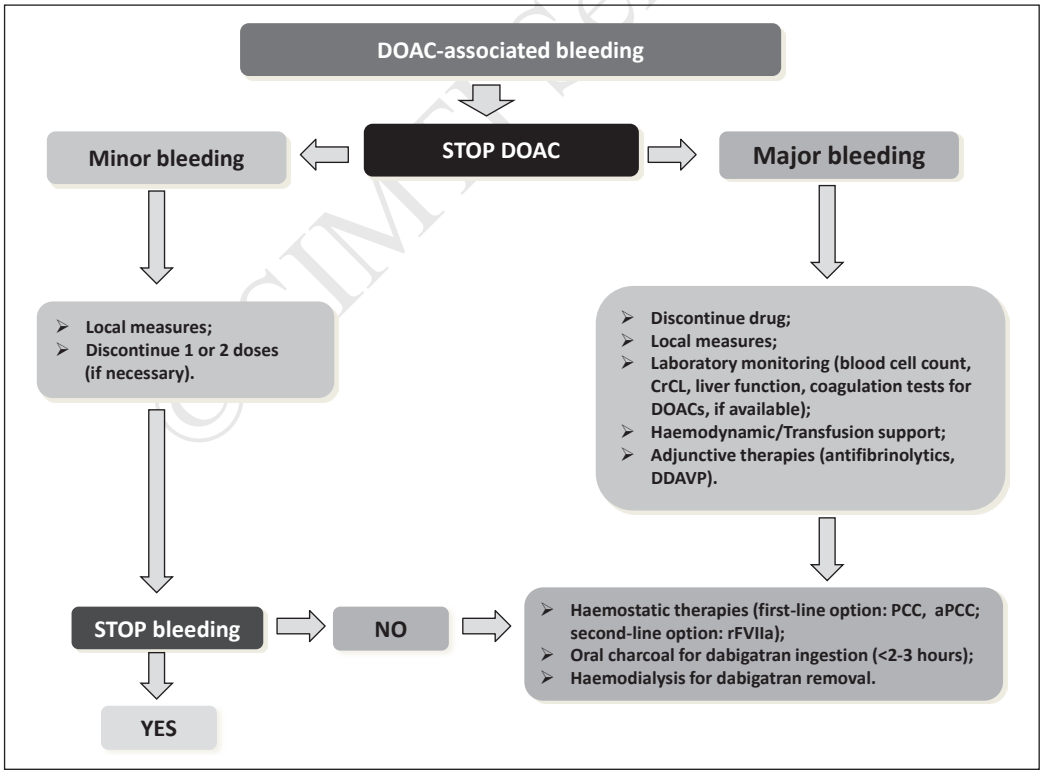

Figure 2 - Treatment algorithm for patients with direct oral anticoagulant-associated bleeding or at high risk of bleeding.
DOAC: direct oral anticoagulant; CrCl: creatinine clearance; DDAVP: desmopressin; PCC: prothrombin complex concentrate; aPCC: activated prothrombin complex concentrate; rFVIIa: recombinant activated factor VII; hs: hours.

PCC contain various amounts of vitamin K-dependent coagulation factors (factors II, IX and X and proteins C and S) and are classified as three-factor PCC or as four-factor PCC, if they contain factor VII[62].

Pre-clinical studies on the efficacy of PCC in the reversal of the anticoagulant effect of DOAC have yielded conflicting results[63]. On the one hand, a mice model of intracerebral haemorrhage[64] and a rabbit model of kidney injury[65] showed good effects of PCC in limiting haematoma growth and blood loss associated with dabigatran while another study demonstrated that four-factor PCC was able to reduce rat (tail vein) bleeding time significantly[66].

On the other hand, successive studies pointed out that PCC had no effect on dabigatran-related bleeding in mice[67] or on the reversal of the effects of rivaroxaban in a rabbit model of hepatosplenic bleeding, despite partial correction of laboratory parameters[68]. Moreover, in separate studies, the addition of PCC to rivaroxaban-spiked plasma *in vitro* did not change abnormal coagulation tests, thromboelastometry or thrombin generation tests[69,70]. An *ex vivo* randomised, double-blind, placebo-controlled study, aimed at reversing the effects of dabigatran and rivaroxaban in healthy male volunteers, showed that four-factor PCC (50 IU/kg) failed to reverse the prolongation of the activated partial thromboplastin time, ecarin clotting time, or thrombin time in participants treated with dabigatran but corrected the prothrombin time prolongation and abnormal endogenous thrombin potential in those treated with rivaroxaban[71]. Four-factor PCC also improved the thrombin peak and velocity indices in thrombin generation of blood from healthy male volunteers pre-treated with apixaban[72].

The result of an open-label, single-centre, parallel-group study showed that both four-factor PCC and three-factor PCC can at least partially reverse the anticoagulant effects of rivaroxaban. Administration of either four-factor or three-factor PCC to 35 healthy volunteers in the presence of rivaroxaban appeared to be safe and well tolerated, with no signs of thromboembolic events[73].

The three-factor PCC was also able to reverse edoxaban-induced thrombin generation inhibition in a phase 1, single-dose, placebo-controlled trial[74]. However, we must underline that all human studies carried out so far in this clinical setting have exploited healthy volunteers without active bleeding. Therefore, we still do not know whether and how the corrections of the laboratory tests modified by DOAC translate into a clinical benefit. Furthermore, at the moment, we do not have robust data to recommend four-factor PCC over three-factor PCC or vice versa in this setting, although data supporting the use of four-factor PCC are probably more consistent[71,72].

Finally, from the analysis of the available literature data, PCC (50 IU/kg) seems to be more effective for bleeding associated with oral anti-FXa inhibitors than for that associated with oral direct thrombin inhibitors. PCC should be preferred over fresh-frozen plasma for DOAC reversal as they provide a more rapid and sustained replacement of multiple factors in a small volume and also theoretically carry a lower risk of transmitting infections because of the viral inactivation process[62].

aPCC (factor VIII inhibitor bypassing activity, FEIBA) contain factors II, VII, IX and X, which are activated during the industrial production process. Several animal and *in vitro* studies on the reversal of the anticoagulant effects of dabigatran, rivaroxaban and apixaban demonstrated that aPCC are able to correct some abnormal clot-based coagulation tests, thromboelastometry parameters and thrombin generation indices[75-78]. In fact, while PCC, aPCC and rFVIIa corrected the prolongation of the prothrombin time and reduced bleeding time in rivaroxaban-treated rats, only aPCC reduced bleeding time in primates treated with rivaroxaban[77]. In an *ex vivo* study of healthy male volunteers, carried out by Marlu and colleagues[79], both four-factor PCC and FEIBA were able to reverse the anticoagulant effect of dabigatran and rivaroxaban but aPCC were more efficacious. Another *ex vivo* experimental study showed that FEIBA, at a dose of 50 IU/kg, corrected thrombin generation in the plasma of patients treated with dabigatran[80]. Another study showed that PCC, aPCC and rFVIIa all corrected the prolongation of prothrombin time when added to plasma from patients receiving rivaroxaban, but only PCC and aPCC modified all abnormal thrombin generation indices[81]. A recent study by Martin and collaborators showed that aPCC was more effective than PCC or rFVIIa in reversing, *in vitro*, the effects of apixaban. aPCC rapidly triggered the development of an apparently normal fibrin network and corrected latency and quantitative parameters, whereas PCC or rFVIIa had only a partial effect[82].

Therefore, aPCC (50 IU/kg, maximum 200 IU/kg/day) seems promising in reversing the effects of DOAC, especially for dabigatran. However, as data from well-designed clinical studies are lacking, the aPCC-associated increased thromboembolic risk should be evaluated carefully.

rFVIIa has also been used to reverse the effect of DOAC. Although it was not able to stop bleeding following treatment with dabigatran or rivaroxaban in animal models, *in vitro* studies suggest a variable effect on rivaroxaban- and apixaban-induced haemostatic abnormalities[64,68,72,83]. Similarly to PCC, rFVIIa also failed to reverse bleeding induced by rivaroxaban overdose[68], while both aPCC and rFVIIa significantly shortened the bleeding time in edoxaban-treated rats[84]. In an *in vitro* study, rFVIIa corrected prothrombin time

prolongation at a low concentration of rivaroxaban (80 ng/μL) and thromboelastometry results at a high concentration of rivaroxaban (200 ng/μL)[70]. In another *in vitro* study analysing the efficacy of PCC, aPCC and rFVIIa in reversing the anti-haemostatic activity of apixaban, rFVIIa was the most effective in correcting clotting time prolongations[72]. In *ex vivo*-treated plasma samples from healthy volunteers rFVIIa was unable to reverse the anticoagulant effect of dabigatran[79]. Although clinical data are lacking, results from pre-clinical studies seem to indicate that rFVIIa is less effective than other haemostatic agents (i.e., activated or non-activated PCC) for the treatment of DOAC-associated bleeding, especially when dealing with oral direct thrombin inhibitors[85]. Furthermore, like aPCC, rFVIIa enhances the risk of thrombosis. Therefore, rFVIIa (90 μg/kg) should be considered as a second-line therapeutic option for the treatment of DOAC-associated bleeding, to be used after the failure of PCC or aPCC (Figure 2).

Specific antidotes

Several specific antidotes for DOAC are currently under development and seem to be promising in early clinical trials evaluating their efficacy and safety[55].

Idarucizumab, a humanised monoclonal antibody fragment (aDabi-Fab), has been produced by Boehringer Ingelheim GmbH (Ingelheim am Rhein, Germany) to reverse the anticoagulant effect of dabigatran and is currently in phase 3 clinical development[86,87]. It has a binding affinity that is about 350 times higher than the binding affinity of dabigatran for thrombin but no procoagulant or anticoagulant effects and a short half-life. A randomised, placebo-controlled, double-blind, proof-of-concept phase 1 study involving 47 healthy male volunteers documented the rapid, complete and sustained reversal of the effects of dabigatran following administration of idarucizumab, with no adverse events[88]. A phase 3 study (RE-VERSE AD; NCT02104947) is currently recruiting patients in more than 35 countries worldwide and aims at assessing the effect of idarucizumab, at a dose of 5 g, on the anticoagulant action of dabigatran in patients treated with dabigatran etexilate who have either uncontrolled bleeding needing urgent medical intervention (group A) or need emergency surgery or procedures necessitating rapid reversal of the anticoagulant effect of dabigatran (group B). An interim analysis including 90 patients who received idarucizumab (51 patients in group A and 39 in group B) showed that the antibody fragment rapidly and completely reversed the anticoagulant activity of dabigatran in 88 to 98% of patients[89]. Similarly to previous studies involving more than 200 healthy volunteers who were treated with aDabi-Fab[88,90,91], no safety concerns were reported. A possible theoretical challenge is linked to the presence of natural antibodies binding to the cleavage site of Fab fragments in about 15% of normal subjects[92]. They would not be able to block the drug effect but the complexes of dabigatran, idarucizumab, and the anti-Fab antibody would no longer be filtered by the kidney, because of their dimension, thus prolonging the resistance to new doses of dabigatran. This problem could be solved simply by changing the anticoagulant, in the case that further anticoagulation is necessary. Another possible very low risk is the formation of anti-idiotype antibodies against this antidote, which may sterically mimic dabigatran and could become an endogenous thrombin inhibitor.

Modified thrombin molecules such as an active site-mutated S195A thrombin (S195A-IIa) and its trypsinised derivative (γT-S195A-IIa) can also play a role in the reversal of dabigatran's effects but clinical data are still lacking[93].

As far as antidote development for the direct FXa inhibitors is concerned, Portola Pharmaceuticals Inc., (San Francisco, CA, USA) has recently produced a modified, recombinant activated FX (andexanet alpha, PRT064445, Annexa™-A), which is catalytically inactive but retains high-affinity binding to factor Xa inhibitors[94]. In a phase 1 study on 32 healthy volunteers randomised to receive single escalating intravenous bolus doses of andexanet alfa or placebo, the anti-FXa activity of rivaroxaban, which was added *ex vivo*, was reversed in a dose-dependent manner with no adverse events[95]. Preliminary results of a phase 2, double-blind, placebo-controlled trial showed that a bolus dose of andexanet alfa antagonised the anti-FXa activity of apixaban and rivaroxaban in healthy volunteers[96,97]. In the randomised, double-blind, placebo-controlled phase 3 ANNEXA-A (Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of FXa Inhibitors - Apixaban) study, evaluating the safety and efficacy of this antidote in older healthy volunteers (50-75 years), andexanet alfa produced rapid, sustained and nearly complete reversal of the anticoagulant effect of apixaban with no serious adverse effects[98,99]. Finally, in January 2015, a phase 3 prospective open-label study to evaluate the effect of andexanet in patients receiving FXa-inhibitors who have acute major bleeding started[100]. However, as according to the currently available data different doses of andexanet alpha seem to be required for the two direct FXa inhibitors apixaban and rivaroxaban[96], it may be challenging to use the appropriate dosage in an emergency clinical condition. An additional possible concern, as with all structurally modified proteins, is immunogenicity of this antidote[92].

Another reversal agent is aripazine, or PER977, a small, synthetic, water-soluble, cationic molecule developed by Perosphere Inc. (Danbury, CT, USA),

which binds non-covalently to anticoagulants, inhibiting the anticoagulant effects of low molecular weight heparins, fondaparinux, the direct oral FXa inhibitors and dabigatran through hydrogen bonding and charge-charge interactions[101]. Unfortunately, at the moment, only limited information about this potential antidote is available. In a human plasma *ex vivo* model, PER977 reversed the anticoagulant effect of rivaroxaban, apixaban, and enoxaparin, measured according to anti-FXa activity, in a dose-dependent manner across a range of concentrations[101]. A phase 1 study evaluating the safety, tolerability, pharmacokinetics and pharmacodynamic characteristics of PER977 administered alone or following a single dose of edoxaban has recently been completed[102], while a phase 2 trial evaluating the safety, tolerability and effect on coagulation tests of escalating doses of PER977 in subjects receiving edoxaban is currently underway[103]. According to the first in vivo human data, "baseline hemostasis was restored from the anticoagulated state within 10 to 30 minutes after administration of 100 to 300 mg of PER977 and was sustained for 24 hours"[104]. Additional phase 2 clinical studies are ongoing. Currently, according to Greinacher *et al*.[92], the main challenges for this antidote are its unclear mode of action and monitoring of reversal therapy, because it may reverse bleeding without reversing the altered clotting assays.

Conclusions

DOAC are at least as effective as VKA for the prevention and treatment of thromboembolism. In addition, post-marketing data show that the safety of DOAC in the real world is similar to that observed in the published, large clinical trials, although particular caution is needed when dealing with elderly patients, who have a higher risk of bleeding, particularly from the gastrointestinal tract. Thanks to their proven efficacy and predictable anticoagulant effect, without need for routine monitoring, the DOAC are gradually replacing VKA for several indications. However, unlike VKA, which can be reversed by PCC, they have the important disadvantage of lacking specific antidotes in the case of emergency situations such as trauma, stroke requiring thrombolysis, and urgent surgery. The progressive development of antidotes for these new drugs which, it is hoped, will become available in the near future will allow better, quicker, and safer management of the reversal of the drugs' effects. Meanwhile, shared treatment policies and algorithms can play a key role in the case emergency reversal is needed.

The Authors declare no conflict of interest.

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