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REVIEW

Direct oral anticoagulants and critical care: a review of literature and current opinion

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Abstract

Since 2008, when the first direct oral anticoagulants (DOACs) were introduced in the Netherlands, there has been a steep rise in the number of patients using these new anticoagulants. Consequently, in critical care we will encounter these patients more frequently. Knowledge of the specialised management strategies, especially of DOAC-related bleeding, is essential. In this article we will review the complications of the use of DOACs and strategies to antagonise their effect in case of major haemorrhage or acute emergency interventions.

Introduction

Since 2008, when the first direct oral anticoagulants (DOACs) were introduced in the Netherlands, the therapy of nonvalvular atrial fibrillation (AF) and treatment and prevention of venous thromboembolism (VTE) altered. Until that moment, the standard therapy for these indications was treatment with vitamin K antagonists (VKAs). The effect of VKAs can easily be antagonised either by administrating vitamin K or if immediate reversal is essential prothrombin complex concentrates (PCC) or plasma. In these settings the ability to monitor the effect of the VKA can be an advantage.

Meanwhile, four DOACs are registered in the Netherlands: Dabigatran, a competitive, reversible, direct inhibitor of thrombin, and the three direct factor Xa (FXa) inhibitors rivaroxaban, apixaban and edoxaban. All four are registered for several indications, including prevention of ischaemic stroke in case of atrial fibrillation and treatment and secondary prevention of recurrent deep venous thrombosis and pulmonary embolism.[1-4]

The registration trials for dabigatran and apixaban in patients with AF show lower rates of systemic embolism and stroke compared with warfarin. For rivaroxaban and edoxaban comparable rates of systemic embolism and stroke compared with warfarin are shown. The rate of major bleeding was similar for dabigatran and rivaroxaban with lower rates of intracranial and fatal bleeding for rivaroxaban. Apixaban and edoxaban both showed a lower rate of cardiovascular causes of mortality and bleeding risk compared with warfarin. All four trials were performed in patients with atrial fibrillation.[1-4]

The major advantage of DOACs, compared with VKAs, is their fixed-dose regimen without the need for routine coagulation monitoring. Their rapid onset and offset of action and short half-life is an advantage as well. Because of the relatively short half-lives of dabigatran and the factor Xa antagonists (12 hours for dabigatran, 7-13 hours for rivaroxaban, 12 hours for apixaban and 10-14 hours for edoxaban) *(table 1)* discontinuation of a DOAC will give relatively quick normalisation of haemostatic function.[5-9]

Table 1. Pharmacological characteristics[9,22,32,63-67]

DOAC	T ½ (h)	Dosage (atrial fibrillation)	Renal elimination (% of total clearance)	Dialysis
Dabigatran	12	150 mg 2dd*	80	Yes
Rivaroxaban	7-13	20 mg 1dd*	33	No
Apixaban	12	5 mg 2dd	25	No
Edoxaban	10-14	60 mg 1dd*	30-50	no

*Dose adjustment in case of renal impairment.

The excellent results in the non-inferiority trials in combination with these favourable drug characteristics resulted in a rapid increase in DOAC users after registration. Since introduction, a total of 129,622 users were registered in the Netherlands in 2016 *(table 2)*, a combination of patients switching from VKAs and new users of anticoagulants.

Despite the evident advantages of the DOACs there have been some major concerns as well. First of all it was unknown how these medications would behave in real-life patients and if their safety profile would remain so favourable as in the strictly

chosen study population. Other major concerns were the absence of readily available monitoring tests and the availability of antidotes.

Table 2. Total number of users of DOACs in the Netherlands per year[68]

		2012	2013	2014	2015	2016
Direct inhibitor of thrombin	Dabigatran	6326	13,053	18,902	26,487	39,562
Direct factor	Rivaroxaban	10,608	12,718	20,620	34,751	56,914
Xa inhibitors	Apixaban	3	730	4766	15,155	31,087
	Edoxaban	-	-	-	7	2059
Total		**16,937**	**26,501**	**44,288**	**76,400**	**129,622**

Concerns regarding DOAC use

Of special concern was the safety profile of the DOACs in elderly patients with possible multi-drug use and/or patients with chronic kidney disease stage IV and V, who were excluded in the registration trials.[1-4] The first observational studies are reassuring with data corresponding with those from the clinical trials, or with even better results with regard to bleeding complications for DOACs compared with VKAs in patients with atrial fibrillation or VTE.[10-13]

Stanton et al. performed a retrospective study on 146 patients with chronic kidney disease stage IV and V using apixaban (in different doses and different duration of use) or warfarin (in different duration of use) for treatment of AF or VTE, or thromboprophylaxis after orthopaedic surgery, which showed a non-significant difference between the groups, with a less frequent occurrence of major bleeding in the apixaban group compared with the warfarin group.[14] In elderly patients (80 years and above) with AF, apixaban also led to a lower rate of major bleeding, again compared with warfarin.[15] Studies on dabigatran in elderly patients show a lower or similar intracranial bleeding risk, but similar or even higher extracranial haemorrhage rates compared with warfarin use.[16-18] It is recommended to adjust the dosage of dabigatran in patients above 80 years.

Furthermore, there are several drugs which interact with DOACs, for instance P-glycoprotein (P-gp) inhibitors such as cyclosporine, erythromycin, azoles but also amiodarone. Co-administration of DOACs and P-gp inhibitors raises the peak concentration of and total exposure to the DOACs.[19-21]

Although, in general, the data of patients on DOACs are reassuring, these effects of drug-drug interactions, age and kidney function could lead to relevant dosing errors in the individual patient, which could easily be missed without routine coagulation monitoring.

Monitoring coagulation status

The absence of the necessity to monitor coagulation is a major advantage in daily practice. However, in complex patients or in acute situations the limited availability of specific coagulation tests can be challenging.

Commonly used and readily available coagulation tests, the prothrombin time (PT) and activated partial thrombin time (APTT), developed for monitoring vitamin K antagonist and heparin treatment, respectively, are only of limited use. Without clear dose-response relations they cannot reflect the coagulation status of the patient and additional coagulation tests are necessary *(table 3)*.

Table 3. Coagulation tests for patients on DOACs

	PT*	APTT*	Anti-Xa**	ECT	dTT
Dabigatran	-	+	-	+	+
Rivaroxaban	+	-	+	-	-
Apixaban	-	-	+	-	-
Edoxaban	-	-	+	-	-

+ adequate test; - test not adequate; *only qualitative; **anti Xa = qualitative, if calibrated: quantitative. DOACs = direct oral anticoagulants; PT = prothrombin time; APTT = activated partial thrombin time; ECT = ecarin clot time; dTT = diluted thrombin time.

Furthermore DOACs reach their peak concentration between 2-4 hours after intake.[8,22-24] If a coagulation test is performed too soon, in particular within two hours after ingestion, the test result may be falsely negative.

In the therapeutic range, dabigatran will not or barely influence the PT but the majority of patients on dabigatran will show a prolonged APTT.[22,25] However, a normal APTT cannot completely exclude anticoagulant activity.[22,25,26] Both the diluted thrombin time (dTT) and the ecarin clotting time (ECT) are specialised, sensitive and quantitative tests to measure the concentration of dabigatran.[22,27] Unfortunately, these tests are not yet readily available in every hospital, but are expected to become more available due to increasing DOAC use.

For the direct factor Xa inhibitors the APTT is not useful.[28-33] In case of rivaroxaban, on-treatment concentrations prolong the PT (without dose-response relation) and normal PT indicates no or only minimal anticoagulant activity. The degree of PT prolongation is dependent on the thromboplastin reagent used.[29] The other direct Xa inhibitors can increase the PT, but only do so in a minority of the patients. A normal PT cannot rule out anticoagulant activity and is therefore not reliable as a screening tool for these FXa inhibitors.[30,31,33] The cause of these differences in effect of the direct FXa inhibitors on PT is unknown.[30]

In most hospitals a rapid anti-FXa assay is available. This test was originally designed for measuring the effect of low-molecular-weight heparin and unfractionated heparin. This uncalibrated anti-FXa assay is, however, only useful for qualitative testing of FXa inhibitors. For quantitative testing of all direct factor Xa inhibitors a calibrated anti-FXa assay must be used, which unfortunately is less widely available.[28,29,31,33-35]

Rotational thromboelastometry (ROTEM) is mainly used to

measure fibrinolysis, hypocoagulability and hypercoagulability during surgical procedures. It can be of some value to monitor coagulation effect of DOACs, although results differ between studies. It seems the ROTEM-based assays can be influenced by DOACs; however a normal result does not exclude a DOAC-induced bleeding tendency.[36-39]

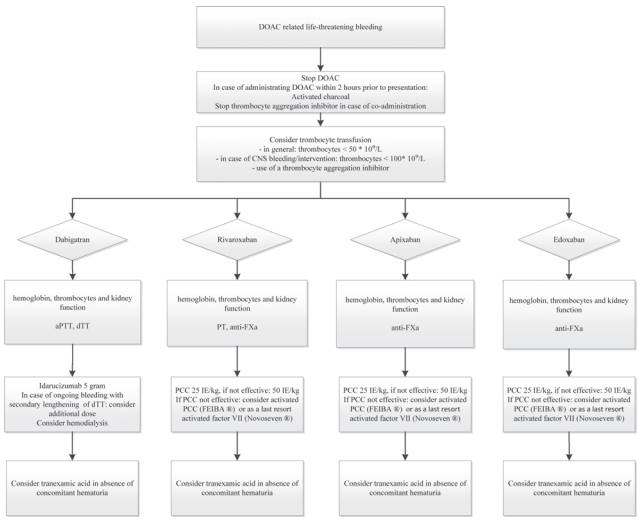

Figure 1. DOAC related life-threatening bleeding

DOAC antidotes

Another major concern after introduction of the DOACS was the unavailability of an antidote. Nowadays one specific antidote, idarucizumab, is available for reversal of dabigatran, and other antidotes are being tested in phase 2 (ciraparantag) and phase 4 (andexanet alfa) trials.

Idarucizumab is a humanised monoclonal antibody fragment that binds with high affinity to free and thrombin-bound dabigatran, antagonising its anticoagulant activity.[40] In a phase I study, idarucizumab gave a complete and direct reversal of the anticoagulant effect of dabigatran. It was well tolerated without serious adverse effects. Reversal of the anticoagulant effect was detectable with dTT and ECT, but also with a lengthened aPTT the clotting time was reversed to normal values.[41]

The RE-VERSE AD study, a phase III multicentre prospective cohort study, included two groups of adult patients on dabigatran with either overt, uncontrollable, or life-threatening bleeding or in need of an urgent invasive procedure.[42] Idarucizumab rapidly and completely reversed the anticoagulant activity of dabigatran in 88-98% of patients. In the patients needing intervention normal intraoperative haemostasis was reported in 92% of the cases. In a minority of the patients dabigatran concentrations increased again at 12 (23%) or 24 (13%) hours after idarucizumab administration, which was detectable in clotting times. The reoccurrence in dabigatran is probably a result of redistribution from the extravascular to the intravascular compartment and the shorter half-life of idarucizumab compared with that of dabigatran.[43] Clinical importance and whether patients could benefit from an additional gift is uncertain but could be considered in ongoing relevant bleeding.[42,44]

Not registered yet, but at the moment being tested in a phase 4 trial, is andexanet alfa (andexanet), a recombinant modified human factor Xa decoy protein. It is enzymatically inactive, but has a high binding activity for direct FXa inhibitors and is also capable of binding indirect FXa inhibitors, making it a potential universal FXa antidote. The ANNEXA-4 trial is still ongoing but preliminary data have already been published.[45] This prospective, multicentre, open label, cohort study included 67 patients with a mean age of 77 years, with considerable cardiovascular disease, with major bleeding associated with intake of FXa inhibitors, to receive andexanet. After bolus administration of andexanet anti-FXa activity decreased compared with baseline by 89% in the rivaroxaban group and 93% in the apixaban group. With continuous infusion these levels remained stable. However, two hours after discontinuation of andexanet anti-FXa activity partially returned to pretreatment values. Whether this is clinically relevant is not clear as clinical haemostatic efficacy, as assessed for 12 hours after the end of the infusion, was excellent or good in 37 of the 47 (79%) patients included in the efficacy analysis. Of note, there were some concerns raised about the rate of thrombotic events (18% after 30 days) in this study. This might be because of discontinuation of the DOAC but an intrinsic prothrombotic effect of andexanet cannot be ruled out at this moment.[46]

Not registered as well, but being tested in phase II trials, is aripazine, also called ciraparantag or PER977. It is a synthetic, small, cationic, water-soluble molecule, which binds specifically to factor Xa inhibitors, the direct thrombin inhibitor dabigatran, and low-molecular-weight heparin and unfractionated heparin. This makes it a potential universal antidote.[47] Results of the First-in-Human phase 1 study are promising, although effect on actual bleeding in patients has not been tested yet.[48,49]

Beside these specific antidotes, PCC could be considered a non-specific antidote. There is one clinical study on administering PCC in the case of life-threatening bleeding in combination with DOAC use. Eerenberg et al. performed a crossover study with healthy individuals on supra-therapeutic levels of dabigatran or rivaroxaban. PCC at a dose of 50 IU/kg corrected the PT for 24 hours in case of rivaroxaban, but there was no correction of APTT in case of dabigatran use.[50] Majeed et al. performed a cohort study on 84 patients with major haemorrhage while using rivaroxaban or apixaban.[51] In 69.1% of patients, administering PCCs (median dose 2000 IU) was effective in achieving haemostasis. The thromboembolism risk was low with two patients developing an ischaemic stroke.

DOACs and critical care

In critical care settings we will encounter more and more known and unknown users of DOACs. Although outcome of patients

on DOACs with severe traumatic bleeding injury or intracranial haemorrhage is more favourable than in patients on vitamin K antagonists, probably because of the relatively short half-lives of DOACs, in critically ill patients it may still be necessary to confirm the presence of and/or antagonise DOAC-induced bleeding tendency.[52-54]

Guidelines for elective surgery and interventions when to stop or how to switch to other medications are readily available. We will discuss the effect of possible DOAC use on diagnostic and therapeutic strategies in the case of trauma, intracranial bleeding and need for emergency interventions. In case of severe trauma or intracranial bleeding and use or potential use of a DOAC, several actions should be taken. First of all, coagulation tests should be performed to demonstrate anticoagulant activity. The limitations of those tests have been discussed above. In the case of use or suspected use of dabigatran or a FXa inhibitor the aPTT, PT, dTT and standard anti-FXa assay should be determined to detect possible anticoagulant activity. At the same time, the haemoglobin, thrombocytes and kidney function should be determined. In particular when using dabigatran, renal impairment will extend the half-life and thus the bleeding tendency.[55,56] In case of thrombocytopenia (< 100 x 109/l) or use of a thrombocyte aggregation inhibitor, thrombocyte transfusion is indicated where contraindications should be weighed against the severity of the bleed. Tranexamic acid could be considered in the absence of concomitant haematuria.[57]

In case of severe bleeding induced by dabigatran, idarucizumab 5 gram intravenously should be administered. In case of ongoing bleeding with secondary lengthening of the dTT an additional gift could be considered. As mentioned above, antidotes are not yet available for the other DOACs and primary treatment consists of administering PCC, although there is limited evidence. If an initial dosage of 25 IU/kg PCC is not effective we first recommend repeating PCC in a dosage of 50 IU/kg. Some treatment protocols mention activated PCC (FEIBA ®) or activated factor VII (Novoseven ®) if PCC treatment fails; however, these therapies are costly and there are no clinical data to support this recommendation.[58,59]

Haemodialysis is a theoretical option for dabigatran removal. Practical use is limited; in acute bleeding it is too time consuming, patients often need transfers for interventions to stop the bleed and haemodynamic stability of the patient can also be an issue.

Besides major bleeding, there are some other situations in which it is important to take DOAC-induced coagulopathy into account. In case of an emergency intervention with high bleeding risk, we recommend to act as above and follow the protocol of major bleeding. There are no controlled data on inserting central venous catheters during DOAC-induced coagulopathy. We suggest to insert the catheter under guidance of ultrasound, to decrease the probably limited complication risks. There are also insufficient data available on inserting an epidural catheter. We suggest to wait at least for 48 hours after the last administration with normalisation of an adequate coagulation test. For dabigatran the APTT, and if available the dTT and ECT, for rivaroxaban the PT and for all direct FXa inhibitors the anti-FXa assay should be performed.

There are limited data on bleeding complications for patients using a DOAC in combination with intravenous thrombolysis for stroke.[60] A recent retrospective study showed no additional risks of systemic thrombolysis in the subgroup of patients on DOACs. This study has several limitations with no information on timing of last DOAC dose and absence of coagulation parameters besides INR, therefore elevated risk of bleeding is not definitively ruled out.[61] To reduce the risk of secondary haemorrhagic conversion several local protocols only recommend systemic thrombolysis if the last DOAC intake is more than four hours ago with normalisation of APTT, PT and anti-FXa parameters.

Data on how to proceed if, despite possible DOAC use, a patient develops a pulmonary embolus are also lacking. Co-administration of thrombolysis could increase the risk of major haemorrhage even further than with thrombolysis alone. We think that in patients in an arrest or peri-arrest situation thrombolysis should not be withheld because of possible concomitant DOAC use. In high to intermediate risk patients without haemodynamic instability, local interventions for removal of pulmonary embolus, if available, could be considered.[62]

In patients admitted to the ICU we advise to stop DOAC use because of practical considerations. Critically ill patients might need multiple interventions, some of which are unplanned. The high incidence of decreased renal function and use of drugs which interact with DOACs are also reasons to withhold DOACs during critical illness.[19-21] When a patient is stable and no interventions are planned in the short term, the earliest moment we would restart is during admission to a medium care unit. It must be taken into account that DOACs will be effective within 2-4 hours, unlike the VKAs.

Conclusion

Because of their convenience and favourable results compared with vitamin K antagonists more patients are using DOACs. Inevitably we will see more of these patients in acute care settings. Critical care clinicians should be aware of possible DOAC use in patients presenting to the emergency room. It is important to realise that the normal standard coagulation test cannot rule out DOAC anticoagulant activity. In patients with major haemorrhage or in need of high-risk interventions, knowledge on how to proceed is essential. Fortunately, nowadays a specific antidote for dabigatran is available. Further development of antidotes for the factor Xa inhibitors is warranted, to make the use of DOACs even safer.

Disclosures

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