

New direct oral anticoagulants – current therapeutic options and treatment recommendations for bleeding complications

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Summary

To date, clinical studies show that the incidence of spontaneous bleeding with new direct oral anticoagulants (DOAs) is comparable to that of established anticoagulants. However, unlike vitamin K antagonists, there are currently no clinically available antidotes or approved reversal agents for new DOAs. Restoring normal coagulation is important in many cases, such as emergency surgeries, serious bleedings, or anti-coagulant overdosing. Attempts have been made to restore normal coagulation after treatment with new DOAs using compounds such as recombinant activated factor VII (rFVIIa), prothrombin complex concentrate (PCC), or FEIBA (factor eight inhibitor bypassing activity). Limited pre-clinical data and even less clinical evidence are available on the usefulness of these methods in restoring normal coagulation for the emergency management of critical bleeding episodes. Evaluating the

utility of DOAs is further complicated by the fact that it is unknown how predictive established test systems are of the bleeding risks. Clinical practice requires further evaluation of the emergency management options for the new DOAs to define the agents and the doses that are most useful. Furthermore, patients receiving long-term treatment with a DOA are likely to undergo elective surgery at some point, and there is lack of evidence regarding perioperative treatment regimens under such conditions. This review summarises potential bleeding management options and available data on the new DOAs.

Keywords

Prophylactic anticoagulation, oral anticoagulant, bleeding complication, treatment recommendation

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Prophylaxis of thromboembolic events – history and current therapeutic options

For almost a century, unfractionated heparins (UFH), low-molecular-weight heparins (LMWH) and vitamin K antagonists (VKA) constituted the main medical armamentarium for anticoagulation of patients at risk of thromboembolic events (1), requiring regular monitoring of the coagulation status to minimise the risk of major bleedings.

Oral drugs are needed for chronic anticoagulation and until recently, VKAs have been the only oral alternative available. The long half-life of VKAs (2) coupled with their significant food interactions can create bleeding problems in interventional settings and have limited their use (3–5). Little advancement has been made in the last few decades in developing new oral anticoagulants with the newest entries into the anticoagulation market being oral direct thrombin inhibitors (DTIs) and oral factor (F)Xa inhibitors.

The increasing need for anticoagulation

The clinical manifestations of arterial and venous thromboembolism such as stroke, pulmonary embolism (PE), venous thromboembolism (VTE) and acute coronary syndromes (ACS), are leading causes of mortality in the Western world (6, 7). The ageing of the population leads to a rising prevalence of diseases requiring chronic anticoagulation, like atrial fibrillation (AF), artificial heart valves and malignant diseases. Stroke prevention in patients with AF is the main indication for oral anticoagulants (8). AF occurs in 1–2% of the general population and its prevalence is estimated to double by 2025 (9). AF patients have a five-fold higher risk of stroke, which is often fatal or disabling (2).

Orthopaedic surgeries, such as hip or knee replacement, are major risk factors for developing PE or VTE. With an increasing number of hip and knee surgeries (>1 million in the USA in 2010 [10]), and an incidence of 40–60% for VTE in untreated patients, there is a significant need for anticoagulation, normally carried out with parenteral drugs such as UFH and LMWH.

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One primary reason for the limited use of oral anticoagulants like VKAs in elderly populations is the physician's concern about anticoagulant-related bleeding, especially intra-cranial haemorrhage (8).

Bleeding events as the major drawbacks for established anticoagulants

For all available anticoagulants, bleeding is the most important adverse event in any type of patient. Co-morbidities, co-medications, age and history of bleeding are the main risk determinants for a given patient. The reported bleeding risk under VKA treatment is variable and high. The recent RE-LY study showed a rate of 3.4% major bleedings per year for warfarin (11), and rates up to 6.5 for major bleedings have been reported (12, 13). For UFH and LMWH, the incidence of major bleeding during the prevention of VTE is between 1.6% and 6% of patients/year (14). Even an antithrombotic agent that is considered safe (ASA; acetylsalicylic acid or aspirin) has an annual risk of major haemorrhage of 1.6% at a 75 mg dose (15). The risk to experience major bleeding is higher for patients who received VKAs than ASA (2.2 vs. 1.3 events per 100 patient-years; hazard ratio [HR], 1.71; 95% confidence interval [CI], 1.21–2.41) (16).

Major bleeding is defined according to the ISTH (International Society on Thrombosis and Haemostasis) recommendations as (17):

- fatal bleeding or
- reduction in haemoglobin level of at least 20 g per litre or
- transfusion of at least two units of blood or
- symptomatic bleeding in a critical area or organ.

Life-threatening bleeding is a subcategory of major bleeding and consists of fatal bleeding, symptomatic intracranial bleeding, bleeding with a decrease in haemoglobin level of at least 50 g per litre, or bleeding requiring transfusion of at least four units of blood. These definitions have been used in most recent clinical studies, such as the RE-LY study (18). However, it must be emphasised that the definition of major bleeding is still controversial (19).

Furthermore, different definitions for major bleeding have been used in studies involving dabigatran, rivaroxaban and apixa-

ban which complicates the comparison of major drawbacks associated with these DOAs.

Recent development of new anticoagulants

Over the last few years, new oral drugs affecting key factors in the coagulation cascade, including FXa and thrombin, have been developed. They either block the formation of thrombin or directly inhibit its activity to regulate blood coagulation and induce platelet aggregation. These new modes of action should be effective for indications that are primarily based on fibrin formation, such as VTE, as well as in settings that are dominated by platelet aggregation, such as arterial thrombotic events. The new direct oral anticoagulants (DOAs) that are currently available are dabigatran (Pradaxa, Boehringer Ingelheim), apixaban (Eliquis, Pfizer, BMS) and rivaroxaban (Xarelto, Bayer, J&J) (20, 21). Another FXa inhibitor, edoxaban (Daiichi Sankyo), is in late-stage development in Europe.

These new drugs have the potential to revolutionise therapy, especially in AF. Regulatory agencies have already approved dabigatran for this indication, while apixaban and rivaroxaban are labelled for the prevention of VTE after elective orthopaedic surgery and are awaiting approval for indication in AF (22, 23).

These new DOAs have some theoretical advantages that separate them from warfarin and UFH/LMWH, especially in chronic indications and older patients (22, 24).

These include:

- rapid onset of action → no need for bridging
- short half-life → easy control of AC effect
- little to no food-drug interaction → no dietary restrictions
- limited drug-drug interactions → few restrictions for co-medication
- predictability of the AC effect → no need for routine coagulation monitoring.

On the other hand, some of their limitations are:

- higher cost
- no monitoring possible if needed
- no specific antidote.

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Target	Thrombin	FXa	FXa	FXa
Half-life (h)	12–17	9–14	9–11	9–13
Dosing	110 – 150 mg bid	2.5 – 5 mg bid	15–30 mg od (Japan only to date)	10 – 30 mg od
Peak plasma conc.	2–3 h	1–3 h	1–3 h	2–4 h
Plasma protein binding	34–35% [34]	87% [32]	40–59% [35]	92–95% [30]
Renal elimination	80%	25%	35%	66%
Metabolism	Potent P-gp inducers / inhibitors	CYP3A4 P-gp inducers / inhibitors	CYP3A4	CYP3A4 P-gp inducers / inhibitors
Coagulation monitoring	Not required	Not required	To be determined	Not required

Table 1: Pharmacokinetic and pharmacodynamic characteristics of new DOAs (modified from [33]).

Characteristics of new DOAs

It is hoped that the new DOAs will change the therapeutic options for anticoagulation because they do not need to be monitored and they show a superior more favourable safety profile with respect to risk of bleeding.

Most anticoagulants require the exclusion of renally impaired patients or dose adjustment of the anticoagulant; UFH is an exception and has no limitations on usage in renally impaired patients.

Rivaroxaban, apixaban, edoxaban and dabigatran have short half-lives, but their renal elimination requires caution and dose adjustment in renally impaired patients, particularly when an exposure-increasing drug-drug interaction cannot be excluded (25–27).

In late 2011, the Food and Drug Administration (FDA) issued a safety review of post-market reports of serious bleeding events with dabigatran, especially in renally impaired patients (28). Dabigatran is 80% renally excreted and its use is contraindicated in patients with severely impaired renal function (CrCl<30 ml/minute [min]). The FXa inhibitor rivaroxaban showed efficacy and safety in AF patients that was similar to warfarin in the ROCKET-AF trial (29) and has lower renal elimination (66%). Renal function needs to be monitored in patients with CrCl<30 ml/min, and dose adjustment might be necessary (30).

The APPRAISE-2 trial had to prematurely stop when the FXa inhibitor apixaban in ACS patients showed an increased incidence of bleeding (31). Although increased bleeding in renally impaired patients has not been observed, apixaban should only be used under tight renal function control and dose adjustment in patients with CrCl<30 ml/min (32).

Renal function tests may not be routinely used in DOA patients, which may lead to increased bleeding incidents.

Several years ago, the development of ximelagatran, a first-generation direct thrombin inhibitor (DTI), stopped due to liver toxicity (36).

The FXa inhibitor rivaroxaban also showed transient increases in plasma levels of liver enzymes, such as alanine aminotransferase, in a small numbers of subjects, but similar increases were also observed in those receiving placebo (37). Because the majority of

clinical studies using the new DOAs have been conducted in patients without liver dysfunction, liver toxicity cannot be excluded as an issue for these new drugs, so routine control of liver function is advised. The low plasma protein binding of dabigatran (► Table 1) indicates that, in the case of a severe bleeding event, the drug could be removed via dialysis or haemofiltration, quickly restoring normal coagulation.

Bleeding risk with new DOAs

The intensity of anticoagulant therapy is strongly correlated with bleeding risk. For example, if the target international normalised ratio (INR) range for warfarin is between 2 and 3, these patients have less than half the incidence of major bleeding when compared with the target INR >3 (38).

The new oral DOAs are speculated to have a more wide therapeutic window than warfarin, leading to a lower incidence of major bleeding. However, the results of large-scale trials indicate that bleeding remains a concern even with the new DOAs (18, 34) (► Table 2). Large studies with rivaroxaban, edoxaban and dabigatran showed that these drugs have incidences of severe bleeding comparable to those of enoxaparin and warfarin.

Several attempts have been made to generate risk schemas for bleeding in patients on anticoagulants. These risk prediction rules show wide differences in risk factors and provide little help to physicians in identifying individual risk (8).

The number of bleeding events is rising due to the ageing of the population and the increasing need for interventional treatment. Although age is considered an independent risk factor for bleeding under anticoagulant therapy, a prospective investigation in close to 800 elderly AF patients > 80 years of age showed that bleeding complications can be kept acceptably low at 2.5 x 100 patient-years through careful management and tight control of renal and liver function (43).

The shorter half-life of the new DOAs might facilitate the management of bleeding events and the control of anticoagulation during interventions or emergency situations. If bleeding still occurs, the lack of specific antidotes limits the therapeutic options (44).

Table 2: Rates of major bleeding complications under different anticoagulant therapies.

Indication	Study	Severe bleeding incidence	Reference
VTE prevention after hip replacement	RECORD 1	Rivaroxaban 10 mg od: 0.3% Enoxaparin 40 mg od: 0.1%	[29,30]
VTE prevention after knee replacement	RECORD 3	Rivaroxaban 10 mg od: 0.6% Enoxaparin 40 mg od: 0.5%	[29,30]
VTE prevention after hip or knee replacement	RE-NOVATE and RE-MODEL	Dabigatran 150 mg od 1.3% Enoxaparin 40 mg od 1.3%	[34,39]
Stroke prevention in atrial fibrillation	RE-LY	Dabigatran 150 mg bd: 3.1% Warfarin od: 3.4%	[34,40]
Secondary prevention of ACS	APPRAISE-2	Apixaban 5 mg bd: 1.3% Placebo: 0.5%	[41]
Stroke prevention in atrial fibrillation	ARISTOTLE	Apixaban 5 mg bd: 2.13% Warfarin: 3.09%	[42]

Due to the highly selective study populations used during the development of the new DOAs, the absolute bleeding risk might be underestimated and can only be measured after exposure of the drugs to larger populations. A registry approach would be very helpful in defining the actual bleeding risk for the new drug classes.

Coagulation tests and the new DOAs

Dabigatran and rivaroxaban alter available coagulation tests, but coagulation test measurements are poorly predictive of the plasma concentrations of these drugs (45).

The new DOAs impair most established tests and are thus unsuitable for monitoring bleeding risk. In a study with orthopaedic surgery patients, rivaroxaban significantly prolonged PT and aPTT clotting times up to 1.4 fold after 2 hours (h) of drug administration. The assays showed high variability in sensitivity that was dependent on the reagents used (46).

New monitoring tests are being developed and available tests, such as the ecarin clotting time (ECT), are being tested for the new DOAs. ECT assesses thrombin activity in plasma and seems to be predictive of dabigatran activity (48), as it prolongs rapidly at low dabigatran levels, and normal ECT indicates no or very low drug levels. Therefore, ECT can be used to estimate dabigatran drug levels in a patient, but the laboratory results have not been shown to correlate with bleeding risk (26). Another well-known test, thrombin time (TT), is very sensitive to dabigatran, and a prolonged TT can demonstrate recent intake of the drug. According to a recent survey, PTT could be used for monitoring dabigatran and to screen for overdoses (47). However, more sensitive tests are ECT and HTI (Hemoclot thrombin inhibitor), and HTI may be considered the gold standard for the monitoring of dabigatran due to its linear correlation at all doses (47) (► Table 3).

Rivaroxaban has been shown to be correlated with the neoplastin-induced prothrombin time (PT), but there are no clinical studies showing the correlation between test results and efficacy or safety (48). No interactions with rivaroxaban were found with an antithrombin (AT) assay dependent on thrombin activity, but AT levels dependent on FXa activity were significantly increased. Thus, rivaroxaban influences FXa-dependent routine coagulation assays in a time-dependent manner (46). Chromogenic assays can also be used to show dose-dependent relationships between anti-FXa activity and rivaroxaban concentration, using rivaroxaban as a calibrator (49). Calibrated anti-FXa assays could serve as an indicator of drug presence and levels, which could help to monitor compliance, but may have no meaning in prediction of bleeding.

Potential reversal agents for the new DOAs

Potential agents for the reversal of the anticoagulation effect of new DOAs were established for the treatment of VKA-induced bleedings and consist of prothrombin complex concentrate (PCC), an activated prothrombin complex concentrate (APCC, FEIBA) and recombinant activated FVII (rFVIIa). Treatment with non-specific antagonists (e.g. PCC and rFVIIa) is proposed in the Summary of Product Characteristics (SPC) for rivaroxaban and apixaban as well as in several publications (50, 51), but the database is fragmentary.

PCC can be divided into “4-factor-concentrates” containing adequate amounts of vitamin K-dependent factors II, VII, IX and X and “3-factor-concentrates” containing significantly lower amounts of FVII.

Limited data are available, but some studies have shown promising results using PCC, FEIBA or rFVIIa (► Table 4). To clarify the reversal potency of available drugs, some studies used supraphysiological doses of DOAs.

Subjects	DOA	Tests	Effect	Reference
Orthopaedic surgery patients	Rivaroxaban 10 mg od	PT	Up to 1.4 fold prolonged	Mani [46]
		aPTT	Up to 1.4 fold prolonged	
		TT	No effect	
		AT	No effect, but AT levels significantly increased	
		FibC	No effect	
		dFIB	Effect reagent dependent	
Human plasma	Dabigatran 4.7 ng/ml – 943.0 ng/ml	aPTT	Prolongation	Douxflis [47]
		TT	Prolongation	
		PT	Prolongation	
		HTI	Prolongation	
		FibC	No effect	

Table 3: Influence of DOAs on *ex vivo* coagulation tests.

AT: antithrombin, aPTT: activated partial thromboplastin time, FibC: fibrinogen levels by Clauss, dFIB: derived fibrinogen, TT: thrombin time, PT: prothrombin time, HTI: Hemoclot thrombin inhibitor.

Reversal of the anticoagulation effects of DOAs by PCC, FEIBA and fresh frozen plasma

PCC in particular has been studied to reverse the anticoagulant effects of DOAs because it contains high concentrations of the coagulation factors II, VII, IX and X, thus stimulating thrombin formation and bypassing the anticoagulant effect of both thrombin and FXa antagonists.

Unfortunately, human data are sparse; to date, only one clinical study has been published. This recent trial in healthy volunteers shows the reversibility of rivaroxaban's anticoagulant activity using PCC. In this randomised, double-blind, placebo-controlled study, 12 healthy male volunteers received rivaroxaban 20 mg twice daily (n=6) or dabigatran 150 mg twice daily (n=6) for 2.5 days, followed by either a single bolus of 50 IU/kg PCC (Cofact) or a similar volume of saline. When based on PT and ETP tests, the

Table 4: Different methods for the reversal of anticoagulation.

Species	Medication	Dose	DOA	Test	Result	Reference
HV	PCC	50 U/kg	rivaroxaban 20 mg bd (human therapeutic dose: 20 mg od)	PT, ETP	Complete reversal	Eerenberg [52]
	PCC	50 U/kg	dabigatran 150 mg bid (human therapeutic dose: 150 mg bid)	PT, ECT, TT	No reversal	
Rats	PCC	50 U/kg	rivaroxaban ED ₅₀ of 1.3 mg/kg	BT, TAT, PT	Complete reversal of TAT and BT, partial of PT	Perzborn [51]
Rabbits	FEIBA		dabigatran 1 µmol/kg bolus + 0.5 µ mol/kg/h infusion for 25 min	PTT, BT	BT reversal	Van Ryn [53]
	PCC			BT	BT reversal	
	rFVIIa			PTT	Partial PTT reversal	
Mice	PCC	100 U/kg	dabigatran 4.5 and 9 mg/kg 5–10-fold the human therapeutic plasma levels	TVBT, ECT, hae- matoma growth	Reduced haematoma growth	Zhou [54]
	Murine FFP	200 µl			No effect	
Human plasma	rFVIIa	8 mg/kg	edoxaban at supratherapeutic concentrations		No effect	Halim [55]
	rFVIIa	0.8 and 1.8 µg/ml	500 and 1,000 ng/ml	PT aPTT anti-Xa	Significant and rapid reversal on all tests	
	FEIBA	0.75 and 1.4 U/ml				
Rabbits	rFVIIa PCC		single bolus of 150 µg/kg rivaroxaban. Plasma levels close to human therapeutic dose	Ear BT Hepatosplenic blood loss aPTT	Decreased ear BT, no effect on blood loss, aPTT decreased	Godier [56]
Human plasma	PCC	0.15, 0.5, 1.5 U/ml	edoxaban 150 – 300 ng/ml (therapeutic to supratherapeutic doses)	PT	Concentration dependent shortening of PT, most effect by rFVIIa	Fukuda [57]
	FEIBA	0.15, 0.5, 1.5 U/ml				
	rFVIIa	100,300, 1,000 ng/ml				
Rats	FEIBA	100 U/kg	edoxaban 1 mg/kg/h	PT	Significant reversal of prolonged BT	
	rFVIIa	1–3 mg/kg				

HV: Healthy volunteers, PT: Prothrombin time, BT: Bleeding time, TAT: Thrombin-antithrombin complex, ECT: Ecarin clotting time, TT: Thrombin time, TVBT: tail vein bleeding time, FFP: fresh frozen plasma, AT: antithrombin, aPTT: activated partial thromboplastin time, FIBc: fibrinogen levels by Clauss, dFIB: derived fibrinogen, PPSB-HT: prothrombin complex concentrate, ETP: endogenous thrombin potential, od: once daily, bid: twice daily.

anticoagulant effect of rivaroxaban was completely reversed in all subjects immediately after infusion of 50 IU/kg PCC. The anticoagulant effect of dabigatran was monitored using aPTT, lag time of the ETP, TT, and ECT. Dabigatran treatment clearly prolonged the aPTT, ETP lag time, TT, and ECT in all subjects. Subsequent administration of 50 U/kg PCC had no effect on these assays. The authors concluded that PCC immediately and completely reverses the anticoagulant effect of rivaroxaban in healthy subjects but has no influence on the effect of dabigatran at the PCC dose used in this study (52) [52]. Several animal studies confirm the efficacy of PCC in reversing the anticoagulant effect of FXa inhibitors such as rivaroxaban (51, 56) or edoxaban (57).

Animal studies also demonstrate the effect of PCC on anticoagulation with dabigatran. Zhou et al. used a murine model of intracerebral haematoma associated with dabigatran and demonstrated that there is strong evidence for PCC and, less consistently, fresh-frozen plasma to prevent excess intracerebral haematoma expansion (54). *In vivo* and *in vitro* coagulation and dabigatran plasma levels were repeatedly measured in C57BL/6 mice receiving dabigatran (4.5 or 9.0 mg/kg). At 30 min after inducing intracerebral hemorrhage (ICH) by striatal collagenase injection, mice received either 100 U/kg PCC, murine fresh-frozen plasma, or recombinant human FVIIa (8.0 mg/kg) intravenously. Twenty-four hours (24 h) later, the ICH volume was quantified on brain cryosections. PCC and, less consistently, fresh-frozen plasma prevented excess haematoma expansion caused by dabigatran, whereas recombinant human FVIIa was ineffective. Prevention of haematoma growth and reversal of tail vein bleeding time by PCC were dose-dependent.

Reversal of the anticoagulation effect of DOAs by rFVIIa

Most studies show that rFVIIa is not as effective as PCC at reversing the anticoagulant effect of DOAs. In a study by Godier et al., rFVIIa significantly reversed ear immersion bleeding time ($p < 0.02$) but failed to reduce haepatosplenic blood loss that was induced by rivaroxaban overdose. In addition, some clinical or lab-

oratory parameters were partially corrected (56). rFVIIa normalised aPTT and corrected several thrombelastographic parameters by decreasing lag time, as previously demonstrated *in vitro* with fondaparinux. Peak height and endogenous thrombin potential were not significantly modified. In a study by Zhou et al., the administration of rFVIIa was ineffective in reversing the anticoagulant effect of dabigatran (54).

The results of a recently published study in a rabbit model using rivaroxaban (56) demonstrated that neither rFVIIa nor PCC fully reversed the bleeding induced by rivaroxaban overdose. PCC and rFVIIa corrected several laboratory parameters but was ineffective in reducing rivaroxaban-induced bleeding *in vivo*. The authors concluded that commonly used laboratory assays failed to predict the *in vivo* effects of reversal agents, suggesting that more robust endpoints are needed to evaluate potential antidotes.

Treatment recommendations for DOA-associated bleeding complications during scheduled surgery

Regardless of the short half-life of DOAs, immediate reversal of the anticoagulant effect is mandatory in case of severe bleeding or emergency surgery.

Based on the limited published preclinical and clinical studies and the pharmacokinetic data of DOAs, some general proposals regarding the treatment of new DOA-associated bleeding events will be discussed in the following section.

Emergency surgery should be delayed for as long as possible (at least 1 or 2 elimination half-lives of the drug), provided that the delay does not imply a risk for the patient. Because dabigatran and rivaroxaban predominantly undergo renal excretion, adequate renal function must be maintained for both drugs. Treatment with the DOA should be discontinued immediately if non-surgical major bleeds occur.

For life-threatening bleeding under dabigatran treatment, haemodialysis and haemofiltration could be options because dabigatran is dialyzable due to its relatively low (35%) plasma protein binding (34, 53, 58). Dialysis is not suitable for rivaroxaban because of its high protein binding of 95% (30).

The application of non-specific antagonists (e.g. PCC and rFVIIa) can be considered after an individual benefit-risk assessment. It must be emphasised that the safety and efficacy of PCC and rFVIIa have not been established in the target population. The arterial risk of rFVIIa in the non-haemophilic population (59) is of concern for elderly patients who frequently suffer from cardiovascular diseases. This population demonstrated the highest risk when the rates of thromboembolic events in 35 rFVIIa placebo-controlled trials in off-label indications were analysed (59). By comparison, the arterial risk of PCC in the target population has not been studied as thoroughly. A venous risk has not been shown in clinical trials, but these trials excluded patients with a history of VTE for whom a DOA could be prescribed. In addition, the dosage

Table 5: How to restore coagulation when bleeding occurs.

Drug	Therapeutic options (not validated by large-scale trials)	Reference
Rivaroxaban	<ul style="list-style-type: none"> • Stop treatment with DOA • PCC • FEIBA • rFVIIa 	[51,52,56] [51] [56]
Edoxaban	<ul style="list-style-type: none"> • Stop treatment with DOA • PCC • FEIBA • rFVIIa 	[57] [55,57] [55,57]
Dabigatran	<ul style="list-style-type: none"> • Stop treatment with DOA • Dialysis • PCC • rFVIIa 	[53] [52,53] [53]

with the best risk-benefit ratio is not known. If used in populations at high risk of arterial thrombosis, it should be considered that dabigatran also is suspected to increase the arterial risk when compared to different anticoagulants (60).

For scheduled surgeries, a treatment regimen is based primarily on the natural clearance of the anticoagulant after preoperative discontinuation of treatment. The therapy-free interval should be estimated taking into account the anticipated bleeding risk (61). The assessment of bleeding risk could be based on risk estimates documented for treatment with VKAs (62) because the future indications for treatment with DOAs are the same.

For procedures with low anticipated bleeding risk that was non-critical in its location and/or easily controlled by simple mechanical haemostasis, the last administration of the DOA should be given 24 h (equivalent to 2–3 mean half-lives) before, and resumed 24 h after, the procedure.

For invasive procedures with moderate or high bleeding risk in patients receiving long-term anticoagulant treatment with a DOA, adequate discontinuation of treatment using the database of average pharmacokinetic variables could be proposed at about 48 h (equivalent to approximately 5 mean half-lives), as drugs are typically almost completely eliminated after this period in the majority of patients.

However, 48 h discontinuation of DOA treatment may be insufficient because covariates such as liver insufficiency, renal insufficiency, drug-drug interactions, and genetic polymorphisms may significantly extend the elimination half-life of the drugs.

Thus, in the absence of a validated antagonist and any clinical experience, discontinuation of treatment five days prior to a scheduled procedure scheduled is recommended, especially for patients with impaired renal or liver function (61). Restarting DOA treatment is proposed at 48 h (day +2) after surgery. For prophylactic dosing, DOA can be restarted 6–10 h after surgery.

For patients at moderate risk of thrombosis, preoperative bridging with heparin may be considered. Postoperative DOA treatment or a curative dose of heparin is advised as soon as the bleeding risk is controlled.

For patients at high risk for thrombosis, bridging may be considered by using heparin administered at the curative dose as two subcutaneous injections per day according to the modalities recommended for VKA bridging (62). Treatment with heparin should be initiated 12–24 h after the last dose of the DOA and should be discontinued before surgery. Restarting heparin treatment after surgery is proposed when the risk of postoperative bleeding is considered to be under control. DOA treatment can be restarted 12 h after the last subcutaneous administration of LMWH if the bleeding risk is controlled with certainty. There should be no overlap between treatment with heparin and a DOA, regardless of the dose and the thromboembolic risk for the patient.

In conclusion, there are only limited preclinical data and one human trial available studying the reversal of anticoagulant effect caused by DOA (► Table 5). Most studies have highlighted the role of PCC, which contains high doses of FX, in reversing the anticoagulant activity of FXa inhibitors; however, PCC does not seem to efficiently reverse the anticoagulant activity of dabigatran. Fur-

thermore, the longer half-time of PCC in comparison to rFVIIa may improve its efficacy. In the absence of efficacious possibilities to restore coagulation under dabigatran, haemodialysis seems to be the first choice. Experience with an increasing number of patients treated with the new DOAs will show whether these drugs can lower bleeding rates. An international registry would greatly help evaluation of the bleeding risk for the new drugs, as well as help analyse the treatment options for bleedings and their follow up.

Conflicts of interest

None declared.

References

1. Wardrop D, Keeling D. The story of the discovery of heparin and warfarin. *Br J Haematology* 2008; 141: 757–763.
2. Camm AJ, Kirchhof P, Lip GY, et al. European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery. Guidelines for the management of atrial fibrillation. The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010; 31: 2369–2429.
3. Alban S. From heparins to factor Xa inhibitors and beyond. *Eur J Clin Invest* 2005; 35 (Suppl 1): 12–20.
4. Hirsh J, Bauer KA, Donati MB, et al. Parenteral Anticoagulants. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Ed.). *Chest* 2008; 133: 141S–159S.
5. Suranyi M, Chow JSF. Review: Anticoagulation for haemodialysis. *Nephrology* 2010; 15: 386–392.
6. Mackman N. Triggers, targets and treatments for thrombosis. *Nature* 2008; 451: 914–918.
7. Heit JA. The Epidemiology of Venous Thromboembolism in the Community. *Arterioscler Thromb Vasc Biol.* 2008; 28: 370–372.
8. Lip GYH, Andreotti F, Fauchier L, et al. Bleeding risk assessment and management in atrial fibrillation patients. Executive Summary of a Position Document from the European Heart Rhythm Association [EHRA], endorsed by the European Society of Cardiology [ESC] Working Group on Thrombosis. *Thromb Haemost* 2011; 106: 997–1011.
9. Lakshminarayan K, Anderson DC, Herzog CA et al. Clinical epidemiology of atrial fibrillation and related cerebrovascular events in the United States. *Neurologist* 2008; 14: 143–150.
10. Lanes S, Fraeman K, Meyers A, et al. Incidence rates for thromboembolic, bleeding and hepatic outcomes in patients undergoing hip or knee replacement surgery. *J Thromb Haemost* 2011; 9 : 325–332.
11. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *Engl J Med* 2009; 361: 1139–1151.
12. Oldgren J, Alings M, Darius H, et al.; on behalf of the RE-LY Investigators. Risks for Stroke, Bleeding, and Death in Patients With Atrial Fibrillation Receiving Dabigatran or Warfarin in Relation to the CHADS2 Score: A Subgroup Analysis of the RE-LY Trial. *Ann Intern Med* 2011; 155: 660–667.
13. Ansell J. Bleeding in Very Old Patients on Vitamin K Antagonist Therapy. *Circulation* 2011; 124: 769–771.
14. Palareti G. Bleeding with anticoagulant treatments. *Hämostaseologie* 2011; 31: 237–242.
15. Mant J, Hobbs FD, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007; 370: 493–503.
16. van Walraven C, Hart RG, Singer DE, et al. Oral anticoagulants vs aspirin in non-valvular atrial fibrillation: an individual patient meta-analysis. *J Am Med Assoc* 2002; 288: 2441–2448.
17. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antithrombotic medicinal products in non-surgical patients. *J Thromb Haemost* 2005; 3: 692–694.
18. Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibril-

- lation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation* 2011; 123: 2363–2372.
19. Rosencher N, Zufferey P, Samama CM. Definition of major bleeding in surgery: an anesthesiologist's point of view: a rebuttal. *J Thromb Haemost* 2010; 8: 1442–1443; author reply 1443–1444.
 20. Ansell J. Factor Xa or thrombin: is factor Xa a better target? *J Thromb Haemost* 2007; 5 (Suppl 1): 60–64.
 21. Goldsack R, Chambers RC, Dabbagh K, et al. Thrombin. *Int J Biochem Cell Biol* 1998; 30: 641–646.
 22. Moser M, Bode C. Anticoagulation in atrial fibrillation – A new era has begun. *Haemostaseologie* 2012; 32: 37–39.
 23. Marijon E, Fauchier L, Le Heuzey JY. New antithrombotic drugs and European approval processes. *Lancet* 2011; 378: 662–663.
 24. Eriksson BI, Quinlan DJ, Eikelboom JW. Novel Oral Factor Xa and Thrombin Inhibitors in the Management of Thromboembolism. *Ann Rev Med* 2011; 62: 41–57.
 25. Guyatt GH, Akl EA, Crowther M, et al. Antithrombotic Therapy and Prevention of Thrombosis. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th ed.). *Chest* 2012; 141 (Suppl 2): 7S–47S.
 26. Ganetsky M, Babu KM, Salhanick SD, et al. Dabigatran: Review of Pharmacology and Management of Bleeding Complications of This Novel Oral Anticoagulant. *J Med Toxicol* 2011; 7: 281–287.
 27. Harder S. Renal Profiles of Anticoagulants. *J Clin Pharmacol* 2012; 52: 964–975.
 28. FDA Drug Safety Communication. Safety review of post-market reports of serious bleeding events with the anticoagulant Pradaxa (dabigatran etexilate mesylate). Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm282724.htm#pat>. Accessed April 2012.
 29. Kwong LM. Therapeutic potential of rivaroxaban in the prevention of venous thromboembolism following hip and knee replacement surgery: a review of clinical trial data. *Vasc Health Risk Manag* 2011; 7: 461–466.
 30. Xarelto Summary of Product Characteristics. Available at: <http://www.xarelto.com/en/information-on-xarelto/summary-of-product-characteristics>. Accessed April 2012.
 31. Tzeis S, Andrikopoulos G. Novel Anticoagulants for Atrial Fibrillation: A Critical Appraisal. *Angiology* 2012; 63: 164–170.
 32. Eliquis Summary of Product Characteristics. Available at: http://www.eliquis.eu/eliquis_smpc.aspx. Accessed April 2012.
 33. Cabral KP, Ansell J, Hylek EM. Future directions of stroke prevention in atrial fibrillation: the potential impact of novel anticoagulants and stroke risk stratification. *J Thromb Haemost* 2011; 9: 441–449.
 34. Pradaxa, summary of product characteristics. Available at: <http://www.pradaxa.com>. Accessed April 2012.
 35. Ogata K, Mendell-Harary J, Tachibana M, et al. Clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers. *J Clin Pharmacol* 2010; 50: 743–753.
 36. Harenberg J, Jörg I, Weiss C. Observations of alanine aminotransferase and aspartate aminotransferase in THRIVE studies treated orally with ximelagatran. *Int J Toxicol* 2006; 25: 165–169.
 37. Kubitz D, Becka M, Wensing G, et al. Safety, pharmacodynamics and pharmacokinetics of BAY 59–7939 – an oral direct factor Xa inhibitor – after multiple dosing in healthy male subjects. *Eur J Clin Pharmacol* 2005; 61: 873–880.
 38. Levine MN, Raskob G, Beyth RJ, et al. Hemorrhagic complications of anticoagulant treatment: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126 (3 Suppl): 287S–310S.
 39. Friedman RJ, Dahl OE, Rosencher N, et al. RE-MOBILIZE, RE-MODEL, RE-NOVATE Steering Committees. Dabigatran versus enoxaparin for prevention of venous thromboembolism after hip or knee arthroplasty: a pooled analysis of three trials. *Thromb Res* 2010; 126: 175–182.
 40. Flaker G, Ezekowitz M, Yusuf S, et al. Efficacy and safety of dabigatran compared to warfarin in patients with paroxysmal, persistent, and permanent atrial fibrillation: results from the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study. *J Am Coll Cardiol* 2012; 59: 854–855.
 41. APPRAISE Steering Committee and Investigators, Alexander JH, Becker RC, Bhatt DL, et al. Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial. *Circulation* 2009; 119: 2877–2885.
 42. Granger CB, Alexander JH, McMurray JJV, et al. for the ARISTOTLE Committees and Investigators. Apixaban versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med* 2011; 365: 981–992.
 43. Poli D, Antonucci E, Grifoni E, et al. Bleeding risk during oral anticoagulation in atrial fibrillation patients older than 80 years. *J Am Coll Cardiol* 2009; 54: 999–1002.
 44. Tafur AJ, McBane R 2nd, Wysokinski WE, et al. Predictors of Major Bleeding in Peri-Operational Anticoagulation Management. *J Thromb Haemost* 2012; 10: 261–267.
 45. Freyburger G, Macouillard G, Labrousse S, et al. Coagulation parameters in patients receiving dabigatran etexilate or rivaroxaban: two observational studies in patients undergoing total hip or total knee replacement. *Thromb Res* 2011; 127: 457–465.
 46. Mani H, Hesse C, Stratmann G, et al. Rivaroxaban differentially influences ex vivo global coagulation assays based on the administration time. *Thromb Haemost* 2011; 106: 156–164.
 47. Douxfils J, Mullier F, Robert S, et al. Impact of dabigatran on a large panel of routine or specific coagulation assays. *Thromb Haemost* 2012; 107: 985–997.
 48. Ahrens I, Lip GYH, Peter K. Anticoagulant drugs in cardiovascular disease. *Thromb Haemost* 2010; 104: 49–60.
 49. Samama MM, Martinoli JL, LeFlem L, et al. Assessment of laboratory assays to measure rivaroxaban – an oral, direct factor Xa inhibitor. *Thromb Haemost* 2010; 103: 815–825.
 50. Levi MM, Eerenberg E, Löwenberg E, et al. Bleeding in patients using new anticoagulants or antiplatelet agents: risk factors and management. *Neth J Med* 2010; 68: 68–76.
 51. Perzborn E, Trabandt A, Selbach K, et al. Prothrombin complex concentrate reverses the effect of high doses of high dose rivaroxaban in rats. *Pathophysiol Haemost Thromb* 2010; 37: YA10-OC251.
 52. Eerenberg ES, Kamphuisen PW, Sijpkens MK, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation* 2011; 124: 1573–1579.
 53. van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost* 2010; 103: 1116–1127.
 54. Zhou W, Schwarting S, Illanes S, et al. Hemostatic therapy in experimental intracerebral hemorrhage associated with the direct thrombin inhibitor dabigatran. *Stroke* 2011; 42: 3594–3599.
 55. Halim AB, Li Y, Stein E, et al. Low Concentrations of rhFVIIa or FEIBA Significantly and Rapidly Reverse the Anticoagulant Effect of Supratherapeutic Edoxaban. Poster at the ASH Congress(?) Dec. 10, 2011 San Diego.
 56. Godier A, Miclot A, Le Bonniec B, et al. Evaluation of Prothrombin Complex Concentrate and Recombinant Activated Factor VII to Reverse Rivaroxaban in a Rabbit Model. *Anesthesiology* 2012; 116: 94–102.
 57. Fukuda T, Honda Y, Kamisato C, et al. Reversal of anticoagulant effects of edoxaban, an oral, direct factor Xa inhibitor, with haemostatic agents. *Thromb Haemost* 2012; 107: 253–259.
 58. Warkentin TE, Margets P, Connolly SJ, et al. Recombinant factor VIIa (rFVIIa) and hemodialysis to manage massive dabigatran-associated postcardiac surgery bleeding. *Blood* 2012; 119: 2172–2174.
 59. Levi MM, Eerenberg E, Löwenberg E, et al. Bleeding in patients using new anticoagulants or antiplatelet agents: risk factors and management. *Neth J Med* 2010; 68: 68–76.
 60. Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. *Arch Intern Med* 2012; 172: 397–402.
 61. Sié P, Samama CM, Godier A, et al. Surgery and invasive procedures in patients on long-term treatment with direct oral anticoagulants: Thrombin or factor-Xa inhibitors. Recommendations of the Working Group on perioperative haemostasis and the French Study Group on thrombosis and haemostasis. *Arch Cardiovasc Dis* 2011; 104: 669–676.
 62. Pernod G, Godier A, Gozalo C, et al. French clinical practice guidelines on the management of patients on vitamin K antagonists in at-risk situations (overdose, risk of bleeding and active bleeding). *Thromb Res* 2010; 126: e167–174.