Review Article

Novel reversal agents and laboratory evaluation for direct-acting oral anticoagulants (DOAC): An update

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ABSTRACT

Novel oral anticoagulants (NOACs) are no longer "novel" but their reversal agents definitely are. Although NOACs enjoy high clinical efficacy, monitoring and reversal of their effect is a challenge which this review attempts to surmount. Ideally, for NOAC activity measurement, specific anti-Factor IIa levels and anti -Factor Xa levels should be monitored (chromogenic assays), but such tests are not readily available. Modifications of the existing coagulation tests catering to this unmet need for quantification of DOAC activity have been reviewed. The available United States Food and Drug Administration (FDA) approved reversal agents, idarucizumab for dabigatrin and andexanet alfa for anti-Xa direct acting oral anticoagulants have given promising results but are prohibitively priced. Medline, Embase, and Scopus databases were thoroughly searched for clinical trials on laboratory investigations and specific as well as non-specific reversal-agents for DOACs.

Key words: Andexanet alfa, idarucizumab, oral anticoagulants, PRT064445, reversal, treatment outcome

INTRODUCTION

Direct acting oral anticoagulants (DOAC) include dabigatran (Pradaxa; direct thrombin (Factor IIa) inhibitor) and rivaroxaban (Xarelto), apixaban (Eliquis), endoxaban (Savaysa) and betrixaban (Bevyxxa) (direct factor Xa inhibitors). Established indications approved by the United States Food and Drug Administration (FDA) include stroke prophylaxis and systemic embolisation in non-valvular atrial fibrillation (NVAF) and venous thromboembolism (VTE) treatment and secondary prophylaxis.[1] In addition, rivaroxaban has obtained FDA approval for acute treatment of acute coronary syndrome. Dabigatran, rivaroxaban and epixaban are FDA-approved for primary prevention of VTE after total hip (35 days) and knee (14 days) replacement too. Warfarin intolerance, inability to adhere to warfarin monitoring requirements, inadequate INR control with warfarin (two INR values greater than 5 or less than 1.5 in the past six months) are other indications.[2-4] when compared to warfarin, DOACs display a decreased intracranial bleed risk.

Lack of specific antidotes was the single largest drawback for DOAC use which has been recently surmounted by the FDA approval of idarucizumab (for dabigatran) in October 2015 and andexanet (for direct Xa inhibitors) in May 2018.[5] A surge in the already burgeoning indications and use of DOACs is expected with the recent breakthrough in launch of specific reversal agents and all anaesthesiologists must be prepared for a greater volume of such patients presenting for elective and emergency surgery. Anaesthesiology is reinventing itself to include perioperative medicine and an in-depth knowledge of DOACs is a step in this direction. Challenges in monitoring and reversal of DOACs have been addressed in this review. Medline, Embase, and Scopus databases were searched using keywords NOAC, DOAC, andexanet alfa, idarucizumab and Prothrombin complex concentrate to locate relevant articles on DOAC monitoring and reversal agents. We

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fully reviewed all relevant articles from our Google, PubMed, ePUB, and EBESCO search after exclusion of animal and *in vitro* human studies to obtain 15 trials on reversal of DOACs.

Nomenclature and historical perspective

Novel oral anticoagulants (NOAC) have been in clinical use since 2010 and hence can no longer be considered novel. Non vitamin -K antagonist oral anticoagulants (NOAC) is the current term in vogue with an intention to keep the acronym NOAC intact. It has been adopted by the CHEST guidelines (2016).[1] This has met with opposition, on the pretext that the uninitiated may take NOAC on its face value as meaning "no anticoagulant" with catastrophic consequences as it signifies an "antonym". Hence, a new term based on mode of action "direct acting oral anticoagulants" (DOAC) has been floated by the International Society on Thrombosis and Haemostasis in 2015,[6] and we shall adhere to DOAC in this review. In fact, we propose a retronym "indirect acting oral anticoagulants" (IOAC) for the classical warfarin which was the first oral anticoagulant to gain FDA-approval in 1954. Target specific oral anticoagulants (TSOAC), oral direct inhibitors (ODI), and specific oral direct anticoagulants (SODA) represent other synonyms for DOAC in scientific parlance.

Clinical profile of DOACs

The clinically relevant pharmacokinetic profile and characteristics of DOACs.[2-10] have been summarised in Table 1. Betrixaban owes its uniqueness to four features: least renal clearance (6-10%), least hepatic metabolism (<1%), the maximum gastrointestinal clearance (>82% eliminated in faeces), and the longest half-life with a reduced peak to nadir drug concentration ratio, making it safe in renal and hepatic impairment patients and has a consistent anticoagulant action over 24 hours.[9,10] The food intake is mandatory with rivaroxaban (bioavailability increases from 66% on empty stomach to 100% with food) but has no effect on epixaban and edoxaban absorption.[2] All the five DOACs (see Appendix) are available in India with betrixaban (the latest one) being manufactured by Avanscure Lifesciences (Gurgaon).

The ideal laboratory investigation for DOAC

There is an unmet need for quantification of DOAC activity for which existing coagulation tests have been modified [Table 2 and Figure 1].[7,11-15] Lack of laboratory guidance complicates the dosing of reversal agents, with possible thrombosis.

For measuring activity of DOACs, specific anti-Factor IIa levels and anti -Factor Xa level monitoring is needed (chromogenic assays), but such tests are not readily available.[9] Bleeding time and clotting time are of no clinical utility. Prothrombin Time (PT) is somewhat useful for monitoring rivaroxaban effect but not for dabigatrin. International normalised ratio (INR) is useful for monitoring warfarin effect but not for DOACs. For dabigatran Partial thromboplastin time (aPTT) proves more sensitive than PT but not for direct Xa inhibitors.[7,11,14] Ecarin clotting time (ECT) and dilute thrombin time (dTT) are helpful for monitoring dabigatrin activity.[15]

Table 1: Characteristics of DOACs

Parameter	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Site of action	Thrombin	Xa	Xa	Xa	Xa
FDA approval	2010	2011	2013	2014	2017
Peak effect (h)	2-3	2-4	1	1.5	3-4
Renal excretion	80%	66%	25%	35%	6-10%
Plasma half life (h)	12-13	9-13	10-14	10-14	20-27
Dose	150mg BD Avoid in CrCl <30 ml	15mg OD Avoid in CrCl <15 ml	5 mg BD Avoid in CrCl <15 ml	60mg OD Avoid in CrCl <15 ml	160mg single dose; Then 80mg OD
Discontinue before surgery (h)					
Bleeding risk high	48-72	72	48	48	48
Bleeding risk low	24-48	24	24	24	24
Reversal Agent (FDA approval)	Idarucizumab (2015)	Andexanet (2018)	Andexanet (2018)	Nil	Nil
Off label use (NON-specific agents)	Haemodialyis	PCC (25-50U/Kg) Activated charcoal Haemodialysis Plasma exchange	PCC	PCC	PCC
Ongoing trials	Aripazine	Aripazine	Aripazine	Aripazine	Aripazine

Rivaroxaban, Apixaban and Edoxaban are not licensed for use with an eGFR <15ml/min; Dabigatran is not FDA approved for use with an eGFR <30ml/min; CrCl – Creatinine clearance; PCC – Prothrombin Complex Concentrate

Table 2: Relevance of available Laboratory coagulation tests in context of DOACs

Lab.Test	Dabigatrin	Rivaroxaban, Apixaban, Edoxaban
aPTT	More sensitive than PT	Low sensitivity
(Partial thromboplastin time)	Qualitative	Not useful
PT/INR	Low sensitivity	Low sensitivity
(Prothrombin time)	Not useful	Qualitative if calibrated agents used
TT*	Over sensitive	N/A
(Thrombin clotting time)	Not useful/Qualitative	
Dilute TT	Highly sensitive Quantitative	N/A
Ecarin Clotting Time	Sensitive Not readily available	Not affected
Chromogenic anti-Factor Xa assay	N/A	High sensitivity Quantitative
Chromogenic anti-Factor IIa assay	High sensitivity Quantitative	N/A
Plasma drug concentration by Liquid chromatography/ tandem mass spectrometry (LC-MS/MS)	High sensitivity Quantitative	High sensitivity Quantitative
Prothrombinase induced CT	Low sensitivity	High sensitivity
TGA	↑lag period↓AUC	↑lag period↓AUC
TEG/TEM		
Rapid TEG	↑R;↓MA	↑ R but low sensitivity
Kaolin TEG	↑R;↓MA high sensitivity	↑R but low sensitivity
ROTEM	↑ACT ;↓MCF	↑ACT but low sensitivity
INTEM	↑ACT ;↓MCF	↑ ACT but low sensitivity
EXTEM	↑ACT ;↓MCF	↑ ACT but low sensitivity
Ecarin TEG	Dose dependent shortening of R time	Dramatic shortening of R time to control levels irrespective of dose

N.A – Not applicable; TGA – Thrombin generation assay; TEG – Thromboelastography ; ROTEM – Rotational thromboelastometery AUC – Area under curve; R – Reaction time; MA – Maximum amplitude; ACT – Activatedclotting time; MCF – Maximum clot firmness; *A normal thrombin time has a high negative predictive value for dabigatran. A normal thrombin time does indicate that there is minimal to no dabigatran present in the blood sample, and this may have some utility

Thromboelastography (TEG) and rotational thromboelastometery (ROTEM)

The viscoelastometric methods for monitoring coagulation have evolved as point-of-care instruments for differential detection of the cellular and plasma subsets of haemostasis. During TEG the cup (with 0.36ml whole blood sample) rotates while during ROTEM the pin (suspended in the sample) rotates. Analogous TEG/TEM-derived parameters comprise reaction time (R)/clotting time (CT)(time period to 2mm amplitude), kinetics (K)/clot formation time (CFT) denoting the period from 2-20mm amplitude, angle alpha (slope of the tracing), and maximum amplitude (MA)/maximum clot firmness (MCF). Intrinsic and extrinsic coagulation triggers can both be utilised. Both INTEM and HEPTEM types of ROTEM utilise contact activation and measure the intrinsic pathway of coagulation. Both EXTEM and FIBTEM subtypes of ROTEM use tissue factor as activator and measure the extrinsic pathway. Kaolin TEG test (using kaolin as activator) is sensitive and useful for monitoring the effects of dabigatran. Reaction time (R) is prolonged for dabigatran. However, for anti-Factor Xa DOACs, both kaolin TEG test and ROTEM (Tem International GmbH, Munich, Germany) INTEM and EXTEM tests lack sensitivity.[13] The rapid TEG test (kaolin and tissue factor as activators) for both intrinsic and extrinsic pathways is more sensitive for anti-Xa inhibitors than single-pathway reagents. In case of an unknown DOAC, an ecarin TEG helps differentiate between anti Factor IIa and the anti-FactorXa inhibitors. Dabigatran consuming patients will display a dose-dependent shortening of the R time, while the patients of rivaroxaban group exhibited dose independent R time shortening to control levels.[13,16]

Thrombin generation assay (TGA) or thrombography provides parameters like peak height, lag time and area under the curve (AUC)/extrinsic thrombin potential (ETP). Lag time is increased while AUC is decreased in patients on DOACs.[16]

The best laboratory investigation when TEG is unavailable would be to measure the serum creatinine levels to rule out renal compromise followed by eliciting a history of last oral intake of the drug. As per pharmacokinetics, roughly five half-lives are required

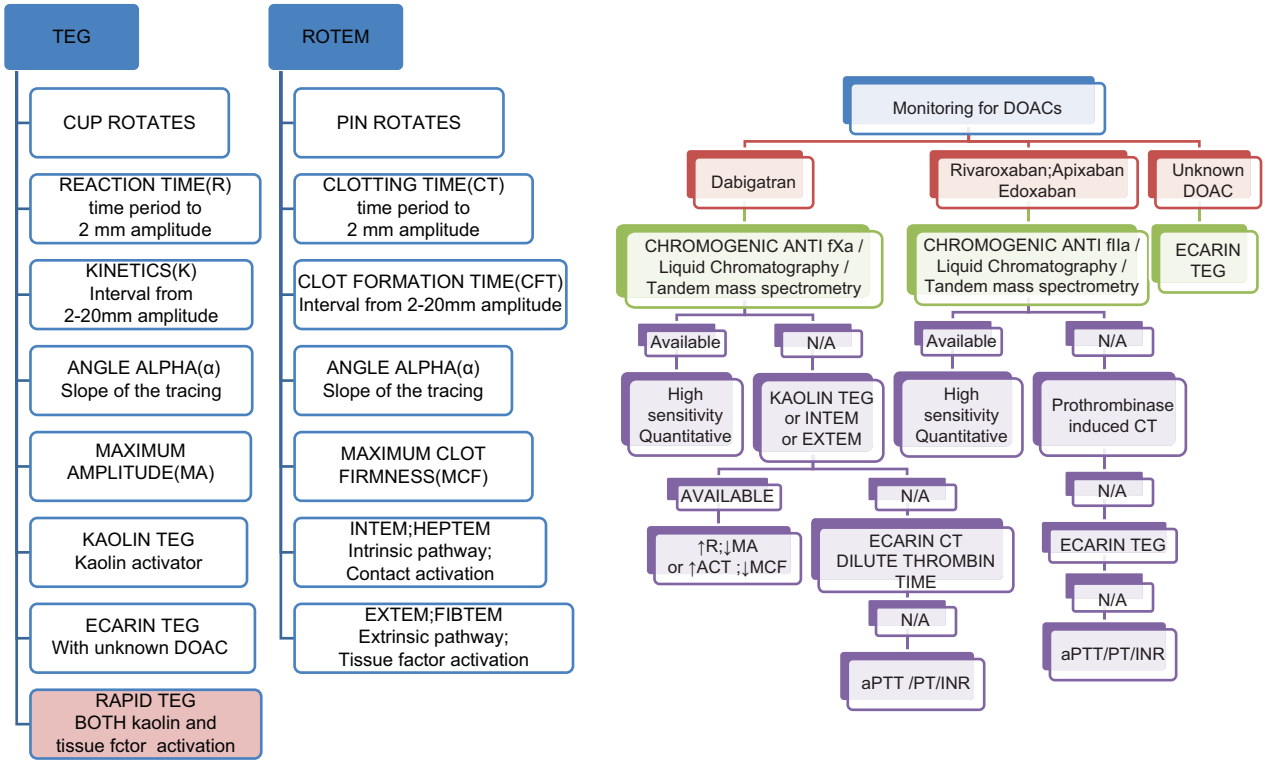

Figure 1: Algorithm for monitoring DOACs

to completely washout any drug from the body. Hence, the product of 'half-life of the DOAC' with a multiplication factor of five gives us the time for which the DOAC needs to be stopped before elective surgery. Reversal agents have an important role to play when one cannot afford to wait for five half-lives (emergency surgery, DOAC induced bleeds, trauma in patients taking DOACs).

Paucity of reversal agents

NOACs are no longer "novel" but their reversal agents definitely are. DOAC reversal agents at a glance [Table 3][17-29] and a summary of 16 human *in vivo* clinical trials involving specific and non-specific DOAC reversal agents[30-46] [Table 4] are presented here for ready referral.

Specific antagonists

Idarucizumab (Praxbind)

The first and only antidote for dabagatrin, idarucizumab manufactured by Boehringer Ingelheim found FDA approval in October 2015.[17] It is distributed in India by Ram Healthcare. The current wholesale price of a pair of 2.5g vials is prohibitively high (2,42,532.44INR/$3482.50).[18] Idarucizumab is a monoclonal antibody fragment that binds to and deactivates dabigatrin.[19] Pollack *et al*.[30] studied Idarucizumab 5g IV for dabigatrin reversal in patients with major bleeding and those scheduled for emergency surgery and found that haemostasis was restored for mean 11.4 h. Glund *et al*.[32] reported that age and kidney function bear no effect on idarucizumab induced reversal of dabigatran anticoagulant effect, which is nevertheless dose dependent. Subtherapeutic idarucizumab (1 g dose) entails a partial return of anticoagulation, as distinct from higher 2.5 or 5 g doses whose effect lasted for mean 24 h. They demonstrated total and persistent dabigatran reversal using activated partial thromboplastin time (aPTT), ecarin clotting time (ECT), diluted thrombin time (dTT), and unbound dabigatran concentrations as measuring parameters. The results of a dosing RCT on healthy volunteers (Van Ryn *et al*. 2018)[33] involving administration of 5-min infusion of increasing doses of idarucizumab or a placebo two hrs post morning dabigatran dose showed a dose-dependent restoration of fibrin formation with 1, 2 or 4 g of idarucizumab to 24%, 45% and 63% respectively, of pre-dabigatran values, half an hour post idarucizumab induced reversal. Fibrinopeptide-A (FPA) was measured via commercial enzyme linked immune sorbent assay (ELISA), ECT and dTT using conventional methods. Plasma dabigatran levels were measured by LC-MS/MS. This establishes that idarucizumab reverses dabigatran-induced inhibition of fibrin deposition

Table 3: DOAC reversal agents at a glance

Property	PCC	Idarucizumab	Andexanet alfa (PRT064445)	Ciraparantag Aripazine/PER997
Chemical structure	Combinations of 3 or 4 clotting factors	Humanised monoclonal antibody fragment	Recombinant factor Xa, Inactivated-zhzo	Small Synthetic cation with 2 arginine units
Manufacturer	Baxter CSL Behring	Boehringer Ingelheim	Portola Pharmaceuticals	Perosphere Pharma
Brand Name	FEIBA Beriplex Kcentra	Praxbind	Andexxa	Not Applicable
Drug reversed	All DOACs Warfarin LMWH	Dabigatran	Rivaroxaban Edoxaban Apixaban Betrixaban Fondaparenux Enoxaparin	All DOACs LMWH; Unfractio-nated heparin
Dose	50 IU/kg	Two doses of 2.5 mg given 15 mins apart	Single IV bolus (400/800 mg) → continuous infusion up to 120 min (4 or 8 mg/min); depending upon the last dose of rivaroxaban (≤10or >10 mg/unknown) or apixaban (≤5 or >5 mg/unknown), and time of the last dose of DOAC (<8 h/unknown or ≥8 h)	Single 100-300mg IV bolus
Onset	10h	<5 min	2 min	5-10 mins
Duration of action	6-72h	24-72h	12h after stopping infusion	24h
Cost per reversal	$108/kg body weight	$3500	$58,000	Not known
FDA approval	NO	YES (2015)	YES (2018)	NO (under fast track review)

PCC – Prothrombin complex concentrate; DOAC – Direct oral anticoagulants; LMWH – Low molecular weight heparin; FDA – US Food and Drug Administration

Table 4: Summary of Human in vivo clinical trials on DOAC reversal agents

Study (Ref)	Indication	*n*	Intervention Arms	Control	Design	Clinical Outcome
Pollack (2015)[30] Interim analysis of 90 patients	Idarucizumab to reverse dabigatrin	51	5g IV Idarucizumab in patients with serious bleeding	nil	Prospective cohort study	Haemostasis restored for mean 11.4h
		39	5g IV Idarucizumab in patients for emergency Surgery			Normal intraop. haemostasis in 33/36 pts.
Pollack (2017)[31] REVERSE AD (phase III study)	Idarucizumab to reverse dabigatrin in bleeding and emergency surgery patients	503	5g IV Idarucizumab in patients with serious bleeding (intracranial, gastrointestinal, intraperi-toneal, intra-pericardial, intraarticular, traumatic)	Nil	Prospective cohort study	A single 5-g dose of idarucizumab was sufficient in 98% of the patients; Reversal sustained for 24 h; Thrombotic events occurred in 24/503 patients within 30 days after treatment and in 34/503 patients within 90 days.
			5g IV Idarucizumab in patients for emergency Surgery			
Glund *et al* (2015)[32]	Idarucizumab to reverse dabigatran in healthy volunteers (18-45y)	110	20 mg to 8 g idarucizumab as a 1-hour intravenous infusion in 10 sequential dose groups, or 1, 2 or 4 g idarucizumab as a 5-minute infusion.	Placebo	Sequential rising dose RCT	Reduction of plasma concentrations to less than 5% of peak within 4h. Idarucizumab (in the absence of dabigatran) had no effect on coagulation parameters or endogenous thrombin potential
Yasaka *et al* (2017)[33]	Safety, tolerability, pharmacokinetics of a range of IV doses of idarucizumab alone/after dabigatran in healthy Japan-ese males	32	Single idarucizumab doses (1, 2, 4 or 8 g [*n*=6/dose group]) or placebo (*n*=2/dose group).	Placebo	Two-part, phase I, placebo-controlled, double-blind, rising-dose RCT	6/60 idarucizumab- treated subjects developed treatment-emergent ADAs (positive titers from 1-40) Idarucizumab at higher doses (4 and 5 g) led to immediate, complete, and sustained reversal of dabigatran-induced anticoagulation for 72 h. At lower (1 and 2 g) doses , a partial return of anti-coagulant effect of dabiga-tran was observed after 1-2 h
		48	Dabigatran (220 mg BD) followed by idarucizumab (*n*=9/dose group) 1, 2, 4 or 5 g (2×2.5 g), or placebo (*n*=3/dose group)			
Glund *et al* (2017)[34]	Idarucizumab to reverse dabigatrin in middle-aged, elderly and renally impaired volunteers	46	Patients received dabigatran etexilate (220 or 150 mg twice daily) for 4 days followed 2 hours later by Idarucizumab doses of 1, 2.5 and 5 g or 2 × 2.5 g 1 h apart, or placebo, as a rapid (5 min) infusion	Placebo	Prospective placebo controlled RCT	Immediate and complete reversal of dabigatran-anticoagulation. Sustained for 24 h with doses of 2.5 or 5 g. Reversal of dabigatran anticoag-ulation by idarucizumab was independent of age and renal function

Contd...

Table 4: Contd...

Study (Ref)	Indication	*n*	Intervention Arms	Control	Design	Clinical Outcome
Van Ryn *et al* (2018)[35]	To study effect of Dabigatran on ability to generate fibrin at a wound site and dabigatran reversal by Idarucizumab, in Healthy Volunteers	35	Baseline FPA noted; Dabigatran (220 mg BD for 4d);FPA noted on day 3 and 4 at 2.5 and 6 hrs post morning dose of dabigatran. On day 4, 5-min infusion of 1, 2 or 4 g of Idarucizumab/ placebo 2 hrs post morning Dabigatran dose was given Scalpel incisions made on the forearm, volar surface. Blood was collected from the wound at each time point over 4 min into vials containing stop solution and frozen until assayed.	Placebo	Prospective Dosing RCT	Mean FPA before DE was 3980±17 ng/ml. Complete inhibition of FPA to 208±28 ng/mL at 2.5 hrs on day 3, corresponding to peak dabigatran levels (210±17 ng/mL). Six hrs post DE, levels were 127±10 ng/mL and FPA was still significantly reduced to 328±35 ng/mL. There was a significant, dose-dependent return of fibrin formation. Anticoagulation (ECT and dTT) was significantly prolonged with dabigatran and reversed to control levels after dosing with 2 or 4 g Idarucizumab
Siegal *et al* (2015)[36]	Andexanet alpha 400mg to reverse apixaban and rivaroxaban	24	5mg BD Apixaban	Patients receiving placebo	2-part placebo controlled RCT	94%↓in anti-FXa activity compared to 21%↓in control group Unbound apixaban↓by 9.3 ng/ml versus 1.9 ng/ml in control group
		27	20mg OD Rivaroxaban	Patients receiving placebo		92%↓in anti-FXa activity compared to 18% in controls Unbound rivaroxaban↓by 23.4 ng/ml v/s 4.2 ng/ml in controls
ANNEXA Trial Part I (Crowther *et al*)[37]	Andexanet bolus to reverse apixaban and rivaroxaban	70	Apixaban followed by 400mg andexanet Rivaroxaban followed by 800mg andexanet	Placebo instead of andexanet	RCT	Anti-fXa levels (Biomarker endpoint)
ANNEXA-R Trial (Crowther *et al*)[38]	Efficacy and safety of andexanet in rivaroxaban reversal in 50-75y old	39	Rivaroxaban 20 mg ODfor 4d followed by either andexanet bolus (800 mg) + andexanet infusion960mg over 2 h or placebo	placebo	Prospective double blind RCT	Greater than 90% reversal of anti-fXa activity
ANNEXA-A Trial (Crowther *et al*)[39]	Efficacy and safety of andexanet for apixaban reversal in older patients	145	Apixaban 5mg BD for 4d Andexanet 400 mg iv bolus then 4 mg/min for 120 min	Placebo	Double blind placebo controlled RCT	Andexanet reversed apixaban anticoagulation within minutes after bolus and for the whole duration of the infusion without toxic effects or thrombotic events
ANNEXA-4 Trial[40] (Ongoing)	Phase 4 Outcomes Study in Bleeding Patients (Still recruiting)	350	Patients receiving fXa inhibitors (Apixaban, Rivaroxaban, Edoxaban) and Enoxaparin presenting with acute major bleeding shall receive andexanet	placebo	Interventional Single arm, Open label study	First primary: Percent change from baseline in anti-fXa activity Second primary: patients achieving "effective haemostasis" (Independent Endpoint Adjudication Committee)
Connolly *et al* (2017)[40]	Andexanet to reverse acute major bleeding within 18 h after Xa inhibitor	67	All patients with major intracranial or gastrointestinal bleed as complication of Anti-Xa received andexanet bolus followed by infusion for 2h	Nil	Multicenter, prospective, open-label, single arm study	Effective haemostasis achieved in 79% of the patients lasting uptil 12h after stoppage of infusion
Ansell *et al* (2014)[41]	PER977 to reverse the anticoagulant effect of edoxaban	80	60 mg edoxaban followed 3h later by single intravenous dose of PER977 (100 to 300 mg)	Placebo followed by PER977	Double blind RCT	↓Whole-blood clotting time to within 10% above the baseline value in ≤10 min, in edoxaban group. In placebo group time to reach that level was much longer (12-15 h).

Contd...

Table 4: Contd...

Study (Ref)	Indication	*n*	Intervention Arms	Control	Design	Clinical Outcome
Eerenberg *et al* (2011)[42]	PCC to reverse dabigatran and rivaroxaban in healthy male volunteers	12	Rivaroxaban 20 mg BD or dabigatran 150 mg BD for 2½ days, followed by either a single bolus of 50 IU/kg PCC (Cofact) or a similar volume of saline. After a washout period, the procedure repeated with the other anticoagulant	Placebo	Placebo-Controlled Crossover RCT in Healthy Subjects	Rivaroxaban induced↑prothrombin time (15.8±1.3s) was immediately and completely reversed by PCC to 12.8±1.0s. ↑Endogenous thrombin potential (ETP) compared with saline
Zahir *et al* (2014)[43]	PCC (Kcentra) to reverse edoxaban	50	Edoxaban 60 mg single dose 2.25 h before PCC 50 IU/kg; 25 IU/kg or 10 IU/kg PCC	Saline placebo	Dosing RCT	No correction of Prothrombin Time compared with saline↑ETP compared with saline
Levi *et al* (2014)[44]	PCC (Kcentra) and Profilnine to reverse rivaroxaban	23	20 mg twice daily for 4 days then 20 mg on day 5 followed by a PCC/saline 50 IU/kg PCC (Kcentra) 50 IU/kg PCC (Profilnine)	Saline placebo	Three arm RCT	PT did not return to baseline; ↑ETP compared with saline; PTTK was Prolonged and No correction of Anti-Xa activity by 4-PCC compared with saline
Majeed *et al* (2017)[45]	PCC effectiveness to manage major bleeding events on rivaroxaban or apixaban	84	Median PCC dose of 2000 IU for major bleeding events (Intra- cranial haemorrhage (70.2%), gastrointesti-nal bleed (15.5%) cases	No control group	Prospective study	PCC to manage major bleeding due to rivaroxaban or apixaban is effective in (69.1%) patients Rate of thromboembolism low when compared to that seen with anticoagulant discontinuation
Song *et al* (2017)[46]	Reversal of apixaban	15	To stuy effects of 2 four factor PCC on apixaban pharmacokinetics and pharmacodynamics	Placebo controlled	Open label 3-period crossover study	Cofact and Beriplex (PCC) reversed apixaban steady state effects in coagulation assessments

Endogenous thrombin potential (ETP) RCT – Randomised clinical trial; PT – Prothrombin time; PTT – Partial thromboplastin time; ETP – Endogenous thrombin potential; 4-PCC, four-factor prothrombin complex concentrate; aPTT – Activated partial thromboplastin time

at the wound-site. In a Japanese study on 80 healthy males (Yasaka *et al*.),[33] 10% of idarucizumab-treated subjects developed anti-idarucizumab antibodies (positive titer range, 1 to 40) in course of therapy. Plasma levels of active dabigatran (unbound fraction) decreased to below detectable limits immediately post-idarucizumab. A six times rise in total dabigatran plasma levels occurred in all dose groups, post idarucizumab infusion, peaking in 30 mins, (the moment dabigatran in the central compartment is exhausted by binding to idarucizumab, rapid redistribution of unbound dabigatran is initiated from the peripheral compartment which again binds to idaricizumab). When participants were administered idarucizumab alone, the coagulation profile (aPTT, dTT, ECT) remained unchanged before and after idarucizumab, regardless of dose. In participants receiving idarucizumab after dabigatran, higher doses of idarucizumab (4 and 2.5 + 2.5g) produced immediate, total, and persistant reversal of dabigatran-induced anticoagulation for up to 72h while at lower doses (1 and 2g) idarucizumab, anticoagulant effect of dabigatran partially returned 1-2h post reversal with idarucizumab.As compared to Glund *et al*.[32] (where 2-g idarucizumab sufficed for persistant reversal in Caucasians) double the dose (4-g idarucizumab) was needed for persistant reversal in Japanese volunteers.

The onset of action of idarucizumab is variously reported to be from immediate to upto 4 hours after administration, and the duration of action is 12h- 72h as per literature review. Nevertheless conflicting case reports from the "real-world use" have recently emerged regarding sustenance of reversal with idarucizumab prompting the need for further dosing studies. A patient with history of atherothrombotic stroke on dabigatran (110mg BD) prophylaxis developed sudden hemiparesis and altepase 0.6 mg/kg was required to be administered after reversal of dabigatran by idarucizumab. Paradoxical elevation of total dabigatran levels, two hours after reversal with idarucizumab occurred while the PTTK values dropped to 30 sec immediately after idarucizumab and 27 sec, 2 h later.[47] Measurement of total dabigatran is therefore totally misleading despite the high performance liquid chromatography and mass spectrometry utilised to obtain it. Unbound dabigatran must be separated by ultrafiltration and measured to obtain the true picture.

A 77-year-old male receiving dabigatran prophylaxis for paroxysmal atrial fibrillation required idarucizumab as antidote owing to, massive dabigatran accumulation due to acute renal failure resulting in acute gastrointestinal bleeding. Fifty minutes post idarucizumab 5g IV, the dabigatran

plasma concentration Dropped from 1630 ng ml^{-1} to undetectable levels of below 30 ng ml^{-1} and bleeding stopped. Eight hours later, there occurred reversal of dabigatran reversal and dabigatran plasma level peaked to 1560 ng ml^{-1}, with simultaneous fall in haemoglobin. Concurrent haemodialysis and haemofiltration reversed the rising trend in dabigatran but the patient was eventually lost due to sepsis and multiorgan failure.[48] Massive dabigatran accumulation as in renal failure should be countered by either repetitive idarucizumab boluses, or combined therapy (reversal agent plus haemodialysis/renal replacement therapy).

Thrombotic events (including three fatal ones) occurred in 34/503 patients (RE-VERSE AD Trial)[31] during the 90 day follow-up post dabigatran reversal with idarucizumab. This warrants resumption of anticoagulation after overcoming the major bleed/emergency surgery. The timing of resumption of DOACs needs to be established by further studies. In the major bleed group, delirium was the most common adverse event (which occurred in 2.3% of the patients) while cardiac arrest and septic shock comprised the commonest adverse event (3.5% and 3.0%, respectively) in the emergency surgery group.

Andexanet alpha (AndexXa/PRT4445)

The single specific reversal drug for direct Xa inhibitors, Andexanet alfa (AndexXa™, Andexanet alfa, Portola Pharmaceuticals, Inc., USA) was recently launched after FDA approval in May 2018.[20] This is a recombinant variation of Xa molecule- a dummy/decoyXa with a serine moiety incorporated. Andexanet has an onset time of 30 mins and a duration of action 4-6 hours. It binds to and blocks rivaroxaban.[21-23] The dosing can be guided by TEG. In the ANNEXA-R trial,[36] all 39 subjects (26andexanet, 13 placebo) were administered rivaroxaban and none of them suffered from infusion-related reactions or serious/severe adverse events. Transient rise in D-dimer (>twice upper normal limit) and F1+2 were observed in a subset of subjects and returned to within normal limits within next 24-72 hours. The mean percent change in anti-fXa from initial level to post-infusion trough was 97% and from initial level to post-bolus trough was 95%. Mean post-infusion nadir (after andexanet administration) for free rivaroxaban concentration was 1.9 ng/mL, which was well below the calculated no-effect rivaroxaban level (4 ng/mL).Thrombin generation was restored to above Mean - 1 SD in all of rivaroxaban treated patients reversed with Andexanet versus none in placebo group. Lasting effect on thrombin generation was not observed. Coagulation profile returned to near normal immediately post andexanet bolus which persisted throughout the 2hr-infusion lasting 1-2 hours post discontinuation. Greater than 90% reversal of anti-fXa activity was observed with no thrombotic events, antibodies to FX or FXa, or neutralizing antibodies to andexanet.

Connolly *et al*.[40] as a pro tem analysis of the ANNEXA-4 Trial,[40] utilised andexanet for arrest of serious bleeding complications (intracranial; gastrointestinal) in 67 patients on direct oral anti-Xa drugs. The mean age of these patients with substantial cardiovascular co-morbidity was 77 years. The mean time elapsed from presentation to andexanet bolus administration was 4.8h. There was an 89% drop in median anti- factor Xa activity from initial levels in patients on rivaroxaban and a 93% drop in patients on apixaban which remained so throughout the 120 min infusion. Twelve hours after stoppage of andexanet infusion, excellent clinical haemostasis was observed in 37 of 47 patients in the efficacy analysis. Incidence of thrombotic complications was 12 in 67 patients (18%) during the month long follow-up. A double-blind, placebo-controlled phase II RCT (NCT03330457) to evaluate the efficacy of andexanet alfa as an antidote for betrixaban in healthy volunteers, is currently ongoing. Another ongoing double-blind, placebo-controlled phase I trial (NCT03083704) aims to assess pharmacokinetics, pharmacodynamics, safety and tolerability of second generation andexanet alfa in healthy volunteers. Andexanet alfa costs $58000per reversal (800mg bolus + 960mg infusion, $3300 per 100 mg vial) which is exorbitantly higher than cost of dabigatran reversal by idarucizumab ($3500 per reversal).[17] Idarucizumab reversal agent is available free if the original molecule is used and patient is registered with the company.

Ciraparantag (Aripazine/PER-997)

PER977 (Perosphere) is a tiny, water-soluble, synthetic cation that binds specifically to DOACs through non-covalent hydrogen bonds and electrostatic interactions.[24,25] It also binds to unfractionated heparin and low molecular weight heparin.[24] As per Ansell *et al*.,[39] the whole-blood clotting time was baseline ± 10% for 24 hours post a solitary PER977 dose to reverse edoxaban. Electron micrographs of blood-clots revealed that edoxaban caused a mean fibrin-fiber diameter shortening by 250-125 nm relative to baseline, which again got normalised half an hour post PER977. Assessment of D-dimer,

prothrombin fragment 1.2, and tissue factor pathway inhibitor levels and whole-blood clotting time revealed no evidence of PER977 related procoagulant activity. Mild circumoral and facial flushing, parageusia and headache were side effects attributable to PER977. 100 to 300 mg of PER977 restored baseline haemostasis from the anticoagulated state within 10 to 30 minutes which was sustained for 24 hours. "Effects of a double-blind, single dose of PER977 administered alone, and following a single dose of edoxaban" (NCT01826266) enrolling 83 patients and "Study of PER977 administered to subjects with steady state edoxaban dosing and re-anticoagulation with edoxaban"(NCT02207257) recruiting 65 participants are two completed RCTs (with results awaited) expected to provide further insight and probably FDA approval for ciraparantag. In the second RCT, subjects were administered a morning dose of 60 mg edoxaban on first and second days. On the third and fourth days, they received an edoxaban bolus (60 mg), followed 180 mins later by a PER977 bolus (25 mg, 50 mg, 100 mg, 300 mg and 600mg) or placebo.

Non-specific antagonists

Early administration of activated charcoal can hamper absorption of DOACs from the gutand can be followed by charcoal filtration.[26] Haemodialysis is partially successful in removing Dabigatrin from the circulation, but is ineffective for anti-Factor Xa DOACs whereas therapeutic plasma exchange maybe employed for urgent rivaroxaban reversal.[26,27] Intermittent haemodialysis reduced dabigatran concentrations by 52%-77% but a rebound reaching 87% within 120 minutes post dialysis was observed in a case series of five patients[28] Recombinant activated factor VII can also be empirically used.[29]

Prothrombin complex concentrate (PCC)

Clotting factor concentration of PCC is roughly 25 times that of normal plasma. Three-factor PCC (Uman Complex D.I.; Kedrion, Castelvecchio Pascoli, Italy) incorporates factors II, IX and X, while four-factor PCC, Beriplex (Kcentra; CSL Behring, King of Prussia, Pennsylvania) has factor VII (fVII) in addition and works in 70% of the patients. Active PCC (FEIBA; Baxter, Deerfield, Illinois) comprises protein C and protein S in addition to the aforementioned four factors with fVII being in active form.[42-46] Factors II and VII possess the longest (60-72 h) and shortest half-life (6 h) respectively, while fIX and fX have half-lives ranging between 12-24 h. Eerenberg *et al*.[42] (2011) demonstrated that, four-factor PCC (Cofact) produced rapid and total reversal of rivaroxaban anticoagulation in healthy participants but failed to influence the anticoagulant effect of dabigatran at the PCC dose (50IU/kg) utilised by them. The endogenous thrombin potential (baseline, 92 ± 22%) was suppressed by rivaroxaban (51 ± 22%) followed by normalisation with PCC (114 ± 26%), while no effect was observed with saline (placebo). Dabigatran prolonged the aPTT, ECT, and thrombin time, which did not revert to baseline with PCC infusion. Both Zahir *et al*.[43] and Levi *et al*.[44] found PCC to be of no clinical importance for DOAC reversal. Levi *et al.* found that Prothrombin Time did not return to baseline (12s) after administering four factor PCC for rivroxaban reversal. Neoplastin PT was recorded as 21 s after rivaroxaban and fell to 17.5 s after PCC. Thromborel S PT was 18s after rivaroxaban and fell to 15.5 after PCC administration. ETP was raised, aPTT was prolonged and neither PCC nor saline restored Anti-Xa activity. Differences in the level of protein S between Cofact and Kcentra (both PCC products) may have shaped their effect on the coagulation parameters studied resulting in different results from these conceptually similar studies. Moreover, the laboratory coagulation tests too, utilize different reagents for the same tests.

Anaesthetic implications

Anaesthesiologists should focus on three main learning objectives. Firstly, time period for which DOACs need to be stopped before performing elective surgery, neuraxial blocks, deep plexus and regional blocks and interventional spinal and pain procedures. Secondly, assessment for requirement of bridging therapy, and finally, management of anticoagulation reversal with specific and non-specific reversal agents in emergency situations.

A tsunami of DOAC patients is expected in the near future due to their desirable drug profile. Increasing medical tourism would likely expose Indian anaesthetists to increasing DOAC patients for elective surgery.

As per the International Society of Thrombosis and Haemostasis (ISTH), to qualify as a major bleed, at least one of two important criteria must be met. First: Any overt bleed causing ≥2 g/dL drop in haemoglobin, or necessitating transfusion of ≥2 units of whole blood or packed red blood cells (PRBCs). Second: Any symptomatic bleed in vital regions (intracranial, intraspinal, intra-articular, intraocular, pericardial, intramuscular producing compartment syndrome,

retroperitoneal). Criteria which make a major bleed life-threatening include symptomatic intracranial bleeding, minimum 5 g/dL fall in haemoglobin, transfusion of ≥4 units of whole blood/PRBCs, requirement of IV inotropic drugs to maintain blood pressure or if the bleeding warrants surgical intervention.

- Patients on DOACs not infrequently present with major bleed warranting surgical intervention or may present for emergency surgery like bone fractures, acute cholecystitis, acute appendicitis, joint and wound infection, incision and drainage of abscesses or acute mesenteric ischemia. India has the dubious distinction of having the highest rate of traumatic brain injury (TBI) and stroke worldwide.[49] India loses 1lac lives annually to TBI which is 25 times higher than the West. Only a percentage of brain damage occurs on primary impact. Progressive damage ensues during the following minutes, hours and days (secondary neurological damage) compounding the mortality and disability. Consequently, early and appropriate management of this emergency is critical and andexanet/idarucizumab reversal can spell the difference between survival and death in TBI patients on DOACs.

The services of an anaesthesiologist in such emergencies are akin to those of a perioperative physician cum cardiologist. In order to independently manage preoperative screening, optimisation and the postoperative course, a sound knowledge of the relevant lab investigations and drug profiles can make the anaesthesiologist self-reliant. Lack of familiarity with pharmacological profile of haemostasis altering drugs may lead to a fresh emergency like spinal haematoma (requiring an MRI for diagnosis followed by emergency laminectomy) in midst of a regional block given for the original emergency surgery.

In ASAIII/IV patients unfit for GA, regional anaesthesia maybe the last resort and reversal of DOAC anticoagulation with idarucizumab or andexanet may prove life-saving.

American Society of Regional Anaesthesia guidelines (ASRA; 2018) on DOACs

Coagulation defects are the principal risk factors for regional anaesthesia. Spinal haematoma is a rare (1 in 150,000 epidurals and 1 in 220,000 spinals) but potentially devastating complication. Minimum time elapsed between the last dose of DOAC and epidural catheter placement/SAB is elaborated in Table 5. Neuraxial blocks appear safe if zero anti-factor Xa activity is documented (tailor made chromogenic anti-factor Xa assay), but the cut off residual level of DOACs acceptable for neuraxial block execution is as yet undetermined. Therapeutic anticoagulation precludes indwelling catheter removal. All DOACs can be resumed 6h after removal of epidural catheter and 24h later in case of a traumatic puncture. This applies to Deep plexus and regional blocks as well.

Summarisation of ASRA 2018 Guidelines[50] as "Thumb rules"

- For simplicity sake, a blanket 72h time interval for discontinuation prior to neuraxial block is applicable to all the DOACs
- All DOACs can be resumed 6h after epidural catheter removal
- In unanticipated administration of DOACs with an indwelling catheter the catheter can be removed 24 h later for all DOACs except betrixaban where a 72 h interval is required.

Guidelines for Interventional pain procedures

Procedure and patient specific factors necessitate distinct guidelines for pain and spine procedures[51] which are divisible into high, intermediate and low bleeding risk categories [Table 5; footnote] The ASRA regional anaesthesia anticoagulation guidelines were essentially judged suitable for the low and intermediate-risk classes, but inappropriate for the high-risk category by the guidelines committee for Interventional spine and pain procedures.

Knowledge of drug half-lives is vital for calculation of the recommended 5 half-life period between cessation of DOACs and medium- and high-risk pain interventions. A 2 half-life period may suffice for low risk procedures after an evaluation, risk assessment, and management decision in consultation with the physician-in-charge decides upon stopping DOACs. Risk categorisation of patients with increased bleeding risk (elderly, bleeding disorder, concomitant anticoagulants/antiplatelets, advanced hepatic or renal disease) posted for low or intermediate-risk interventions should be stepped up to intermediate or high risk, respectively.

In patients at high risk for VTE, a bridging therapy with LMWH can cover the DOAC-free period, and the LMWH can be discontinued 24h prior to the pain intervention. DOACs may be resumed 24h after interventional pain procedures. Alternatively, in individuals with

Table 5: Recommended time intervals for discontinuation and resumption of DOACs

DOAC	DOSE	Discontinue before neuraxial/ plexus block (ASRA 2018)	Resumption after epidural catheter removal/block		Discontinue before pain intervention (Interventional Spine & Pain Guidelines 2018)	
			Clean	Traumatic	High risk* medium risk†	Low‡ risk
Dabigatran	All doses	4-5d	6h	24h	5x T1/2	2×T1/2
	Renal Impairment	6d			4d	2d
Rivaroxaban	Prophylactic (5mg/d)	24h	6h	24h	5×T1/2	2×T1/2
	CrCl <50 mL/min	44-65h			3d	24-26h
	Therapeutic (>10 mg/d)	44-65h				
Apixaban	Prophylactic (2.5mg/d)	28h	6h	24h	5×T1/2	2×T1/2
	S. creatinine ≥1.5mg/dL or Age ≥80y or Body weight ≤60kg	40-75h			3d	26-30h
	Therapeutic (>5mg/d)	40-75h				
Edoxaban	Prophylactic (<30mg/day)	20-28h	6h	24h	5×T1/2	2×T1/2
	CrCl 15-49 mL/min	40-70h			3d	20-28h
	Body weight <60 kg Concomitant P-gp inhib.					
	Therapeutic (>30mg/d)	40-70h				
Betrixaban	All doses	72h	6h	24h	5×T1/2	2×T1/2
	CrCl <15-29 mL/min Concomitant P-gp inhib.	76-135h			6d	3d

DOAC – Direct acting oral anticoagulant; ASRA – American Society for Regional Anaesthesia; CrCl – Creatinine clearance; P-gp inhib – Permeability Glycoprotein inhibitors; T1/2 – Plasma half life. *High risk procedure category: Spinal cord stimulation trial and implant, dorsal root ganglion stimulation, intrathecal catheter and pump implant, vertebroplasty, kyphoplasty, percutaneous decompression laminotomy, epiduroscopy and epidural decompression; †Intermediate risk procedure category: interlaminar cervical, thoracic, lumbar and sacral (C, T, L, S) epidural steroid injection (ESIs), transforaminal ESIs (C, T, L, S), cervical facet medial branch nerve block (MBNB), radio frequency ablation (RFA), intradiscal procedures (C, T, L), sympathetic blocks (stellate, thoraic, splanchnic, celiac, lumbar, hypogastric), trigeminal and sphenopalatine ganglia blocks; ‡Low risk procedure category: peripheral nerve blocks, peripheral joint, musculoskeletal and trigger point injections including piriformis and sacroiliac joint injection, sacral lateral branch blocks, thoracic and lumbar facet MBNB and RFA, peripheral nerve stimulation trial and implant, pocket revision and implantable pulse generator or intrathecal pump replacement.

heightened risk of VTE, half the usual dose of DOAC may be ingested 12 hours following the pain procedure. Most of the case reports of spinal hematoma in patients on NOACs (2 from dabigatran, 7 from rivaroxaban and 1 from apixaban) describe spontaneous haematomas. Only in 2 patients (both on rivaroxaban), the timing of the rivaroxaban can be questioned. In the first patient, the hematoma was probably due to the additive anticoagulant effect of 40 mg enoxaparin and 7 mg warfarin stopped just 24 h before rivaroxaban. In the second patient, the interval between stoppage of rivaroxaban and removal of the catheter was 18 hours (2 half-lives) while that between epidural catheter removal and rivaroxaban resumption was 6 hours. At peak effect of rivaroxaban (2-3 h), the clot was barely stable.

SUMMARY

Anaesthesiology is reinventing itself to include perioperative medicine and an update on the fast-evolving field of DOACs is a felt need. PCC as reversal agents for DOAC do not hold much clinical value as per the available recent clinical trials. Idarucizumab and andexanet look promisingly effective but are priced prohibitively. Further trials on these novel reversal agents, after addressing the cost-factor, is the need of the hour. Dose of antidote for sustained reversal and pin-pointing the ideal time frame for re-initiation of DOACs after reversal (to avoid thrombotic complications) are other unresolved issues.

Two novel reversal agents for the "not so novel" DOACS have been approved off late by the FDA and a third one (ciraparantag) is in the pipeline. Owing to launch of specific reversal agents, anaesthesiologists can expect a tsunami of patients on DOAC prophylaxis presenting for elective or emergency surgery or with DOAC related bleeding complications or unrelated trauma. Idarucizumab and andexanet look promisingly effective but are priced prohibitively. The ideal dose of antidote for sustained reversal and pin-pointing the ideal time frame for re-initiation of DOACs after reversal (to avoid thrombotic complications) are unresolved issues yet.

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Conflicts of interest

There are no conflicts of interest.

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APPENDIX

Drug names with Manufacturer name in journal format

Dabigatran: (Pradexa™, Dabigatranetexilate, Boehringer Ingelheim Pharmaceuticals, Inc.)
Rivaroxaban: (Xarelto™, Rivaroxaban, Bayer AG, Germany)
Apixaban: (Eliquis™, Apixaban, Bristol-Myer Squibb company/Pfizer Inc., USA)
Andexanet: (AndexXa™, Andexanet alfa, Portola Pharmaceuticals, Inc., USA)
Edoxaban: (LiXiana™, Edoxaban Tosilate Hydrate, Daichi Sankyo Europe GmbH)
Betrixaban: (BevyxXa™, Betrixaban maleate, Portola Pharmaceuticals, Inc. USA)
Idarucizumab: (Praxbind™, Idarucizumab, Boehringer Ingelheim Pharmaceuticals, Inc.)