INTRODUCTION

Direct acting oral anticoagulants (DOAC) include dabigatran (Pradaxa; direct thrombin (Factor IIa) inhibitor) and rivaroxaban (Xarelto), apixaban (Eliquis), fondaparinux (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. In addition, rivaroxaban has obtained FDA approval for acute treatment of acute coronary syndrome. Dabigatran, rivaroxaban and apixaban 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 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 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
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 Avansure 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 dabigatran. 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]

| 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   | 15mg OD     | 5 mg BD  | 60mg OD  | 160mg single dose; Then 80mg OD |
| Discontinue before surgery (h) Bleeding risk high | 48-72 | 72 | 48 | 48 | 48 |
| Discontinue before surgery (h) 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) | Haemodialysis 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
Thromboelastography (TEG) and rotational thromboelastometry (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.

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

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

N.A – Not applicable; TGA – Thrombin generation assay; TEG – Thromboelastography ; ROTEM – Rotational thromboelastometry AUC – Area under curve; R – Reaction time; MA – Maximum amplitude; ACT – Activated clotting 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.
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 dabigatran, 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 dabigatran.[19] Pollack *et al.*[20] studied Idarucizumab 5g IV for dabigatran 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.

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**Figure 1:** Algorithm for monitoring DOACs

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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 | Dabigatran | Rivaroxaban Edoxaban Apixaban Betrixaban Fondaparinux 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 (≤10 or >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) [31] Interim analysis of 90 patients | Idarucizumab to reverse dabigatran | 51 | 5g IV Idarucizumab in patients with serious bleeding | nil | Prospective cohort study | Haemostasis restored for mean 11.4h Normal intraop. haemostasis in 33/36 pts. |
| Pollack (2017) [31] REVERSE AD (phase III study) | Idarucizumab to reverse dabigatran in bleeding and emergency surgery patients | 503 | 5g IV Idarucizumab in patients with serious bleeding (intracranial, gastrointestinal, intraperi-tonal, intra-pericardial, intra-articular, 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. |
| 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 Japanese males | 32 | Single idarucizumab doses (1, 2, 4 or 8 g [n=6/dose group]) or placebo (n=2/dose group). 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) | Placebo | Two-part, phase I, placebo-controlled, double-blind, rising-dose RCT | 6/60 dabirucizumab- treated subjects developed treatment-emergent ADAs (positive titers from 1-40) Dabirucizumab 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 |
| Glund et al (2017) [34] | Idarucizumab to reverse dabigatran 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 | 35 | Baseline FPA noted; Dabigatran (220 mg BD for 4d); FPA noted on day 3 and 4       | 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 92%↓ in anti-FXa activity compared to 18%↓ in controls Unbound rivaroxaban↓ by 23.4 ng/ml vs 4.2 ng/ml in controls Anti-Fxa levels (Biomarker endpoint) |
| ANNEXA Trial Part I (Crowther et al)[37] | Andexanet bolus to reverse apixaban and rivaroxaban | 70 | Apixaban followed by 400mg andexanet                                              | Placebo instead of andexanet | RCT                  | AntiFXa levels (Biomarker endpoint) |
| ANNEXA-R Trial (Crowther et al)[38] | Efficacy and safety of andexanet in rivaroxaban reversal in 50-75y old patients | 39 | Rivaroxaban 20 mg OD for 4d followed by either andexanet bolus (800 mg) + andexanet infusion 960mg 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 Xa 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)[41]    | 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 until 12 h 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). |

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at the wound-site. In a Japanese study on 80 healthy males (Yasaka et al.),[32] 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 idarucizumab). 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 persistent 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.[33] (where 2-g idarucizumab sufficed for persistent reversal in Caucasians) double the dose (4-g idarucizumab) was needed for persistent 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 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 haemodilysis 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,\(^{39}\) 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 $56000 per 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 gut and can be followed by charcoal filtration. Haemodialysis is partially successful in removing Dabigatran from the circulation, but is ineffective for anti-Factor Xa DOACs whereas therapeutic plasma exchange maybe employed for urgent rivaroxaban reversal. 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. Recombinant activated factor VII can also be empirically used.

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. 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. (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. and Levi et al. 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 s 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,
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. 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 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 which are divisible into high, intermediate and low bleeding risk categories. 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
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.)

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