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Measurement and Reversal of the Direct Oral Anticoagulants

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Abstract

Direct oral anticoagulants (DOACs) offer non-inferior efficacy and improved safety compared to vitamin K antagonists (VKAs) for prevention and treatment of venous thromboembolism and prevention of stroke and systemic embolism in non-valvular atrial fibrillation. Unlike VKAs, DOACs do not require routine laboratory monitoring of anticoagulant effect and dose adjustment. In certain situations, however, laboratory assessment of anticoagulant effect may be desirable. Here we review the utility of currently available assays for assessment of DOAC effect and recommend an optimal assessment strategy for each drug, including calibrated dilute thrombin time or ecarin-based assays for dabigatran and calibrated anti-Xa activity assays for the factor Xa inhibitors. We also discuss reversal strategies, both specific and non-specific, for each drug, including the preferential use of idarucizumab for reversal of dabigatran and two agents, andexanet and ciraparantag, currently under development for reversal of rivaroxaban, apixaban and edoxaban.

Keywords

Apixaban; Dabigatran; DOACs; Edoxaban; Measurement; Reversal; Rivaroxaban

1.0 Introduction

Since 2010, four direct oral anticoagulants (DOACs) have become available in North America, Europe, and elsewhere. Dabigatran, a direct thrombin inhibitor, and rivaroxaban, apixaban and edoxaban, direct factor Xa inhibitors, are approved in various jurisdictions for treatment and secondary prevention of venous thromboembolism (VTE), prevention of stroke and systemic embolism in non-valvular atrial fibrillation (AF), and prevention of VTE

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Conflict of Interest Statement

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after major orthopedic surgery. DOACs offer non-inferior efficacy and a number of advantages over vitamin K antagonists (VKAs), including decreased bleeding,[1] lack of requirement for routine laboratory monitoring of anticoagulant effect and dose adjustment based on laboratory measurement, simplified perioperative management, and fewer drug and dietary interactions. On the basis of these advantages, both the American College of Chest Physicians (ACCP)[2] and the Anticoagulation Forum[3] released updated guidelines in 2016 recommending DOACs over VKAs for patients with non-cancer associated VTE.

The DOACs are not without limitations, however, including difficulty measuring and interpreting anticoagulant effect and, for the anti-Xa agents, lack of a clear reversal strategy. In this article we review current data regarding laboratory measurement of anticoagulant effect and reversal strategies for these agents.

2.0 General Principles of Measurement

Liquid chromatography/tandem mass spectrometry (LC-MS/MS) is the reference standard method for DOAC measurement.[4] LC-MS/MS has been used to define expected steady-state plasma DOAC levels in pharmacokinetic studies (Table 1).[5–8] These studies show that DOAC levels vary widely from peak to trough. For twice daily drugs such as dabigatran and apixaban, there is approximately a 2-fold difference between the median peak and trough concentrations. For once daily drugs such as rivaroxaban and edoxaban, the difference is 8 to 10-fold. While comparisons of median peak and trough values provide a sense of the expected variation in drug levels within an individual patient, percentile ranges shed light on the striking interindividual variation in DOAC levels. For instance, peak dabigatran levels vary by a factor of ~7 from the 5^{th} to 95^{th} percentile. Trough rivaroxaban levels vary 14.5-fold over this range (Table 1).

Although limited data linking DOAC levels with clinical outcomes have been published,[9, 10] therapeutic ranges over which clinical outcomes are optimized have not been defined for these agents. In lieu of therapeutic ranges, we use the concept of “on-therapy range.”[11] We define the on-therapy range for a given DOAC at a given dose as the interval delineated by the 5^{th} percentile trough and the 95^{th} percentile peak plasma level. Care must be taken with timing of these measurements, particularly as trough levels may be misleading if drawn well after the time of the next expected dose. By definition, the large majority of patients in steady state will have levels in the on-therapy range at any time during treatment. Very low drug levels below the 5^{th} percentile trough may be regarded as below the ontherapy range and very high levels above the 95^{th} percentile peak as above the on-therapy range.

2.1 Indications for DOAC measurement

Laboratory measurement of the anticoagulant effect of DOACs is not routinely recommended, but may be helpful in certain circumstances. In the emergent setting, such as trauma, urgent/emergent surgery and recent stroke within the thrombolytic therapy window, rapid assessment of anticoagulant effect has the potential to guide clinical management. In other circumstances, such as the frail elderly, patients with extremes of body weight, impaired or hyper-renal function, overdose, gastrointestinal malabsorptive disorders, and

suspected drug interactions, assessment of plasma levels may be desirable to detect potentially below on-therapy or above on-therapy levels.[12]

2.2 Characteristics of an ideal assay

To measure DOAC levels accurately, an assay result (or a mathematical adjustment of the assay result) must show a high degree of linearity with drug concentration, as measured by LC-MS/MS and have minimal inter- and intra-assay variability. Because there are situations when it may be desirable to measure below on-therapy, on-therapy, or above on-therapy levels, an ideal assay should show linearity across a broad range of drug concentrations. The assay should be sufficiently sensitive to the lowest clinically relevant concentrations of drug. It should also be highly specific for the drug of interest such that it is not influenced by other anticoagulants or by biological variables known to affect coagulation assays such as lupus anticoagulants and clotting factor deficiencies. Finally, because there may be an emergent indication for measurement, an assay should be available 24 hours a day, 7 days a week, with a short turnaround time.

Unfortunately, no currently available assay meets these idealized criteria. As discussed in detail below, widely available assays such as the prothrombin time (PT) and activated partial thromboplastin time (APTT) do not show sufficient sensitivity and linearity. Specialized assays have enhanced operating characteristics, but are not widely available.[13]

3.0 General Principles of Reversal

Indications for DOAC reversal include serious bleeding and need for an emergent, unplanned procedure. Appropriate use of any reversal strategy requires careful consideration of risks (including thrombosis) and benefits and should take into consideration the necessity of reversal and time since last dose, as well as drug-specific half-life. For bleeding patients, supportive care measures including local control, hemodynamic support, transfusions and early involvement of interventionalists should be utilized and may be all that is needed to control most bleeds. Use of reversal agents should be reserved for cases of serious or life-threatening hemorrhage in which supportive measures are inadequate and for emergent procedures that cannot be delayed.

Strategies for DOAC reversal include drug removal, bypass agents (which activate coagulation downstream of or through pathways unaffected by the drug in question), and specific reversal agents that sequester and neutralize the anticoagulant. Examples of these strategies are shown in Table 2. Removal strategies have important limitations. Because DOACs are absorbed rapidly from the gastrointestinal tract, activated charcoal is generally only useful for impeding absorption when administered within 1–2 hours of ingestion. Hemodialysis removes approximately half of circulating dabigatran over 1.5–5 hours[14] but placement of a dialysis catheter may be problematic in an anticoagulated patient and a rebound increase in plasma dabigatran levels may be observed as redistribution from the extravascular space occurs. The factor Xa inhibitors are not efficiently removed by hemodialysis because they are more heavily protein-bound.

The mechanism by which bypass agents may promote hemostasis in DOAC-treated patients is unclear since DOACs inhibit coagulation downstream from the points at which some or all bypass agents activate coagulation. For example, dabigatran inhibits thrombin, which is downstream from factor VIIa, the active ingredient in recombinant factor VIIa. Evidence on bypass agents for DOAC reversal is conflicting and is limited to in vitro analyses, animal bleeding models, and healthy volunteer studies.[15] Use of bypass agents for reversal of DOACs in bleeding patients has not been systematically investigated. Specific sequestration agents are either recently approved (e.g. idarucizumab) or in clinical development (e.g. andexanet alfa, ciraparantag). As detailed below, these agents correct coagulation parameters in DOAC-treated patients within minutes of infusion. More data are required to define their safety and efficacy.

4.0 Dabigatran

Dabigatran is a direct thrombin inhibitor. The half-life of dabigatran in individuals with normal renal function is approximately 12–14 hours with 80% renal elimination. The standard dose of dabigatran for both AF and VTE in patients with normal renal function is 150 mg BID. In some jurisdictions, a dose reduction to 110 mg BID is recommended in patients judged to be at increased risk for bleeding including those ≥ 75 years of age. In the US, a dose of 75 mg BID is recommended in AF patients with a creatine clearance (CrCl) of 15 to 30 mL/minute.[16] The on-therapy range in AF patients taking dabigatran 150 mg twice daily for at least one week is 31–443 ng/mL (Table 1).[5, 17]

4.1 Measurement of Anticoagulant Effect

4.1.1 Thrombin time—The thrombin time (TT) is exquisitely sensitive to dabigatran. Depending on which reagent is used, dabigatran concentrations as low as 25 ng/mL (below the on-therapy range) may result in an unmeasurable TT (i.e. plasma will not clot after addition of thrombin).[18–21] The TT is therefore not useful for quantification of dabigatran. The TT has one important use: a normal value excludes clinically relevant levels of dabigatran. The converse, however, is not true. The TT may be prolonged in the presence of clinically relevant or inconsequential levels of dabigatran.

4.1.2 Dilute thrombin time—The inordinate sensitivity of the TT may be overcome by diluting the plasma sample with normal plasma. This method, known as the dilute thrombin time (dTT), may be modified from in-house thrombin time assays or purchased commercially (HEMOCLOT, HYPHEN BioMed, Neuvillesur-Oise, France). When the dTT is calibrated for dabigatran measurement, it demonstrates high linearity (R^2 0.96–1.0) with drug levels determined by LC-MS/MS across and above the on-therapy range, with weaker correlation at low (< 50–100 ng/mL) and high (> 500ng/mL) dabigatran levels.[22–25] The dTT is not widely available. In a survey of coagulation laboratories in Australia and New Zealand, only 9 of 592 centers offered the assay.[26]

4.1.3 Ecarin-based assays—Ecarin is a metalloproteinase that cleaves prothrombin to an active intermediate called meizothrombin. Dabigatran inhibits meizothrombin, much as it inhibits thrombin, a property which can be exploited for measurement of dabigatran in

ecarin-based assays. Two such assays are available. In the ecarin clotting time (ECT), ecarin is added to citrated blood or plasma and time to clot formation is measured. In the ecarin chromogenic assay (ECA), meizothrombin generation is measured with a chromogenic substrate in the presence of an excess of purified prothrombin.[27, 28] Both the ECT and ECA demonstrate high sensitivity to dabigatran with strong linear correlation (R^2 0.94–1.0) across and above the on-therapy range.[29, 30] As with the dTT, correlation is weaker at extreme drug levels (< 40ng/mL or > 940ng/mL).[29, 31] The ECT and ECA are not widely available and are limited by lack of standardization and variability in sensitivity to dabigatran among different lots of ecarin.[24, 30]

4.1.4 Activated partial thromboplastin time—The APTT exhibits a curvilinear relationship with dabigatran concentration with a flattening of the dose-response curve at dabigatran levels greater than 200–300 ng/mL.[17] This precludes accurate quantification of dabigatran, particularly at higher concentrations.

Commercial APTT reagents show marked variation in their sensitivity to dabigatran. In a study of 9 different APTT methods, the APTT of plasma spiked with dabigatran 120 ng/mL ranged from 26.0 to 91.9 s.[32] As recommended by the International Society on Thrombosis and Haemostasis, coagulation laboratories should perform dose-response studies using calibration standards to define the sensitivity of their particular method to dabigatran.[33] A caveat of this approach is that in vitro dose-response curves may not simulate the relationship between coagulation tests and dabigatran levels in ex vivo samples.[23]

The APTT is insufficiently sensitive to dabigatran to exclude on-therapy drug levels. Multiple studies have demonstrated normal APTT results in the presence of trough-like dabigatran concentrations.[22, 29, 34, 35] In one study of ex vivo plasma samples from patients taking dabigatran 150 mg BID at steady state, 18% of subjects had a normal APTT at trough.[29]

4.1.5 Prothrombin time—The PT is even less sensitive to dabigatran than the APTT and may be normal in the presence of on-therapy or even above on-therapy dabigatran concentrations. In an ex vivo study of samples from 35 patients taking dabigatran 150 mg BID, the PT was normal in 29% of samples at trough.[29] As with APTT reagents, commercial thromboplastin reagents vary widely in their sensitivity to dabigatran. In a study involving 71 laboratories, the PT of a sample spiked with dabigatran 300 ng/mL ranged from 15.7 to 50.2 s, depending on the reagent.[32] Another study of AF patients demonstrated that the international normalized ratio (INR) remained within normal limits at concentrations as high as 400 ng/mL (near the upper limit of the on-therapy range).[22]

4.1.6 Other Assays—Clotting time may be prolonged on rotational thromboelastometry (ROTEM) in the presence of therapeutic levels of dabigatran, but this is nonspecific and rarely accompanied by changes in other ROTEM parameters.[36] Dose-dependent prolongation of kaolin test reaction time and time to maximum rate of thrombus generation may be expected on thromboelastography (TEG) in the presence of concentrations between 50 and 500 ng/mL, though the TEG platform is limited by high interindividual variability and lack of specificity.[37] The Dilute Russell Viper Venom Time (DRVVT) is also prolonged

in the presence of dabigatran, but often overestimates the true plasma level.[38] Urine-based assays may be useful for identifying whether the patient has taken dabigatran recently when history is not available, but correlate poorly with plasma drug levels.[39] A chromogenic anti-IIa assay is also under investigation and appears to correlate with HPLC-MS/MS (r^2 0.81) but data are limited and the assay is not widely available.[40]

4.2 Reversal

4.2.1 Idarucizumab—Dabigatran is currently the only DOAC with an approved specific reversal agent. Idarucizumab was approved for use in the United States and Europe in late 2015. It is a humanized monoclonal antibody fragment with high affinity for dabigatran, administered in two 50 mL bolus infusions no more than 15 minutes apart for a total fixed dose of 5 g.[40, 41] It was approved based on interim results of the REVERSE-AD trial,[42] a multicenter open-label prospective cohort study which enrolled 90 patients judged to require reversal of dabigatran effect. Arm A included patients with overt, uncontrollable or lifethreatening bleeding. Arm B included patients requiring surgery or other invasive procedures that could not be delayed for at least 8 hours and for which normal hemostasis was required. The study did not include a placebo control arm due to ethical concerns of offering an inactive treatment to patients with life-threatening bleeding. The primary efficacy outcome was normalization of coagulation parameters. Secondary endpoints included time to cessation of bleeding in Arm A and quality of intraoperative hemostasis in Arm B.

Normalization of the dTT and/or ECT occurred in 88–98% of patients and was demonstrated within minutes of idarucizumab infusion. Median time to cessation of bleeding in Arm A was 11.4 hours and could not be judged in some patients. In the absence of a control group, it is not possible to determine whether idarucizumab hastened achievement of hemostasis. In Arm B, intraoperative hemostasis was judged to be normal in 92% of subjects. Idarucizumab was well-tolerated. There were no infusion reactions and only one thrombotic event within 72 hours of infusion. Idarucizumab did not induce thrombin generation in healthy volunteers.[41]

Two important observations from the REVERSE-AD trial are worth highlighting. A baseline blood sample was drawn at study entry and sent to a central laboratory for analysis. The results were not available to investigators at the time subjects were enrolled in the study. Post hoc analyses of these baseline samples revealed that the dTT and ECT were normal in 24% and 10% of patients at enrollment, respectively. These data suggest that up to a quarter of subjects enrolled in REVERSE-AD may have had clinically insignificant dabigatran levels at study entry and were therefore unlikely to benefit from idarucizumab. Also noteworthy, 6 (7%) and 16 (18%) patients had an increase in dabigatran levels at 12 and 24 hours after administration of idarucizumab, respectively. These late increases in plasma dabigatran concentration may reflect redistribution of dabigatran from extravascular tissues into the intravascular compartment after idarucizumab has been cleared from the circulation. They raise the possibility that some patients could be at risk for delayed bleeding and would benefit from readminstration of idarucizumab. Of course availability of specialized assays such as the dTT or ECT are necessary for identifying patients who may benefit from initial administration or redosing of idarucizumab. In centers where these assays are not

immediately available, such decisions are challenging and must be made on an empiric basis.

The REVERSE-AD study is ongoing with a target enrollment of 500 subjects (clinicaltrials.gov identifier NCT02104947). More data on the efficacy and safety of idarucizumab are expected upon its completion.

4.2.2 Other Reversal Strategies—Hemodialysis removes roughly 50% of dabigatran over 1.5–5 hours,[14] but is often impractical because of bleeding risk with catheter placement and time required between line insertion and completion of dialysis. Data on the use of bypass agents for dabigatran reversal is limited to in vitro, animal, and healthy volunteer studies. The safety and efficacy of these agents in bleeding patients is unknown.

With the availability of idarucizumab, the role of hemodialysis and bypass agents in dabigatran reversal is limited to patients who continue to bleed despite administration of idarucizumab or situations in which it is unavailable. All patients should be managed with maximal supportive measures. Idarucizumab should be reserved for those with critical bleeding (i.e. organ- or life-threatening bleeding) or an emergent procedure (e.g. trauma surgery, management of an acute abdomen, etc.) that cannot be delayed for at least 8 hours. If bleeding persists after administration, continued attempts at supportive care as well as careful consideration of any other possible etiologies of coagulopathy (disseminated intravascular coagulation, liver injury, etc.) are warranted. In the case of delayed rebleeding, additional doses may be considered, although there is currently scant evidence to support this practice. Resumption of anticoagulation should be considered on a case by case basis. The relatively short half-life (45 minutes)[41] renders idarucizumab unlikely to interfere with resumption of dabigatran.

5.0 Anti-Xa Agents

5.1 Rivaroxaban

Rivaroxaban is a competitive inhibitor of free and clot-based factor Xa. The half-life is approximately 6–13 hours in patients with normal kidney function with 36% renal clearance. On-therapy levels range from 6–419 ng/mL in pharmacokinetic studies of patients taking 20 mg daily in steady-state (Table 1).[6,43] In patients with acute VTE, rivaroxaban is administered at a dose of 15 mg BID for the first three weeks of treatment. In patients with AF and in patients with VTE who have completed three or more weeks of treatment, 20 mg daily is recommended. A reduced dose of 15 mg daily is recommended for AF patients with renal insufficiency. A dose of 10 mg daily is recommended for thromboprophylaxis after major orthopedic surgery.[44]

5.2 Apixaban

Apixaban is a direct inhibitor of factor Xa which is metabolized by multiple routes with minimal dependence on renal function. Drug half-life is approximately 12 hours and on-therapy levels range from 41–321 ng/mL in pharmacokinetic studies of AF patients receiving 5 mg twice daily (Table 1).[5,45] Apixaban is administered at a dose of 10 mg twice daily in patients with acute VTE and reduced to 5 mg BID after the initial seven days of

therapy. Further de-escalation to 2.5 mg BID is appropriate for secondary VTE prevention in some patients whose event was ≥ 6 months ago. The standard dose is 5 mg BID in AF patients. A reduced dose of 2.5 mg BID is appropriate in AF patients with two or more of the following: age ≥ 80 years, body weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dL. A dose of 2.5 mg BID is also recommended for VTE prophylaxis following total knee and hip arthroplasty.[46]

5.3 Edoxaban

Edoxaban is a direct inhibitor of factor Xa with a half-life of approximately 10–14 hours. Roughly 50% of metabolites are renally cleared and on-therapy levels range from 10–250 ng/mL in AF patients taking 60 mg daily (Table 1).[7,12] The standard dose is patients with AF and VTE is 60 mg. A reduced dose of 30 mg daily is used in VTE patients with a weight ≤ 60 kg and in VTE or AF patients with a CrCl of 15–50 mL/minute. Edoxaban in contraindicated in AF patients with a CrCl > 95 mL/minute.[47]

5.4 Measurement of Anticoagulant Effect

5.4.1 Anti-Xa activity—Anti-Xa activity assays calibrated with drug-specific standards show a high degree of linear correlation (R^2 0.83–1.0) across the on-therapy range for rivaroxaban, apixaban, and edoxaban.[48–51] Correlation is somewhat reduced at below on-therapy and above on-therapy levels for rivaroxaban and apixaban[35, 49] and at levels > 200–300 ng/mL for edoxaban.[52, 53] Drug-specific calibration increases accuracy for purposes of quantification, but is likely not necessary to exclude clinically relevant levels of drug and is not widely available.[54] In a 2013 survey of coagulation laboratories, 300 centers reported offering an anti-Xa assay for measurement of heparin, but only 9 had established standard curves for quantification of rivaroxaban.[54] In the absence of a drug-specific calibration curve, use of a curve calibrated for unfractionated or low molecular weight heparin is a reasonable surrogate for excluding drug levels ≥ 25–30 ng/mL.[53] Rivaroxaban and apixaban exhibit similar anti-Xa activity by in vitro methods, suggesting that a common calibrator may be feasible. Commercial edoxaban calibrators are not yet available.

5.4.2 Prothrombin time—Rivaroxaban prolongs the PT in a concentration-dependent manner. PT reagents vary markedly in their sensitivity to rivaroxaban. One study demonstrated coefficients of variation as high as 29.7% when local PT reagents were used to measure rivaroxaban concentrations in spiked plasma samples. This was reduced to a maximum of 7.5% when a central reagent was used.[55] Interassay variability was reduced by use of an international sensitivity index specific for rivaroxaban, but not by conversion to an INR used for warfarin monitoring.[56] Sensitivity indices to factor Xa inhibitors have not been defined for most PT reagents. The PT has insufficient sensitivity to exclude on-therapy levels of rivaroxaban. In a study of ex vivo samples from patients taking rivaroxaban 20 mg daily at steady state, 19% to 93% of samples at trough had a normal PT, depending on the reagent.[57]

A linear relationship is also noted between edoxaban concentration and the PT. As with rivaroxaban, the PT is insufficiently sensitive to edoxaban to exclude low on-therapy levels and wide variation in sensitivity is observed among different thromboplastin reagents.[58]

Concentrations of edoxaban ranging from 97 to 406 ng/mL are required to double the PT from baseline, depending on the reagent.[59, 60]

The PT is less sensitive to apixaban than it is to rivaroxaban and edoxaban, probably because apixaban binds to factor Xa more slowly.[61] Most PT reagents are inadequately sensitive to detect not only on-therapy, but even above on-therapy levels of apixaban with minimal change in values up to concentrations of 200 ng/mL in both patient and spiked samples.[35, 62]

Laboratories should conduct dose-response studies to define the in vitro sensitivity of their PT method to rivaroxaban and apixaban.[33] Unfortunately, edoxaban calibration standards are not yet commercially available for this purpose. As with dabigatran, in vitro dose-response curves may not simulate the relationship between coagulation tests and rivaroxaban levels in ex vivo samples.[23] The same limitation is likely to apply to apixaban- and edoxaban-spiked samples as well, though systematic comparisons with ex vivo samples have not been published.

5.4.3 Activated partial thromboplastin time—The APTT is less sensitive than the PT to factor Xa inhibitors and, in general, does not have a role in the laboratory assessment of anticoagulation with these agents. A normal APTT does not exclude on-therapy drug levels of rivaroxaban. In a study of ex vivo samples from patients taking rivaroxaban 20 mg daily, 56% to 89% of samples had a normal APTT at trough, depending on the APTT reagent.[57] A normal APTT does not exclude on-therapy levels of edoxaban and apixaban and may not exclude above ontherapy levels of these drugs. Plasma samples needed to be spiked to edoxaban concentrations of 304 to 400 ng/mL to double the APTT from baseline.[60] Apixaban levels of 500 ng/mL (well above the on-therapy range) only marginally increased the APTT.[63]

5.4.4 Other Assays—As with dabigatran, ROTEM and TEG may be anticipated to reflect the presence of on-therapy or above on-therapy levels of Xa inhibitors, but are nonspecific and lack precision.[37, 64] DRVVT assays also demonstrate prolongation in the presence of anti-Xa inhibitors but, as with dabigatran, tend to overestimate drug concentration.[38] Concentrations of rivaroxaban and apixaban as measured by urinary assays are 5- to 15-fold higher as compared to plasma.[65]

5.5 Reversal

5.5.1 Andexanet Alfa and Ciraparantag—To date, no specific reversal agents for factor Xa inhibitors have received regulatory approval, but two agents are under clinical investigation.

Andexanet alfa is a recombinant factor Xa protein that lacks catalytic and membrane-binding activity, rendering it unable to participate in coagulation, but retains the ability to bind and sequester factor Xa inhibitors.[66] Andexanet was demonstrated to decrease anti-Xa activity in 101 rivaroxaban- and apixaban-treated healthy volunteers enrolled in separate double-blind placebo-controlled studies (ANNEXA-A and ANNEXA-R).[56] Initial reduction in anti-Xa activity was seen minutes after bolus injection, but was short lived due to the short half-life of andexanet (~1 hour). When the bolus was followed by a continuous infusion,

suppression of anti-Xa activity persisted for the duration of the infusion. A similar timeline was seen for correction of thrombin generation indices. Andexanet was well-tolerated. There were no serious or severe adverse events. One subject in ANNEXA-A and one subject in ANNEXA-R had infusion reactions (urticaria). There were no thrombotic events, though a possible prothrombotic signal was detected in some subjects with increased D-dimer and prothrombin F1.2 levels. Increases in thrombin generation, in some cases 1–2 standard deviations above the mean, were also observed. These changes may result from binding of andexanet to the endogenous anticoagulant protein, tissue factor pathway inhibitor and/or other mechanisms.[66] Clinical implications of this prothrombotic signal in the inherently high-risk patients who are prescribed anticoagulation remain uncertain. More data on the efficacy and safety of andexanet will be provided by an ongoing prospective single arm trial of andexanet in patients with acute major bleeding on direct or indirect anti-Xa agents (clinicaltrials.gov identifier NCT02329327). Andexanet is currently under review for accelerated approval by the US Food and Drug Administration.

Ciparantag (PER977) is a small synthetic cationic molecule that binds non-covalently to oral factor Xa inhibitors as well as dabigatran, unfractionated heparin, low molecular weight heparin, and fondaparinux. It has been demonstrated to effectively reverse the anticoagulant effect of rivaroxaban, apixaban and edoxaban in animal bleeding models and to normalize the whole blood clotting time in edoxaban-treated healthy volunteers.[67] Clinical efficacy in bleeding patients has yet to be evaluated.

One of the challenges posed by ciraparantag is its effect on laboratory testing. Ciraparantag binds to contact pathway activators (e.g. Celite, Kaolin) and in vitro anticoagulants (e.g. citrate, EDTA, heparin), thus interfering with assays that use these reagents. A point-of-care whole blood clotting time that overcomes these limitations is in development for measurement of anticoagulants in the presence of ciraparantag.[58]

5.5.2 Bypass agents—Until specific reversal agents become available, bypass agents may be considered in the setting of critical bleeding when supportive measures are inadequate. High quality data on these approaches are lacking. Available evidence on use of bypass agents for reversal of factor Xa inhibitors is derived from in vitro studies, ex vivo studies of healthy volunteers, and animal studies, all of which have key limitations and are unlikely to fully simulate in vivo bleeding in patients.[15]

Prothrombin complex concentrates (PCC) are plasma-derived concentrates of the vitamin K-dependent clotting factors. Four-factor PCCs contain factors II, VII, IX, and X as well as protein C and protein S. Three-factor PCCs are similar in composition, but contain little or no factor VII. PCCs have been shown to correct the PT and some abnormal thrombin generation parameters in healthy subjects treated with rivaroxaban and apixaban.[68–70] Four-factor formulations appear to be more effective as compared to three factor PCCs for correcting the PT (2.5 s reduction vs. 0.6 s reduction in PT in a head-to-head comparison in healthy, rivaroxaban-treated volunteers), but less effective for correcting thrombin generation indices in patients taking rivaroxaban.[70, 71] Data on efficacy for restoration of hemostasis are limited, but reduced bleeding duration was demonstrated with PCC as compared to placebo in edoxaban-treated healthy volunteers undergoing punch biopsy.[72] Data on use of PCC in

DOAC-treated bleeding patients are currently lacking, as are data on risk of thromboembolism, although a 4% incidence of VTE has been reported with the use of PCC for reversal of VKA.[73]

Activated PCC (APCC) is a plasma-derived concentrate of factors II, VII, IX, and X, which are activated during the manufacturing process. APCC has been demonstrated to correct the PT and some thrombin generation indices in healthy subjects treated with rivaroxaban, but an effect on anti-Xa activity was not demonstrated.[74] In theory, measurement of anti-Xa activity may be unreliable in this setting because the test reagent, factor Xa, is supplemented through infusion of APCC. In volunteers treated with apixaban, APCC induced normalization of thrombin generation indices and partial correction of the PT and APTT.[69, 70] As with PCC, data on use of APCC in the management of DOAC-treated bleeding patients is lacking. Hemophilia patients treated with APCC have a thrombotic rate of 4.05 per 10^5 infusions,[75] but thrombotic risk has not been assessed in subjects on DOAC therapy.

Recombinant human VIIa (rhVIIa) corrected the PT and some thrombin generation indices in healthy volunteers treated with rivaroxaban, but had no effect on anti-Xa activity.[76, 77] In subjects treated with apixaban, rhVIIa improved some thrombin generation indices as well as the PT and APTT.[70] No data in bleeding subjects are available. Off-label use of rhFVIIa was associated with an increased risk of arterial thrombosis compared with placebo in a meta-analysis of randomized clinical trials.[78]

6.0 Summary

DOAC levels vary widely within individual patients from peak to trough and between different patients (Table 1). Although routine laboratory monitoring of anticoagulant activity is not indicated, there are special situations in which laboratory measurement may be desirable. Suggested assays for detection and quantification of DOACs are shown in Table 3. For patients taking dabigatran, a normal TT excludes the presence of clinically relevant levels of drug, although a prolonged TT may occur in the absence of clinically significant levels. The dTT or ecarin-based assays are recommended for measurement of drug levels. For patients treated with direct factor Xa inhibitors, an anti-Xa activity assay calibrated with the drug of interest is the test of choice for measurement of anticoagulant effect. If an anti-Xa assay is unavailable, the PT may be considered as a screening test for rivaroxaban or edoxaban, with the understanding that a normal PT may not exclude on-therapy levels of drug, particularly if an insensitive reagent is used. The PT and APTT have insufficient sensitivity to be useful in patients taking apixaban. Interpretation of coagulation assays in patients taking a DOAC is summarized in Table 4.

Although DOACs are associated with a reduced rate of bleeding compared with VKAs, reversal may be indicated in special situations including serious bleeding or need for an emergent procedure. In DOAC-treated patients with bleeding, first-line therapy consists of supportive care measures including local control, volume resuscitation, transfusion support, and early involvement of interventionalists. In many cases, these measures alone will suffice. In cases of severe or life-threatening bleeding, reversal strategies including removal,

bypassing agents and sequestration may be employed (Table 2). In the case of dabigatran, reversal with idarucizumab should be added to supportive care. In patients on rivaroxaban, apixaban, or edoxaban with severe or life-threatening bleeding, we suggest reversal with 4-factor PCC 50 IU/kg despite a lack of high-quality evidence and the potential for increased thrombotic risk. Specific reversal agents for factor Xa inhibitors including andexanet alfa and ciraparantag are in development and may ultimately replace PCC and other non-specific reversal strategies.

Key challenges lie ahead in the measurement and reversal of the DOACs. In the current landscape, the most suitable assays for DOAC measurement are not widely available and the most accessible assays are not very good. Further work is needed to develop assays that can accurately measure DOAC levels at or near the point-of-care. The dawn of specific reversal agents for the DOACs is now upon us. More data are needed on the efficacy and safety of these drugs and how to select appropriate patients to receive them.

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Practice Points

- Calibrated dilute thrombin time and ecarin-based assays are the tests of choice for measurement of dabigatran.
- Calibrated anti-Xa activity assays are the tests of choice for measurement of rivaroxaban, apixaban, and edoxaban.
- Most DOAC-related bleeding can be managed with supportive care alone.
- Idarucizumab is the agent of choice if reversal of dabigatran is required.
- We suggest PCC 50 IU/kg for reversal of factor Xa inhibitors, though high quality evidence is lacking.
- Specific reversal agents for factor Xa inhibitors are in clinical development.

Research agenda

- Develop assays that accurately measure DOACs and can be made widely available.
- Define the efficacy and safety of specific reversal agents for the DOACs.

Table 1

Steady-State Peak and Trough Levels of Approved DOACs

Drug	Dose	Time to Peak	Median Peak (5th to 95th percentile)	Median Trough (5th to 95th percentile)	References
Dabigatran	150 mg BID	1–2 hours	184 ng/mL (64–443)	90 ng/mL (31–225)	4, 16
Rivaroxaban	20 mg daily	2–4 hours	270 ng/mL (189–419)	26 ng/mL (6–87)	6, 34
Apixaban	5 mg BID	3–4 hours	171 ng/mL (91–321)	103 ng/mL (41–230)	5, 36
Edoxaban	60 mg daily	1–2 hours	170 ng/mL (120–250)[a]	22 ng/mL (10–40)[a]	7, 11

[a]Interquartile range

Table 2

DOAC reversal strategies

Strategy	Example
Removal	Activated charcoal Hemodialysis (dabigatran only)
Bypassing	Prothrombin complex concentrate Activated prothrombin complex concentrate Recombinant factor VIIa
Sequestration	Idarucizumab (dabigatran only) Andexanet alfa (factor Xa inhibitors) Ciraparantag

Table 3
Preferred assays for detection and quantification of DOACS

Purpose of testing	Dabigatran		Xa Inhibitors	
	Test of Choice	Alternative	Test of Choice	Alternative
Exclusion of on-therapy or above on-therapy levels	TT, dTT, ECT, ECA	APTT*	Anti-Xa assay	PT*
Quantification	dTT, ECT, ECA	None	Anti-Xa assay	None

*Tests are inadequately sensitive to conclusively rule out clinically relevant anticoagulant effect.

Table 4
Interpretation of coagulation assays in DOAC-treated patients

Below on-therapy, on-therapy, and above on-therapy ranges are listed in Table 1 and relate specifically to the doses shown in Table 1.

Test	Dabigatran		Xa Inhibitors	
	Normal	**Abnormal/Prolonged** *	**Normal**	**Abnormal/Prolonged** *
APTT	Does not exclude on-therapy levels	On-therapy or above on-therapy levels likely present	Does not exclude on-therapy levels	On-therapy or above on-therapy levels likely present
PT	Does not exclude on-therapy levels	On-therapy or above on-therapy levels likely present	Does not exclude on-therapy levels	On-therapy or above on-therapy levels likely present
TT	Excludes clinically significant levels	Below on-therapy, on-therapy, or above on-therapy levels likely present	Not Useful	Not Useful
dTT	Likely excludes clinically significant levels	May be used to quantify drug levels	Not Useful	Not Useful
Ecarin-based assay	Likely excludes clinically significant levels	May be used to quantify drug levels	Not Useful	Not Useful
Test	**Dabigatran**		**Xa Inhibitors**	
	< Lower Limit of Quantification	**Analytical Measurement Range**	**< Lower Limit of Quantification**	**Analytical Measurement Range**
Anti-Xa assay (UFH/LMWH calibrated)	Not Useful	Not Useful	Likely excludes clinically significant levels	May be used to estimate drug levels
Anti-Xa assay (DOAC calibrated)	Not Useful	Not Useful	Likely excludes clinically significant levels	May be used to quantify drug levels

* Alternative etiologies for coagulopathy should also be considered (e.g. disseminated intravascular coagulation, liver injury, etc.)

DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; UFH, unfractionated heparin