Assessing and Reversing the Effect of Direct Oral Anticoagulants on Coagulation

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Direct oral anticoagulants have improved anticoagulation options for many patients, but they present challenges regarding monitoring and reversal of anticoagulant activity. Anesthesiologists are likely to encounter patients taking direct oral anticoagulants in a variety of clinical settings including scheduled procedures, emergency procedures, trauma, and critical care units. This review focuses on the pharmacokinetics of direct oral anticoagulants, testing methods to assess anticoagulant activity, and the use of reversal agents, to give the practicing anesthesiologist the necessary knowledge to manage situations encountered in clinical practice.

The direct oral anticoagulants are approved and prescribed for a number of indications to prevent and treat thromboembolic disease. Large phase III randomized controlled trials comparing direct oral anticoagulants to either vitamin K antagonists or low-molecular-weight heparin have demonstrated similar or better safety and efficacy for many indications. The direct thrombin inhibitor dabigatran and the Xa inhibitors apixaban, rivaroxaban, and edoxaban have been approved by the U.S. Food and Drug Administration and European Medicines Agency for treatment of venous thromboembolism and prevention of stroke in nonvalvular atrial fibrillation.[1–4] Dabigatran, apixaban, and rivaroxaban are approved for venous thromboembolic prophylaxis after hip and knee replacement surgery.[1–3] Rivaroxaban and apixaban are approved for extended venous thromboembolic prophylaxis.[2,3] Rivaroxaban and an additional Xa inhibitor, betrixaban, are Food and Drug Administration–approved for extended venous thromboembolic prophylaxis in medically ill, hospitalized patients.[2,5] Low-dose rivaroxaban at 2.5 mg twice daily in combination with low-dose aspirin has been approved by the Food and Drug Administration to reduce the risk of cardiovascular death, myocardial infarction, and stroke in patients with chronic coronary artery disease or peripheral artery disease.[2]

Direct Oral Anticoagulant Properties

The direct oral anticoagulants have rapid onset of anticoagulant activity, reaching peak anticoagulant effect within 0.5 to 4 h of ingestion. The half-lives are also relatively short and considerably shorter than the pharmacodynamic effects of vitamin K antagonists. In patients with normal renal function, the half-life of each direct oral anticoagulant can predict the duration of anticoagulant effect, with prolonged anticoagulation occurring with impaired renal function. The direct oral anticoagulants have variable renal clearance with the greatest (80%) for dabigatran (table 1).[1] The direct oral anticoagulants have short half-lives, averaging 12 h (table 1).[2–4] The exception is betrixaban with a half-life of 19 to 27 h, with effects lasting up to 4 days after the last ingestion.[5,6] Delayed clearance and elevated drug concentrations can also be seen as a consequence of drug–drug interactions, particularly with drugs that strongly inhibit the P-glycoprotein transporter and cytochrome P450 systems.[7]

Direct Oral Anticoagulant Plasma Concentrations

The predictable pharmacokinetics of the direct oral anticoagulants and their wide therapeutic window allow for standard fixed dosing without monitoring as with vitamin K antagonists. Mean peak and trough concentrations have been reported (table 1), but they are not targeted or validated levels because clinical studies of efficacy and safety were not based on achieving specific plasma levels. As a result, specific monitoring of anticoagulant levels to optimize care has yet to be determined.[8,10] Patients treated with rivaroxaban or apixaban for venous thromboembolism may have higher levels during the initial 7 to 21 days of treatment when dosing is higher, an important consideration when these patients present requiring emergency surgery.[2,3]

Clinically Relevant Drug Levels

Although monitoring direct oral anticoagulant levels has been suggested to optimize efficacy and safety for subpopulations of patients with atrial fibrillation or venous thromboembolism, determining the plasma concentration at presentation with bleeding or need for emergent surgery serves a different purpose. Studies identifying the threshold concentration that is clinically relevant resulting in impaired hemostasis have not been performed. Expert consensus opinion has empirically set thresholds based on the aggregate knowledge of trough levels, but there is significant

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Table 1. Pharmacokinetic Properties and Laboratory Tests for Direct Oral Anticoagulants[1-7]

	Pharmacokinetic Properties					Laboratory Testing					
	Time to Peak, h	Half-life, h	Peak Concentration, ng/ml	Trough Concentration, ng/ml	Renal Clearance, %	Routine Assay	Limitations of Routine Assay	Sensitive Assay	Limitations of Sensitive Assay	DOAC Specific Assay	Limitations of DOAC Specific Assay
Dabigatran	2	12–17	AF*: 175 VTE†: 175	AF: 91 VTE: 60	80	aPTT	Insensitive at high and low dabigatran concentrations	TT	Positive test may be seen with drug levels that do not impact hemostasis	Dabigatran drug level using calibrator‡	Variable availability; not FDA/EMA-approved
Apixaban	3	~12	AF: 171 VTE: 132	AF: 103 VTE: 63	27	PT	Insensitive, sensitivity lowest for apixaban	Anti-Xa level for UFH/LMWH	Positive test may be seen with drug levels that do not impact hemostasis	Chromogenic anti-Xa level with Xa inhibitor specific calibrators	Variable availability; not FDA/EMA-approved
Betrixaban	3–4	19–27	36§	N/A	11						
Edoxaban	1–2	10–14	AF: 170 VTE: 234	AF: 36 VTE: 19	50						
Rivaroxaban	2–4	5–13	AF: 246 VTE: 270	AF: 44 VTE: 26	67						

Appropriate tests are categorized as routinely available and direct oral anticoagulant (DOAC) specific. Median plasma drug concentrations are derived from randomized clinical trials, with data from almost 30,000 patients randomized to a direct oral anticoagulant for stroke prevention in atrial fibrillation (AF) and 13,000 in the venous thromboembolism (VTE) trials. Patients were on full intensity dose unless they had decreased renal function.

*Denotes data from AF clinical trials. †Denotes data from VTE clinical trials. ‡Data from VTE prophylaxis clinical trial. §Dilute thrombin time (TT), ecarin clotting time, or chromogenic direct thrombin assay, all with calibrators to determine dabigatran concentration.

aPTT, activated partial thromboplastin time; EMA, European Medicines Agency; FDA, Food and Drug Administration; LMWH, low-molecular-weight heparin; N/A, not applicable; PT, prothrombin time; UFH, unfractionated heparin.

uncertainty about these threshold levels, because no validation studies have been performed. For patients who present with bleeding, direct oral anticoagulant concentrations of more than 50 ng/ml are considered high enough to warrant use of a reversal agent, whereas the threshold for major surgery has been set at a maximum of 30 ng/ml.[11,12] However, for individual patients, these threshold values may be inappropriate, and clinical judgment is required.[13]

Measurement of Direct Oral Anticoagulant Concentration

Routine Coagulation Tests

Clinical coagulation studies such as prothrombin time (PT), activated partial thromboplastin time (PTT), thrombin time, and anti-Xa levels are routinely determined for heparins, but they have limited utility for quantitative measurements of direct oral anticoagulants. Most institutions do not have rapidly available thrombin time or anti-Xa testing. The threshold for detection of low or high direct oral anticoagulant concentrations with PT and activated PTT assays depends on the assays and are insensitive to clinically relevant direct oral anticoagulant concentrations, especially at the level of 50 mg/ml, which has been suggested as the threshold for use of specific reversal agents, or at 30 ng/ml, which is the upper limit that has been suggested for safely proceeding to surgery.[11,12] With dabigatran, a prolonged activated PTT is an indication of an anticoagulation effect, but a normal activated PTT can be seen with levels in the 50 ng/ml range[7,13,14]; also, the activated PTT will plateau at high concentrations.[15,16] For Xa inhibitors, the PT may be elevated, but multiple factors influence this test, especially in patients after traumatic injury.[15,16] Sensitivity to PT measurements also varies across different laboratories based on reagent use.[14] Even with the same reagents, sensitivity varies with different Xa inhibitors and is lowest with apixaban—patients can have significant apixaban concentrations inhibiting hemostasis yet a normal PT.[15,17,18]

For dabigatran, the thrombin time is so sensitive that even inconsequential levels will cause prolongation.[14] The thrombin time allows a dabigatran effect to be excluded but provides no insight into the degree of anticoagulation. Anti-Xa levels calibrated for heparins serve a similar role for Xa inhibitors. Anti-Xa levels are highly sensitive to the presence of a Xa inhibitors, but the result—reported in units for heparins—is poorly correlated with Xa inhibitor concentration and varies with reagents.[19,20] However, the anti-Xa assay used for low-molecular-weight heparin can be used as a qualitative assay to exclude the presence of a Xa inhibitors, as with the thrombin time with dabigatran. If the level is less than 0.1 U, it can be assumed that no drug activity is present. This approach has been used to allow the administration of thrombolysis to stroke patients who would otherwise have been ineligible.[21]

Caution should be used when interpreting the results of any anticoagulant tests, because all coagulation tests, either routine clinical labs or direct oral anticoagulant specific (with some exceptions), can be affected by other anticoagulants including unfractionated heparin, low-molecular-weight heparin, or the direct thrombin inhibitors such as argatroban or bivalirudin or by inherited or acquired factor deficiencies.

Direct Oral Anticoagulant Specific Assays

The gold standard assay that determines quantitative Xa inhibitor levels, liquid chromatography–tandem mass spectroscopy, is impractical for routine clinical use. The specific assays furthest along in development include a dilute thrombin time and the use of an ecarin-based chromogenic assay for dabigatran and anti-Xa assays using chromogenic substrates with drug-specific calibrators for Xa inhibitors that can be used to determine peak and trough values, such as between 50 and 500 ng/ml, with a different set able to detect direct oral anticoagulant concentrations of less than 50 ng/ml.[22–24]

Although assays to quantitate direct oral anticoagulants are commercially available and have European Conformity certification, none have received regulatory approval in the United States; many U.S. commercial and academic center clinical labs are running the tests for "research purposes."[25] (Personal oral communication July 2018 from Thomas Lee Ortel, M.D., Ph.D., Division of Hematology in the Department of Medicine, Duke Cancer Institute, Durham, North Carolina and personal written communication October 24, 2019 from Elizabeth Vancott, M.D., Massachusetts General Hospital, Harvard Medical School Boston, Massachusetts.) The turnaround time for tests sent to a commercial vendor is days to weeks, whereas even in academic clinical labs, the turnaround time can be long enough to prohibit their use in emergency care situations. Like the PT and activated PTT assays, the specific assays require processing time to separate plasma for testing. Some centers have demonstrated that results can be obtained within 35 min in real-world settings,[26] although even a 35-min turnaround time may not be appropriate. Point-of-care tests currently in development using whole blood or urine samples report results within 10 min, allowing rapid detection of the presence of a direct oral anticoagulant to determine whether reversal is needed.[27–29]

Clinical Factors

Trauma patients and those with life-threatening bleeding may require reversal agents if suspected or determined to have impaired coagulation, regardless of the need for surgery. Additional development of and increased familiarity with rapid direct oral anticoagulant testing along with the potential use of reversal agents preprocedure are needed. Until such testing is available, the following approaches may help guide clinical decisions regarding timing of procedures and need for potential reversal.

Timing of Last Ingestion

The full anticoagulant effect is not likely to be present if the last ingestion was greater than 24 h and the metabolic

pathways of elimination are normal. Prolonged anticoagulation is expected in patients with acute kidney injury or with impaired baseline renal function. If possible, delaying surgery for 24 to 48 h after last ingestion if the patient is on full-dose anticoagulant allows for drug clearance. For patients on reduced anticoagulation doses, such as for extended venous thromboembolic prophylaxis, delaying for 12 to 24 h may be appropriate depending on the bleeding risk of the procedure.[30] Although guidelines continue to support the use of activated charcoal if the last ingestion has been within 2 to 3 h of presentation,[24] aspiration risk must be considered.

Assessing the Need for Reversal Agents

The need and availability of an anticoagulant reversal should be assessed. If the patient does not have life-threatening bleeding and can be supported with routine clinical care or does not have an emergent need for high-risk invasive procedures, administration of a reversal agent is not indicated.[11]

Specific Reversal Agents

The specific reversal agents for dabigatran and the anti-Xa inhibitors idarucizumab and andexanet alfa, respectively, have Food and Drug Administration and European Medicines Agency approval, based on multicenter prospective single arm open label trial results. The lack of a comparator arm in both trials is considered a flaw in trial design by some; however, when the trials were designed, it was deemed to be unethical to randomize bleeding patients to placebo.[31] Differences in the trial designs led to different label indications, with andexanet restricted to patients with life-threatening bleeding,[13] whereas idarucizumab is also approved for use to reverse dabigatran anticoagulation before surgery.[29]

Idarucizumab

The humanized monoclonal antibody idarucizumab binds dabigatran with high affinity, removing it from circulation.[32] It is packaged as two vials of 2.5 g that can be rapidly infused in 5 to 10 min.[33] In clinical trials, all patients received the 5-g dose, because this dose was deemed effective for dabigatran concentrations as high as the 99th percentile in the atrial fibrillation trial.[32] In bleeding patients, idarucizumab resulted in median time to hemostasis of 2.5 h; 68% had cessation of bleeding within 24 h.[32] For the 43% requiring emergent surgery or invasive procedures but not bleeding, the median time to surgery after administration of the first vial was 1.6 to 3.3 h.[32,34] Hemostasis was judged to be normal by 93% of the surgeons in the 195 patients treated with idaucizumab. In a subanalysis, idarucizumab resulted in normal hemostasis in 91% of the 140 major surgery cases, which included 49 abdominal, 45 orthopedic, 34 vascular, and 8 neurosurgical cases.[34] These patients also received a variety of blood products. In a small number of patients, resurgence of dabigatran levels and anticoagulant effect was evident at 12 to 24 h,[32–37] important to consider in the postoperative period. Some data support the use of subsequent doses of idarucizumab for high-risk patients. Hemodialysis provides an alternative method for dabigatran elimination either alone or in combination with idarucizumab.[35,38,39]

Andexanet Alfa

Andexanet alfa is a factor Xa decoy molecule with high affinity for Xa inhibitors lacking catalytic activity[40] with approval for use in patients with life-threatening bleeding taking apixaban or rivaroxaban. Enrollment in the phase 3 trial was limited to patients with life-threatening bleeding (64% intracranial, 26% gastrointestinal) with no plans for surgery within 12 h. Andexanet alfa is not approved for use to reverse anticoagulation before surgery.[41] The numbers of patients treated with edoxaban, betrixaban, and low-molecular-weight heparin were insufficient to assess efficacy and safety.[41] Because of its short half-life, it is given as a bolus followed by a 2-h continuous infusion.[40] High- or low-dose selection for both the bolus and the infusion is based on time since last ingestion, dose, and type of Xa inhibitor.[40] In the phase III trial, this dosing resulted in excellent or good hemostasis in 82% of patients at 12 h after infusion.[41] Two hours after the continuous infusion is completed, the anticoagulant activity is the same as if the patient received placebo, a factor to consider in cases of ongoing bleeding, intentional overdose, or high bleeding risk.[41]

Although andexanet is not approved for use to allow emergency surgery, reports in bleeding patients treated with andexanet who subsequently required surgery have been published.[42] Twelve patients underwent invasive procedures after andexanet, 75% were treated with andexanet to control the index bleeding event. Neurosurgical procedures included endoventricular drain placement (2), craniotomy (3), and C-spine decompressive laminectomy (2). The administration of andexanet was timed so that the first incision was made after initiating or completing the bolus in eight patients. The procedure was completed before the end of the continuous infusion in eight cases. Two cases required intraoperative support with a combination of different products including erythrocyte, plasma, cryoprecipitate, and prothrombin complex concentrates. As a result of this experience, two important perspectives need to be considered. Andexanet reverses the Xa inhibition of any anticoagulant that binds to Xa, including unfractionated heparin. The cardiac surgical patient requiring cardiopulmonary bypass required 90,000 units of unfractionated heparin to achieve and maintain the target activated clotting time.[43] Patients subsequently requiring heparin anticoagulation such as percutaneous coronary intervention will require larger doses of heparin to achieve adequate anticoagulation or an alternative anticoagulant.[42,43,44] The standard anti-Xa assay cannot be used to gauge the reversal effect of because of technical limitations.[45] As a reminder, andexanet alfa's suppression of anticoagulation is maximal over the first 2 h and gone at 4 h, potentially a problem for lengthy procedures, postoperative management, or long delays in initiating procedures after

andexanet administration. The efficacy and safety of andexanet to reverse Xa inhibitor anticoagulant effects in patients without bleeding before emergency surgery or procedural intervention has not yet been investigated in a formal clinical trial.

Nonspecific Reversal Agents

Although specific reversal agents have been studied in prospective clinical trials, they may not be available at all facilities. The reversal of Xa inhibitors poses the biggest challenge because they are more frequently prescribed than dabigatran. Strategies to deal with bleeding patients evolved using prothrombin complex concentrate before the availability of andexanet alfa. Several reports and consecutive case series have used prothrombin complex concentrate at 25 to 50 U/kg or a fixed dose of 1,500 to 2,000 units for patients with life-threatening bleeding with good hemostasis achieved in 68 to 69%; however, it must be noted that in many of the cases, it was up to the local provider to determine whether reversal was indicated and what dose should be used.[24,46,47] In one study, patients were enrolled only after receiving prothrombin complex concentrates.[47] The effectiveness of prothrombin complex concentrate to reverse Xa inhibitors is debated, because no direct comparison with andexanet has been performed. A retrospective study assessed the use of prothrombin complex concentrates for reversing warfarin in 264 patients compared to 40 patients taking apixaban and 40 taking rivaroxaban. No statistically significant differences in overall mortality at 30 days were seen, although there were numeric differences with 30-day mortality for patients on warfarin: 22.3% compared to 32.5% and 33.5% for patients on rivaroxaban and apixan.[48] Whether prothrombin complex concentrate reverses the anticoagulant effect or simply provides more hemostatic substrate is unknown. Although *in vitro* data demonstrate that prothrombin complex concentrate can restore coagulation tests to normal in the setting of a Xa inhibitors in volunteers,[49] there may be a dose-dependent effect[50] or lack of efficacy on punch biopsy bleeding with high Xa inhibitor concentrations.[51] A systematic review of the use of prothrombin complex concentrate to reverse Xa inhibitors in the setting of major bleeding could not reach a definitive conclusion regarding efficacy.[52]

Fresh frozen plasma has no role in reversing direct oral anticoagulants, because the concentration of clotting factors is insufficient to overcome the anticoagulation effect even with high volume. Although agents other than idarucizumab to reverse dabigatran have shown good hemostasis in *in vitro* models or small studies,[9,53] idarucizumab has a long duration of effect, demonstrated perioperative efficacy, and safety; it should be used when reversal of dabigatran is needed. Although activated prothrombin complex concentrates have been studied in animal models and healthy volunteers,[54,55] the associated prothrombotic risk *versus* benefit of any procoagulant should be considered.

Clinical guidelines recommend idarucizumab as first-line therapy to reverse dabigatran and andexanet alfa to reverse rivaroxaban and apixaban, although some societies, such as the American Society of Hematology (Washington, D.C.), give both agents a conditional recommendation.[23,56–58] Cost considerations have played a large role in the decision about whether to add specific reversal agents to the formulary in the United States. The price of standard-dose andexanet can be 5 to 10 times more than four-factor prothrombin concentrates or idarucizumab, depending on total dose and agent. Clinicians should know what is available for use at their institution and be familiar with institutional guidelines for use.

Clinical Situations

Elective Surgery

For planned procedures, direct oral anticoagulants can be held for 1 to 2 days depending on the bleeding risk of the procedure.[12] Based on published data, elective surgery should be postponed for patients who did not stop direct oral anticoagulant for the appropriate time period, and reversal agents should not be given to facilitate elective surgery. In most patients, bridging with heparin or low-molecular-weight heparin does not alter outcomes but may be associated with an increased risk of bleeding as noted.[12] In a large well conducted study in atrial fibrillation patients, a standard perioperative approach was used, with plasma concentrations of direct oral anticoagulants measured after holding the prespecified times of 1 day for patients with normal renal function undergoing low–bleeding risk procedures and 2 days for high–bleeding risk procedures.[12] Drug levels were not known at the time of the procedure. Only 4.5 to 12.9% of patients had immediate preoperative direct oral anticoagulant concentrations greater than the empirically determined threshold of 50 ng/ml when held for 1 day for low-risk procedures, whereas 85.3 to 98.9% of patients holding for 2 days before a high–bleeding risk procedure had an immediate preoperative level of less than 30 ng/ml. Depending on the direct oral anticoagulants and time held, 0.55 to 21.9% of patients had levels between 30 and 49.9 ng/ml. For patients with decreased renal function, hold times were longer. An important caveat is that these time frames are not in agreement with American Society of Regional Anesthesia and Pain Medicine (Pittsburgh, Pennsylvania) recommendations for neuraxial procedures, which recommend holding for 3 to 5 days depending on anticoagulant and renal function.[59] Because 9.9 to 21.9% of patients with normal renal function who held for 1 day for low–bleeding risk procedures had drug concentrations between 30 and 49.9 ng/ml, holding for longer time periods seems prudent if neuraxial anesthesia is to be used. Rapid turnaround time direct oral anticoagulant levels would be useful in this situation.[60]

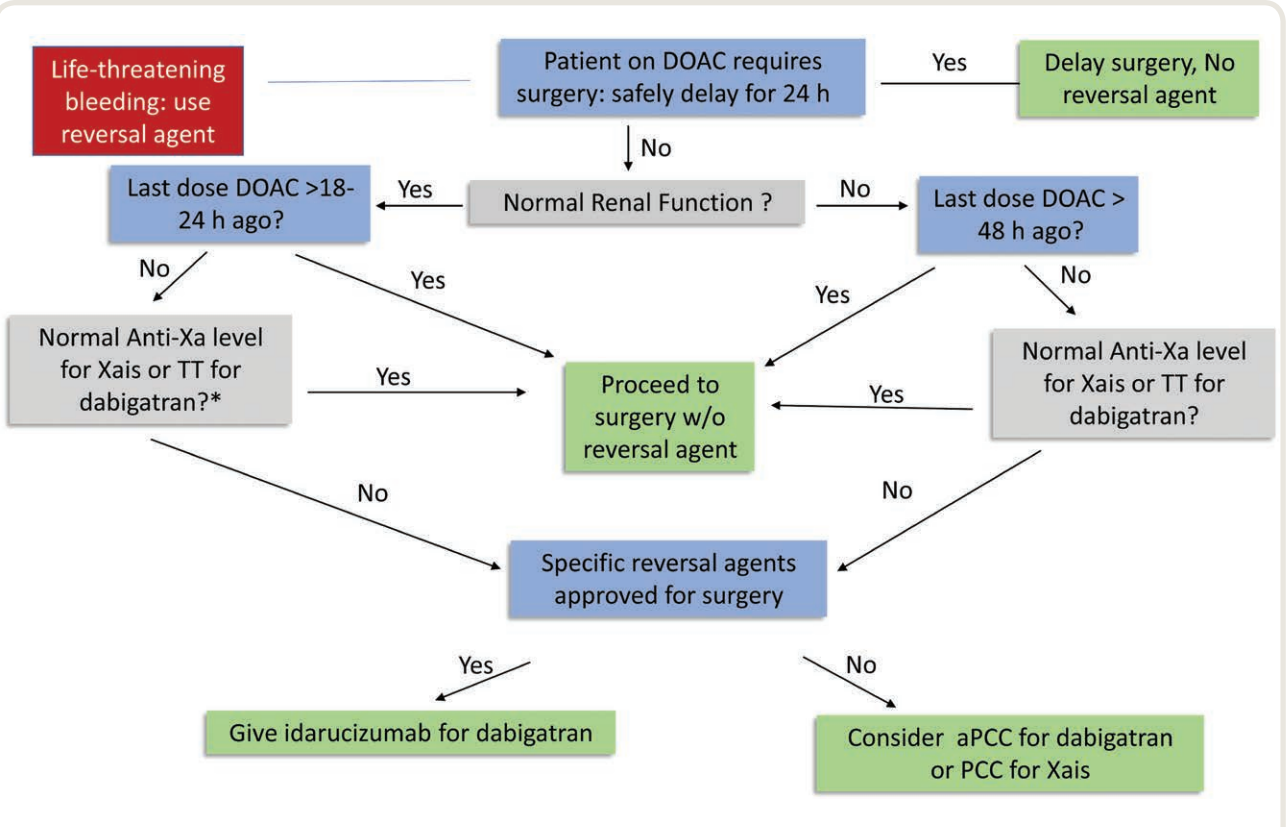

Fig. 1. Clinical decision pathway for direct oral anticoagulants (DOAC) reversal. The steps in this pathway can be followed to assess patients taking direct oral anticoagulants to determine if the patient can proceed to surgery or undergo significant invasive procedures with minimal impairment of hemostasis by direct oral anticoagulants, or whether reversal agents use should be considered. For patients with life-threatening bleeding, reversal agents should be used first according to label. *If anti-Xa level or thrombin time is not available 24 h per day, administer reversal agent based on renal function and time since last ingestion. aPCC, activated prothrombin complex concentrate; PCC, prothrombin complex concentrate; TT, thromboplastin time; Xais, factor Xa inibitors.

Urgent and Emergent Surgery

For patients with ingestion of direct oral anticoagulants within the last 24 h for whom surgery cannot be postponed, an assessment of drug activity should ideally be attempted to determine the necessity of reversing anticoagulation (table 1). Some patients must proceed to the operating room before lab results are available, in which case clinical judgment incorporating timing of last direct oral anticoagulant ingestion, renal function, and the type of procedure should be used to determine whether to reverse anticoagulation. Results that return after the procedure has started are still useful to guide care. For high–bleeding risk procedures or surgery in a critical site, empiric use of reversal agents should be considered, keeping in mind the caveats about use.[24,56–58]

Trauma and Clinically Significant Bleeding

In patients with trauma or life-threatening bleeding and recent or unknown time of direct oral anticoagulant ingestion, specific approved reversal agent based on clinical trial data and endorsement by society guidelines should be considered.[24,32,41,56–58] The use of assays for qualitative drug effect, if they can be obtained rapidly such as within 30 min, may prevent unnecessary reversal agent administration.[8,21,54,60] Timing of such testing could be incorporated into workflow, such as samples sent to the lab while patient is getting scanned for in intracranial hemorrhage with results available when scanning is finished. Because specific direct oral anticoagulant level testing with rapid turnaround time is not currently available in most U.S. institutions, the tests outlined in table 1 can be used to determine whether there is anticoagulant activity present. If rapid results from these tests are not available, then clinical judgment is required regarding use of specific reversal agents, focusing on life-threatening bleeding first and the necessity of surgery second.

Conclusions

Managing patients taking direct oral anticoagulants who unexpectedly present with the need for emergency surgery can be challenging. Priority should be given to managing life-threatening bleeding in the setting of direct oral anticoagulant coagulopathy followed by evaluation for the need

for surgery. Figure 1 outlines a potential decision tree that can be considered for management based on available data. Although the use of reversal agents informed by drug levels is ideal practice, the current limitations of testing should not limit administration or cause delay in cases of life-threatening bleeding or emergency surgery. In high-acuity situations, immediate use of reversal agents with dosing based on the specific direct oral anticoagulant and clinical guidelines should be considered.[24,56–58] In situations where approved reversal agents are not available, the use of alternatives can be considered based on limited data. Improved testing and new reversal agents are in development; until they are available, the information in this review should help guide clinical practice.

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Competing Interests

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