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Review

Discontinuation and management of direct-acting anticoagulants for emergency procedures☆,☆☆,★

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ABSTRACT

Patients taking direct oral anticoagulants (DOACs) who then need an emergency invasive procedure require specialized management strategies. Appropriate patient evaluation includes assessment of the current anticoagulation state, including timing of the last dose. DOACs require particular coagulation assays to measure anticoagulation levels accurately, although standard coagulation screening tests may provide qualitative guidance. Specialty societies have endorsed general recommendations for patient management to promote hemostasis in anticoagulated patients requiring surgery or other invasive procedures. These include general stopping rules (such as ≥24 hours for low-risk procedures and ≥48 hours for high-risk surgery with normal renal function) for elective procedures. Bridging therapy when oral anticoagulant treatment is interrupted has recently been questioned, depending on the clinical scenario. Novel agents for the reversal of DOAC-induced anticoagulation have recently been developed. Idarucizumab, a humanized monoclonal antibody fragment that selectively binds dabigatran, was recently approved for clinical use in patients with life-threatening or uncontrolled bleeding, and for patients requiring emergency interventions. Idarucizumab can streamline the pre- and periprocedural anticoagulation management of dabigatran-treated patients, as it provides fast, complete, and sustainable reversibility. Andexanet alfa is an inactive, decoy factor Xa (FXa) molecule that binds FXa inhibitors, and ciraparantag is a synthetic molecule designed to bind fractionated and unfractionated heparins, and each of the currently approved DOACs. As clinical development of the additional anti-FXa-specific anticoagulant reversal agents proceeds, the respective role of each in the management of emergency bleeding events and invasive procedures will be better defined, and it is hoped they will make important contributions to patient care.

When administered to reduce the risk of stroke in patients with nonvalvular atrial fibrillation (NVAF), the direct oral anticoagulants (DOACs) are also associated with clinically important reductions in the frequency of major bleeding, including life-threatening bleeding events and, especially, intracranial bleeding, when compared with patients receiving warfarin [1-4]. Still, these events do occur, and the clinician may be faced with a need to reverse anticoagulation resulting from a bleeding event or need for emergency surgery.

In such situations, the timing of the last DOAC dose allows estimation of the time required for elimination from the plasma, and is therefore an important consideration. Plasma concentrations of anticoagulants generally decrease to minimally effective levels within 3-5 half-lives, but the exact timing may vary depending upon the agent and the patient's overall clinical status. Recommendations based on pharmacokinetic and pharmacodynamic studies have been made about the optimal time for stopping DOAC-related anticoagulation [5-8]. In addition, a patient's renal function is an important consideration for elimination of most of the DOACs, especially dabigatran, because lower creatinine clearance (CrCl) rates are associated with elevated serum concentrations [9,10]. Potential interactions with concomitant medications must also be considered, although for the most part, the DOACs are reported to have fewer drug—drug interactions than do the vitamin K antagonists (VKAs) [5-8].

The management of patients who are treated with DOACs and later require an emergency procedure due to trauma or other emergencies continues to evolve with the development of experience and definitive management strategies. This brief review will discuss topics known to impact clinical care in DOAC-treated patients who require surgery or invasive procedures, including assessing the current anticoagulation

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effect, their periprocedural management, current protocols for temporary discontinuations in DOAC therapy, and the utility of particular DOAC reversal agents.

1. Measurement of Anticoagulation with the DOACs

Routine monitoring of anticoagulation is not generally recommended or required for patients treated with any of the approved DOACs. However, in patients who are in need of an emergency surgical or invasive procedure, an on-demand assessment of the current level of anticoagulation effect is important [11,12]. It should be kept in mind that key information to guide the interpretation of results from individual coagulation tests in these patients includes timing of the last dose of the specific anticoagulant and the patient's renal function [11].

There are a number of general considerations when assessing the anticoagulation effects of individual DOACs, including the individual drug in question, and the relevant coagulation assay that should be used to assess its effects. The international normalized ratio (INR) was developed to monitor anticoagulation associated with the VKAs, and is not as reliable an assay for the assessment of the anticoagulant effects of some factor Xa (FXa) inhibitors (apixaban) or dabigatran [13]. The prothrombin time (PT) may provide a potential indication of the anticoagulant effects of FXa inhibitors, but the assay is relatively insensitive [13]. For example, the PT is not sufficiently sensitive to reliably measure apixaban levels in therapeutic ranges [14,15]. Similar results have been reported when the PT assay has been used to assess anticoagulation with rivaroxaban, where PT results correlated poorly with rivaroxaban concentrations [16]. In addition, results of this assay can vary depending on the batch of individual reagents used to process the samples [13,16].

Specialized anti-FXa assays, which are distinct from those used for low-molecular-weight heparin (LMWH), have been developed recently and are recommended for quantitative measurements of rivaroxaban and apixaban [17,18] and edoxaban [7]. However, for optimal performance and accuracy, these assays will require individual calibration to each specific drug [13,16].

The PT assay is generally not sensitive enough to reliably measure clinically relevant dabigatran concentrations, but responses may be increased with high levels of dabigatran [15]. A normal activated partial thromboplastin time assay can be used as a screening tool to determine a potential anticoagulation effect due to dabigatran, although this is not the most sensitive assay available [13]. The thrombin time is a sensitive assessment of dabigatran anticoagulation, but this assay can overestimate dabigatran levels at high concentrations and is, therefore, most useful as a qualitative tool [13]. The dilute thrombin time (dTT), as measured by the HEMOCLOT assay (HYPHEN BioMed, Neuville-sur-Oise, France), best correlates with dabigatran plasma concentrations and is, therefore, a more reliable measure of the anticoagulant effect of dabigatran. However, this assay is not currently approved in the United States [13,19]. In the European Union, measuring dTT with the calibrated HEMOCLOT thrombin inhibitor assay is recommended as the tool of choice for assessing the anticoagulation effect of dabigatran [20]. Also in EU, the ecarin clotting time assay is often used in a fashion similar to the dTT to assess anticoagulant effects of dabigatran [21]. A summary of the coagulation assays for each approved agent is provided in Table 1[5-8,17,20,22].

2. Periprocedural Management

A recent analysis from the Randomized Evaluation of Longterm anticoagulation therapY (RE-LY) study (dabigatran vs VKA in patients with NVAF) reported similar rates of perioperative bleeding and thromboembolism in warfarinand dabigatran-treated patients [23]. Similar results have also been reported in studies of "real-world" populations at high risk for thromboembolic and bleeding events for dabigatran [24] and rivaroxaban [25] in general clinical practice.

Clinical decisions about the management of DOAC-treated patients who require an invasive procedure should be based in part on the patient's renal function, the length of time from last DOAC administration, concomitant medications that the patient is taking, and their overall risk of procedural bleeding [26]. For example, in patients with moderate renal impairment (CrCl 30-50 mL/min), medications such as the P-glycoprotein (P-gp) inhibitors dronedarone or systemic ketoconazole may increase exposure to dabigatran and potentially lead to hemostatic dysfunction [5]. Similar concerns have been raised for co-administration of FXa inhibitors and agents that are strong dual inhibitors of Cytochrome P450 3A4 and P-gp (eg, ketoconazole, itraconazole, ritonavir, and clarithromycin for apixaban) [6]; and diltiazem, verapamil, dronedarone, and erythromycin for rivaroxaban [8]. Co-administration of P-gp inhibitors such as amiodarone, cyclosporine, dronedarone, erythromycin, ketoconazole, quinidine, and verapamil has been reported to increase edoxaban exposure [7]. Concomitant use of rifampin, a P-gp inducer, is also contraindicated in patients treated with edoxaban [7].

Recommendations for DOAC treatment interruption have been made previously, especially for surgical patients, and are summarized below. The European Society of Anaesthesiology and the French Working Group on Perioperative Haemostasis (GIHP) recommend interruption of DOAC therapy ~24 hours (2 or 3 half-lives) prior to a procedure that carries a low bleeding risk, but 5 days prior to an intervention with a medium or high bleeding risk, dependent on the DOAC and factors such as the patient's renal function [27,28]. The European Heart Rhythm Association's guide to DOAC use suggests a general stopping rule of ≥24 hours for low-risk procedures and ≥48 hours for high-risk surgery. However, longer delays are suggested for patients with a CrCl of <80 mL/min taking dabigatran and those with a CrCl of 15-30 mL/min who are administered FXa inhibitors [26]. Other expert consensus documents recommend at least a 24—48-hour discontinuation window for a particular DOAC based on the specific agent, renal function, and high vs low risk of procedural bleeding [29]. Specific guidance for discontinuation and bridging for each approved agent are presented in Table 2[5-8,30-33]. It is important to keep in mind that additional studies to assess standardized perioperative management protocols in DOAC-treated patients are ongoing, and the results from these studies are expected to refine our understanding of this clinical challenge [29,34].

Table 1
Appropriateness of Assays for Monitoring the Activity of Direct Oral Anticoagulants [5-8,17,20,22]

Drug	Quantitative Assays (Provide an Estimate of Anticoagulant Drug Levels)	Qualitative Assays (Indicate Presence or Absence of Drug Effect)	Not Recommended
Direct FXa inhibitors (apixaban, rivaroxaban, or edoxaban)	Specific, calibrated anti-FXa assays	Prothrombin time assay obtained in seconds with sensitive reagents	Insensitive prothrombin time, activated partial thromboplastin time, dilute thrombin time or thrombin time assays, or heparin-specific assays such as the activated clotting time assay
Direct thrombin inhibitor (dabigatran)	HEMOCLOT dilute thrombin assay, ecarin clotting time	Activated partial thromboplastin time, thrombin time, activated clotting time assay	Chromogenic anti-FXa assays

FXa = factor Xa.

Table 2
Discontinuation Guidance

	Apixaban [6,30,31]	Dabigatran [5,30,32]	Edoxaban [7,30,31]	Rivaroxaban [8,30,33]
Discontinuation for surgery or other interventions	In cases where there is a low risk of bleeding or when a potential bleeding event would be in an easily controlled noncritical location, apixaban should be discontinued at least 24 h prior to elective surgery or invasive procedures. In cases with a moderate or high risk of unacceptable or clinically significant bleeding, apixaban should be discontinued at least 48 h prior to elective surgery or invasive procedures.	Dabigatran should be discontinued 1-2 d (CrCl of ≥50 mL/min) or 3-5 d (CrCl of <50 mL/min) in advance of any invasive or surgical procedures. For patients who require complete hemostasis, such as those undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port, longer discontinuation times should be considered. Use of idarucizumab, a specific dabigatran anticoagulation reversal agent, should be considered in cases where emergency surgery or urgent procedures are needed.	Edoxaban should be discontinued at least 24 h prior to invasive or surgical procedures because of the risk of bleeding.	If anticoagulation must be discontinued to reduce the risk of bleeding with surgical or other procedures, rivaroxaban should be stopped at least 24 h prior to the procedure to reduce the risk of bleeding.
Bridging	Bridging anticoagulation is generally not required during the 24-48 h after stopping apixaban in advance of a procedure.	If dabigatran is discontinued for other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant, and then restart dabigatran as soon as medically appropriate.	Administer a parenteral anticoagulant and then switch to oral edoxaban if oral medication cannot be taken during or after surgical intervention.	If oral medication cannot be taken during or after surgical intervention, consider administering a parenteral anticoagulant.
Specific reversal agent	Specific FXa reversal agent (andexanet alfa) is under accelerated development and FDA review. Ciraparantag, an agent to reverse the anticoagulant effects of both LMWH and UFH, and all 4 currently approved DOACs is currently under development.	Use the approved and available specific reversal agent (idarucizumab) in case of emergency surgery or urgent procedures when reversal of the anticoagulant effect of dabigatran is needed. Ciraparantag, an agent to reverse the anticoagulant effects of both LMWH and UFH, and all 4 currently approved DOACs, is currently under development.	Specific FXa reversal agent (andexanet alfa) is under accelerated development and FDA review. Ciraparantag, an agent to reverse the anticoagulant effects of both LMWH and UFH, and all 4 currently approved DOACs is currently under development.	Specific FXa reversal agent (andexanet alfa) is under accelerated development and FDA review. Ciraparantag, an agent to reverse the anticoagulant effects of both LMWH and UFH, and all 4 currently approved DOACs is currently under development.
Restarting DOAC	As soon as adequate hemostasis has been established after any surgical or other procedure, apixaban should be restarted.	Restart dabigatran as soon as medically appropriate, or 24 h after idarucizumab reversal.	Edoxaban can be restarted after the surgical or other procedure as soon as adequate hemostasis has been established noting that the time to onset of pharmacodynamic effect is 1-2 h.	Rivaroxaban should be re-started after any invasive procedures as soon as appropriate hemostasis is established. It should be noted that the time to onset of therapeutic effect is brief.
Warnings	Premature discontinuation of apixaban increases the risk of thrombotic events. Epidural or spinal hematomas may occur in patients treated with apixaban who are receiving neuraxial anesthesia or undergoing spinal puncture. An increased rate of stroke was observed during the transition from apixaban to warfarin in clinical trials in atrial fibrillation patients.	Premature discontinuation of any oral anticoagulant, including dabigatran, increases the risk of thrombotic events. Epidural or spinal hematomas may occur in patients treated with dabigatran who are receiving neuraxial anesthesia or undergoing spinal puncture.	Edoxaban has reduced efficacy in NVAF patients with a CrCl of >95 mL/min, and should not be used in this population. Premature discontinuation of edoxaban increases the risk of ischemic events. Epidural or spinal hematomas may occur in patients treated with edoxaban who are receiving neuraxial anesthesia or undergoing spinal puncture.	Premature discontinuation of any oral anticoagulant, including rivaroxaban, increases the risk of thrombotic events. Epidural or spinal hematomas have occurred in patients treated with rivaroxaban who are receiving neuraxial anesthesia or undergoing spinal puncture.

CrCl = creatine clearance; DOAC = direct oral anticoagulant; FDA = U.S. Food and Drug Administration; FXa = factor Xa; LMWH = low-molecular-weight heparin; NVAF = nonvalvular atrial fibrillation; UFH = unfractionated heparin.

3. Interruption of Oral Anticoagulation and Bridging/Switching Between Anticoagulants

Earlier guidelines for periprocedural management of patients on oral anticoagulation supported the discontinuation of oral anticoagulation with warfarin and recommended the use of LMWH or unfractionated heparin to bridge patients with atrial fibrillation who are at elevated risk for thromboembolic events [35,36]. More recently, the need for anticoagulant bridging to allow invasive procedures to continue has been called into question [37,38]. In fact, current guidelines from the American Academy of Neurology state that bridging therapy with heparin is probably associated with an increased bleeding risk when compared with warfarin discontinuation [39]. These recommendations are supported by a recent report from the BRIDGE Investigators, who state that stopping warfarin (without bridging with LMWH), was noninferior to bridging therapy when warfarin treatment was interrupted for an elective operation or other elective invasive procedure [40].

Similar guidance is emerging for patients who are anticoagulated with any of the currently approved DOACs, where the limited data available suggest that bridging with another anticoagulant provides limited, if any, benefit to the patient. An example of this can be found in a recent sub-analysis of data from the RE-LY study, where dabigatran-treated patients who had treatment interruption for an elective procedure experienced more major bleeding events with bridging therapy than patients who did not receive bridging therapy, with no significant effect on arterial thromboembolism [41]. Anticoagulation with dabigatran should begin as soon after the procedure as is medically possible [5]. Related guidance is also provided by the manufacturer of apixaban [6] and also does not recommend bridging therapy during DOAC treatment interruptions. For patients on either edoxaban [7] or rivaroxaban [8],

treatment should be stopped at least 24 hours prior to an invasive or surgical procedure. A parenteral anticoagulant can be administered if needed until an oral anticoagulant can be re-administered.

There is ongoing interest about the clinical need for bridging therapy with heparin or other parenteral agents during DOAC treatment interruptions for invasive or surgical procedures. Randomized and controlled clinical trials currently underway, such as the BRUISE CONTROL-2, are expected to provide evidence-based clinical guidance for the management of DOAC-treated patients who are facing invasive or surgical procedures [42].

4. Reversal of DOAC-Induced Anticoagulation with Specific Agents

Several reversal agents to rapidly counter the anticoagulation effects of DOACs are in development, and the respective roles for each will eventually be defined through formal studies and clinical experience. A specific reversal agent for dabigatran, idarucizumab, is a humanized monoclonal antibody that selectively binds dabigatran and reverses dabigatran-induced anticoagulation. In the RE-VERSE AD (A Study of the RE-VERSal Effects of Idarucizumab on Active Dabigatran) study, idarucizumab reversed the anticoagulant effects of dabigatran in patients with amajor bleeding event, or who were in need of an urgent invasive procedure (within 8 hours) [22,43]. Idarucizumab has recently been approved by the U.S. Food and Drug Administration and the European Medicines Agency for the reversal of dabigatran-related anticoagulation in cases where emergency surgery or urgent procedures are required, or in cases of life-threatening or uncontrolled bleeding [32].

Andexanet alfa is in advanced clinical trials as a specific reversal agent of FXa inhibitors, including apixaban, edoxaban, and rivaroxaban, and enoxaparin [44,45]. However, it should be noted that clinical trial data have not yet been published where andexanet alfa was studied for the reversal of anticoagulation in surgical patients, where emergency surgery or urgent procedures are required, or in cases of life-threatening or uncontrolled bleeding. Andexanet alfa is a bioengineered human FXa decoy protein that has been modified to delete the native catalytic activity while retaining the high-affinity binding of FXa inhibitors within the enzymatic active site. By binding to circulating FXa inhibitors, andexanet alfa makes endogenous FXa available to contribute to the coagulation cascade [45].

Another potential approach is ciraparantag (PER977), a small cationic and water-soluble molecule that was designed to bind with high affinity to unfractionated heparin and LMWH by forming noncovalent hydrogen bonds and strong chargeecharge interactions [30]. Ciraparantag binds in a similar way to the oral FXa inhibitors, edoxaban, rivaroxaban, and apixaban, and to the oral thrombin inhibitor dabigatran, potentially achieving potent and rapid reversal of their anticoagulant effects [30].

As clinical experience with the reversal agents grows, the respective role of each reversal agent in the management of emergency bleeding events and surgical procedures will be better defined over the next few years, leading to important contributions in the care of patients with NVAF and other thromboembolic challenges [46].

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