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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.

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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.

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

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]

PERIPROCEDURAL MANAGEMENT

A recent analysis from the Randomized Evaluation of Long-term anticoagulation therapY (RE-LY) study (dabigatran vs VKA in patients with NVAF) reported similar rates of perioperative bleeding and thromboembolism in warfarin- and 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