The direct oral anticoagulants (DOACs), which include dabigatran, rivaroxaban, apixaban, and edoxaban, were designed to be given in fixed doses without routine coagulation monitoring. When administered in this manner in trials that included >71,000 patients with atrial fibrillation and >27,000 patients with venous thromboembolism, the DOACs were at least as effective as vitamin K antagonists but were associated with less serious bleeding, particularly less intracranial bleeding. Eliminating coagulation monitoring simplifies anticoagulation therapy. This feature, together with their proven efficacy and safety, explains why guidelines give preference to the DOACs over vitamin K antagonists for stroke prevention in atrial fibrillation and for the treatment of venous thromboembolism.

Although routine coagulation monitoring is unnecessary, there is an urgent need for readily and rapidly available tests to measure the DOACs. This need will increase with the introduction of costly reversal agents such as idarucizumab for dabigatran and andexanet alfa for rivaroxaban, apixaban, and edoxaban. Idarucizumab is already licensed, and andexanet is undergoing regulatory review and could be approved later this year. What tests are currently available, and why do we need new ones?

Although currently available global tests of coagulation such as the activated partial thromboplastin time (aPTT) and prothrombin time (PT) can be useful to assess the anticoagulant effects of dabigatran and some of the oral factor Xa inhibitors, respectively, the sensitivity of these tests is variable and reagent dependent. Regardless of reagent, the PT is less responsive to apixaban and edoxaban than to rivaroxaban. Unfortunately, because sensitivity to the DOACs is rarely considered when reagents are chosen, the utility of the tests may change when laboratories order new lots of reagents. This not only complicates interpretation of test results over time in a single laboratory, but also renders between-laboratory comparisons difficult. These issues highlight the need for standardized tests.

The DOACs have half-lives of ≈12 hours. Consequently, circulating drug levels and their subsequent effects on the aPTT and PT depend on when the blood sample was collected relative to the timing of the last drug dose. Even when measured soon after drug intake, a prolonged aPTT in patients taking dabigatran or an elevated PT in those on rivaroxaban, apixaban, or edoxaban gives no information about how much drug is in the circulation, and a normal test result does not exclude the presence of drug. Therefore, more accurate tests are needed. Such tests are currently available in research facilities and include the diluted thrombin time and ecarin clot time or ecarin chromogenic assay for dabigatran, as well as chromogenic anti–factor Xa assays for rivaroxaban, apixaban, and edoxaban. Unfortunately, these tests are not widely available, and even if available, the turnaround time is often too slow to be useful. This needs to change.

**Urgent Need to Measure Effects of Direct Oral Anticoagulants**

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Key Words: anticoagulant

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In patients taking rivaroxaban, apixaban, or edoxaban, the PT will not identify patients requiring reversal with andexanet or inform the timing of urgent surgery. In the ongoing Prospective, Open-Label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor Who Have Acute Major Bleeding (ClinicalTrials.gov Unique identifier NCT02329327), andexanet is administered as a bolus followed by a 2-hour infusion. Although blood is collected for central laboratory determination of anti–factor Xa activity, the treating physician cannot access this information. Instead, the dose of andexanet is determined by which oral factor Xa inhibitor the patient is taking and the time from the last dose. If implemented in practice, this approach could lead to unnecessary administration or underdosing of andexanet if the clinical information is incorrect. Therefore, unless anti–factor Xa levels are available locally, the treating physician has no way to determine whether reversal is warranted, to calculate the appropriate andexanet dose, and to monitor the extent of reversal. Although the cost of andexanet has not been revealed, it will be at least as expensive as idarucizumab, which costs about $3500 per dose in the United States. Therefore, ready access to rapidly available, calibrated tests is needed to ensure that reversal agents are given appropriately.

Can we achieve this goal? All modern coagulometers are capable of performing chromogenic assays with a turnaround time similar to that for the aPTT or PT, and anti–factor Xa assays are already available for quantifying levels of heparin or low-molecular-weight heparin. Commercial anti–factor Xa assays for rivaroxaban and apixaban and a diluted thrombin time and ecarin chromogenic assay for dabigatran are available, and an anti–factor Xa assay for edoxaban soon will be available. Calibration of these assays into practice requires their regulatory approval for clinical use and their widespread introduction into busy emergency departments. We urge regulatory agencies and hospitals to get on board to make this happen.

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Table. Assays Available to Measure Plasma Levels of the DOACs

<table>
<thead>
<tr>
<th>Target</th>
<th>Drug</th>
<th>Test</th>
<th>Manufacturers</th>
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</thead>
<tbody>
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<td>Thrombin</td>
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DOAC indicates direct oral anticoagulant.

Why is the need for these tests so urgent? Quantification of plasma concentrations of the DOACs is critical when assessing their potential contribution to serious bleeding, when making decisions about the timing of urgent surgery or interventions, or when determining whether patients with acute ischemic stroke can safely be given fibrinolytic therapy. Patients with elevated drug levels in these settings may benefit from the administration of a reversal agent, whereas those with little or no circulating drug will not. In urgent situations, clinicians may administer reversal agents without waiting for the results of laboratory testing, but how do we otherwise identify patients who need reversal, and how do we monitor the extent of reversal achieved when reversal agents are given?

Idarucizumab is licensed for dabigatran reversal in patients with life-threatening bleeding or in those requiring urgent surgery or intervention. An elevated aPTT at baseline provides sufficient grounds to administer idarucizumab, but a normal aPTT may not exclude the potential benefit from reversal because the aPTT is less responsive to dabigatran than the ecarin clot time. This concept is supported by data from the first 90 patients enrolled in the RE-VERSE AD (Reversal Effects of Idarucizumab on Active Dabigatran) study; at baseline, 25 of these patients had a normal aPTT, whereas only 9 had a normal ecarin clot time. Therefore, more sensitive tests than the aPTT are needed to best identify patients who will benefit from idarucizumab and to monitor their response to treatment.

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REFERENCES
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