Direct Oral Anticoagulants

Monitoring Anticoagulant Effect

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KEYWORDS

• Oral anticoagulants • Coagulation testing • Trough level • Anticoagulant effect

KEY POINTS

- The direct oral anticoagulants (DOACs), dabigatran, apixaban, edoxaban, and rivaroxaban, were approved for prevention and treatment of venous thrombosis and for prevention of embolic stroke in patients with atrial fibrillation, without need to monitor drug activity levels.
- Clinical circumstances exist where laboratory measures of drug activity may help guide clinical care.
- Trough drug levels correlate best with bleeding risk, although values measured in patients on the medications vary widely.
- Screening laboratory tests differ in their sensitivity to the drugs and knowledge of the assays available and laboratory-specific performance is required.
- Direct oral anticoagulants can affect clot-based coagulation assays performed, including tests for thrombophilias, factor levels, and thromboelastography, and results of those tests should be interpreted with caution in patients on DOACs.

INTRODUCTION

Direct oral anticoagulants (DOACs) inhibit coagulation through factor Xa (apixaban, edoxaban, rivaroxaban) or thrombin (dabigatran) (**Fig. 1**), and do not require antithrombin for activity as is needed for the heparins and fondaparinux. DOACs are approved for prevention and treatment of venous thromboembolism and for treatment of patients with atrial fibrillation. Clinical trials were designed and regulatory approval given without a need for dose adjustment based on laboratory testing. In clinical trials use of these agents was associated with less or similar bleeding and thrombotic complications compared with warfarin.[1–8] However, in certain clinical settings measurement of anticoagulant activity is desired to help inform patient care. These include life-threatening bleeding, emergency surgery, renal impairment, liver failure, in patients taking medications that affect DOAC plasma concentrations, recurrent thrombosis or bleeding on recommended doses, or extremes of body weight (**Box 1**).

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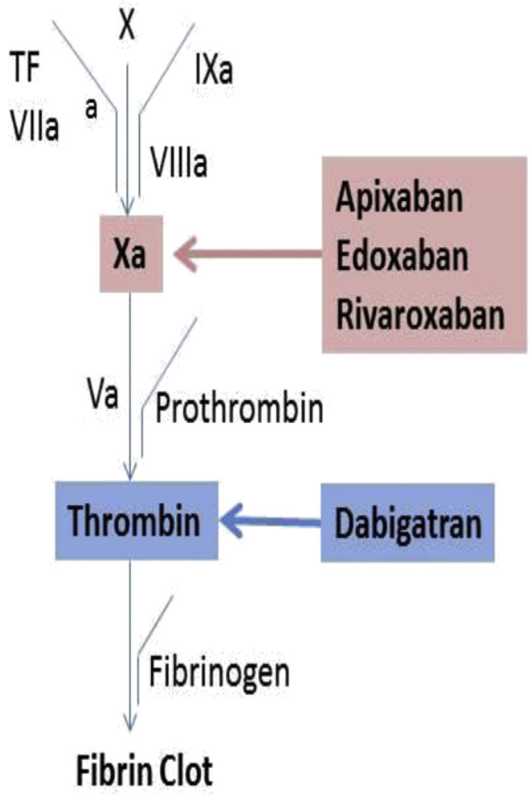

Fig. 1. Sites of action of DOACs. TF, tissue factor. [a] This activation pathway is inhibited on formation of an Xa-tissue factor pathway inhibitor-VIIa-TF complex.

True therapeutic ranges based on clinical outcomes have not been established for these agents. Levels that correlate with efficacy and/or adverse outcomes are just now being studied. Instead we have levels that were measured in study populations on standard dosing, most commonly at peak and trough concentrations using liquid chromatography/tandem mass spectrometry (LC-MS/MS) methodology. Of note, these levels vary widely across study participants.[9–12] Instead of therapeutic levels, the terms on-therapy drug concentrations or on-therapy levels are more accurate.

Box 1 **Reasons for measuring DOAC anticoagulant activity**
Major bleeding
Emergent need for surgery
Renal impairment
Severe liver failure
Potential drug-drug interactions
Bleeding or thrombosis on therapy
Extremes of body weight