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Laboratory Measurement of the Anticoagulant Activity of the Non–Vitamin K Oral Anticoagulants

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ABSTRACT

BACKGROUND Non-vitamin K oral anticoagulants (NOACs) do not require routine laboratory monitoring. However, laboratory measurement may be desirable in special situations and populations.

OBJECTIVES This study's objective was to systematically review and summarize current evidence regarding laboratory measurement of the anticoagulant activity of dabigatran, rivaroxaban, and apixaban.

METHODS We searched PubMed and Web of Science for studies that reported a relationship between drug levels of dabigatran, rivaroxaban, and apixaban and coagulation assay results. Study quality was evaluated using QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2).

RESULTS We identified 17 eligible studies for dabigatran, 15 for rivaroxaban, and 4 for apixaban. For dabigatran, a normal thrombin time excludes clinically relevant drug concentrations. The activated partial thromboplastin time (APTT) and prothrombin time (PT) are less sensitive and may be normal at trough drug levels. The dilute thrombin time (R^2 = 0.92 to 0.99) and ecarin-based assays (R^2 = 0.92 to 1.00) show excellent linearity across on-therapy drug concentrations and may be used for drug quantification. For rivaroxaban and apixaban, anti-Xa activity is linear (R^2 = 0.89 to 1.00) over a wide range of drug levels and may be used for drug quantification. Undetectable anti-Xa activity likely excludes clinically relevant drug concentrations. The PT is less sensitive (especially for apixaban); a normal PT may not exclude clinically relevant levels. The APTT demonstrates insufficient sensitivity and linearity for quantification.

CONCLUSIONS Dabigatran, rivaroxaban, and apixaban exhibit variable effects on coagulation assays. Understanding these effects facilitates interpretation of test results in NOAC-treated patients. More information on the relationship between drug levels and clinical outcomes is needed. (J Am Coll Cardiol 2014;64:1128–39) © 2014 by the American College of Cardiology Foundation.

Dabigatran etexilate, an oral prodrug of the direct thrombin inhibitor dabigatran, and the oral direct inhibitors of factor Xa, rivaroxaban and apixaban, are approved in the United States, Europe, and Canada to prevent stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF). They are also variably licensed for treatment of venous thromboembolism (VTE) and prevention of VTE after major orthopedic surgery (MOS) in certain jurisdictions. We refer to these

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agents collectively as non-vitamin K oral anticoagulants (NOACs) in this paper. Synonymous terms preferred by other researchers include direct-acting oral anticoagulant agents and new, novel, or target-specific oral anticoagulant agents (1).

Unlike warfarin and other vitamin K antagonists (VKAs), the NOACs are administered in fixed doses and do not require routine laboratory monitoring (2–4). However, measurement of their anticoagulant activity may be desirable in special clinical settings such as bleeding; the pre-operative state; breakthrough thrombosis; and suspected overdose, noncompliance, or drug interactions and in certain populations, including those with extremes in body weight and in the elderly and patients with renal insufficiency in whom there is a risk of drug accumulation. Assessment of anticoagulant effect may also be important in patients with AF presenting with acute ischemic stroke before administration of thrombolytic therapy (5).

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Numerous studies on use of coagulation assays for measurement of NOAC activity have been published recently, although a systematic review has not been undertaken. The objective of our analysis was to summarize current evidence regarding laboratory measurement of NOAC anticoagulant activity and to provide evidence-based guidance to practicing cardiologists on the interpretation of coagulation tests in NOAC-treated patients.

METHODS

LITERATURE SEARCH. We performed a systematic review of the literature to examine current evidence for laboratory measurement of the NOACs. A search of PubMed and Web of Science from inception through December 1, 2013, was undertaken separately for dabigatran, rivaroxaban, and apixaban using the following key words: "name of drug" AND ((laboratory measurement) OR (laboratory monitoring)).

STUDY SELECTION. Articles were examined, first by title and abstract and then by review of the complete paper as indicated. Additional articles were sought by reviewing bibliographies. Liquid chromatography/tandem mass spectrometry (LC-MS/MS) is the reference method for measurement of the plasma concentration of NOACs (6). Studies that reported the relationship between drug (or active metabolite) levels in human plasma, as measured directly using LC-MS/MS or indirectly using LC-MS/MS-validated calibration standards and 1 or more clinical coagulation assays, were eligible for inclusion. We excluded animal studies, abstracts only, and non-English language publications.

DATA EXTRACTION. We extracted key characteristics from eligible studies and recorded them in an evidence table. These included author, year of publication, setting, NOAC (i.e., dabigatran, rivaroxaban, or apixaban), reference method for measurement of drug levels, range of drug concentrations studied, test material (i.e., ex vivo patient plasma, ex vivo healthy control plasma, or spiked normal plasma), dose (for studies using ex vivo plasma only), indication (for studies using ex vivo patient plasma only), number of samples (for studies using individual [i.e., unpooled] plasma only), coagulation assays and reagents, and descriptors of the relationship between drug level and coagulation assay (e.g., R^2 values, range of linearity).

QUALITY ASSESSMENT. Study quality was evaluated using QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2), a standardized tool for quality assessment of studies of diagnostic accuracy. The tool comprises 4 domains: patient selection, index test, reference standard, and flow and timing. Risk of bias is assessed across all domains; the first 3 domains are also assessed with respect to applicability to clinical practice (7).

RESULTS

DABIGATRAN. Dabigatran etexilate, an oral nonpeptide prodrug, is rapidly converted to the active drug dabigatran by ubiquitous esterases. Dabigatran directly inhibits both free and clot-bound thrombin. It has relatively poor bioavailability (approximately 6.5%) and is eliminated predominantly by the kidneys (80%). In individuals with normal renal function, the half-life of dabigatran is 12 to 14 h. Prolonged clearance and bioaccumulation are observed in patients with renal insufficiency (8). In patients with nonvalvular AF and normal kidney function, the dose is 150 mg twice daily, which is reduced in patients with renal insufficiency.

Peak levels of dabigatran occur 2 to 3 h after ingestion. Steady-state peak and trough concentrations in patients with AF and normal renal function taking dabigatran 150 mg twice daily are shown in **Table 1** (8). Substantial interindividual variability in drug exposure is observed. In the PETRO (Prevention of Embolic and Thrombotic Events in Patients

ABBREVIATIONS AND ACRONYMS

ACT = activated clotting time
AF = atrial fibrillation
APTT = activated partial thromboplastin time
ECA = ecarin chromogenic assay
ECT = ecarin clotting time
NOAC = non-vitamin K oral anticoagulant
PiCT = prothrombinase-induced clotting time
POC = point of care
PT/INR = prothrombin time/international normalized ratio
TT = thrombin time
VKA = vitamin K antagonist