

Algorithm for Rapid Exclusion of Clinically Relevant Plasma Levels of Direct Oral Anticoagulants in Patients Using the DOAC Dipstick: An Expert Consensus Paper

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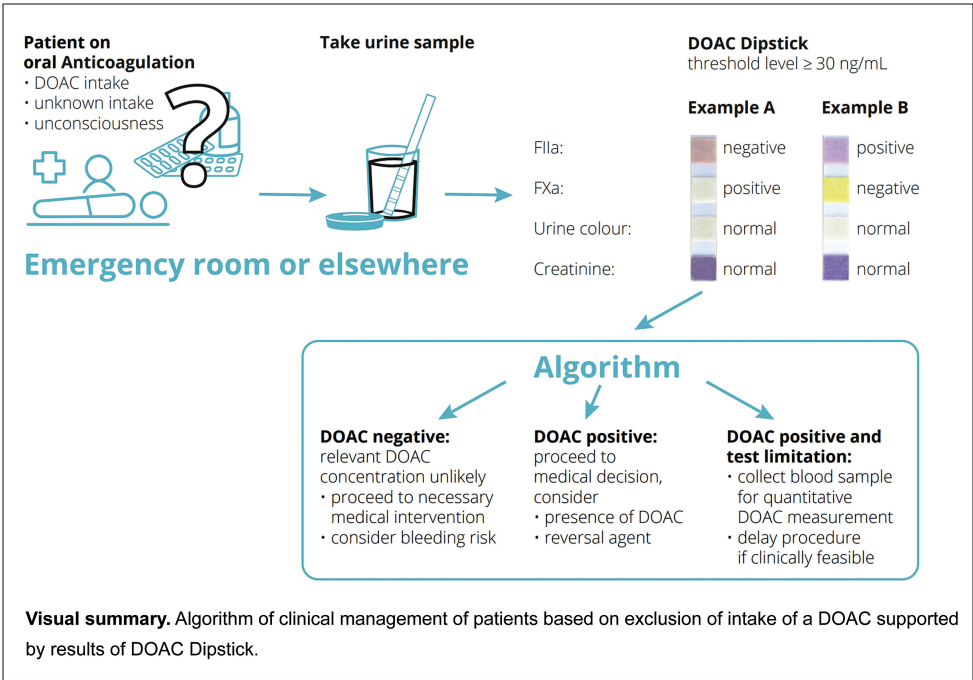
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Abstract

Background With the widespread use of direct oral anticoagulants (DOACs), there is an urgent need for a rapid assay to exclude clinically relevant plasma levels. Accurate and rapid determination of DOAC levels would guide medical decision-making to (1) determine the potential contribution of the DOAC to spontaneous or trauma-induced hemorrhage; (2) identify appropriate candidates for reversal, or (3) optimize the timing of urgent surgery or intervention.

Methods and Results The DOAC Dipstick test uses a disposable strip to identify factor Xa- or thrombin inhibitors in a urine sample. Based on the results of a systematic literature search followed by an analysis of a simple pooling of five retrieved clinical studies, the test strip has a high sensitivity and an acceptably high negative predictive value when compared with levels measured with liquid chromatography tandem mass spectrometry or calibrated chromogenic assays to reliably exclude plasma DOAC concentrations ≥ 30 ng/mL.

Conclusion Based on these data, a simple algorithm is proposed to enhance medical decision-making in acute care indications useful primarily in hospitals not having readily available quantitative tests and 24/7. This algorithm not only determines DOAC exposure but also differentiates between factor Xa and thrombin inhibitors to better guide clinical management.

Keywords

- ▶ direct oral anticoagulants
- ▶ point-of-care tests
- ▶ urine
- ▶ plasma
- ▶ pooled analysis

Introduction

Direct oral anticoagulants (DOACs) are used to prevent and treat thromboembolic events in individuals with atrial fibrillation (AF) and venous thromboembolism (VTE). DOACs are at least as efficacious as vitamin K antagonists (VKAs) and are associated with lower rates of spontaneous and life-threatening bleeding. Consequently, recent guidelines and position papers have recommended DOACs over VKAs for a broad spectrum of clinical indications.^{1,2}

The management of patients treated with DOACs who experience spontaneous, peri-interventional or trauma-related bleeding or require urgent surgery or other interventions remains challenging.³ Unlike VKAs, DOAC levels are not routinely monitored and cannot be determined with global tests of coagulation such as the prothrombin time or activated partial thromboplastin time.^{4,5} Instead, the levels must be determined by liquid chromatography tandem mass spectrometry (LC-MS/MS) or with specialized assays, such as calibrated chromogenic assays. Some position papers have suggested measuring DOAC levels in patients presenting to emergency departments with serious bleeding, acute ischemic stroke or when major surgical interventions or other invasive procedures associated with high bleeding risk are needed.¹ Various DOAC threshold plasma levels, ranging from ≤ 20 to ≤ 100 ng/mL, have been proposed to guide the administration of intravenous thrombolysis in DOAC-treated patients with an acute ischemic stroke.^{6,7} Plasma DOAC concentrations exceeding 50 to 75 ng/mL may warrant the administration of reversal agents in patients with life-threatening bleeding,^{8,9} whereas DOAC concentrations below 30 to 50 ng/mL are considered acceptable in patients requiring urgent surgery or interventions associated with a medium to high risk of bleeding.^{10,11}

Algorithms have been developed to help health care providers interpret the results of coagulation tests.^{12–16} Whereas conventional assays measure the anticoagulant effects of DOACs in plasma, the DOAC Dipstick (DOASENSE, Heidelberg, Germany) is a point-of-care test that uses a disposable test strip to detect DOACs in urine and to differentiate between dabigatran and activated factor X (FXa) inhibitors. Capitalizing on its ease of use and rapid turnaround time, we propose a simple algorithm that uses the DOAC Dipstick test to rapidly exclude the presence of clinically relevant plasma DOAC levels.

The DOAC Dipstick Method

The DOAC Dipstick tests for the presence of DOACs in urine samples and is approved for use in Europe, Australia, and Brazil. The test strip has four distinct pads: pad #1 contains 3,5-dinitrobenzoic acid in alkaline medium to semi-quantitatively measure creatinine; pad #2 does not contain any reagents and is used to determine the influence of urine color on test result validity; pad #3 contains a FXa-specific peptide and a chromophore which will produce color in the presence of FXa inhibitors; and pad #4 contains a thrombin specific peptide and a chromophore which will produce color in the presence of a thrombin inhibitor.¹⁷ Once collected, a single

| Pad | | Example A | Example B |
|--------------------------|----------|-----------|-----------|
| 4 = Thrombin inhibitor: | negative | | positive |
| 3 = Factor Xa inhibitor: | positive | | negative |
| 2 = Urine colour: | normal | | normal |
| 1 = Creatinine: | normal | | normal |

Fig. 1 Color label of DOAC Dipstick results for negative and positive thrombin- and factor Xa inhibitor pad results (example A) and a positive and a negative thrombin- and factor Xa inhibitor pad results (example B) in the presence of normal creatinine pad and of normal urine color pad results.

DOAC Dipstick is immersed in the urine for 2 to 3 seconds, ensuring that all pads are exposed to urine. Excess urine is blotted using a tissue without touching the pads. The strip is then placed on a flat surface, to await the 10 minutes reaction time at room temperature (15–25°C). Evaluating the dipstick too early may yield false-positive (FP) results if the chemical reactions have not yet reached a plateau. Reading the test strip too late (20 minutes or later) may also cause false-positive (FP) results because of a nonspecific chemical reaction between reaction partners (unpublished data from J.H.). If a DOAC is present, there is a specific color change on the respective test pad, which can be identified visually or with a semiautomated strip reader to determine qualitative results. A color label of reactions for the DOAC test is provided on the reagent vial to assist visual interpretation (► Fig. 1).

An abnormal urine color may potentially effect test pad results. The DOAC Dipstick color pad (pad #2) addresses whether urine color might influence pad interpretation. If the color of this pad is darker than the color provided on the reagent vial color panel for pad #2, then results for all the other pads (creatinine, FXa, and thrombin) may not be accurate and make the test invalid. Reduced renal function may also affect the test pad results accuracy. If the result for pad #1 (creatinine) is “low” or lighter than the respective color on the vial color panel, the urine creatinine is low indicating renal insufficiency. In cases of renal insufficiency, there may be FN reactions for pad 3 or pad 4, and alternative blood testing methods are required.

One study demonstrated the relationship between DOAC Dipstick and urine concentrations of DOAC as well as the agreement of visual interpretation of test pad results between testing centers.¹⁸ The specificity of the DOAC Dipstick test to oral anti-FXa medications was confirmed in urine samples from drug-naïve individuals, and urine samples containing DOAC, heparin, or nadroparin.^{19,20}

Methods

A systematic literature search was performed between 1993 and June 2023 to identify relevant studies in PubMed (MEDLINE) and Cochrane Library databases. The literature search was performed in collaboration with librarians at the Faculty of

Table 1 Search string of systematic review of the literature according to Martini et al²¹

| |
|---|
| ("direct oral anticoagulant_"[tiab] OR doac_[tiab] OR "new oral anticoagulant_"[tiab] OR Noac_[tiab] OR "Dabigatran"[mh] OR "Rivaroxaban"[mh] OR "apixaban"[nm] OR "Rivaroxaban"[nm] OR "Dabigatran"[nm] OR "edoxaban"[nm] OR "apixaban"[tiab] OR "Rivaroxaban"[tiab] OR "Dabigatran"[tiab] OR "edoxaban"[tiab]) AND ("Point-of-Care Testing"[Mesh] OR Plasma[Mesh] OR Serum[Mesh] OR Urine[Mesh] OR "Point of care"[tiab] OR Plasma[tiab] OR Serum[tiab] OR Urine[tiab] OR Dipstick_[tiab] OR "Blood Coagulation Tests"[Mesh] OR "Coagulation"[tiab] OR "Mass Spectrometry"[Mesh] OR "Mass Spectrometry"[tiab] OR "International Normalized Ratio_"[tiab] OR INR[tiab] OR "Partial Thromboplastin Time"[tiab] OR aptt[tiab] OR Ptt [tiab] OR "Prothrombin Time_"[tiab] OR Pt[tiab] OR Thromboelastography[tiab] OR Thromboelastometry[tiab] OR "Thrombin Time_"[tiab] OR "whole blood clotting"[tiab] OR "chromogenic"[tiab] OR Hemoclot[tiab]) AND ("sensitivity and specificity"[Mesh] OR sensitiv_[tiab] OR "predictive value_"[tiab] OR accurac_[tiab] OR diagnosis [Subheading:noexp] OR diagnos_[tiab] OR specificity[tiab]) |
|---|

Medicine of the University of Heidelberg. The reference lists of all included papers were hand-searched to identify other relevant articles. The search string is listed in ►Table 1.²¹ Inclusion criteria were the determination of DOACs in urine samples of patients treated with rivaroxaban, apixaban, edoxaban, and dabigatran. Duplicate publications, meta-analyses, reviews, case reports, and studies that measured DOACs only using coagulation and chromogenic tests, chromatography methods or blood-based point-of-care tests were excluded. Studies that reported DOAC Dipstick results from urine samples and LC-MS/MS or hemostatic assay results for plasma samples were screened for inclusion. Abstracts, reviews, and meta-analyses were excluded. Publications were screened by two independent researchers (J.H., S.H.) discrepancies were resolved by discussion and eligible studies were included in the analysis by simple pooling.

For the data from the clinical studies, reported in the publications, we decided to analyze by simple pooling to determine DOAC Dipstick performance in terms of sensitivity, negative predictive value (NPV), positive predictive value (PPV), and specificity. In a sub-analysis, the plasma concentrations of rivaroxaban, apixaban, and edoxaban were used to determine FXa DOAC urine dipstick pad performance. We calculated unweighted mean values of these statistics with 95% confidence intervals (CIs) using Stata 17.0 for Mac (H.H.) and independently confirmed by SAS version 4.5 (S.H., C.W.).

Results

One thousand and two hundred six eligible studies were found in the database search. After removing duplicate publications, reviews, case reports, studies that used other hemostatic methods for detection of DOACs, other indications than anticoagulation for AF and deep vein thrombosis, investigated effect of antidotes with other hemostatic methods, and use of prototype urine test strips, five clinical studies were eligible for inclusion in the pooled analysis that assessed plasma concentrations of DOACs and DOAC Dipstick results (►Fig. 2).^{20,22–25}

All identified studies used ≥30 ng/mL as a clinically significant threshold. True positives (TPs) are defined as DOAC Dipstick positive with plasma DOAC concentration ≥30 ng/mL while true negatives (TNs) are defined as DOAC Dipstick negative with plasma concentrations <30 ng/mL. A FN result represents a negative DOAC Dipstick in a patient with a plasma DOAC concentration ≥30 ng/mL. A FP result indicates a positive DOAC Dipstick in a patient with plasma concentration

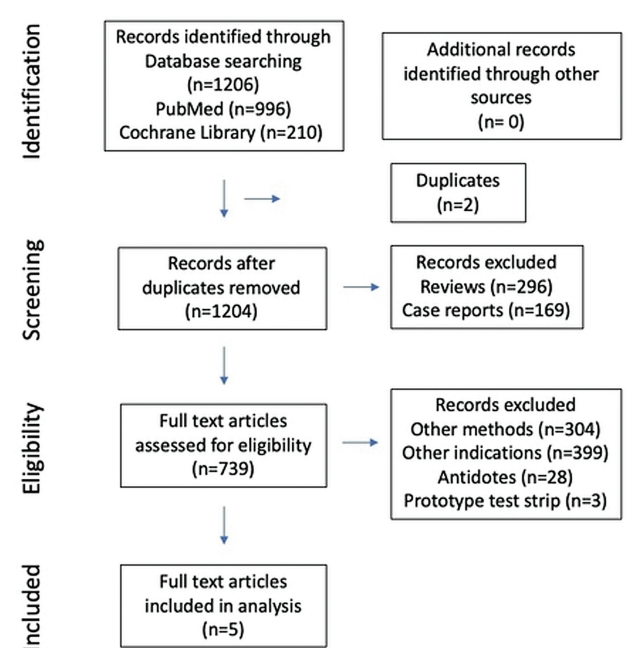


Fig. 2 Flowchart of the results of systematic review of the literature and reasons for exclusion of publications for analysis by simple pooling.

<30 ng/mL. DOAC concentrations were measured using either LC-MS/MS, representing the gold standard,²³ or a calibrated chromogenic assay.^{20,22,24,25} A summation of the DOAC Dipstick performance characteristics for each study is provided in ►Table 2. Studies that included DOAC-naïve normal subjects (controls) were excluded in this analysis.^{20,25}

Study #1: A single-center, prospective cohort study that recruited subjects from the neurology and cardiovascular disease departments, included those taking DOACs (n = 31 on apixaban, n = 53 on rivaroxaban, and n = 44 on dabigatran).²²

Study #2: A prospective, single-center, cohort type cross-sectional diagnostic study assessed the performance of the DOAC Dipstick in patients taking DOACs and were admitted to an emergency care unit with AF, VTE, or ischemic stroke (n = 65 on apixaban, n = 77 on edoxaban, n = 92 on rivaroxaban, and n = 31 on dabigatran).²³

Study #3: Described as a clinical pilot study, DOAC-treated adult inpatients or outpatients from internal medicine or cardiology departments were recruited. There were 10

Table 2 True positive (TP), false negative (FN), false positive (FP), and true negative (TN) results of visual evaluation of DOAC Dipstick factor Xa- and thrombin inhibitor pad colors using a threshold of <30 ng/mL plasma DOAC concentration for true negative and ≥30 ng/mL drug concentration for true-positive dipstick results

| Author year, reference | Factor Xa pad | | | | Thrombin pad | | | |
|---------------------------------|---------------|----|----|----|--------------|----|----|-----|
| | TP | FN | FP | TN | TP | FN | FP | TN |
| Margetić 2022 ²² | 56 | 0 | 22 | 6 | 27 | 0 | 16 | 1 |
| Merrelaar2022 ²³ | 190 | 5 | 22 | 48 | 26 | 0 | 5 | 234 |
| Örd 2022 ²⁰ | 18 | 0 | 2 | 0 | 3 | 0 | 0 | 0 |
| Papageorgiou 2023 ²⁴ | 102 | 3 | 12 | 3 | 0 | 0 | 0 | 0 |
| Tan 2023 ²⁵ | 35 | 1 | 1 | 1 | 2 | 1 | 0 | 0 |
| Sum | 401 | 9 | 59 | 58 | 58 | 1 | 21 | 235 |

Abbreviations: DOAC, direct oral anticoagulant; FN, false negative; FP, false positive; TP, true positive; TN, true negative.

patients treated with apixaban, 10 patients treated with rivaroxaban, and 3 patients treated with dabigatran.²⁰

Study #4: A prospective observational cohort study of consecutively enrolled outpatients treated with apixaban ($n = 43$) or rivaroxaban ($n = 77$) for recurrent VTE.²⁴

Study #5: A single-center, prospective, two-armed observational study comprising an acute arm including 17 patients with nonvalvular AF and ischemic stroke with an indication for thrombolysis (apixaban $n = 11$, rivaroxaban $n = 5$, and dabigatran $n = 1$) and a subacute arm including 24 AF patients on secondary prophylaxis for ischemic stroke ($n = 21$ with apixaban, $n = 1$ with rivaroxaban, $n = 2$ with dabigatran).²⁵

The individual values of each study for TP and FP and for TN and FN results of the direct oral FXa and thrombin inhibitor pads of the dipstick are summarized in ▶Table 1. There were 10 subjects in each of two studies^{20,25} that were not receiving a DOAC and served as controls. These subjects were excluded from the analysis. Consequently, the reported number of patients differs from those of the two publications.

In one study,²³ 4.8 and 3.0% of patients were excluded due to abnormal urine color and creatinine pad “low,” respectively. In another study,²⁰ 8.7% of patients had reduced creatinine clearance, a rivaroxaban plasma level <30 ng/mL, a positive FXa pad that was assessed as a FP dipstick result (▶Table 2, ▶Supplementary Table S1, available in the online version), and a creatinine pad that was not assessed. In the remaining studies, no abnormal urine color pads and creatinine pad “low” were observed.

In four studies,^{20,22,24,25} urine dipstick results were compared with plasma DOAC concentrations determined using DOAC-specific calibrated chromogenic anti-Xa assays and in one study,²³ plasma concentrations of FXa DOACs and of dabigatran ($n = 265$ each) were determined by LC-MS/MS (▶Table 2). In total, there were $n = 842$ ($n = 577$ plus $n = 265$) evaluations of urine dipstick pads from all five studies.

The sensitivity was >97% (lower 95% CI >90%) for both DOAC classes (▶Table 3). The NPV value for the FXa pad was 87% (95% CI: 76–94%) and for the thrombin inhibitor pad was >99% (95% CI: 98–100%) (▶Table 3). The PPV for the DOAC Dipstick was similar to the NPV for FXa inhibitors and less

robust for thrombin inhibitors confirming that the primary utility of a negative urine DOAC Dipstick pad result is to identify clinically relevant DOAC concentrations at a threshold of ≥30 ng/mL in the blood. There was a discordance of specificity between DOAC classes for unclear reasons, with the FXa inhibitor pad exhibiting less specificity (more FP results) than the thrombin inhibitor pad (▶Table 2).

The sub-analysis for rivaroxaban, apixaban (5 studies),^{20,22–25} and edoxaban (1 study)²³ showed a difference in their performance, with comparatively lower NPV for apixaban (81.8%) than for rivaroxaban (97.9%) or edoxaban (100%). The other statistical parameters ranged between 53 and 84% (▶Supplementary Tables S1 and S2, available in the online version).

Algorithm Using the DOAC Dipstick

Based on the available studies, we propose an algorithm, reported in a simpler form,²⁶ that uses the DOAC Dipstick to assist in the management of critically ill patients presenting to hospitals or urgent care centers not having available specific DOAC test within a short time frame and 24/7

Table 3 Sensitivity, negative predictive value (NPV), positive predictive value (PPV), and specificity values of DOAC Dipstick performance using a threshold of <30 ng/mL plasma DOAC concentration for true negative and ≥30 ng/mL drug concentration for true-positive dipstick results from cited clinical studies^{20,22–25}

| | Direct oral factor Xa inhibitors Mean (95% CI) | Direct oral thrombin inhibitor Mean (95% CI) |
|---------------------------|---|---|
| Sensitivity | 97.8 (95.6–99.0) | 98.3 (91.0–100) |
| Negative predictive value | 86.6 (76.0–93.7) | 99.6 (97.7–100) |
| Positive predictive value | 87.2 (83.7–90.1) | 73.4 (63.7–83.2) |
| Specificity | 50.0 (40.2–59.0) | 91.8 (87.7–94.0) |

Abbreviations: CI, confidence interval.

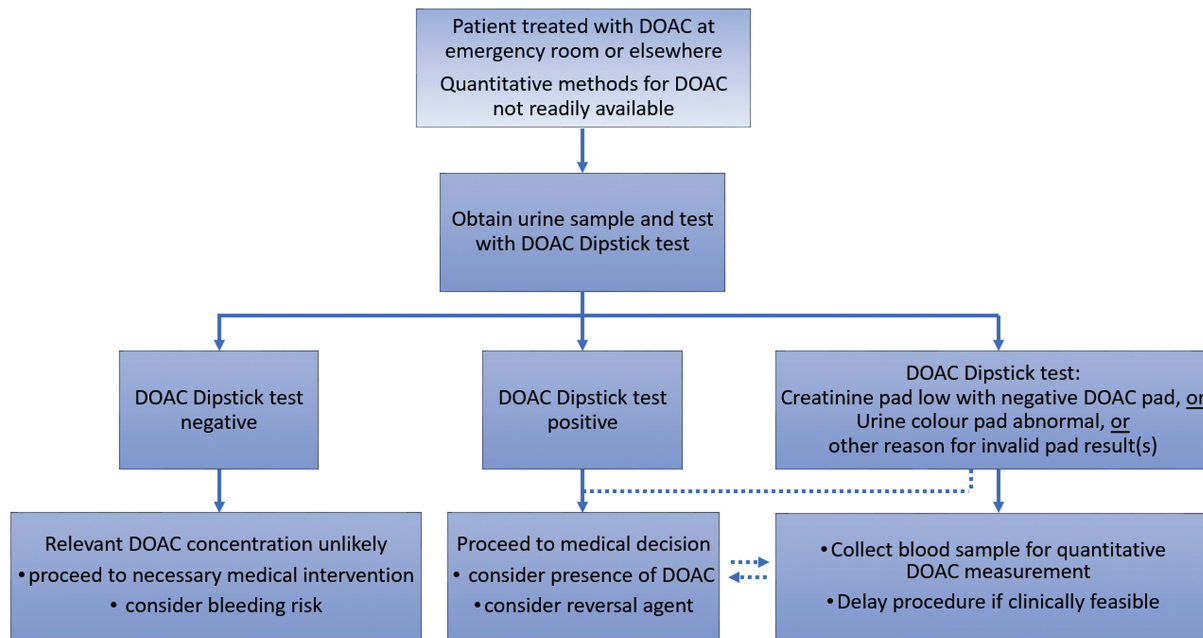


Fig. 3 Algorithm for the rapid and reliable exclusion of clinically relevant concentrations at ≥ 30 ng/mL of DOACs using the DOAC Dipstick. NOTE: dashed lines for additional testing should only be considered if the laboratory can provide suitable quantitative measurements within 30 minutes of receipt. DOAC, direct oral anticoagulant.

(► **Fig. 3**). If the test is negative (with normal creatinine pad results), then clinically significant DOAC levels (≥ 30 ng/mL) have been excluded. If the thrombin inhibitor or FXa pad indicates positivity, the algorithm options are dependent on the laboratory's capacity to provide a timely (within 30 minutes of receipt) quantitative DOAC measurement. If the laboratory can provide timely quantitative DOAC measurements, these results may provide additional guidance for determining the suitability of medical or surgical interventions, including DOAC reversal strategies. If timely testing cannot be performed by the laboratory, the decision to proceed with medical or surgical intervention should be based on the patient's clinical history, including reversal strategies. The proper course of action will depend on a host of factors including type of procedure needed, urgency of procedure, and on the availability of reversal agents. Unreliable dipstick results because of a low creatinine pad, abnormal urine color pad, or other reasons for invalid pad results, e.g., expiry date of test strip passed or incorrect handling, should be interpreted as "positive" in the algorithm.

Discussion

Accurate and rapid detection of DOACs in the circulation remains a major challenge in patients presenting with major bleeding or with thrombotic events during treatment, or requiring urgent surgery or an invasive procedure. Although LC-MS/MS is the gold standard for quantifying DOAC levels in the plasma, this technique is not widely available and has a slow turnaround time. More rapid methods for assessing plasma concentrations of DOACs such as hemostatic assays and rotational thromboelastography (ROTEM) using global or specific activators for blood clotting, have been

described.^{4,12,13} However, these methods still require the acquisition of a blood sample, transportation of the blood sample to the testing laboratory, processing of the blood to yield a suitable sample for testing (plasma), and the necessary instrumentation with suitable performing reagents. In contrast, the urine dipstick method can be readily tested at the patient's bedside, without the need for sample processing or specialized equipment. Given the DOAC Dipstick's high sensitivity (to both direct oral FXa- and thrombin inhibitors) and ability to differentiate dabigatran from oral FXa inhibitors, this method is also suitable for screening patients where medication history may not be reliable or readily available. The result of the urine dipstick may be helpful in clinical circumstances if the dipstick test result supports a treatment decision for the patient and is particularly suitable for hospitals or urgent care centers where a specialized coagulation testing is not available or not available 24/7.

We describe an easy-to-use algorithm using the DOAC Dipstick based on the high NPV, thus excluding significant blood concentrations of DOACs using the patient's urine. This algorithm can enhance medical decision-making in acute care indications by distinguishing whether drug exposure is either an oral direct FXa- or thrombin inhibitor. This allows administration of the correct reversal agent when indicated, and can improve the timing of invasive medical diagnostic and therapeutic interventions. For time-sensitive interventions such as thrombolysis for acute ischemic stroke, the "reverse and lyse" strategy is commonly used for patients presumed to have recently ingested a DOAC.²⁷ Data from a recent retrospective real-world practice study suggests that clinicians appear to be effectively selecting those patients with recent DOAC exposure who are at an appropriately low risk for intravenous thrombolysis. The dipstick will exclude

DOAC concentrations ≥ 30 ng/mL, even though proposed thresholds for thrombolysis are higher. Thus, the dipstick may act as a green light for thrombolysis treatment if negative, but DOAC Dipstick results may also be useful in cases where the risk and benefit of thrombolysis are not as straightforward.²⁸ This also relates to medical diagnostic and therapeutic interventions, balancing the patient's bleeding risk and the urgency of the patient's intervention against the result of the dipstick with the threshold level being 30 ng/mL. The result of the dipstick needs to be interpreted in relation to the clinical picture of the patient. Along with DOAC Dipstick information, further decision-making can likely be improved based on additional variables such as type of DOAC, time of last intake, concomitant disease states, and interfering medications. Information from family members can also be helpful, especially in unconscious or cognitively impaired patients.

Other algorithms for assessing DOAC exposure have been described, including the use of a hemostatic assay with targeted thresholds of <30 and <50 ng/mL.¹² An algorithm for ROTEM uses different blood coagulation activators and specific clotting times at threshold values of <30 and <50 ng/mL.^{13–15} Another algorithm for bleeding patients suspected of taking DOACs involves initial testing with the DOAC Dipstick followed by ClotPro testing for positive dipstick results.¹⁶ A potential advantage to this approach is that viscoelastic measurements can assess other hemostatic dysfunctions unrelated to DOAC presence or effect.

Several limitations exist of DOAC Dipstick testing. The 87% NPV for exclusion of FXa inhibitors by the dipstick may result in inadequate medical decisions in 13% of patients, if the treating physician relies only on the urine dipstick test result. There is less apixaban excreted in urine than rivaroxaban or edoxaban,^{19,22,23} consistent with apixaban's primary hepatic clearance mechanism.¹² Detailed data on appearance of DOACs in plasma and urine following oral intake, the influence of active DOAC metabolites on the urine dipstick test, and of off-label uses or doses of these drugs remain to be investigated.

There are a few additional limitations for the proposed algorithm. For anuric patients, blood samples will need to be collected to assess DOAC exposure. For patients who are unable to provide spontaneous urine on their own, a urinary catheter may be placed if clinically indicated for other medical reasons. However, in these catheterized patients, the urinary DOAC concentration may not be accurately reflected by the urine dipstick test if an extended period of time has elapsed since the catheter drainage bag was last emptied. The performance of the DOAC Dipstick in urine samples collected from children has not yet been evaluated.

Other technical considerations for use of this algorithm would be the strict adherence to dipstick testing conditions. In busy emergency or urgent care settings, or in conditions where poor lighting or visual evaluation may be compromised (i.e., color blindness), the use of the DOAC Dipstick photometric reader may be of value to ensure proper adherence to the manufacturer's instructions for use of the urine dipstick for DOAC screening.

Conclusion

The DOAC Dipstick algorithm is a simple, rapid method of delivering DOAC results using patient urine. Advantages of the method are that it does not require knowledge of the specific DOAC taken by the patient, is a point-of-care format, and has a rapid turnaround time, thereby enabling its use even in small facilities such as community hospitals. This test excludes clinically relevant blood concentrations of DOACs, which can speed up clinical decision-making in critical medical situations such as major bleeding, acute ischemic stroke with consideration for intravenous thrombolysis, or urgent surgical procedures.

What is known about this topic?

- Direct oral anticoagulant (DOAC) agents are widely used to treat and prevent thrombotic events.
- There is an urgent need for a rapid and sensitive assay to exclude clinically relevant plasma levels of DOACs to guide medical decision-making.
- The DOAC Dipstick tests for the presence or absence of DOACs in urine samples on a disposable test strip at a plasma threshold of ≥ 30 ng/mL.

What does this paper add?

- Pooled analysis of five available studies, comparing DOAC Dipstick with LC-MS/MS or DOAC-calibrated chromogenic assays, indicates an acceptably high negative predictive value for exclusion of DOACs requiring verification of a match with the patient's clinical picture.
- The DOAC Dipstick excludes clinically relevant blood concentrations of DOACs at a threshold of ≥ 30 ng/mL, which may support clinical decision-making in critical medical situations, such as excessive bleeding, prior to intravenous thrombolysis, or before urgent surgical procedures.

Authors' Contribution

Conception of the work: initially by J.H., S.H., A.M., M.S., C.W. and a DOAC POCT meeting held on the occasion of the XXIII ISTH congress by all authors. Two-thirds of the authors participated in person and one-third virtually and approved the conception. Acquisition of data: I.C., P.C., H.H., S.H., A.M., M.P., M.S., J.V., C.W. Statistical analysis: H.H., S.H., C.W. Laboratory methods: J.D., J.V., I.C., P.C., A.M., M.S., M.P. Drafting: J.H., R.C.G., A.C., C.B., I.P., S.P., J.W. Reviewing: All authors. Agreement and final approval: All authors.

Conflict of Interest

J.H. is general manager and founder of DOASENSE GmbH, J.D. is CEO of Qualiblood SA. All other authors declare no conflicts of interest.

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