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DOAC Dipstick Testing Can Reliably Exclude the Presence of Clinically Relevant DOAC Concentrations in Circulation

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Abstract

In certain clinical situations, it is necessary to determine whether clinically relevant plasma levels of direct oral anticoagulants (DOACs) are present. We examined whether qualitative testing of DOACs in urine samples can exclude DOAC plasma concentrations of $\geq$30 ng/mL. This prospective single-center cohort study included consecutive patients treated with an oral direct factor Xa inhibitor (DXI) (apixaban, $n = 31$, rivaroxaban, $n = 53$) and direct thrombin inhibitor (DTI) (dabigatran, $n = 44$). We aimed to define the negative predictive value (NPV) and other statistical parameters of detecting DXIs and DTIs by DOAC Dipstick at plasma concentrations of $\geq$30 ng/mL. We also determined the best-fit threshold plasma levels using chromogenic substrate assays by logistic regression analysis. Between July 2020 and July 2021, 128 eligible patients (mean age 66 years, 55 females) were included into the study. The NPVs and sensitivities for DXI and DTI of DOAC Dipstick were 100% at $\geq$30 ng/mL plasma, for specificities 6 and 21% and for positive predictive values 62 and 72%, respectively. All diagnostic statistical tests improved to values between 86 and 100% at best-fitting plasma thresholds of $\geq$14 ng/mL for DXI and $\geq$19 ng/mL for DTI. Visual analysis using the DOAC Dipstick was 100% in agreement with that of the optoelectronic DOASENSE Reader for all the three DOACs.

Keywords
- oral anticoagulants
- DOAC Dipstick
- urine samples

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DOAC Dipstick testing can reliably exclude the presence of DOACs in urine samples at best-fitting thresholds of >14 and >19 ng/mL in plasma. The performance of the DOAC Dipstick at detecting lower DOAC concentrations in plasma requires confirmation.

Introduction

In recent years, direct oral anticoagulants (DOACs) have been widely used to prevent and treat thromboembolic diseases.[1,2] Treatment with DOACs does not require routine coagulation monitoring. However, there are special clinical conditions when the plasma DOAC concentration should be determined, such as bleeding, thromboembolic events during therapy, emergency surgery, invasive procedures, reduced drug elimination associated with renal or liver failure, and suspected noncompliance or overdose.[3,4]

Although DOACs significantly influence the results of coagulation tests, these assays are not appropriate for quantifying drug concentration and assessing anticoagulant effects, nor for excluding the presence of clinically relevant drug concentrations in the blood because of differences in responsiveness to individual commercial reagents.[5,6] We need to be able to accurately quantify DOAC plasma concentrations in patients to make important clinical decisions in certain situations, and different methods have been developed to do this. Of these methods, liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) is the most accurate[7–9] but can only be used in specialized laboratories because of high complexity and long turnaround times.[10,11] Therefore, assays on automated coagulation analyzers were introduced to quantify DOACs in plasma for clinical routine use.

Attempts have also been made to create a rapid screening assay, such as a point-of-care test, that can determine whether clinically relevant concentrations of DOACs are present in circulation. A rapid qualitative assay that can reliably determine whether DOACs are present in circulation would help treat patients on DOACs in emergency situations.[12] The in vitro diagnostic DOAC Dipstick (DOASENSE GmbH, Heidelberg, Germany) was recently developed to qualitatively detect DOACs in urine samples.[13,14] The DOAC Dipstick strip can detect the direct thrombin inhibitor (DTI) dabigatran on a thrombin inhibitor (THR) pad and the direct factor Xa inhibitors (DXIs) rivaroxaban, apixaban, and edoxaban on a factor Xa inhibitor (FXA) pad.[14] The test has a turnaround time of approximately 10 minutes and a positive or negative result can be determined by visually identifying pad colors or by using a semi-automated DOASENSE Reader (DOASENSE GmbH, Heidelberg, Germany). The primary purpose of the DOASENSE Reader is to exclude clinically relevant DOAC concentrations in the blood in urgent clinical situations. The clinically relevant threshold for DOAC concentrations in circulation is considered to be ≥30 or ≥50 ng/mL.[15,16] These limits were proposed for patients with serious bleeding. A DOAC concentration of >50 ng/mL was regarded as high enough to support antidote administration, whereas in those requiring an urgent major surgery, a DOAC-specific antidote should be considered to be administered at a plasma concentration of 30 ng/mL and higher.

The aim of this study was to evaluate whether the DOAC Dipstick can be used to exclude plasma concentrations of ≥30 ng/mL for dabigatran, rivaroxaban, and apixaban. DOAC plasma concentrations were determined in blood samples by specific quantitative chromogenic substrate assays and were compared at a plasma level of ≥30 ng/mL with qualitative results of DOAC concentrations in urine samples detected by the DOAC Dipstick. In addition, we estimated in this population the thresholds of plasma DOAC concentrations for the DOAC Dipstick by logistic regression analysis.

Methods

Study Design

This single-center, prospective, controlled cohort study recruited patients from the departments of neurology and cardiovascular diseases at Sestre Milosrdnice University Hospital Center between July 2020 and July 2021. The institutional ethics committee approved the study protocol on June 6, 2020. All patients provided written informed consent according to the ethical guidelines of the Declaration of Helsinki.

The inclusion criteria were age ≥18 years, treatment with dabigatran, rivaroxaban, or apixaban for at least 1 week, and written informed consent. Exclusion criteria were known renal insufficiency (creatinine clearance <30 mL/min/1.73 m^2), incapacity to understand and sign the informed consent, and DOAC intake less than 12 hours before plasma and urine sampling.

Demographic data (age, sex), type of DOAC, indication for anticoagulant therapy, time of last drug intake, time of blood and urine collection, and concomitant diagnoses and medications were documented by the study personnel. All data were entered into Excel 2017 (Microsoft). DOAC Dipstick test results obtained by visual evaluation and by the DOASENSE Reader were digitally photographed and kept in a specific case report form.

Participants and Methods

Blood and urine samples were taken from participants in the morning before the next drug dose was taken. Patients provided urine samples approximately 10 to 15 minutes after blood sampling. All patients were treated with the following approved DOAC doses: rivaroxaban 20 mg ($n = 41$) or 15 mg ($n = 13$) once daily, apixaban 5 ($n = 26$) or 2.5 mg ($n = 7$) twice daily, and dabigatran 150 mg ($n = 28$) or 110 mg ($n = 16$) twice daily.

Collection and Processing of Urine Samples

Urine samples were collected in a sterile 100-mL polypropylene urine beaker with integrated transfer device (Cat. No. 724310, Greiner Bio-One, Austria) and then transferred to 10-mL Vacuette Urine tubes with a round base (Cat. No. 455007, Greiner Bio-One, Austria) using plastic syringes. Aliquots were immediately frozen at −80°C in the same laboratory for further quantitative determination of DOAC concentration. Additional two 5-mL aliquots of urine were taken from the 100-mL urine beaker and transferred to new Vacuette Urine tubes (Greiner Bio-One, Austria) and tested immediately with the DOAC Dipstick by study personnel.

Collection and Processing of Blood Specimens

Venous blood was collected in 3.2% sodium citrate (volume 3.5 mL) containing vacutainers (Greiner Bio-One, Kremsmünster, Austria) and centrifuged within 1 hour of blood drawing at $3,500 \times g$ for 10 minutes at room temperature to obtain platelet-poor plasma. Concentrations of DOACs in plasma samples were determined on the same day and within 4 hours of blood collection. An additional tube of venous blood was collected in a vacutainer with no additives (Greiner Bio-One, Kremsmünster, Austria) and centrifuged at $3,500 \times g$ for 10 minutes at room temperature to obtain serum. The creatinine concentration and the estimated glomerular filtration rate (eGFR) were determined in serum samples using the eGFR CKD-EPI method within 6 hours of sample collection.

Performance of the DOAC Dipstick Test

DOAC Dipstick testing in urine has already been described in detail.[13] The DOAC Dipstick strip has four pads for qualitative testing: the THR pad (for detecting dabigatran), the FXA pad (for detecting rivaroxaban, apixaban, and edoxaban), a urine color pad (to check the urine color is normal), and a creatinine pad (to check creatinine levels are normal). In brief, all four pads on the strip were completely immersed in freshly collected urine for 2 to 3 seconds and incubated at room temperature for 10 minutes. The test pad colors were evaluated visually by two independent observers and compared with the reference scale attached to the test strip tube. Results were also analyzed using the semi-automated DOASENSE Reader. The test strip was photographed and the DOASENSE Reader results were printed out immediately after analysis for documentation.

Quantitative Determination of DOACs in Plasma and Urine Samples

Dabigatran, rivaroxaban, and apixaban were quantified using a coagulation analyzer BCSXP (Siemens Healthineers, Marburg, Germany) according to the manufacturer's protocol. Dabigatran concentrations were measured using the Innovance DTI chromogenic assay (Siemens Healthineers, Marburg, Germany) calibrated with Dabigatran Standards (Ref. No. OPOL93) (Siemens Healthineers, Marburg, Germany). Rivaroxaban and apixaban were measured using the Innovance Heparin assay (Siemens Healthineers, Marburg, Germany) calibrated with BIOPHEN Rivaroxaban Calibrator Low (Ref. No. 226001), BIOPHEN Rivaroxaban Calibrator (Ref. No. 222701), BIOPHEN Apixaban Calibrator Low (Ref. No. 226101), and BIOPHEN Apixaban Calibrator (Ref. No. 226201). All BIOPHEN calibrators are products of HYPHEN BioMed (Neuville-sur-Oise, France). All three DOAC assays were verified on the BCSXP analyzer as described earlier.[17]

DOAC concentrations are much higher in urine than in plasma,[14] so urine samples were prediluted with saline (0.9% NaCl) at ratios of 1:5 to 1:50 before DOACs were quantified using the coagulation analyzer BCSXP.

Statistical Analysis

All statistical calculations were performed with SAS software, release 9.4 (SAS Institute Inc., Cary, North Carolina, United States). Quantitative variables are presented by their mean values and 95% confidence intervals. Qualitative data are described by absolute and relative frequencies. To compare two groups, two-sample *t*-test, Chi-squared test, or Fisher's exact test was used, as appropriate. Mean values of the plasma or urine groups were compared using one-way ANOVAs.

Plasma DOAC concentrations were categorized as negative and positive according to a threshold of $\geq$30 ng/mL, and then compared with the FXA and THR pad results of DOAC Dipstick. Agreement between these two methods has been quantified by the Kappa coefficient. Furthermore, the Kappa coefficient was used to evaluate the interrater agreement between DOASENSE Reader and visual evaluation of the pads of DOAC Dipsticks.

Logistic regression analyses with the binary outcome DOAC present or absent were performed together with receiver operating curve (ROC) analyses to find best-fitting thresholds for plasma concentrations for FXA and THR pads. For each ROC analysis, the area under the curve (AUC) was assessed as a measure of goodness of the associated statistical model. A ROC analysis determines specified thresholds by the maximum value of the sum of sensitivity and specificity. It should be mentioned that slightly different thresholds would change values only marginally. The DeLong test has been used to compare two ROC curves.[18] For each threshold, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were assessed. In general, a test result with a *p*-value less than 0.05 was considered as statistically significant.

Results

A total of 131 plasma samples were collected during the study; samples from one patient were excluded because the urine color pad indicated an "abnormal" result (urine bilirubin: 361 µmol/L; normal: <3.4 µmol/L) and samples from two patients had to be excluded because the creatinine pad indicated a "low" result. A total of 128 evaluable samples were collected; 44 of these from patients treated with dabigatran, 53 from patients treated with rivaroxaban, and 31 from patients treated with apixaban. Demographic data of the participants are presented in ►**Table 1**. Patients with nonvalvular atrial fibrillation were treated more frequently

Table 1 Demographic data of the participants

Biographic data	DXI group	DTI group	All	*p*-Values
n	84	44	128	
Male/female (*n*/*N*)	47/37	26/18	73/55	0.733
Age (y), mean (95% CI)	64 (60–68)	67 (63–74)	66 (62–67)	
Apixaban, *n*	31		31	
Rivaroxaban, *n*	53		53	
Dabigatran, *n*		44	44	
NVAF, *n*	44	35	79	0.003
VTE, *n*	31	2	33	<0.001
Ischemic stroke, *n*	6	7	13	0.714
Other[a], *n*	6	0	6	0.093

Abbreviations: CI, confidence interval; DXI, direct factor Xa inhibitor; DTI, direct thrombin inhibitor; NVAF, nonvalvular atrial fibrillation; VTE, venous thromboembolism.
[a]Transient ischemic attack, cardiomyopathy (ejection fraction < 30%).

Table 2 Concentrations of dabigatran, rivaroxaban, and apixaban in plasma and urine samples collected from participants before their morning dose of the anticoagulant

DOAC	*n*	Mean (95% confidence interval) (ng/mL)		*p*-Values
		Plasma	Urine	
Dabigatran	44	37.8 (33.1–42.5)	3,954.3 (3,213.3–4,695.3)	<0.001
Apixaban	31	44.2 (37.8–50.6)	1,169.9 (883.8–1,456.0)	<0.001
Rivaroxaban	53	32.6 (27.8–37.5)	1,214.8 (853.0–1,576.5)	<0.001

Abbreviation: DOAC, direct oral anticoagulant.

with dabigatran and patients with venous thromboembolism more frequently with rivaroxaban and apixaban.

The concentrations of rivaroxaban, apixaban, and dabigatran in plasma and urine are presented in ►**Table 2**. DOAC concentrations were 20- to 100-fold higher in urine samples than in plasma samples and were highest for dabigatran followed by rivaroxaban and apixaban.

The results for correct and false evaluations of the FXA and DTI DOAC Dipstick pads at a ≥30 ng/mL plasma threshold are shown in ►**Table 3**. The best-fitting threshold of plasma levels was ≥14 ng/mL for DXI and ≥19 ng/mL for DTI. The numbers of accurate negative evaluations of the FXA and DTI pads were identical at both thresholds. At a threshold of ≥14 ng/mL, 1/7 test results was false negative for DXI (14%). There were too few patients ($n = 1$) to calculate the correct NPV for the DTI pad.

The AUC, sensitivity, specificity, NPV, and PPV values for DXI and DTI at thresholds of ≥30 ng/mL for DXI and DTI and at the best-fit threshold of ≥14 ng/mL for DXI and ≥19 ng/mL for DTI are presented in ►**Table 4**.

The ROC analysis showed an AUC of 0.859 for detecting DXI and of 0.814 for detecting DTI with the DOAC Dipstick at a threshold of ≥30 ng/mL (►**Table 4**). Sensitivities and NPVs were 100% for DXI and DTI and PPVs and specificities were 62 and 72% and 6 and 21% by logistic regression analysis for both DOACs. At a threshold of ≥14 ng/mL for DXI, the AUC was 0.994, and PPV and specificity increased to 85 and 99%, respectively. The AUC for DTI could not be determined at a threshold of ≥19 ng/mL and the other statistical parameters were 100%. The AUC of DXI at ≥30 ng/mL was significantly different to that at ≥14 ng/mL ($p < 0.001$) and could not be determined for DTI because there were not enough data (►**Table 4**).

There were no differences between the visual evaluations of the two independent observers for the FXA and THR DOAC Dipstick pads (kappa value of 1.0).

Discussion

The objective of this study was to examine whether the commercial DOAC Dipstick test can exclude the presence of clinically relevant plasma DOAC concentrations of 30 ng/mL or lower by rapid testing of urine samples. If so, the DOAC Dipstick may be able to assist rapid medical decision making in emergency clinical situations such as before urgent major surgical and/or diagnostic interventions or administration of reversal agents in the perioperative setting. To do this, we compared the quantitative plasma concentrations of DOACs, determined by a chromogenic substrate assay, for qualitative detection of DXI and DTI. We used a threshold of ≥30 ng/mL

Table 3 Comparison of DOAC Dipstick results with plasma DOAC concentrations for DXI ($n = 84$) and DTI ($n = 44$) according to plasma thresholds of ≥30 ng/mL and of ≥14 or ≥19 ng/mL

Threshold	Dipstick negative (*n*)	Conc., mean (95% CI) (ng/mL)	Dipstick positive (*n*)	Conc., mean (95% CI) (ng/mL)	Agreement (%) κ (95% CI)
DXI					
<30	6	8.7 (5.4–11.9)	22	20.3 (18.5–22.1)	74 κ = 0.27 (0.09–0.45)
≥30	–	–	56	46.5 (42.6–50.3)	
<14	6	8.7 (5.4–11.9)	1	12	99 κ = 0.92 (0.76–1.0)
≥14	–	–	77	39.4 (35.6–43.3)	
DTI					
<30	1	17	16	25.4 (23.7–27.1)	64 κ = 0.07 (−0.06–0.20)
≥30	–	–	27	45.9 (40.2–51.7)	
<19	1	17	–	–	100 κ = 1.0 (NA)
≥19	–	–	43	38.3 (33.6–43.0)	

Abbreviations: CI, confidence interval; Conc., concentration; DTI, direct thrombin inhibitor; DXI, direct factor Xa inhibitor; NA, not available; **κ,** kappa value.

Table 4 Area under the curve (AUC) according to the receiver operating curve (ROC) analysis and statistical parameters for DXI ($n = 84$) and DTI ($n = 44$) at thresholds of ≥30 ng/mL and thresholds of ≥14 and ≥19 ng/mL in plasma

DOAC	Threshold (ng/mL)	AUC ROC (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	*p*-Value 30 vs. 14 ng/mL
DXI	≥30	0.859 (0.809–0.909)	100 (93.6–100)	21.4 (8.3–41.0)	71.8 (60.5–81.4)	100 (54.1–100)	
DTI		0.814 (0.741–0.887)	100 (87.2–100)	5.9 (0.2–28.7)	62.8 (46.7–77.0)	100 (2.5–100)	
DXI	≥14	0.994 (0.981–1.0)	100 (95.3–100)	85.7 (42.1–99.6)	98.7 (93.1–100)	100 (54.1–100)	<0.001
DTI	≥19	n.a.	100 (91.8–100)	100 (2.5–100)	100 (91.8–100)	100 (2.5–100)	

Abbreviations: CI, confidence interval; DOAC, direct oral anticoagulant; DTI, direct thrombin inhibitor; DXI, direct factor Xa inhibitor; NPV, negative predictive value; PPV, positive predictive value.

as described in the literature and a more precise threshold determined by ROC analysis. Blood samples were collected before patients took their DOAC in the morning to obtain samples with concentrations close to the clinically relevant threshold of ≥30 ng/mL.[6]

We showed that DOAC concentrations were 20- to 100-fold higher in urine than in plasma. This has only been described for dabigatran,[19] apixaban, and rivaroxaban in few patients or has only been calculated[20] using plasma[7,8] or urine concentrations.[9,21,22] The high DOAC concentration we observed in urine may be explained by the high renal elimination rates of 80% for dabigatran, 33% for rivaroxaban, and 25% for apixaban,[8] and by the pharmacokinetics of DOACs. Higher concentrations of dabigatran than rivaroxaban and apixaban in urine have been shown using LC-MS/MS and chromogenic substrates.[9] These results support our findings.

A threshold of >30 ng/mL DOACs in plasma is currently regarded as relevant for clinical decisions in emergency situations. At values of 30 ng/mL and higher, DXI- and DTI-specific antidotes should be administered before performing an urgent major surgical intervention or in cases of severe hemorrhage.[8] In these urgent situations, it is essential to be able to rapidly and accurately test for DOACs. Specific chromogenic substrate assays have a turnaround time of 60 minutes or longer, which is not feasible for everyday use in urgent situations. Point-of-care tests can give results faster. Thrombin generation assays may reliably detect DOAC concentrations of 30 ng/mL in whole blood and 50 ng/mL in plasma.[23] However, these coagulation tests have limitations[23] and restricted availability. Recently, it was reported that for patients taking dabigatran, a normal thrombin clotting time or a negative DOAC Dipstick test result may justify to withhold a reversal agent or reversal would not be

warranted in a patient taking DXI with a negative DOAC Dipstick test result or a heparin anti-Xa level below the lower limit of quantification.[24] In a perioperative setting it was suggested that drug level >30 ng/mL may justify to postpone a high bleeding risk operation or to administer a reversal agent before surgical intervention.[25] If such test is not available in a short turnaround time a negative DOAC Dipstick test result would justify withholding a reversal agent for DXI and DTI and to perform urgent major surgery in patients.[26] In this study, we showed that the DOAC Dipstick can reliably detect clinically relevant plasma DOAC concentrations reported in the literature using urine samples. This means that, in the clinical situation, a positive DOAC Dipstick test shows that DOACs are present in the patient's blood and that specific quantitative DOAC determination in plasma should be performed as the next step in clinical decision making or in the case of a patient being considered for reversal, there may be no further testing needed.[14]

There is still some debate about which plasma DOAC concentrations are clinically relevant; both 30 and 50 ng/mL have been reported as clinically relevant to support decision-making processes.[23] In the present study, plasma samples were collected in the morning, before the next dose of DOAC was taken, to ensure plasma levels were as low as possible since the last intake. A strength of the study is that samples were obtained at trough plasma concentration and to enrich the population for DOAC levels closely above the prespecified threshold of interest. Consequently, plasma levels in our patients were relatively low compared with those reported in the literature.[7,8,14] These low concentrations allowed us to identify threshold levels for DXI (14 ng/mL) and DTI (19 ng/mL) determined by logistic regression analysis. Because of the pharmacokinetics of DOACs, the concentration in urine is higher than in plasma, and DOACs can be detected in urine using the DOAC Dipstick test. Additional studies are needed to confirm these results and to validate their clinical importance.

We also observed a high interrater agreement for the visual analysis of DXI and DTI pad colors on the DOAC Dipstick.[21] However, visual interpretation of the DOAC Dipstick may be difficult in stressful circumstances such as in the intensive care unit or in the presence of warm artificial light. In these cases, a semiautomatic reader can be used to interpret the results; we showed here that the reader results are 100% in agreement with the visual evaluation of DOAC Dipstick pads.

Accurate results are highly important and a false-negative result could have severe consequences. We did not observe any false-negative results when detecting DOACs at clinically relevant plasma concentrations (≥30 ng/mL) and also at ≥14 ng/mL using the DOAC Dipstick. The creatinine pad and the urine color pad can exclude the possibility of false-negative results—we excluded two patients with a "low" result on the creatinine pad and one patient with an "abnormal" result on the urine color pad.[14]

There are some limitations to the present study. First, we did not confirm DOAC concentrations in urine samples by LC/MS-MS. However, measurements of DOACs in urine using LC-MS/MS and specific chromogenic substrate methods have been shown to give similar results.[9] Second, the study included a relatively small number of patients and the statistical significance of test results in patients treated with dabigatran could not be determined. However, this is the first study reporting detection of DOACs in plasma and urine samples taken at the same time from the same patient. We observed higher than expected concentrations of DOACs in urine, which may explain this limitation. This requires further investigation. Third, our patients were on known and stable anticoagulation with DOACs and caution is required when transferring the results to patients from an emergency department. Other potential limitations for routine clinical use of the dipstick urine assay include the time and dose of the last DOAC intake, when the bladder was last voided, and patient's renal and liver function.

In conclusion, our study has confirmed that the DOAC Dipstick can be used to exclude the presence of clinically relevant DXI and DTI levels (≥30 ng/mL) in patient urine. A positive DOAC Dipstick test result suggests that DOACs are present in circulation at clinically relevant levels and that DOACs should be quantified in plasma as the next step in clinical decision making.

What is known about this topic?

- Quantitative determination of DOAC concentrations in plasma can be performed by specific chromogenic substrate assays on automated coagulation analyzers.
- DOAC concentrations are much higher in urine than in plasma due to their high renal elimination rates (80% for dabigatran, 33% for rivaroxaban, and 25% for apixaban) and the pharmacokinetics of DOACs.
- The in vitro diagnostic DOAC Dipstick test in urine samples can detect the direct thrombin inhibitor (DTI) dabigatran on a thrombin inhibitor (THR) pad and the direct factor Xa inhibitors (DXIs) rivaroxaban, apixaban, and edoxaban on a factor Xa inhibitor (FXA) pad.

What does this paper add?

- DOAC Dipstick testing in urine can reliably exclude the presence of clinically relevant concentrations (≥30 ng/mL) of dabigatran, rivaroxaban, and apixaban in blood.
- The DOAC Dipstick test may help the rapid medical decision making in emergency clinical situations in patients treated with DOAC drugs.
- A positive DOAC Dipstick test result suggests that DOACs are present in circulation at clinically relevant levels and that DOACs should be quantified in plasma as the next step in clinical decision making.

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Conflict of Interest

S.M., I.C., A.L.H., M.B.P., S.S.G., A.C.G., D.D.B., P.M., S.H., and C.W. have nothing to declare. J.H. is the founder and general manager of DOASENSE.

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