White Paper DOAC Dipstick

Important publications
on the DOAC Dipstick and DOASENSE Reader

Uwe Spannagel, Remi Corlin, Frieder Loesel, Job Harenberg

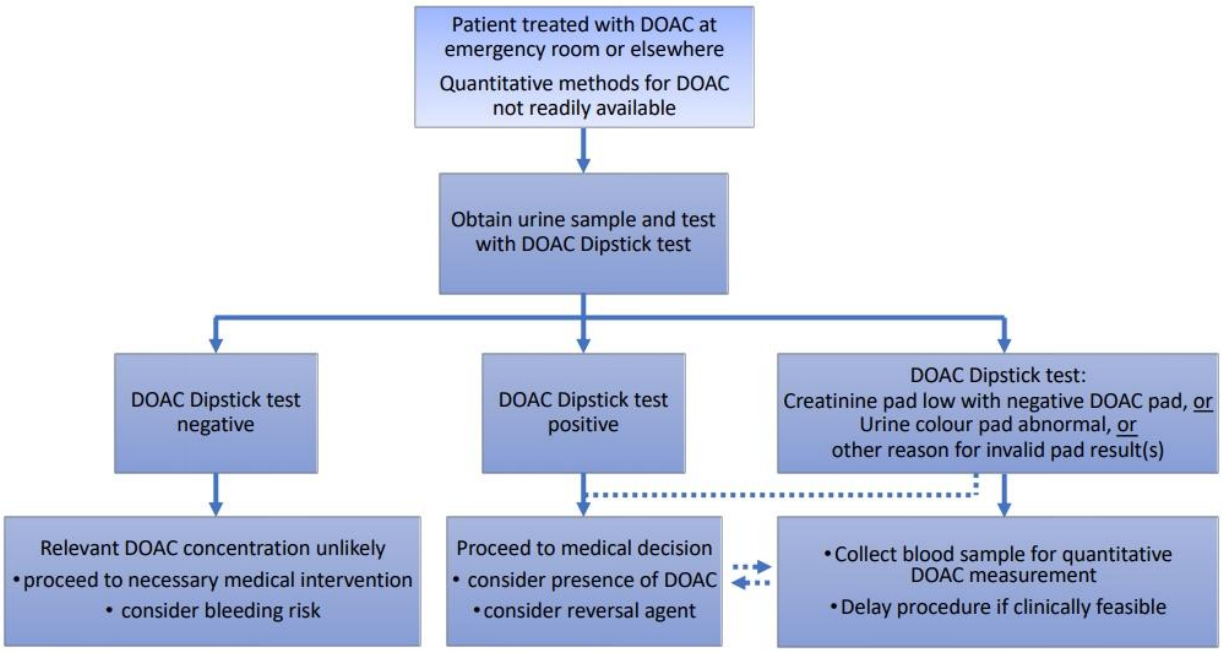
Content:

Introductory Remarks & Summary:

The fast and reliable detection of Direct Oral Anticoagulants (DOACs) with a Point-of-Care-Test (POCT) has been an unmet medical need until now. DOASENSE has addressed this problem with the development of the *DOAC Dipstick*, providing a rapid POCT method for many indications and hospitals.
DOACs are predominantly excreted unchanged in urine and can be diagnosed very reliably within only 10 minutes with the IVDR/CE-certified, commercially available *DOAC Dipstick* and the optional, also IVDR-compliant optoelectronic *DOASENSE Reader*. In the following, we summarize important studies on the *DOAC Dipstick* and the *DOASENSE Reader* that have been published in international scientific journals. In each case, we also provide an online link that can be used to access the full publications.
The publications from multiple centers now uniformly show >95% sensitivity and an equally high negative predictive value at a plasma concentration of DOACs of 30 ng/ml. This results in a high degree of certainty for patients and the treating physician regarding the question of whether a DOAC is present in the plasma - and if so, which type of DOAC (for further literature, see https://doasense.de/resources.html).
For clinical decision making the clinical picture of the patient has to be considered and the *DOAC Dipstick* test can contribute as an important decision support.
For example, the *DOAC Dipstick* test can provide decision support for physicians in the following clinical pictures:

- Patients with severe bleeding:
    - In case of negative detection of a DOAC, the result supports the clinically indicated treatment, e.g., that no DOAC antidote is required.
    - If positive for a DOAC, the result supports administration of an antidote or mechanical intervention. A quantitative test can further help guide the physician's decision.
- Patients with indication for an intervention, e.g., in trauma surgery or neurology:
    - If negative for a DOAC, the result supports the indication for surgical intervention or therapy with a fibrinolytic agent.
    - If positive for a DOAC, the result supports postponement of surgery, mechanical intervention for stroke, or administration of a DOAC antidote. An additional quantitative test can help guide the physician's decision.

These procedures are illustrated in the following flowchart and were published in 2024, see section IV:



In Germany, the *DOAC Dipstick* test is now used at more than 300 hospitals, and it is used internationally in Australia, Austria, Brazil, the Czech Republic, Estonia, France, Italy, Lithuania, Portugal, Spain, and an increasing number of other countries. Several publications by internationally recognized user groups document consistent results of the *DOAC Dipstick* test, and the DOASENSE POCT has been included in various international guidelines, thereby reinforcing the safety and importance of *DOAC Dipstick* for the diagnosis of DOACs in general medicine, emergency medicine, trauma surgery, neurology and cardiology.

I. Accuracy of a Rapid Diagnostic Test for the Presence of Direct Oral Factor Xa or Thrombin Inhibitors in Urine — A Multicenter Trial

Job Harenberg, Jan Beyer-Westendorf, Mark Crowther, Jonathan Douxfils, Ismail Elalamy, Peter Verhamme, Rupert Bauersachs, Svetlana Hetjens, Christel Weiss

Thromb Haemost 2020;120:132–140.

After several preliminary studies with prototypes since 2014 and after regularly reproducible results were achieved for the detection of all DOACs approved in Germany with the *DOAC Dipstick* in urine, a large clinical study could be set up in 2017. This study was conducted in 18 centers in Germany. These were specialist practices as well as clinics with extensive study experience. Of 914 patients included, 880 could be evaluated. About half of the patients received a DXI (n=451) and half a DTI (n=429).

Urine from all patients taking DOACs was analyzed for the presence of DOACs using the *DOAC Dipstick*. In addition, the urine samples were analyzed for DOACs in a central laboratory using mass spectroscopy. The primary endpoint of the study was the rate of true positive and true negative results from the visual reading of the *DOAC Dipstick* compared to the results obtained from the patients' urine samples by mass spectroscopy. In addition, inter-center variations were analyzed to detect any center effects (= kappa).

The results were as described below. The critical correct negative predictive value was 96.1 % for DXI and 99.6 % for DTI. A kappa of 94.5 % and 98.7 % means that all centers performed equally well.

	Factor Xa Inhibitor pad		**Thrombin Inhibitor pad**	
	Mean	95% CI	Mean	95% CI
Sensitivity	0.962	0.941; 0.978	0.995	0.983; 0.999
Specificity	0.984	0.967; 0.993	0.991	0.978; 0.998
Accuracy	0.973	0.960; 0.982	0.993	0.985; 0.998
NPV	0.961	0.939; 0.977	0.996	0.984; 0.999
PPV	0.984	0.968; 0.994	0.991	0.976; 0.998
Kappa	0.945	0.924; 0.967	0.987	0.976; 0.997

CI = Confidence interval
NPV = negative predictive value
PPV = positive predictive value
Kappa = Measure of agreement

Table *– Important results of the multicenter study*

Conclusion:

The DOAC Dipstick **is very well suited to exclude relevant DOAC concentrations within 10 minutes, so that physicians can initiate lysis or surgery.**

- **Simple and fast point-of-care diagnostics of DOACs possible for the first time**
- **Very high sensitivity and specificity of the *DOAC Dipstick test***
- **No laboratory required**

Online link to the publication: https://doi.org/10.1055/s-0039-1700545

II. Detection of Direct Oral Anticoagulants in Patient Urine Samples by Prototype and Commercial Test Strips for DOACs – A Systematic Review and Meta-analysis

Andrea Martini, Job Harenberg, Rupert Bauersachs, Jan Beyer-Westendorf, Mark Crowther, Jonathan Douxfils, Ismail Elalamy, Christel Weiss, Svetlana Hetjens

TH Open 2021;5:e438–e448.

This meta-analysis investigated the extent to which the results of the preliminary studies are consistent with prototypes of the *DOAC Dipstick* for point-of-care diagnostics of DOACs in urine and confirm the findings of the aforementioned multicenter study.
Three further studies with a total of 658 patients under DXI and 586 patients under DTI were identified, which were examined and evaluated with the prototype of the *DOAC Dipstick.* Thus, the results of a total of 1,109 patients under DXI and 1,015 patients under DTI were available for the meta-analysis.
The pooled analysis of the studies with the results of the prototypes and the commercially available *DOAC Dipsticks* was 96.8 and 97.9 % for sensitivity and specificity, respectively, for DXI and 99.3 and 99.3 % for DTI.

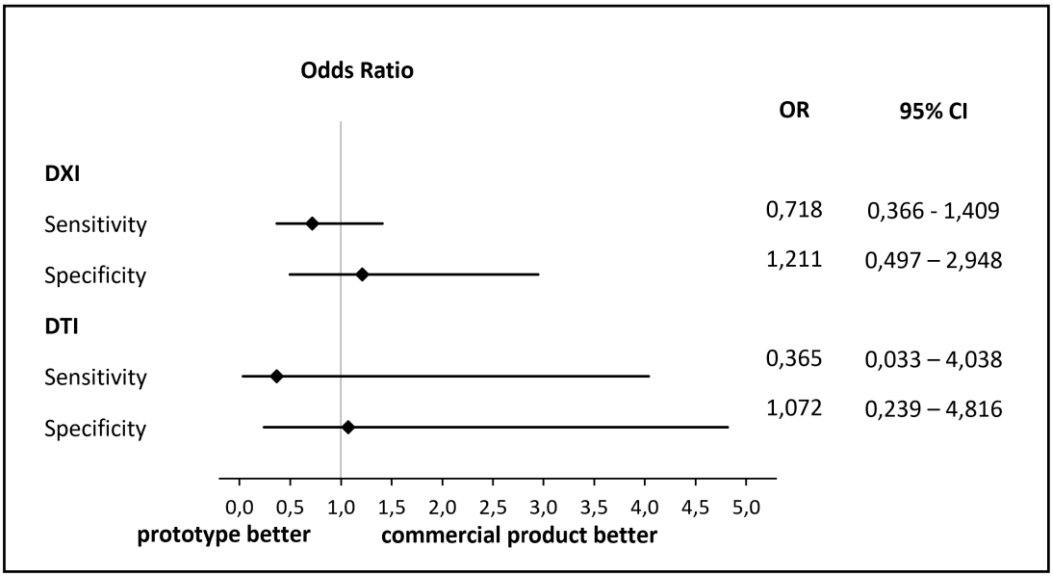


Figure *- Sensitivity and specificity for the detection of DXIs and DTI for the commercial DOAC Dipstick and the prototype. Odds ratios (OR) greater than 1 indicate that the sensitivity or specificity is higher for the commercial DOAC Dipstick product compared to the prototype, and vice versa.*

Conclusion:

- **The initial prototype *DOAC Dipsticks*, which were produced before commercial approval, demonstrated the same high quality and reliability for DOAC point-of-care diagnostics as the CE-certified commercial products now being distributed.**
- **This further broadens the available scientific data basis on POC diagnostics with the *DOAC Dipstick* technology.**

Online link to the publication: https://doi.org/10.1055/s-0041-1732437

III. Performance Characteristics of DOAC Dipstick in Determining Direct Oral Anticoagulants in Urine

Job Harenberg, Andrea Martini, Shanshan Du, Sandra Krämer, Christel Weiss, Svetlana Hetjens
Clin Appl Thromb Hemost. 2021 Jan-Dec;27, doi: 10.1177/1076029621993550

Laboratory-based coagulation tests for heparins (UFH and NMH), fondaparinux, vitamin K antagonists (VKA) as well as for direct oral anticoagulants (DOACs) have become widely established in clinical and laboratory routine, are very specific and well reproducible by different users. However, it was relatively unknown until now, how specific the *DOAC Dipstick* is with regard to anticoagulants other than DOACs. Likewise, how and whether the results differ when interpreting the *DOAC Dipstick* by different users.
In this study of 108 patients, it was shown that there was no interaction between UFH, NMH, fondaparinux or VKA and the *DOAC Dipstick.* Abnormal urine staining, which could distort the result of the *DOAC Dipstick,* was reliably detected, so that these dipsticks were not evaluated. The interobserver variability also was very low. This confirmed the results of the multicenter study with 900 patients published in 2020.

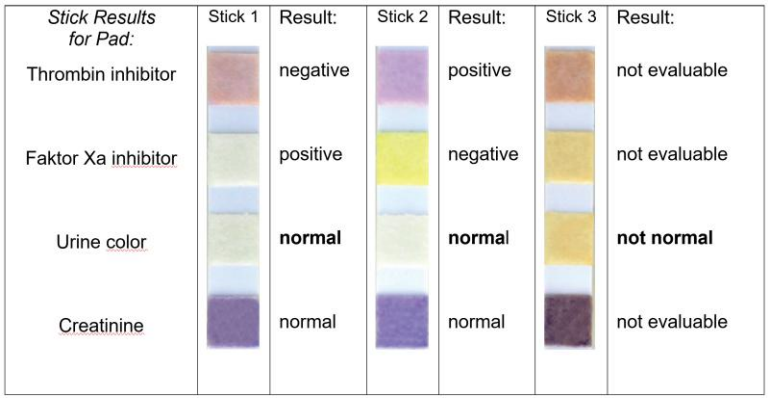


Figure *– Digital photos of test strips after incubation with urine from patients. Stick 1: Patient undergoing treatment with rivaroxaban, Stick 2: Patient undergoing treatment with dabigatran, Stick 3: Patient undergoing therapy with rivaroxaban and dark discolored urine, pad urine color "not normal" and colors of the other pads therefore "not evaluable".*

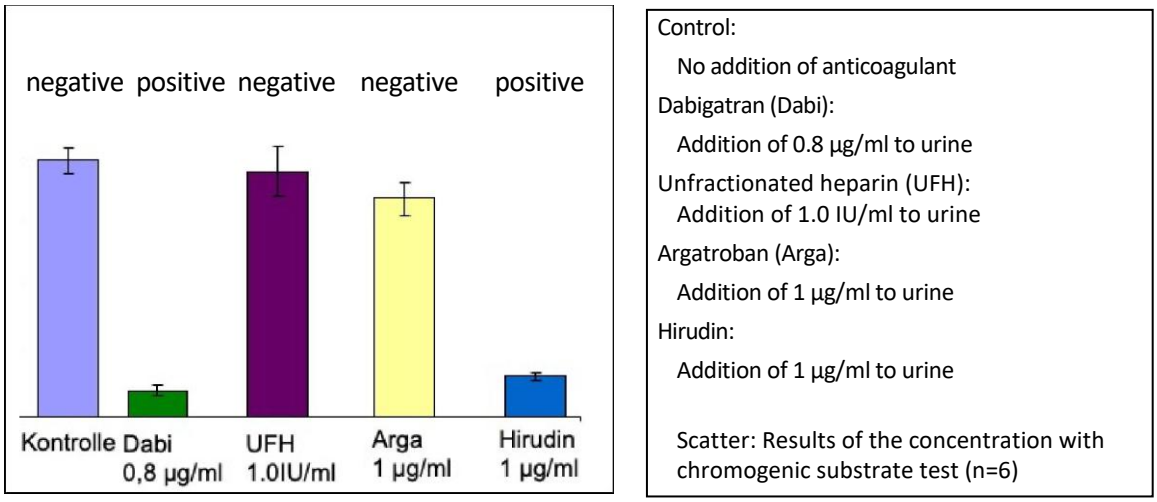


Figure *– Influence of addition of dabigatran, unfractionated heparin (UFH), argatroban and hirudin to urine of healthy subjects on thrombin pad of DOAC Dipstick (n=6)*

Conclusion:

- **The *DOAC Dipstick* reacts highly specifically with DOACs. Other relevant anticoagulants do not interfere with the results.**
- **Different observers achieve identical test results with the *DOAC Dipstick*.**

Online link to the publication: https://doi.org/10.1177/1076029621993550

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

Harenberg J, Gosselin RC, Cuker A, Becattini, Pabinger I, Poli S, Weitz JI, Ageno W, Bauersachs R, Ćelap I, Choi P, Douketis J, Douxfils J, Elalamy I, Fareed J, Falanga A, Favalor E, Gerotziafas GT, Herkner H, Hetjens S, Klamroth R, Heubner L, Langer F, Lip GYH, Mac Grory B, Margetić S, Merrelaar A, Pikta M, Renne' T, Schwameis M, Schulman S, Strbian D, Tafur A, Violi F, Vassart J, Walenga J, Weiss C

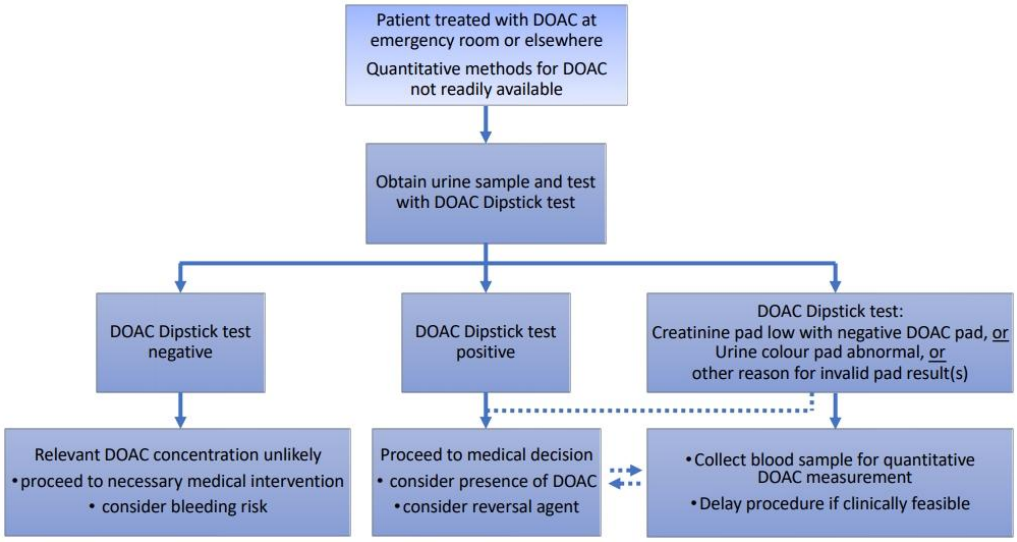
Thromb Haemost 2024 Mar 8. doi: 10.1055/a-2261-1811.

Following the publication of five scientific papers from different countries on the performance of the *DOAC Dipstick* in patients in cardiology (Margetic, Örd), neurology (Margetic, Örd, Tan) and the emergency department (Merrelaar), an international group of experts decided to summarize the study data in a special form of meta-analysis: a pooled analysis.

The sensitivity and the negative predictive value at the **plasma threshold value of ≥30ng/mL** of DOACs are circled in red in the following table:

	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)
NPV	86.6 (76.0 – 93.7)	99.6 (97.7 – 100)
PPV	87.2 (83.7 – 90.1)	73.4 (63.7 – 83.2)
Specificity	50.0 (40.2 – 59.0)	91.8 (87.7 – 94 .9)

Based on the results of the pooled analysis, the authors of this consensus paper developed **a simple and practicable algorithm for treatment decisions** to identify the absence or presence of DOACs in patients:



Conclusion:

- **This is the first meta-analysis of DOACs determined by a DOAC POCT method for several indications at a plasma threshold ≥30ng/mL.**
- **The plasma threshold was determined by LC-MS/MS and chromogenic assays in plasma to define the *DOAC Dipstick's* performance values.**
- **This test is particularly suitable in situations where quantitative tests for DOACs are not readily available.**

Online link to the publication: https://doi.org/10.1055/a-2261-1811

V. DOAC Dipstick testing can reliably exclude the presence of clinically relevant DOAC concentrations in circulation

Sandra Margetić, Ivana Ćelap, Arijana Lovrenčić Huzjan, Marijana Bosnar Puretić, Sandra Šupraha Goreta, Anesa Čajević Glojnarić, Diana Delić Brkljačić, Pavao Mioč, Job Harenberg, Svetlana Hetjens, Christel Weiss

Thromb Haemost. 2022,122(9):1542-1548.

Another important question is how well the *DOAC Dipstick* in urine detects the critical threshold value > 30 ng/ml and < 30 ng/ml of DOACs in plasma. A working group from Zagreb / Croatia succeeded in determining the correlation in a clinical study: The DOAC value of 30 ng/ml in plasma is recognized by experts as the threshold value below which no significant anticoagulant effect can be expected and therefore surgical interventions, lysis therapy or a PDA can be performed.
This is the first study to compare or correlate urine levels of DOACs with simultaneously determined levels in plasma. In total, samples from 128 patients treated with apixaban (n=31), rivaroxaban (n=53) or dabigatran (n=44) were analyzed. The main objective was to show that clinically relevant DOAC concentrations of > 30 ng/ml in plasma can be excluded with the *DOAC Dipstick* (negative predictive value; NPV).
The result showed that all DOAC plasma concentrations above a value of 30 ng/ml were detected as correct positive with the *DOAC Dipstick.* Regardless of whether it was a direct oral FXa (DXI) or thrombin inhibitor (DTI). Thus, the negative predictive value (NPV) and the sensitivity were 100%.

Comparison of INR with DOAC concentration in plasma and DOAC Dipstick in Urine

	INR (VKA)	DOAC concentration	Dipstick
Surgery / lysis / PDA usually feasible	< 1.7	< 30 ng/ml plasma	negative

Table *– Critical thresholds of anticoagulation by vitamin K antagonists and DOACs below which surgical intervention can usually be performed*

In addition to the visual reading of the *DOAC Dipstick*, it was also analyzed with the optoelectronic *DOASENSE Reader*. Here, the agreement between visual and electronic analysis was also 100%.

Conclusion:

This study was the first to prove that negative results with the *DOAC Dipstick* from urine samples – read both visually and by means of the electronic *Reader* – never exceeded the clinically relevant threshold value of 30 ng/ml in plasma. In this respect, surgical interventions, lysis treatments and PDAs are usually possible without further quantitative laboratory tests.

- **Negative predictive value (NPV) and sensitivity of *DOAC Dipstick* was found to be 100% compared to quantitative DOAC measurement**
- **Critical DOAC threshold of 30ng/ml plasma is reliably determined with the *DOAC Dipstick***

Online link to the publication: https://doi.org/10.1055/a-1753-2748

VI. Performance of a Qualitative Point-of-Care Strip Test to Detect DOAC Exposure at the Emergency Department: A Cohort-Type Cross-Sectional Diagnostic Accuracy Study

Anne E. Merrelaar, Magdalena S. Bögl, Nina Buchtele, Marieke Merrelaar, Harald Herkner, Christian Schoergenhofer, Job Harenberg, Jonathan Douxfils, Romain Siriez, Bernd Jilma, Alexander O. Spiel, Michael Schwameis

Thromb Haemost. 2022, 122(10):1723-1731.

The use of the *DOAC Dipstick* in emergency medicine is of crucial importance for patients, since the therapeutic decisions depending on whether a patient has been taking a DOAC must be made here particularly quickly and safely.

The research group of Merrelaar et al. from Vienna studied the *DOAC Dipstick* test from urine samples with plasma concentrations of apixaban, edoxaban, rivaroxaban, and dabigatran for thresholds of 30 ng/ml plasma and others in nearly 300 patients in the emergency department of a large hospital. Plasma concentrations were measured using mass spectrometry as the gold standard method.

The results show a high sensitivity of >95% with the *DOAC Dipstick* at the threshold of 30 ng/ml in plasma for all DOACs in patients after admission to the emergency department.

The authors demonstrate the high sensitivity, specificity, negative and positive predictive value of the test for FXa and thrombin inhibitors here also for patients in the emergency department. They are in general agreement with the results of patients from specialist outpatient clinics (Harenberg et al. 2020) and from neurological and cardiology departments (Margetic et al. 2022). However, due to the small number of factor Xa pads of patients under treatment with dabigatran (n=31) to be evaluated compared with oral factor Xa inhibitors (n=234), the statements on specificity and, to a certain extent, also for the negative predictive value and the positive predictive value of the factor Xa pad are of somewhat limited validity, also with regard to the corresponding parameters from previous studies.

In case of a positive test result of the *DOAC Dipstick*, the authors suggest a quantitative DOAC determination in blood, if the possibility for a rapid determination exists.
If the test is negative, emergency surgery and other urgent interventional procedures, such as thrombolysis, can usually be performed promptly without further quantitative DOAC confirmation testing.

The authors conclude that the *DOAC Dipstick* test is a particularly safe decision aid for physicians in emergency medicine and supports decisions in triage of patients.

Conclusion:

This study demonstrates for the first time that the *DOAC Dipstick* test can be used safely and reliably in the emergency department of a large hospital.

- **All DOACs were reliably detected with the *DOAC Dipstick* at a threshold of 30 ng/ml plasma.**
- **This means that a negative or a positive result from the *DOAC Dipstick* can significantly support clinical therapy options in emergency care.**
- **The DOASENSE POCT can also accelerate patient care in emergency medicine.**

Online link to the publication: https://doi.org/10.1055/s-0042-1750327

VII. Assessment of Direct Oral Anticoagulant Status Using the DOASENSE Dipstick in Thrombolysis Eligible Patients with Stroke: Proof-of-Concept Study

Peter Shuangyue Tan, Peter SW Park, Ross Cody, Tanya Frost, Bailey McNamara, Marija Borosak, Philip MC Choi

Stroke. 2023;54: e142-e144.

This is the first publication in a major peer-reviewed journal on a study using the *DOAC Dipstick* test in a stroke center setting, where every minute counts in therapeutic decision making, e.g. proceeding with thrombolysis. Thrombolysis in acute stroke may be safe depending on the direct oral anticoagulant (DOAC) plasma concentration level, but timely access to DOAC lab assays is limited. Thresholds of plasma concentrations are still controversial for conduction of intravenous thrombolysis in patients with ischemic stroke, or for administration of DOAC antidotes.

The authors performed a single-center, prospective, 2-armed observational study at a high-volume primary stroke center in Australia.
The acute arm recruited patients eligible for thrombolytic therapy (n=17; Rivaroxaban, Apixaban, Dabigatran). Expedited plasma DOAC level determination and *DOAC Dipstick* tests were performed during the acute stroke assessment. The subacute arm recruited ischemic stroke inpatients, following DOAC initiation for secondary prevention (n=24) by assessing plasma DOAC level at 4 to 6 hours following ingestion to determine the agreement of results. DOAC levels (threshold >30 ng/mL) were determined by chromogenic substrate tests and *DOAC Dipstick* test following the instructions for use.

Results

- Median time to result for plasma DOAC level versus *DOAC Dipstick* test:
  52 min (interquartile range, 38–67) for lab assay; versus
  20 min (interquartile range, 17–24) for *DOAC Dipstick*, including urine acquisition time.
- 95% (16/17) and 92% (22/24) agreement between the *DOAC Dipstick* results and DOAC plasma level >30 ng/mL for all DOACs in the acute and subacute treatment arm.
- No false negatives in the acute arm.
- Two false negative results with corresponding plasma levels of 56 and 58 ng/mL in the subacute arm: an apixaban case in which diluted urine was collected from an indwelling catheter bag and a dabigatran case in an elderly lady with urinary incontinence.
- 10 patients not on DOAC tested negative on *DOAC Dipstick* and plasma concentration.

The authors conclude that their study provides preliminary evidence for using the *DOAC Dipstick* test to identify patients for prompt thrombolysis, who would have been excluded otherwise (based on their clinical history alone).

Conclusion:

This is the first study on the use of the *DOAC Dipstick* test in a stroke center.

- **Rapid determination of DOAC status may improve targeting of reversal agent administration, minimizing thrombolysis delay.**
- **Data provide preliminary evidence for using the *DOAC Dipstick* test strips to identify patients for prompt thrombolysis.**

Online link to the publication: https://doi.org/10.1161/STROKEAHA.122.041555

VIII. Evaluation of DOAC Dipstick Test for Detecting Direct Oral Anticoagulants in Urine Compared with a Clinically Relevant Plasma Threshold Concentration

Lenna Örd, Toomas Marandi, Marit Märk, Leonid Raidjuk L, Jelena Kostjuk, Valdas Banys, Karit Krause, Marika Pikta

Clin Appl Thromb Hemost, 2022, Volume 28: 1-8. doi: 10.1177/10760296221084307.

The aim of this study was to evaluate the possible uses and limitations of the *DOAC Dipstick* and to compare the visual analysis with that of the *DOASENSE Reader*.

Plasma and urine samples were collected from 23 patients who were reliably taking DOACs. The DOAC concentrations in plasma and urine were determined using chromogenic substrate tests and also in urine using the *DOAC Dipstick*. Plasma concentrations were dichotomized at a threshold of ≥30 ng/mL. In addition, the patient samples were compared with samples from a control group that did not take anticoagulants (n=10), as well as with DOASENSE control urines.

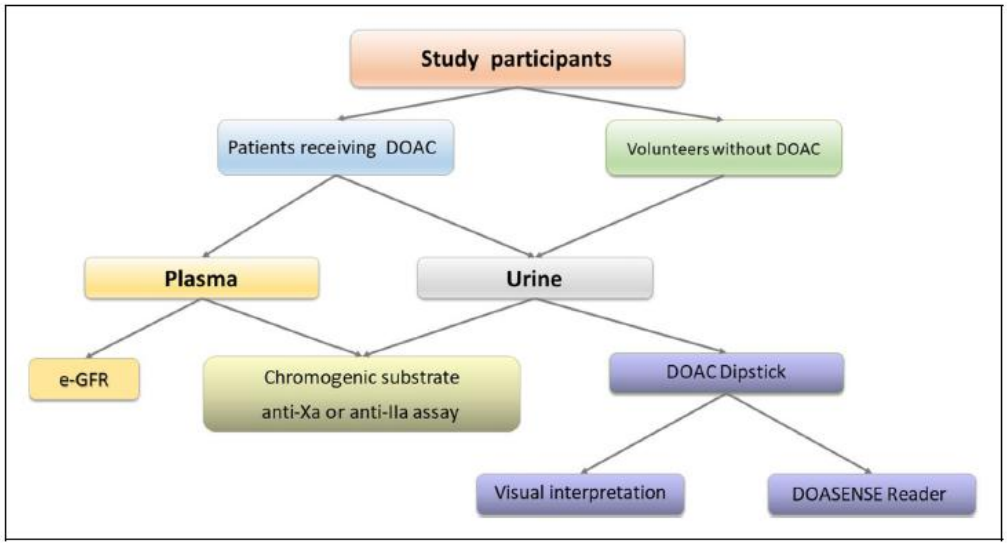


Figure *– Study design*

Results: The results of the *DOAC Dipstick* test were positive in 21/23 patient urine samples with a DOAC plasma concentration of ≥30 ng/ml and in 2/23 patient urine samples with a DOAC plasma concentration of <30 ng/ml.
The interindividual agreement between three observers was over 90% for the visual analysis of the patient urine samples and 100% for the analysis of the patient urine using the *DOASENSE Reader*. Likewise in the control group without DOACs, as well as in the control urines.
The *DOAC Dipstick* detects DOACs in urine very reliably from a plasma threshold of ≥30 ng/ml. All measurement methods, from urine with the *DOAC Dipstick*, or the *DOASENSE Reader* or alternatively from plasma, showed a very high level of agreement. The measurements with urine and plasma of the control group without DOACs and the control urines confirmed the result.

Conclusion:

- **The *DOAC Dipstick* is able to quickly and reliably detect or exclude DOAC concentrations that are above or below the critical threshold of 30ng/ml, either with purely visual reading or using a reader.**
- **If the *DOAC Dipstick* test is negative, the patient can usually be referred immediately for an intervention such as lysis or surgery. If the test is positive, depending on the urgency, it can be repeated after some time or, if available, a quantitative test can be followed.**

Online link to the publication: https://doi.org/10.1177%2F10760296221084307

IX. Comparison of the DOAC Dipstick Test on Urine Samples With Chromogenic Substrate Methods on Plasma Samples in Outpatients Treated With Direct Oral Anticoagulants

Loula Papageorgiou, Svetlana Hetjens, Jawed Fareed, Sanny Auge, Laetitia Tredler, Job Harenberg, Christel Weiss, Ismail Elalamy, Grigorios T. Gerotziafas

Clin Appl Thromb Hemost, 2023, Vol 29: 1-7. doi: 10.1177/10760296231179684.

In this publication, the authors focus on another important topic of DOAC therapy and the benefits of *DOAC Dipstick*: **Adherence**

The background is that the *DOAC Dipstick* is an easy-to-use, non-invasive test that is suitable for assessing adherence to DOAC therapy in outpatients. In real life, adherence to DOAC therapy is reported to be only 70% and decreases over the years and with increasing age.
The authors aimed to show that *DOAC Dipstick* in a specialized center may be sufficient to improve treatment adherence.

Methods: This prospective, single-center, non-interventional study was conducted in a specialized hemostaseology outpatient clinic in Paris in 120 patients treated with apixaban (n=43) and rivaroxaban (n=77) and evaluated the outcomes of *DOAC Dipstick* with a DOAC plasma concentration of a threshold of >30 ng/ ml. Indications for DOAC therapy were atrial fibrillation and prophylaxis of recurrent venous thrombosis or pulmonary embolism, particularly in patients with cancer-related thrombosis.

Results: At a threshold of >30 ng/ml plasma 102/105 patients had true positive *DOAC Dipstick* results and only 3/105 patients had false negative results. In 10 patients with positive dipstick results, the plasma concentrations of apixaban and rivaroxaban were between 20 and 30 ng/ml. This shows the high sensitivity of *DOAC Dipstick* and that a negative result of *DOAC Dipstick* really captures clinically relevant low and high values of plasma concentrations of apixaban and rivaroxaban.

The sensitivity and positive predictive value (PPV) of *DOAC Dipstick* were high: 97.1 % (95 % confidence interval: 91.9-99.4) and 89.5 % (82.3-94.4) respectively.

There was complete agreement between two independent observers in the interpretation of the test strips.

Conclusion:

This study demonstrates for the first time that:

- **The *DOAC Dipstick* has proven to be a valuable, sensitive, and accurate tool for patient-friendly assessment of adherence to DOACs, that can be used by general practitioners at primary care level.**
- **The results demonstrate excellent performance at a clinically relevant plasma concentration of 30 ng/ml.**
- **Repeated use of the *DOAC Dipstick* POCT may improve adherence to DOAC therapy.**

Online link to the publication: https://doi.org/10.1177/10760296231179684

X. The DOAC (direct oral anticoagulant) Dipstick reliably excludes residual FXa inhibitors levels in the preoperative setting

Julie Vassart, Alfonso Tafur, Marisa Durante, Anne-Yseult Boucher, Laure Morimont, Jeanine M. Walenga, Job Harenberg, Jonathan Douxfils

Thromb Res 2024 Jul;239:109023. doi: 10.1016/j.thromres.2024.04.029.

The importance of rapid determination of direct oral anticoagulants (DOACs) using the *DOAC Dipstick* is described in this publication prior to elective knee or hip replacement. Patients with deep vein thrombosis or atrial fibrillation and anticoagulation with apixaban (n=37) and rivaroxaban (n=16) were included in the study before operation.
Methods: DOACs are measured in urine using DOAC Dipstick and in plasma using mass spectrometry.
Results: Sensitivity, specificity, negative (NPV) and positive predictive value (PPV) of *DOAC Dipstick* are given in the table at different cut-off values of DOACs in plasma.

Table *– The sensitivity and NPV are 100% at the limit values of 30 and 50 ng/mL. Specificity and PPV are lower at 54% to 83%.*

MW=mean value
PPV/NPV= positive/negative predictive value

Threshold	≥20 ng/mL MW	≥30 ng/mL MW	≥50 ng/mL MW
Sensitivity, %	94	100	100
Specificity, %	83	71	64
PPV, %	70	60	54
NPV, %	97	100	100

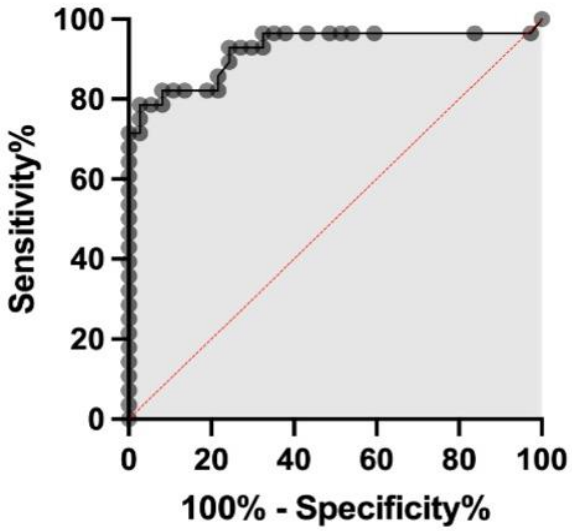


Figure *– The area under the curve (AUC) of the 'Receiver Operating Curve' (ROC) is 93%. This value is very high for a method comparison of coagulation analysis results with DOACs*

Conclusion:

- **This is the first publication on results of the plasma threshold value of DOACs at 30ng/mL with DOAC POCT in surgical medicine compared to plasma concentration measured by mass spectrometry.**
- **The high NPV is significant in the preoperative phase for immediate surgical intervention or its postponement.**
- **Sensitivity and NPV of *DOAC Dipstick* are equally high at 30 ng/mL plasma in preoperative medicine as in non-surgical diseases**

Online link to the publication: https://doi.org/10.1016/j.thromres.2024.04.029

XI. Trend-setting resolution of the Federal Joint Committee (G-BA) of 8 April 2021 on the new guideline for the care of femur fractures close to the hip joint and specifically on the handling of anticoagulant medication

The Federal Joint Committee (G-BA) is the highest-level decision-making body of the joint self-administration in the German health system. It determines, in the form of guidelines, which medical services the insured can claim. In addition, the G-BA decides on quality assurance measures for practices and hospitals.
In this decision, the G-BA specified the SOP for handling anticoagulant medication – especially regarding direct oral anticoagulants (DOAC). An "*earliest possible assessment regarding anticoagulant medication*" must be carried out. If patients on anticoagulation do not have reliable information on the last time they took the medication, clinics should carry out an additional assessment of the coagulation status with "*suitable test procedures*" - also for DOACs.
In the **supporting reasons for** the G-BA decision, it states in a quintessence: "*For all four common DOACs, a urine dipstick test with color coding is also available, which indicates with **very high reliability** whether relevant drug concentrations are present in the urine"* and "***The test accuracy in the study was high (sensitivity and specificity >95% each).** ... **Thus, the test is basically suitable as an on-site test in emergency situations***".

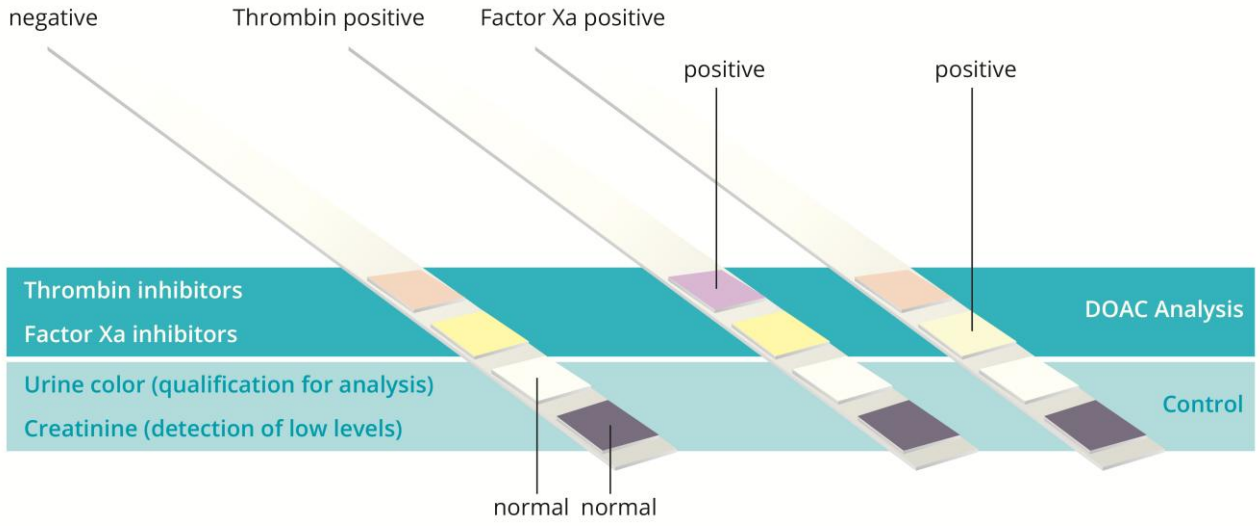


***Figure** - Functional principle of the DOAC Dipstick test strip*

<u>Conclusion</u>:
The GB-A requires the earliest possible coagulation diagnostics also for DOACs and lists the *DOAC Dipstick* as suitable test.
Even if the medication history is supposedly reliable, it is known from studies that up to one third of patients do not take prescribed DOACs or no longer take them regularly after just one year. With the *DOAC Dipstick,* these patients can be reliably identified, they can receive surgery more quickly and thus morbidity and mortality can be reduced.

- **Reliable coagulation diagnostics for the assessment of the earliest possible time of surgery are necessary.**
- ***DOAC Dipstick* designated as the only point-of-care test with very high reliability by GB-A.**

Online link to the publication: https://www.g-ba.de/beschluesse/4655/

XII. DOAC Dipstick for detecting direct oral anticoagulants

National Institute for Health and Care Excellence (NICE) of the UK NHS
Medtech innovation briefing [MIB248], February 2021

The National Institute for Health and Care Excellence (NICE) is an agency of the Department of Health (DH) in the UK. It serves both the English and Welsh National Health Services (NHS). It publishes guidelines in various areas, e.g. on the use of new procedures within the NHS. The evaluation is primarily based on evaluations of effectiveness and cost-effectiveness.
NICE experts agree that the *DOAC Dipstick* technology is a novel concept for detecting direct oral anticoagulants (DOACs). The experts pointed out that the technology is innovative compared to standard care because it does not require blood sampling or laboratory analysis. In addition, *DOAC Dipstick* diagnostics are much faster and easier to perform than the usual laboratory tests, which are also not available everywhere. The *DOAC Dipstick* could one day replace the usual DOAC diagnostics. Competing technologies are not known to the NHS.
The technology could be resource-efficient if it leads to earlier clinical decisions, improve clinical outcomes for patients and reduce the length of hospital stay. The cost of the test is inexpensive at around £15 per dipstick compared to £34 for standard clotting tests in the laboratory.

Conclusion:
NICE is on par with the GB-A in Germany in its positive assessment of the *DOAC Dipstick*. The *DOAC Dipstick* could one day replace standard laboratory diagnostics for DOACs in the UK.

- **Non-invasive, innovative aspect of the *DOAC Dipstick* in DOAC POC diagnostics.**
- **Very good study data basis with > 1,000 patients.**
- **Not inferior to the gold standard mass spectroscopy.**

Online link to the publication: https://www.nice.org.uk/advice/mib248

XIII. 2021 Australasian Anesthesia Blue Book

After the initial market launch of the *DOAC Dipstick* and the optoelectronic *DOASENSE Reader* for POC diagnostics of DOACs in Germany in 2019, the market launch in other European and non-European countries, such as Australia, is progressing.
In 2021, the *DOAC Dipstick* was included in the prestigious Australasian Anesthesia Blue Book in the chapter "*Dose monitoring of DOACs*". It described that urine testing with the *DOAC Dipstick* has several advantages over blood sampling or DOAC plasma testing and is probably the best POC diagnostic tool in an emergency situation, as the result is available within only 10 minutes. If the result is positive and further laboratory tests are required, the type of DOAC identified by the dipstick can be specifically investigated.
If the *DOAC Dipstick* is negative, surgical interventions can be performed without further quantitative DOAC laboratory tests. Similarly, spinal anesthesia can be performed. This is possible because there is a high correlation between urine and plasma levels measured in parallel.

Conclusion:

- **The *DOAC Dipstick* is already used in several non-European countries and is recommended by various professional societies.**

Online link to the publication (please see the "Blue Book 2021" links on that page):
https://www.anzca.edu.au/safety-and-advocacy/advocacy/college-publications/australasian-anaesthesia-(the-blue-book)

XIV. DOASENSE test is listed in the Anaesthesia Guidelines in Estonia

In 2022, the Estonian Society of Anaesthesiologists updated its guidelines for the management of antithrombotic drugs in planned and emergency surgery.
Of interest and particular relevance is Table 10 on Page 14 of the new document, listing that DOASENSE's *DOAC Dipstick* test can exclude the presence of Dabigatran (Anti-Thrombin) or Rivaroxaban, Apixaban and Edoxaban (Anti-Factor Xa), or assist in the decision to administer a reversal agent.

Conclusion:

This is another example of the ongoing acceptance and adoption of the DOASENSE test in emergency and elective surgery:

- **as an alternative to laboratory quantitative assays for the exclusion of DOACs**
- **as a qualitative assay that may guide the administration of the relevant antidote (Praxbind or Ondexxya)**

Online link to the guideline:
https://anest.ee/ravijuhised/ then click on ***Uus!*** *Antitrombootilised ravimid plaanilises ja erakorralises kirurgias*
or here: https://doasense.de/files/2023-11_EST-Guideline.pdf

XV. DOASENSE's DOAC Dipstick is the recommended Point-Of-Care Test for the prescription of Andexanet alpha (Ondexxya) in Tuscany (Italy)

In August 2023 the highest regional health authorities in Tuscany (Italy) enacted a new procedure for the appropriate prescription of ONDEXXYA that is recommended to all professionals involved. It clearly stipulates the DOASENSE *DOAC Dipstick* and provides detailed guidance across three distinct documents:
A letter was sent to all regional Emergency Departments, stipulating that "in the decision-making process for the prescription of the ONDEXXYA drug, the use of the following test is indicated: test strip for DOACs – DOASENSE Dipstick Ref 001". Further, the letter continues: "We hereby recommend that the companies and organisations in question make available the diagnostic indicated above in all the Emergency Urgent Structures of the Region, together with the specific reader."
An order form was designed to be used by clinicians to support the prescription of ONDEXXYA. The section "DOSAGE NAO" (Dose of DOAC) lists the two options for testing, i.e. plasma level >30ng/mL or Urinary (POCT) positive.
Finally detailed guidelines were drafted for indications for use of Andexanet Alfa. Page 8 provides an algorithm to support the prescription of the drug showing the same two alternatives for the testing: plasma level >30ng/mL or Urinary (POCT) positive.

Conclusion:

- **Andexanet alpha is approved but not yet reimbursed in Italy. Its prescription is now conditioned to the adherence to this protocol in Tuscany, which requires evidence of active presence of a qualified anti-factor Xa test.**
- **Acknowledging the challenge to obtain quantitative results within the time required for a decision, this decision instructs all regional emergency departments to be equipped with the *DOAC Dipstick* test and with the *DOASENSE Reader* for documentation of printed results.**

Online link: https://doasense.de/files/2023-11_IT-Recommendation.pdf

XVI. DOAC Dipstick test included in new Guideline published by the European Society of Anaesthesiology and Intensive Care

Clinical guideline on reversal of direct oral anticoagulants in patients with life threatening bleeding

Grottke, Oliver; Afshari, Arash; Ahmed, Aamer; Arnaoutoglou, Eleni; Bolliger, Daniel; Fenger-Eriksen, Christian; von Heymann, Christian

Eur J Anaesthesiol 2024, 41: 327-350

The European Journal of Anaesthesiology published a new *"Clinical guideline on reversal of direct oral anticoagulants in patient with life threatening bleeding"*
This is the first international guideline to include the DOASENSE test for DOACs and represents a new and strong recognition by the clinical community of the important clinical gap that the *DOAC Dipstick* test fills when there is no quantitative DOAC-specific test available in time. The publication stated the following:

- *"**In the absence of specific coagulation testing, DOAC dipstick testing can be suggested to demonstrate the presence of DOACS**. (Level 2C)"*
- *"Finally, **a urine dipstick test might be used to detect DOAC in emergency settings and before urgent surgery within a few minutes. Studies including a total of more than 1000 patients and a meta-analysis showed that sensitivity, specificity, accuracy and predictive values and agreement between determination of DOAC levels in urine using the DOAC dipsticks were noninferior or superior as compared with mass spectroscopy**."*

It is of further interest, that the guideline disqualifies *"nonspecific viscoelastic coagulation monitoring to reliably detect DOAC levels."* It also endorses specific viscoelastic Ecarin/Russell's viper venom tests. But, as a reminder, Haemonetics announced the commercial discontinuation of the *ClotPro* device, graded "2C" by the guideline authors.

Online link: https://doi.org/10.1097/EJA.0000000000001968

SEE ALSO:

XVII: Clinical guideline on reversal of direct oral anticoagulants in patients with life threatening bleeding: use of a urine dipstick

Job Harenberg, Florian Langer, Jürgen Koscielny

Eur J Anaesthesiol 2024; 41:713-4

In this letter to the editor of European Journal of Anaestesiology, the authors updated with provided data the grading of *DOAC Dipstick* published in the guideline *"Clinical guideline on reversal of direct oral anticoagulants in patient with life threatening bleeding"* as follows:

- The new data on *DOAC Dipstick* indicated evidence from randomized, controlled clinical trials (Level 1B) and from observational studies (Level 2A) on the 30 ng/mL plasma cut-off value
- This new data should assign evidence at least as Level 2A to *DOAC Dipstick*

Conclusion:

- **This is the first international guideline to include the *DOAC Dipstick* test of DOASENSE for determination of presence of DOACs in bleeding emergencies if quantitative tests are not readily available.**
- **The guideline and additional publication acknowledge the quality of the *DOAC Dipstick* test and the respective clinical studies.**

Online link: DOI: 10.1097/EJA.0000000000002021

XVIII: Recent guideline from the British Society of Haematology on the measurement of direct oral anticoagulants lists the DOASENSE point-of-care test

Baker P, Platton S, Arachchillage DJ, Kitchen S, Patel J, Riat R, Gomez K.

Br J Haematol. 2024 Oct;205(4):1302-1318

Online link: https://onlinelibrary.wiley.com/doi/10.1111/bjh.19729

AND

XIX: Urgent Reversal of Direct Oral Anticoagulants in Critical and Life-Threatening Bleeding: A Multidisciplinary Expert Consensus

Rodrigues A, Gonçalves LR, Gregório T, Baldaia C, Santo GC, Gouveia J.

J Clin Med. 2024 Nov 14;13(22):6842. doi: 10.3390/jcm13226842

Online link: https://www.mdpi.com/2077-0383/13/22/6842

Conclusion:

- **The recommendations of the British Society for Haematology and of a Portuguese Expert Consensus both state that the presence of Factor Xa and thrombin DOACs can be excluded reliably by *DOAC Dipstick*, corresponding to a blood level of < 30 ng/mL.**
- **More and more guidance, guidelines and recommendations are published where *DOAC Dipstick* is mentioned as an alternative reliable method to exclude clinically relevant plasma level of DOACs, specifically in emergency medicine or when quantitative laboratory methods are not readily available.**

XX: IVDR certification of the DOASENSE DOAC point-of-care test

In early 2025 the Notified Body DEKRA issued IVDR certificates for the *DOAC Dipstick*, confirming that the test complies with European requirements of the IVDR (EU) 2017/746 Regulation (Class C device).
The optional *DOASENSE Reader* has been compliant with the IVDR since 2022 (Class A device).

EU Certificate

for the assessment of the technical documentation

according to Regulation on In-vitro Diagnostic Medical Devices (EU) 2017/746 Annex IX Chapter II

As a Notified Body of the European Union, DEKRA Certification GmbH certifies, that the manufacturer

DOASENSE GmbH

Single Registration Number (SRN): DE-MF-000015367
Waldhofer Straße 102, 69123 Heidelberg, Germany

that the technical documentation of the product(s) described in the annex complies with the provisions of the Regulation on In-Vitro Diagnostic Medical Devices (EU) 2017/746. The certificate is based on the results of the assessment of the technical documentation according to the Regulation on In-Vitro Diagnostic Medical Devices (EU) 2017/746 Annex IX Chapter II, which are recorded in the report referred to in the annex.

Product: DOAC Dipstick

EU Certificate no.: 51551-71-A0-00

Certificate valid from: 2025-02-21
Certificate valid to: 2030-02-20

Benannt durch/Designated by Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten
BS-IVDR-100

Digitally signed by Andre Schmitz
Date: 2025-02-21 14:38:00 +01:00

DEKRA Certification GmbH, Stuttgart, 2025-02-21
Notified Body ID number: 0124

DEKRA Certification GmbH * Handwerkstraße 15 * D-70565 Stuttgart * www.dekra-certification.de/medizinprodukte

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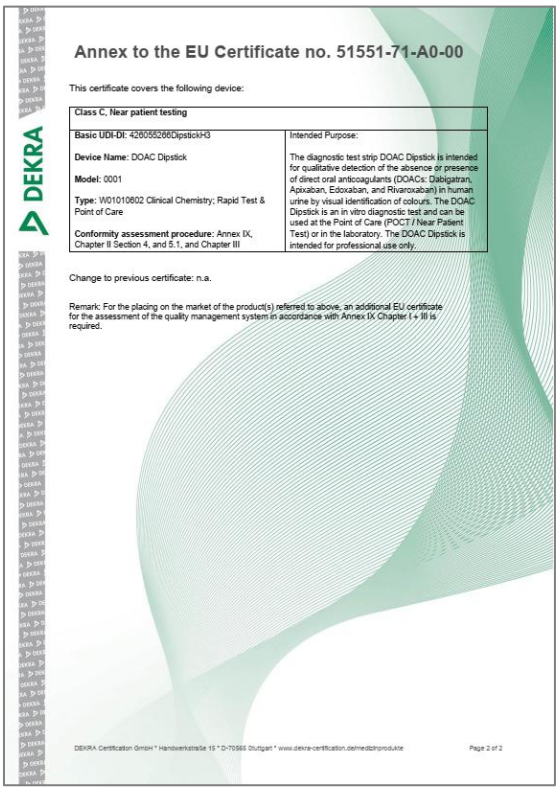

Annex to the EU Certificate no. 51551-71-A0-00

This certificate covers the following device:

Class C, Near patient testing	
Basic UDI-DI: 426055266DipstickH3 **Device Name:** DOAC Dipstick **Model:** 0001 **Type:** WI01010602 Clinical Chemistry; Rapid Test & Point of Care **Conformity assessment procedure:** Annex IX, Chapter II Section 4, and 5.1, and Chapter III	Intended Purpose: The diagnostic test strip DOAC Dipstick is intended for qualitative detection of the absence or presence of direct oral anticoagulants (DOACs: Dabigatran, Apixaban, Edoxaban, and Rivaroxaban) in human urine by visual identification of colours. The DOAC Dipstick is an in vitro diagnostic test and can be used at the Point of Care (POCT / Near Patient Test) or in the laboratory. The DOAC Dipstick is intended for professional use only.

Change to previous certificate: n.a.

Remark: For the placing on the market of the product(s) referred to above, an additional EU certificate for the assessment of the quality management system in accordance with Annex IX Chapter I + III is required.

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EU Certificate

for the assessment of the quality management system

according to Regulation on In-vitro Diagnostic Medical Devices (EU) 2017/746 Annex IX Chapter I+III

As a Notified Body of the European Union, DEKRA Certification GmbH certifies, that the manufacturer

DOASENSE GmbH

Single Registration Number (SRN): DE-MF-000015367
Waldhofer Straße 102, 69123 Heidelberg, Germany

applies a quality management system according to Annex IX Chapter I+III of the regulation on in-vitro diagnostic medical devices (EU) 2017/746 for the devices listed in the annex. This certificate is based on the assessments listed in CNo51551-00 and is only valid in conjunction with the successful completion of the annual surveillance audits.

EU Certificate no.: 51551-70-00-00

Certificate valid from: 2025-02-21
Certificate valid to: 2028-04-04

Benannt durch/Designated by Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten
BS-IVDR-100

Digitally signed by Andre Schmitz
Date: 2025-02-21 14:37:43 +01:00

DEKRA Certification GmbH, Stuttgart, 2025-02-21
Notified Body ID: 0124

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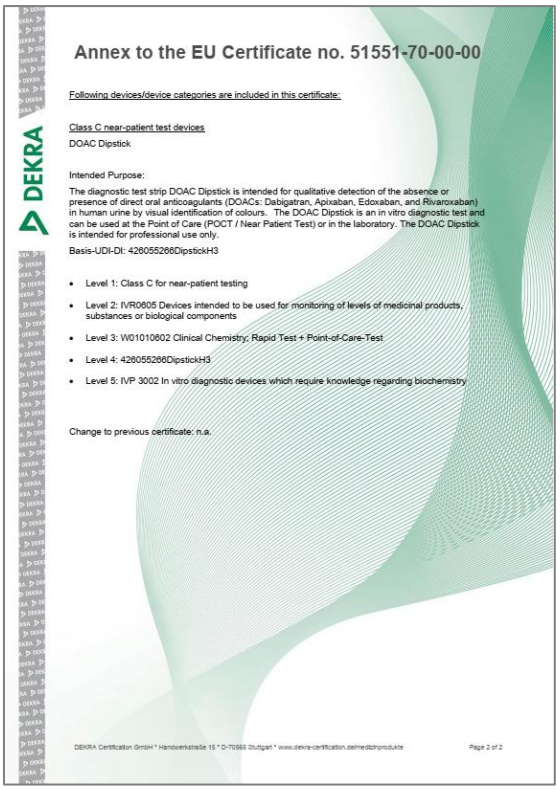

Annex to the EU Certificate no. 51551-70-00-00

Following devices/device categories are included in this certificate:

Class C near-patient test devices

DOAC Dipstick

Intended Purpose:

The diagnostic test strip DOAC Dipstick is intended for qualitative detection of the absence or presence of direct oral anticoagulants (DOACs: Dabigatran, Apixaban, Edoxaban, and Rivaroxaban) in human urine by visual identification of colours. The DOAC Dipstick is an in vitro diagnostic test and can be used at the Point of Care (POCT / Near Patient Test) or in the laboratory. The DOAC Dipstick is intended for professional use only.

Basis-UDI-DI: 426055266DipstickH3

- Level 1: Class C for near-patient testing
- Level 2: IVR0605 Devices intended to be used for monitoring of levels of medicinal products, substances or biological components
- Level 3: WI01010602 Clinical Chemistry; Rapid Test + Point-of-Care-Test
- Level 4: 426055266DipstickH3
- Level 5: IVP 3002 In vitro diagnostic devices which require knowledge regarding biochemistry

Change to previous certificate: n.a.

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ANNEX:
Further citations of *DOAC Dipstick* publications in the scientific literature

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Clin Appl Thromb Hemost. 2022 Jan-Dec;28:10760296221096422. doi: 10.1177/10760296221096422.

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