White Paper DOAC Dipstick

Important studies on the DOAC Dipstick and DOASENSE Reader in the international trade press

Uwe Spannagel, Frieder Loesel, Job Harenberg

Content:

I. 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 CE-certified, commercially available *DOAC Dipstick* and the optional 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).

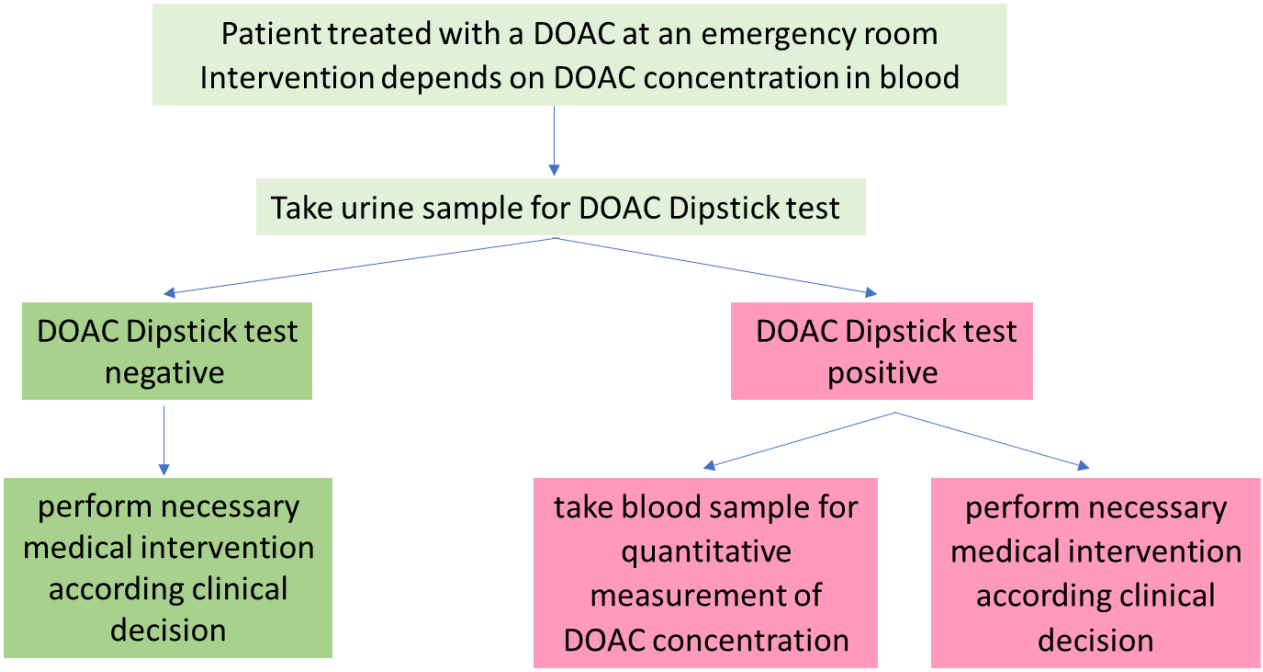
For clinical decision making the clinical picture of the patient has to be considered and the *DOAC Dipstick* test can contribute as an important decision support.

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:



In Germany, the *DOAC Dipstick* test is now used at more than 200 hospitals and it is used internationally in Australia, Brazil, France, Italy, Lithuania, Austria, Spain, the Czech Republic and an increasing number of other countries. Several publications by internationally recognized user groups document consistent results of the *DOAC Dipstick* test, thereby reinforcing the safety and importance of *DOAC Dipstick* for the diagnosis of DOACs in general medicine, emergency medicine, trauma surgery, neurology and cardiology.

II. 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 1 – *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

III. 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.

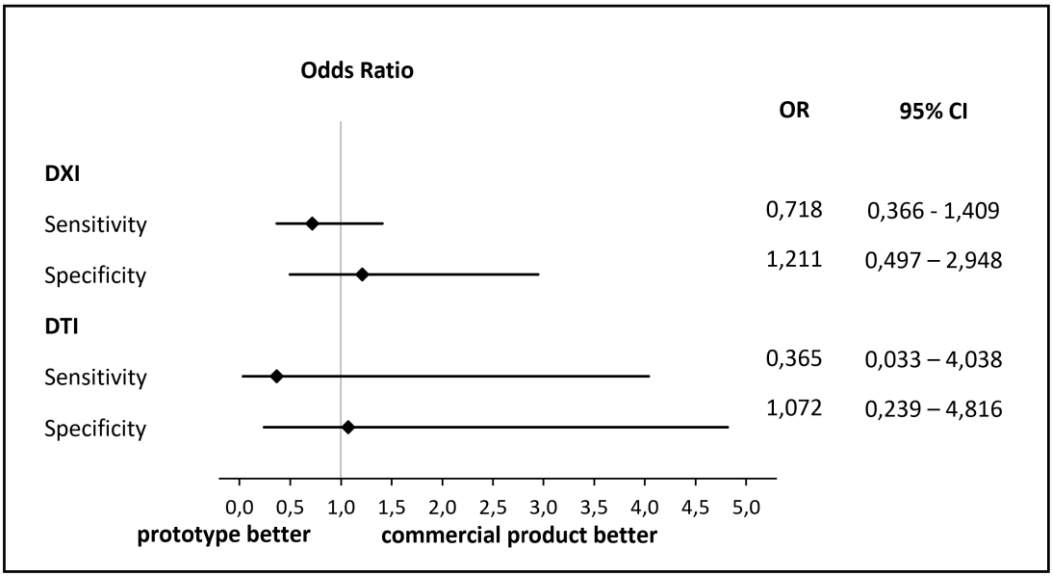


Figure 1 *- Sensitivity and specificity for the detection of DXIs and DTI for the commercial DOAC Dipstick and the prototype. Odds ratios (OR) greater than 1 indicate that the sensitivity or specificity is higher for the commercial DOAC Dipstick product compared to the prototype, and vice versa.*

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

IV. 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

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.

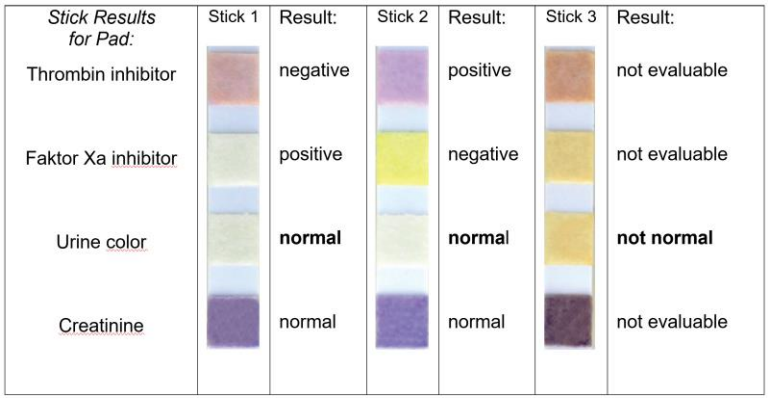


Figure 2 – *Digital photos of test strips after incubation with urine from patients. Stick 1: Patient undergoing treatment with rivaroxaban, Stick 2: Patient undergoing treatment with dabigatran, Stick 3: Patient undergoing therapy with rivaroxaban and dark discolored urine, pad urine color "not normal"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

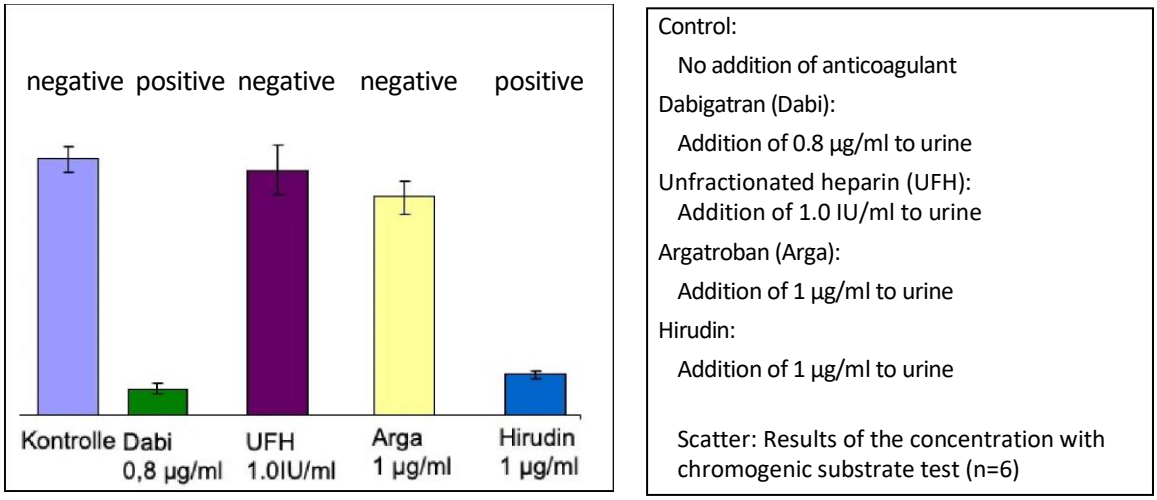


Figure 3 – *Influence of addition of dabigatran, unfractionated heparin (UFH), argatroban and hirudin to urine of healthy subjects on thrombin pad of DOAC Dipstick (n=6)*

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

V. 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***".

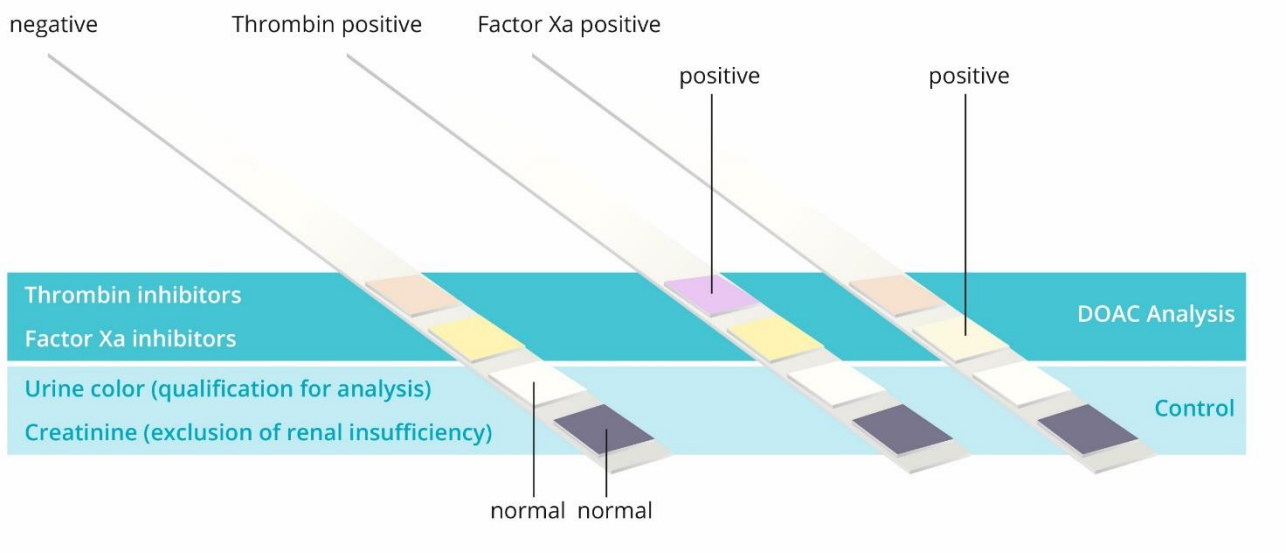


Figure 4 *- Functional principle of the DOAC Dipstick test strip*

<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 actually 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/

VI. 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

VII. 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:
https://www.anzca.edu.au/resources/college-publications/australasian-anaesthesia-(the-blue-book)/blue-book-2021.pdf

VIII. Modern diagnostics in emergency medicine

Niederdöckl J, Buchtele N, Schwameis M, Domanovits H

Wien Klin Wochenschr 133, 249–266 (2021).

In Austria, the working group of the authors successfully conducted a study with approx. 300 patients in the emergency department of the University Clinic for Internal Medicine using the *DOAC Dipstick* in Vienna.

The increasing use of point-of-care testing in emergency medicine has led to a reduction in time delays in patient treatment and can improve the patient's medical outcome.

The good experience gained in the study prompted the authors to include the *DOAC Dipstick* in their review paper "*Modern diagnostics in emergency medicine*".

The *DOAC Dipstick* allows rapid and accurate detection or exclusion of DOACs after only 10 minutes from the patient's urine.

Severe trauma, bleeding complications and immediate surgical interventions require prompt diagnosis for the presence of anticoagulants.

Conclusion:

- **The urine-based *DOAC Dipstick* can thus become a valuable, readily available tool in the diagnosis of DOACs in clinical practice as well as in emergency medicine.**

Online link to the publication: https://doi.org/10.1007/s00508-020-01657-2

IX. 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 Jan 27

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 2 *– 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

X. 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, July 4

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

XI. 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;54:00–00.

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

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