

White Paper DOAC Dipstick

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

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I. Introductory Remarks:

Direct oral anticoagulants (DOACs) were introduced to the market in Germany in 2008. The first approved product was dabigatran (Pradaxa®) as a thrombin inhibitor, followed by rivaroxaban (Xarelto®), apixaban (Eliquis®) and edoxaban (Lixiana®). In the meantime, they have a majority market share compared to vitamin K antagonists and are predominantly used for stroke prophylaxis in atrial fibrillation, for primary and secondary prophylaxis of deep vein thrombosis and pulmonary embolism, but also for postoperative thromboembolism prophylaxis in major orthopaedic surgery.

As a rule, coagulation monitoring is not required when DOACs are administered. In certain situations, such as stroke before planned lysis, before major surgery with increased risk of bleeding and other indications, this may nevertheless be necessary. The usual point-of-care coagulation tests are not suitable for DOACs, and many laboratories, especially in smaller hospitals, cannot carry out the quantitative special coagulation tests. Moreover, in urgent interventions the time until the results are available – usually more than 1 hour – is much too long.

Since DOACs are predominantly excreted unchanged in the urine (Figure 1), they can now be diagnosed very reliably within only 10 minutes using the *DOAC Dipstick*, which has been commercially available for some time, and the optional optoelectronic *DOASENSE Reader* (Figure 2).

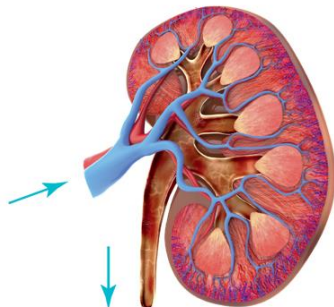


Figure 1 – Excretion of DOACs via urine by glomerular filtration



Figure 2 – DOAC Dipsticks and the DOASENSE Reader

In the following, we summarize important studies on the *DOAC Dipstick* and the *DOASENSE Reader* that have been published. In each case, we also provide online links that can be used to access the full publications and highlight key points at the bottom.

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

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.

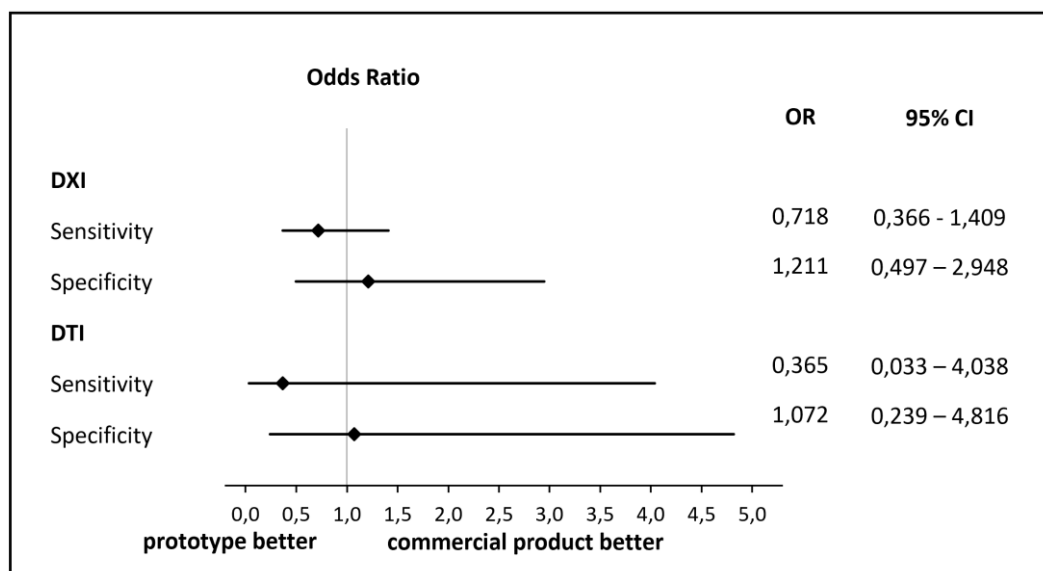


Figure 3 - Sensitivity and specificity for the detection of DXIs and DTI for the commercial *DOAC Dipstick* and the prototype. Odds ratios (OR) greater than 1 indicate that the sensitivity or specificity is higher for the commercial *DOAC Dipstick* product compared to the prototype, and vice versa.

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.

Stick Results for Pad:	Stick 1	Result:	Stick 2	Result:	Stick 3	Result:
Thrombin inhibitor		negative		positive		not evaluable
Faktor Xa inhibitor		positive		negative		not evaluable
Urine color		normal		normal		not normal
Creatinine		normal		normal		not evaluable

Figure 4 – 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".

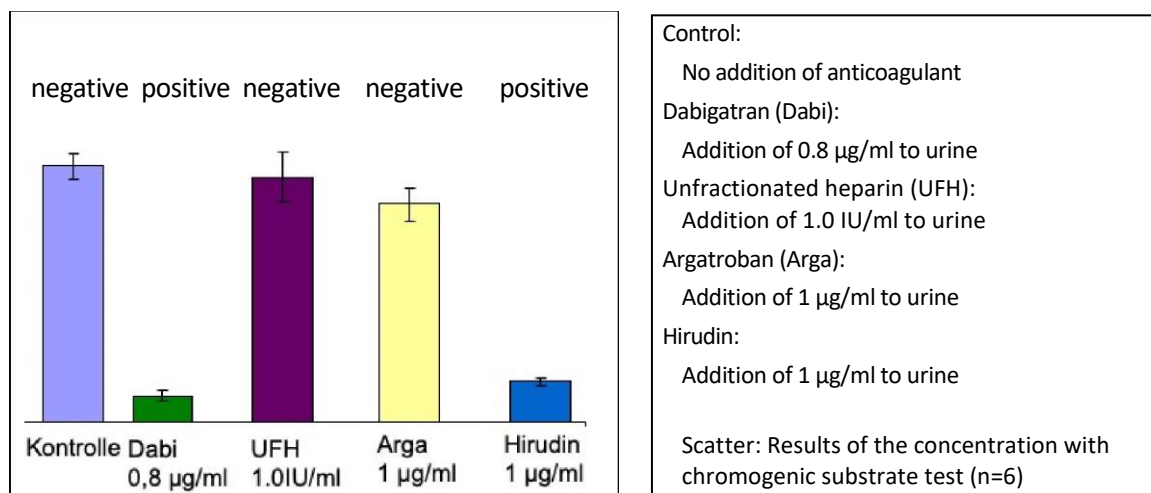


Figure 5 – Influence of addition of dabigatran, unfractionated heparin (UFH), argatroban and hirudin to urine of healthy subjects on thrombin pad of DOAC Dipstick (n=6)

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".

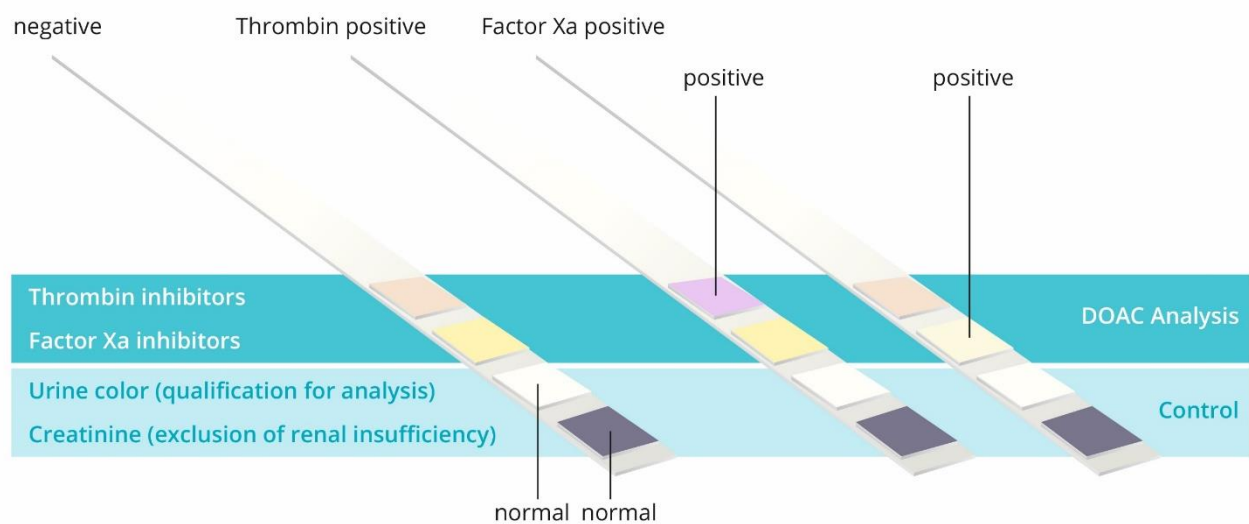


Figure 6 - Functional principle of the DOAC Dipstick test strip

Conclusion:

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](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 DOAKs 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 Čelap, 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>