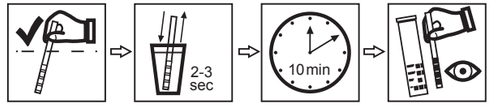
DOAC Dipstick

CE 0124

DIAGNOSTIC TEST FOR DOACs IN URINE

IVD | REF 0001 | Σ 12



EN

Intended Use:
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.

Summary and Explanation
The clinical importance of positive results of a DOAC in human urine relates to the presence of DOACs in blood. DOACs are excreted rapidly into urine starting 1 to 2 hours after intake of the medication. A specific and rapid detection indication by a point of care test may support diagnosis of anticoagulant therapy with DOACs especially in emergency medicine. Medical decision-making may be accelerated. Typical indications are patients with ischemic or haemorrhagic stroke with indication for fibrinolytic therapy or administration of a specific antidote, major traumas, emergency procedures, spontaneous thrombotic and bleeding events during oral anticoagulant therapy, and situations without available medication history. The kidney excretes creatinine and DOACs into urine. Their excretion decreases with impairment of renal function. Consequently, DOACs accumulate in blood with decrease of renal function. Therefore, the parameter creatinine was included on the DOAC Dipstick. If creatinine pad shows result „low“, false negative results of DOACs may be detected in urine samples using DOAC Dipstick.

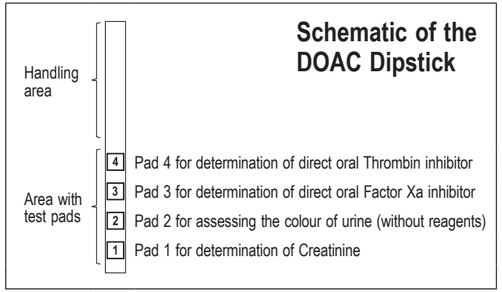
Material Provided with the Test

Test strip:	12
Test strip tube container with printed colour scale and cap:	1
Instructions for Use:	1

Materials Required but Not Provided
Clean container made of polypropylene for urine sample collection.
Timer.

Principle of the DOAC Test Strip
The test consists of a change of colour upon reaction of Factor Xa or Thrombin on the release of the chromophore bound to a substrate. The release of the chromophore is negatively related to the amount of DOAC in urine. Colours for oral direct Factor Xa and Thrombin inhibitors are different. The colour of the pads on the test strips changes within 10 min and can be identified by naked eye. The colours allow the detection of DOACs in a urine sample, with interpretation as “negative” in the absence of a DOAC and as “positive” in the presence of a DOAC. Respective colours for comparison are printed on the test tube containing the test strips.

The DOAC Dipstick has four different test pads used for analysis, as follows:



Principle of Tests & Active Reagents

Thrombin Inhibitors - Thrombin releases a chromophore from a Thrombin-specific peptide that is inhibited in the presence of a direct oral Thrombin inhibitor.

Factor Xa Inhibitors - Factor Xa releases a chromophore from a Factor Xa-specific peptide that is inhibited in the presence of a direct oral Factor Xa inhibitor.

Urine Colour - This pad does not contain any reagents and is used for assessing the impact of the colour of the patient urine used.

Creatinine - The test is based on reaction of creatinine with 3.5-dinitrobenzoic acid in alkaline medium (Benedict-Behre reaction).

Warning and Precautions
Do not use expired devices.
Do not reuse the test components.
Follow good laboratory practice and safety guidelines. Wear lab coats, disposable latex gloves and protective glasses where necessary.

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Used test strips must be treated as hazardous waste according to national biohazard and safety guidelines or regulations.
All reagents of this kit have been found to be uninfectious. However, materials contaminated with human urine can be infectious. For this reason, used test strips should be treated as potential biohazards in use and for disposal.
If contamination of clothing occurs: Rinse skin with water or shower.
Avoid contact with skin and eye. If skin irritation occurs: Consult a physician in all serious cases of health damage. In case of an accidental ingestion wash out the mouth and drink approximately 0.5 l of water. In case of eye contact, rinse the eye quickly and thoroughly using a stream of clean water.

Procedure Notes Before Performing the Test
Do not use test strips with an expiry date that has already passed.
Carefully read the instructions for use before starting the test.
The instructions must be followed exactly to obtain accurate results.
This test is for professional in vitro diagnostic use only.
Do not touch test pads of the strip. Handle the test strips only at the handling area opposite to the area with the test pads.
Do not open the tube containing the test strips unless you are ready to conduct the test.
Remove only as many test strips as required and reseal the tube immediately with the cap. The cap contains a desiccant.
Perform testing in ambient temperature (20±5°C).

Collection of Urine Sample:
1. Each urine sample must be collected in a clean container made of polypropylene. Only freshly collected urine may be used. If urine samples are collected by urinary catheter, the maximum time between collection in the catheter and testing is two hours.
2. Shake the container lightly before dipping the test strip.
3. Use urine within two hours after collection.

Assay Procedure - Use of Test Strips:
1. Immerse the test strip for 2 to 3 seconds into the urine sample so that all test pads are completely covered by the urine.
2. After removing the test strip from the urine, some liquid may be attached at the borders or edges of the test strips. Wipe off the excess urine on a tissue to absorb runoff. The test pads should not be touched.
3. Place the test strip on a flat surface, so that you can see the test pads, and wait for 10 minutes (incubation time of tests). Use a timer to control the time.
4. After 10 minutes incubation time immediately compare the test pads by naked eye to the corresponding colour scales on the label of the tube container. Refer to the next section regarding the visual determination of the colours.

Visual Determination and Interpretation of Colours of DOAC Dipstick
Colours must be compared to colours of the colour scale printed on the label of the container by naked eye. As an alternative to visually determining the colours of pads 1, 3 and 4, the semi-automatic DOASENSE Reader (DOASENSE REF 0002) can also be used.

Test Pad 1 (Creatinine):
- The colour of pad 1 corresponds to colours **“normal”** (“norm.”) on the tube label → creatinine in urine is normal. Pad 3 and pad 4 can be evaluated.
- The colour of pad 1 is darker than the colours **“norm.”** on the tube label → high creatinine does not affect DOAC excretion into urine. Pad 3 and pad 4 can be evaluated.
- The colour of pad 1 is **“low”** or lighter than the respective colour of the tube label → creatinine in urine is low, indicating impairment of renal function. A check of the kidney retention parameters in the patient’s serum should be considered. **Colours of pad 3 and pad 4 may be false negative.**

Test Pad 2 (Urine colour):
- The colour of the pad is white as the respective colour marked **“norm.”** on the tube label → the results of pad 1, 3 and 4 are valid.
- The colour of the pad is darker than the colour printed on the tube label → colours of pad 1, pad 3 and pad 4 may be distorted. The test is invalid.

Test Pad 3 (medication Apixaban, Edoxaban, Rivaroxaban):
- The colour of pad 3 clearly is yellow as the respective colour marked **“neg.”** on the tube label → direct oral Factor Xa inhibitor is absent in the urine sample.
- The colour of pad 3 is less yellow than the colour marked **“neg.”** on the tube label, and thus the result is **“pos.”** → direct oral Factor Xa inhibitor is present in urine.
- The colour of pad 3 is white as the respective colour marked **“pos.”** on the tube label → direct oral Factor Xa inhibitor is present in urine.

Test Pad 4 (medication Dabigatran):
- The colour of pad 4 is ochre as the respective colour marked **“neg.”** on the tube label → direct oral Thrombin inhibitor is absent in the urine sample.
- The colour of pad 4 is between the ochre colour marked **“neg.”** and the rose colour marked **“pos.”** on the tube label → direct oral Thrombin inhibitor is present in urine.
- The colour of pad 4 is **rose** as the respective rose colour marked **“pos.”** on the tube label → direct oral Thrombin inhibitor is present in urine.

If pad 3 and pad 4 are both “pos.”, then the test is invalid, because it is unlikely that a person is treated with both types of DOACs.

Limitations
The test results are qualitative. No quantitative interpretation should be made based on the test results.
The results always must be interpreted and evaluated in connection with other clinical information by a physician before diagnosing. No treatment decisions should be made solely based on the outcome of a DOAC Dipstick analysis. Additional laboratory analysis (e.g. determination of blood coagulation parameters) may be required. Due to possible limitations of detecting creatinine in urine, an additional check of kidney retention parameters in patient’s serum should be considered.
Persons with colour vision deficiency or colour blindness must not perform the DOAC Dipstick test.
A recently voided urinary bladder may impact the detectable DOACs in the urine.

Expected Values and Reference Ranges
Creatinine - Reference Range: 0.25 – 3.0 g/l, (2.2 – 26.5 mmol/l) (Ref.: Needleman). Note: The lighter “normal” reference colour for the Creatinine pad on the tube label represents a concentration of 0.25 g/l creatinine in the urine sample.
DOACs - Normal values are below 5 ng/ml (LC-MS/MS method). Patients under DOAC treatment typically display values above 200 ng/ml (Ref.: Schreiner).

Performance Characteristics
The visual analysis of the colours of the DOAC Dipstick corresponds to results “negative” and “positive”. The cut off value of Apixaban, Edoxaban, and Rivaroxaban for “negative” is < 100 ng/ml, and the cut off value for “positive” is > 200 ng/ml. The cut off value of Dabigatran for “negative” is < 50 ng/ml and for “positive” > 125 ng/ml. In the ranges between the cut off values the colours of the results for the DOACs may be identified as either “negative” or “positive”. Data were obtained in artificial urine and normal human urine spiked with concentrations of DOACs ranging from 0 to 1500 ng/ml. Using urine samples of patients treated with Apixaban, Edoxaban, Rivaroxaban, and Dabigatran, sensitivities and specificities were all > 95% (Ref.: Harenberg 2020).
Concentrations of DOACs in urine are higher due to the lower volume of urine compared to the volume of distribution of DOACs in blood, and were below 5 ng/ml (LC-MS/MS method) in patients not treated with DOACs and typically above 200 ng/ml for all DOACs during treatment and 12 or 24 hours after intake of medication (mean values 5.600 ng/ml Dabigatran, 2.700 ng/ml Rivaroxaban, 1.800 ng/ml Apixaban, n = 29 each) (Ref.: Schreiner).

Interferences
No information is reported in the literature on drug-drug and drug-other compounds interactions in urine – except the coloured compounds in urine described above. The number of interactions tends to be low to very low due to the high specificity of the enzymes with the respective substrates. No interaction occurs between the components of pad 3 with pad 4 and vice versa.
Heparins, low-molecular-weight heparins, e.g. enoxaparin, and fondaparinux do not react on pads 3 and 4 (Harenberg 2017).
Coloured compounds in urine such as bilirubin, urobilinogen and blood (macrohaematuria) may modify the results of pad 1, pad 3 and pad 4. The impact of the colour of the urine sample can be assessed by pad 2 (see above for interpretation).
Creatinine - In urines with high buffering capacity false low reading may be obtained. With high concentrations of ketone bodies (> 50 mmol/l) false normal reading may occur. Blood > 2000 Ery/µl may cause false normal results.

Storage Conditions
The recommended storage temperature of the closed test-strip tube container is between +2 °C to +30 °C. DOAC Dipsticks may be used until the expiration date printed on the label. After opening, the tube must be closed tightly immediately after removing of the strips used for evaluation, and the closed tube has to be stored away from direct sunlight at temperatures not exceeding +30 °C.
Storage above +30 °C will adversely affect the stability and test performance of the product.
After first opening the tube, the DOAC Dipsticks remaining in the tube can be used for max. 3 months. Do not use any DOAC Dipsticks remaining in the tube after 3 months after first opening.

Vigilance
Any serious incident in relation to this device shall be reported without any delay to the manufacturer and the national authority of the state in which the user/patient is located.

References
CLSI. Urinalysis; Approved Guideline - Third Edition. CLSI document GP16-A3; 2009. · Harenberg J et al. Thromb Haemost 2020, 120:132-40. · Schreiner R et al. Res Pract Thromb Haemost 2017;1(Suppl.1):PB 491. · Harenberg J, et al. Res Pract Thromb Haemost 2017;1(Suppl.1): PB 454. · Harenberg J, et al Clin Chem Lab Med. 2016;54:275-83. · Du S, et al. Clin Chem Lab Med. 2015;53:1237-47. · Harenberg J, et al. Semin Thromb Hemost. 2015;41:228-36. · Favaloro EJ, et al. Semin Thromb Hemost. 2015;41:208-27. · Harenberg J, et al. Thromb J. 2013 Aug 1;11(1):15. · Needleman SB, et al. J Forensic Sci. 1992;37:1125-1133.

WI7.5-3-EN-Rev04 – Date of revision: 2024-04-26

SYMBOLS USED

CE 0124	CE Mark - Device complies with European requirements of the IVDR (EU) 2017/746 Regulation	LOT	Lot Number		Device for near-patient testing
IVD	In Vitro Diagnostics	REF	Catalogue Number		Device not for self-testing
	Manufacturer		Storage Temperature		Do not reuse
Σ n	Content is sufficient for <n> tests		Expiry Date		See Instructions for Use

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