NICE advice

DOAC Dipstick for detecting direct oral anticoagulants

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is the DOASENSE DOAC Dipstick. It is used for detecting direct oral anticoagulants (DOACs) in urine.
- The **innovative aspects** are that the technology is a point-of-care test with results available within 10 minutes. The test is also a non-invasive method of detecting DOACs compared with standard laboratory tests that involve collecting a blood sample.
- The intended **place in therapy** would be instead of standard laboratory tests used to detect DOACs in emergency settings, or before elective surgery for people taking DOACs.
- The **main points from the evidence** summarised in this briefing are from 3 studies involving over 1,000 people taking DOACs. They suggest that the DOAC Dipstick test can detect DOACs in urine with non-inferior (for factor Xa inhibitors) or superior (for thrombin inhibitors) specificity and sensitivity, compared with liquid chromatography-tandem mass spectrometry.

- **Key uncertainties** around the evidence or technology are that the evidence is limited in quantity and quality. There is currently no evidence assessing the effect of the test on clinical decision making and long-term clinical outcomes in the NHS.
- The **cost** of the DOAC Dipstick is £15 per strip (excluding VAT).

The technology

The DOAC Dipstick (DOASENSE GmbH) is a single-use, point-of-care dipstick test that is used to detect direct oral anticoagulants (DOACs) in urine. The urine dipstick test detects DOACs (both factor Xa inhibitors and thrombin inhibitors) based on colour-changing chemical reactions that happen on the surface of the DOAC Dipstick test pads. Each dipstick test strip contains 4 test pads to detect:

- direct oral thrombin inhibitors (dabigatran – pad 4)
- direct oral factor Xa inhibitors (apixaban, edoxaban and rivaroxaban – pad 3)
- urine colour (validation pad to help exclude abnormal urine colour that can affect results – pad 2)
- creatinine (validation pad to help exclude impaired renal function that can affect results – pad 1).

The test is done by immersing the test strips in a urine sample for 2 to 3 seconds, removing excess liquid using a tissue, and placing on a flat surface for 10 minutes. Then results can be determined. Colour identification can be done with the naked eye using the corresponding colour scales on the tube label, or with an automated reader (DOASENSE Reader).

According to the product's instruction for use, the cut-off value of apixaban, edoxaban and rivaroxaban for a negative test result is less than 100 ng/ml, and the cut-off value for a positive test result is over 200 ng/ml. The cut-off value of dabigatran for a negative result is less than 50 ng/ml and for a positive result it is more than 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.

Innovations

The company states that the DOAC Dipstick is the only test approved for point-of-care testing of DOACs. Results are available within 10 minutes, which may lead to more timely medical treatment decisions. This could include administering a reversal agent for thrombin or factor Xa inhibitors, or directing a person to surgery. In addition, the DOAC Dipstick is a less invasive method of DOAC testing compared with currently available laboratory tests for DOAC detection, which may involve collecting blood samples from people.

Current care pathway

DOACs are a group of anticoagulating substances that directly inhibit specific clotting factors such as factor Xa and thrombin. They are used to prevent and treat thromboembolism across various clinical indications. The 4 DOACs currently licensed in the UK are apixaban, dabigatran etexilate, edoxaban and rivaroxaban. Routine coagulation monitoring for people taking DOACs is not needed. However, there are some clinical situations when the measurement of DOAC activity may be useful to help with clinical decision making and subsequent management:

- In people admitted to emergency departments with an acute bleed, to understand whether anticoagulation is the cause of the bleed.
- In people needing emergency surgery to understand whether the person has taken DOACs before the procedure.
- Before elective surgery in people on DOAC therapy, to rule out the presence of residual DOACs.

Laboratory tests are available that may provide useful information about the levels of DOAC in blood in these situations. Liquid chromatography with tandem mass spectrometry (LC-MS/MS) is considered gold standard for the measurement of DOACs. However, LC-MS/MS is not widely available, needs a relatively high level of expertise and is time-consuming. Other more accessible laboratory tests are available, including:

- thrombin time
- prothrombin time

- activated partial thromboplastin time
- plasma-diluted thrombin time or direct thrombin inhibitor assay (Hemoclot)
- drug-specific anti-Xa assays (available for rivaroxaban, apixaban and edoxaban).

Experts who commented on this briefing said that the availability of these laboratory tests may vary between centres. Specific assays can accurately quantitate drug levels, however they can be expensive, they are not available in all laboratories and require particular expertise.

Due to its high degree of specificity, sensitivity, selectivity and reproducibility, LC-MS/MS is considered the gold standard method for the measurement of DOACs.

The DOACs have differing impacts on the common tests of haemostasis and it is important that clinicians are familiar with the sensitivity of the reagents used in their laboratory to individual DOACs.

Each DOAC is known to produce unique effects on coagulation assays. The sensitivities of these tests can vary widely depending on the DOAC drug and reagents used and cannot be standardised across laboratories. Some tests (such as prothrombin time and activated partial thromboplastin time) may not be reliable to detect therapeutic concentrations of all DOACs. Experts who commented on this briefing said that the availability of these laboratory tests may vary between centres.

In emergency situations, when a person is suspected to have taken a DOAC recently before admission, an appropriate reversal agent may be given. This depends on the DOAC taken (idarucizumab is used for dabigatran, andexanet alfa for apixaban or rivaroxaban, and prothrombin complex concentrate is used when specific reversal agents are not available).

The following publications have been identified as relevant to this care pathway:

- British Society for Haematology guideline on the measurement of non-coumarin anticoagulants and their effects on tests of haemostasis (2014)
- NICE's guideline on routine preoperative tests for elective surgery. This does not recommend routine haemostasis testing before elective surgery but states that if people on anticoagulants need their clotting status checking, this can be done using point-of-care testing.

- NICE's key therapeutic topic on anticoagulants, including direct-acting oral anticoagulants (DOACs) (last updated September 2019), summarises recommendations from NICE technology appraisals about anticoagulants and DOACs.
- International consensus statement on the peri-operative management of direct oral anticoagulants in cardiac surgery (2018). Does not recommend routine coagulation testing in people taking DOACs having elective cardiac surgery, unless there are factors that may increase the risk of bleeding. The recommendations state however, that monitoring of DOAC levels are helpful in emergency cases, in patients with an unclear history of DOAC intake, and in patients with organ dysfunction.
- NICE's evidence summary on the reversal of the anticoagulant effect of dabigatran: idarucizumab.
- NICE's technology appraisal guidance on andexanet alfa for reversing anticoagulation (guidance in development, expected to publish April 2021).

Population, setting and intended user

According to the company, there are currently more than 1 million people having DOAC therapy in the UK. Licensed oral anticoagulants that are used in the UK include warfarin, and the DOACs apixaban, dabigatran etexilate, edoxaban and rivaroxaban. The most common adverse effect of anticoagulants is bleeding, ranging from mild events to serious and fatal haemorrhage. The DOAC Dipstick is intended to test for DOACs in people arriving at emergency departments with acute bleeding or haemorrhagic stroke, or in people needing emergency surgery when the presence of DOACs needs to be ruled out. DOAC Dipstick can also be used to rule out the presence of residual DOACs in people before elective surgery. The test would be done in secondary care by healthcare professionals working in emergency, stroke or surgical departments. According to experts who commented on this briefing, the test is simple to do and would be done by healthcare assistants or nursing staff.

Costs

Technology costs

The DOAC Dipstick test costs around £15 per strip (excluding VAT). The technology is available in packs of 12 test strips. The test is not yet launched in the UK. The company

states that the technology is expected to be available in the UK by February 2021.

Costs of standard care

The unit cost of a standard laboratory haemostasis test is approximately £34. This includes the cost of the test itself (£30; cost taken from NICE's guideline on routine preoperative tests for elective surgery and inflated to 2019 prices) and the cost of staff time and equipment needed to collect the blood sample (£4; NHS reference costs 2018/19 for phlebotomy).

Resource consequences

The technology could be resource releasing if it results in earlier clinical decisions that lead to improvements in clinical outcomes for patients and reductions in length of hospital stay. The company also states that the DOAC Dipstick may allow increased flexibility in operating room scheduling, which could free up recovery and intensive care unit beds earlier. There is no published evidence to support these claims. Experts who commented on this briefing said the test is a simple point-of-care test and appears to be easy to do and interpret, with minimal training needed.

Regulatory information

The DOAC Dipstick test is a CE-marked in vitro diagnostic (class general or self-certified).

Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Anticoagulant therapy is used for preventing and treating thromboembolism across various clinical indications. The prevalence of many of these conditions increases with age. Other risks factors for these conditions may include the sex of the individual, family history and family origin, pregnancy, immobility, and other comorbidities such as obesity and cancer. Age, sex, family origin, pregnancy and disability are protected characteristics under the Equality Act 2010.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

Three studies are summarised in this briefing, involving over 1,000 people taking direct oral anticoagulants.

The evidence base comprises 1 multicentre, prospective observational study published as a full text article, a single-centre, prospective, observational study and a case report of 1 patient (both published as conference abstracts).

A review was identified that described the functionality of the DOAC Dipstick, the testing procedure and the available evidence for the test (Harenberg et al. 2019). An abstract was also identified that described the design of an ongoing prospective, single cohort study in people with atrial fibrillation or history of venous thromboembolism on DOAC therapy who need treatment interruption (Tafur et al. 2019). These have not been reviewed further in this briefing.

The clinical evidence and its strengths and limitations is summarised in the overall assessment of the evidence.

Overall assessment of the evidence

The available evidence for the DOAC Dipstick is relatively limited in terms of quality and quantity. Two of the 3 studies included in this briefing were presented in abstract form with limited information, which made thorough critical appraisal difficult (Jilma et al. 2019 and Harenberg et al. 2017). Results from Harenberg et al. (2020), a multicentre observational study, suggest that the sensitivity and specificity of the technology in detecting DOACs in urine is non-inferior to that of liquid chromatography-tandem mass spectrometry (LC-MS/MS) for factor Xa inhibitors and superior to that of LC-MS/MS for thrombin inhibitors.

Most of the studies were done in Germany and there was no evidence from the UK, which may limit generalisability to the NHS. The managing director and founder of the DOAC Dipstick test was an author for all the studies. There were no independent studies identified using the technology. There is currently no evidence assessing the effect of the test on resource use and clinical outcomes for patients.

Harenberg et al. (2020)

Study size, design and location

A multicentre, prospective, open-label observational study of 914 people having treatment with direct oral factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban) or a direct oral thrombin inhibitor (dabigatran) at 18 centres in Germany.

Intervention and comparator

DOAC Dipstick test compared with LC-MS/MS.

Key outcomes

Of the 914 people in the study, 880 people were included in the per-protocol analysis (451 in the direct oral factor Xa inhibitor group and 429 in the direct oral thrombin inhibitor group). The sensitivity, specificity, accuracy, and predictive values were non-inferior to that of LC-MS/MS for detecting factor Xa inhibitors (at least 95% with a 0.5% margin, $p<0.04$) and superior to that of LC-MS/MS for detecting thrombin inhibitor (significant at a proportion of 97.5%; $p<0.001$). The agreement (kappa value) between results of the dipstick test and LC-MS/MS were 0.945 for detecting factor Xa inhibitors and 0.987 for detecting thrombin inhibitor. Receiver operating curves showed c-values of 0.989 for factor Xa inhibitor detection and 0.995 for thrombin inhibitor detection (a c-value of 1 indicates a 'perfect' test result). The intention-to-analyse analysis confirmed the results of the per-protocol analysis. Visual evaluation of the factor Xa and thrombin inhibitor pads were not different between centres.

Strengths and limitations

The study author is the managing director and founder of the DOAC Dipstick. The time since the bladder was previously emptied was not considered or standardised in the study. The thrombin pad served as a negative control for the factor Xa inhibitor test and

vice versa. The study did not involve people not taking direct oral anticoagulants. The design of this study was previously described in an abstract by Harenberg et al. (2019).

Jilma et al. (2019)

Study size, design and location

Case report of an 81-year-old man with chronic direct oral anticoagulant intake at an emergency department in Vienna, Austria.

Intervention and comparator

DOAC Dipstick test. No comparator.

Key outcomes

The patient, who was included in an ongoing cohort study, was taking rivaroxaban 20 mg once daily and was also diagnosed with acute pre-renal kidney injury (plasma creatinine 5 mg/dl, blood urea nitrogen 130 mg/dl). The DOAC Dipstick results were interpreted to be negative for the presence of rivaroxaban and normal for levels of creatinine in the urine. The control test pad (which is designed to detect abnormal urine colour) turned yellow, indicating that the person had dark-coloured urine. The case report highlights the effect of dark-coloured urine on the DOAC Dipstick results.

Strengths and limitations

This was a single person case report, which is regarded as relatively low-grade level of evidence. The results were presented in abstract form with limited information, which made thorough critical appraisal difficult. The case report was from a person treated in Austria, which may limit generalisability to the NHS. One of the authors is the managing director and founder of the DOAC Dipstick.

Harenberg et al. (2017)

Study size, design and location

Single centre, prospective, observational study of people having treatment with apixaban

5 mg twice daily, rivaroxaban 20 mg once daily or dabigatran 110 mg or 150 mg twice daily, as well as people without anticoagulant therapy (n=29 for each group).

Intervention and comparator

The DOAC Dipstick test compared with liquid chromatography-tandem mass spectrometry.

Key outcomes

The authors stated that the reliability (kappa index) and validity of the test were 100% (95% confidence intervals 74% to 100%) for detecting apixaban, rivaroxaban or dabigatran. The ranges of results analysed by ImageJ software did not overlap for negative or positive results on the point-of-care test pads for either DOAC type. Validity was calculated using concentrations of DOACs measured with LC-MS/MS. Concentrations were below 10 ng/ml in control samples, 202 ng/ml to 6.667 ng/ml in samples from people taking apixaban, 169 ng/ml to 9.579 ng/ml in samples from people taking rivaroxaban and 1.057 ng/ml to 15.996 ng/ml in samples from people taking dabigatran.

Strengths and limitations

Results suggest that the point-of-care test could offer a rapid, reliable and valid detection of DOACs. Results were presented in abstract form and are also described in Harenberg et al. (2019). There was limited information on the demographics of the people involved and possible confounding factors. Two independent observers visually assessed the coloured test pads using a CMYK scale. The test strips were also photographed in a lightbox and colours analysed by the ImageJ software program.

Sustainability

The technology's external packaging and dipstick container are made from recyclable materials. The dipstick container is made from polypropylene and is free from bisphenol A. The company claims that adopting the DOAC Dipstick point-of-care test may help reduce the environmental impact by decreasing the number of laboratory tests needed. There is no published evidence to support this claim.

Recent and ongoing studies

No ongoing or in-development trials were identified by NICE when searching key clinical trial registries. The company stated that there are a total of 5 ongoing studies evaluating the DOAC Dipstick. These are being done in Germany, France, Austria, the US and Croatia. They include people having major orthopaedic surgery, outpatients with venous thromboembolism and people admitted to emergency departments.

Expert comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

The technology is not yet available in the NHS. Three out of 4 experts had not used this technology before. One of the experts was familiar with the technology and had been provided with a prototype.

Level of innovation

Most of the experts agreed that the technology was a novel concept for detecting direct oral anticoagulants (DOACs), with 2 experts adding that it is a first-in-class procedure. Experts noted that the technology was innovative compared with standard care because it does not need venepuncture or laboratory-based analyses. One expert also noted that, if urine samples were easy to collect, the DOASENSE test would be faster than standard care. One expert thought it would replace standard care. None of the experts were aware of any competing technologies in the NHS that have a similar mode of action. However, 1 expert said that other point-of-care tests are available (such as thromboelastography and rotational thromboelastometry) but that these need blood samples.

Potential patient impact

The main benefits for patients identified by the experts include earlier detection of DOACs, leading to more timely clinical decision making and appropriate emergency treatment. One expert said that in elective cases a negative test result would assure surgeons and when a positive test result is given the procedure could be delayed. This would help to reduce the risk of bleeding complications during surgery. One expert noted that more patients could

have access to testing with the technology compared with standard laboratory-based DOAC testing, which has limited availability in most hospitals.

People at risk of haemorrhagic stroke or bleeding during surgery, people with head injuries, and people presenting to emergency departments with acute bleeding or haemorrhagic stroke who are confused were identified as people who would particularly benefit from the technology. One expert felt the technology could be used in the hyperacute phase of management for people with ischaemic stroke on DOACs. They stated that if a reliable point-of-care test was available it could help stroke specialists decide whether to offer these people alteplase, which is currently contraindicated in people who have taken DOACs in the previous 48 hours.

Potential system impact

Potential system benefits identified by the experts include a reduced number of phlebotomy blood samples taken, reduced hospital or GP visits for blood sampling, and helping relieve some pressure on laboratory technicians. However, 1 expert stated that a blood test may still be needed to test for residual warfarin. Other benefits were more appropriate management for patients who present with an acute bleed or need emergency surgery and safer management for people having elective surgery.

One expert said that the test would initially be used alongside standard testing but may replace standard care once there is confidence in the test results. Another expert noted that it would be an addition to standard care because DOACs are not routinely tested for. One of the experts noted that because it is a screening tool, positive test results may need further testing to assess the quantity and type of DOAC in the blood.

One expert believed the technology would lead to cost savings overall, while another felt the technology would cost the same as standard care because positive tests would need further testing. Overall, the experts did not think adopting the technology would have a negative impact on resource use, and minimal training would be needed. One of the experts said that the technology could be taken up quickly by emergency departments, as well as outpatient and inpatient services. This is because it is simple to do and not labour intensive.

General comments

The experts were not aware of any NHS centres currently using the technology.

The accuracy and reliability of the test were key uncertainties identified by 2 of the experts. Experts highlighted potential harm for people with an inaccurate test result. This includes planned procedures that carry a bleeding risk being done in people with a false positive result and people not having appropriate or timely treatment because of a false negative result. One expert stated that if the test were shown to be reliable and reproducible, with a low false negative rate, it could be a cost-effective way to screen for DOACs. However, another expert felt that the test would only be useful in people presenting to emergency departments in whom a medical history is uncertain and who are unable to provide further clarity (that is, they are confused or cognitively impaired), and very occasionally in people who had been involved in a traffic accident who are unable to communicate about their medication history. This expert did not see a place for the technology in people having elective surgery.

One expert highlighted that the current evidence base is limited, relies on insufficient patient numbers and has not been done in the intended population. They stated that for the test to be routinely adopted, a prospective randomised controlled trial is needed that shows efficacy compared with standard care by evaluating the effect of using the test on clinical outcomes.

Expert commentators

The following clinicians contributed to this briefing:

- Aamer B Ahmed, consultant cardiothoracic anaesthetist, honorary associate professor, department of anaesthesia and critical care, Glenfield hospital, University Hospitals of Leicester NHS Trust. Has no direct or indirect financial or non-financial interests.
- Prasanna Aghoram, consultant physician and clinical stroke lead, Darent Valley Hospital. Did not declare any interests.

- Beverley Hunt, professor of thrombosis and haemostasis, King's College London, consultant at Guy's and St Thomas' NHS Foundation Trust, thrombosis and haemophilia centre St Thomas' Hospital. Medical director of Thrombosis UK (2002 to ongoing), a member of (from 2015) and chair of the steering committee for World Thrombosis Day (2019 to ongoing).
- Tim Chesser, consultant orthopaedic trauma surgeon, North Bristol NHS Trust. Did not declare any interests.

Development of this briefing

This briefing was developed by NICE. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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