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The Pointy End of Point-of-Care Testing for Direct Oral Anticoagulants

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Direct oral anticoagulants (DOACs), also sometimes called 'NOACs' (variably for novel, new, or non-vitamin K antagonist oral anticoagulants), represent an increasingly applied form of anticoagulant therapy for an ever-expanding range of indications.^{1,2} Routine haemostasis (coagulation) assays are variably sensitive to DOACs,^{3,4} and cannot be reliably used for measuring their concentration. Although routine monitoring of DOACs is not generally required, there are many plausible situations in which knowledge of patient's anticoagulant status may be clinically useful, including unconscious patients presenting as a trauma and bleeding, or patients presenting for emergency surgery, known or unknown to be on an anticoagulant, as well as patients developing thrombosis while on treatment and women with possible pregnancy whereby the effect of these drugs on the foetus is still unknown.^{3,4} Accordingly, sensitive and specific methods for assessing DOACs are increasingly employed in clinical practice. DOACs mainly segregate into one of two agent classes, namely anti-thrombin (anti-activated factor II; anti-FIIa, such as dabigatran) and anti-activated factor X (anti-FXa, such as rivaroxaban, apixaban, edoxaban). Like most tests of haemostasis, laboratory-based assays typically utilize citrate anticoagulated plasma to measure DOAC activity.^{3,4} The most commonly applied tests respectively are laboratory-performed direct thrombin inhibitor and chromogenic anti-FXa assays.^{3,4}

Point-of-care (POC) tests represent an additional strategy for measuring DOACs. Proponents of POC testing cite faster test times at 'bedside', potentially useful for emergency or surgical use where despatch to a laboratory and availability of finally issued results may exceed clinical desirability. Sometimes, specific laboratory tests for DOACs may also only be available on restricted days or times or at central sites. There are several current and emerging strategies for DOAC testing, including POC.^{3–11} However, the research

group headed by Harenberg has taken a unique strategy to develop a POC for DOAC testing using urine as the biological material and a method they have called 'DOAC Dipstick'.⁵ The basis for the test is that some 30 to 80% of DOACs are excreted into the urine, and that sensitive and specific tests for either anti-FIIa or anti-FXa in urine can therefore be developed. With this assay, the dipstick contains a matrix where specific enzymes and substrates directed against DOACs are immobilized to enable detection of both types of agents (anti-FIIa or anti-FXa) on the same dipstick, at the same time, but using separate pads. The dipstick also contains additional pads to control for colour of urine and assess urine creatinine concentration, which respectively help to avoid false positives and identify impaired renal function.

It is therefore of interest that the Harenberg group have published the results of a multicentre trial on the methodology in the current issue of the journal.¹¹ This report provides important confirmatory evidence on the reliability of this POC system to specifically identify (or exclude) the presence of current anti-FIIa or anti-FXa DOACs in urine, with different operators and remarkably high negative and positive predictive value. This article represents the last in a series of publications by the authors around this technique,^{5,11} and importantly identifies a milestone in this journey, initially conceived as an idea in 2013.^{12,13}

Like all journeys related to the field of haemostasis, this will no doubt be one that continues. 'Stagnation' reflects a dangerous term in haemostasis. Pathophysiologically, stagnation in blood flow may lead to thrombosis according to the classical Virchow's triad. Metaphorically, stagnation in innovation leads to a separate kind of arrest, namely that of progress. The journey of anticoagulation therapy is itself interesting and on-going. DOACs represent the new kid on the antithrombotic block, with four such agents now imbedded in clinical practice, but several others are potentially

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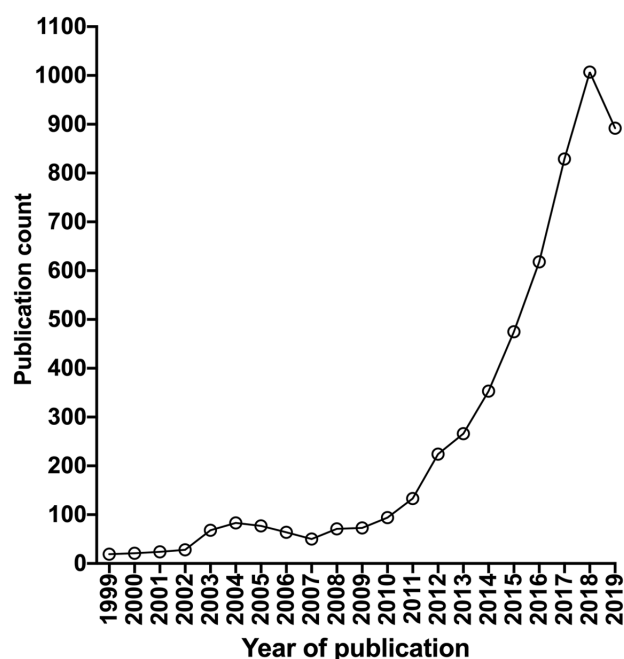


Fig. 1 The ever-expanding literature involving direct oral anticoagulants (DOACs). A simple PubMed search of 'DOAC', 'NOAC' and 'direct oral anticoagulants' (even recognizing that this would not capture all possible derivations of DOACs) identified over 5,600 entries, with the growth over the past 20 years identified here. The count for 2019 represents only a partial year (up to 17th September).

emerging.¹⁴ A PubMed search of 'DOAC', 'NOAC' and 'direct oral anticoagulants' (albeit recognized to not capture all possible derivations of DOACs) identifies over 5,600 entries, with the explosion in recent entries evident in ►Fig. 1. Several such papers have recently appeared in this journal, but perhaps most relevant to the current in focus publication of Harenberg and team, are those related to tests performed for DOACs, or otherwise adversely affected by DOACs.

One standout in particular is the recent International Council for Standardization in Haematology recommendations for laboratory measurement of DOACs,³ which also recognize the availability of POC tests such as DOAC Dipstick. As already mentioned, several papers have also been recently published around other novel approaches to DOAC testing.^{7–10}

Along with clinical benefits of DOACs come some negative issues around 'test interference'.^{15–18} For example, tests used in investigating lupus anticoagulant (LA), especially the activated partial thromboplastin time and the dilute Russell viper venom time, are very sensitive to the presence of all DOACs,^{4,15,16} and may lead to both false positive and false negative test results for LA,¹⁶ although this effect can be abrogated by using various DOAC 'neutralisers'.^{16,17} DOACs may also interfere with other tests such as anti-thrombin assays.^{4,18} In this case, the interference is class-specific, as anti-FIIa agents interfere with anti-FIIa-based anti-thrombin assays and anti-FXa agents interfere with anti-FXa-based anti-thrombin assays.

In conclusion, DOACs currently represent the main class of clinical anticoagulants, surpassing the use of vitamin K antagonist therapy in many geographic and clinical settings.^{1,2} Although they do not require routine monitoring by DOAC

testing, there may be occasions in which testing may be useful and drive a clinical response that depends on whether or not DOACs are identified, or if high levels of DOACs are identified, and so on.^{3,4} DOAC Dipstick testing using urine represents one strategy for assessing the presence or absence of DOACs quickly and accurately, and using a potentially less invasive technique, also overcoming some potential pre-analytical limitations of drawing blood (i.e. patients with small or difficult veins, haemolysis, sample contamination, sample stability, etc.).^{5,11–14} Some additional aspects of the robustness of the test may also have to be clarified in due course, such as the impact of urine dilution or concentration, the potential interference of urine components (i.e. erythrocytes, leukocytes, microorganisms, casts) as well as from other substances and drugs excreted with the urine. Naturally, there are also other emerging strategies,^{6–10} and the goal-posts may also be shifting with emergence of even 'newer' DOACs.¹⁴ Finally, strategies to test for DOACs may become eventually surpassed by strategies to permit other haemostasis tests to be performed without inadvertent interference of DOACs, given especially that performance of 'thrombophilia tests' is inevitable on patients on anticoagulant therapy.^{15–18}

Note

The views expressed in this editorial are those of the authors, and are not necessarily those of NSW Health Pathology or the University of Verona.

Conflict of Interest

None declared.

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