

Laboratory Options for Assessing the Effects of Direct Oral Anticoagulants in Estonia

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Summary

Introduction. Direct oral anticoagulants (DOACs) are widely used for the management of thromboembolic disorders, particularly in preventing and treating venous thromboembolism and stroke in patients with atrial fibrillation. While routine laboratory monitoring of DOACs is generally not recommended, certain clinical scenarios necessitate their assessment. In Estonia, an increasing demand exists for laboratory-based evaluation of DOAC levels to support clinical decision-making. This study aims to develop a standardized protocol for laboratory assessment of DOAC therapy based on the currently available assays.

Materials and Methods. A comprehensive review of laboratory methods for DOAC assessment in Estonia was conducted, analyzing qualitative and quantitative assays, including anti-Xa activity, thrombin time, and chromogenic assays. The study also evaluated the applicability of the DOAC Dipstick (DOASENSE GmbH, Germany) as a point-of-care test for qualitative urine analysis. International

guidelines and expert consensus documents were reviewed to establish a standardized laboratory assessment protocol.

Results. DOAC measurement techniques vary in availability and reliability across Estonian laboratories. Plasma-based methods provide precise quantification but are not universally accessible, while urine-based DOAC Dipstick testing offers a rapid alternative for excluding clinically significant DOAC levels. The study proposes a standard operating protocol, integrating these methodologies to improve DOAC assessment in clinical practice.

Conclusions. Establishing a standardized protocol for DOAC laboratory assessment in Estonia enhances clinical decision-making by providing reliable and accessible testing methods. The integration of plasma and urine-based assays ensures a comprehensive evaluation of DOAC therapy, but further research is required to optimize clinical applicability and patient outcomes.

Keywords: direct oral anticoagulants, laboratory, monitoring, emergency care.

INTRODUCTION

Direct oral anticoagulants (DOACs) are extensively used for the management of thromboembolic events and as prophylaxis, particularly in the prevention and treatment of venous thromboembolism and stroke in patients with non-valvular atrial fibrillation [1]. Currently, direct factor

Xa (FXa) inhibitors, including apixaban (APBN), edoxaban (EDBN), and rivaroxaban (RXN), as well as the direct thrombin inhibitor (DTI) dabigatran (DBTN), are approved for use in Estonia. Moreover, data from the Estonian Agency of Medicines indicate a continued rise in the use of DOACs across the country [2]. Figure 1 illustrates a similar trend in all Baltic countries.

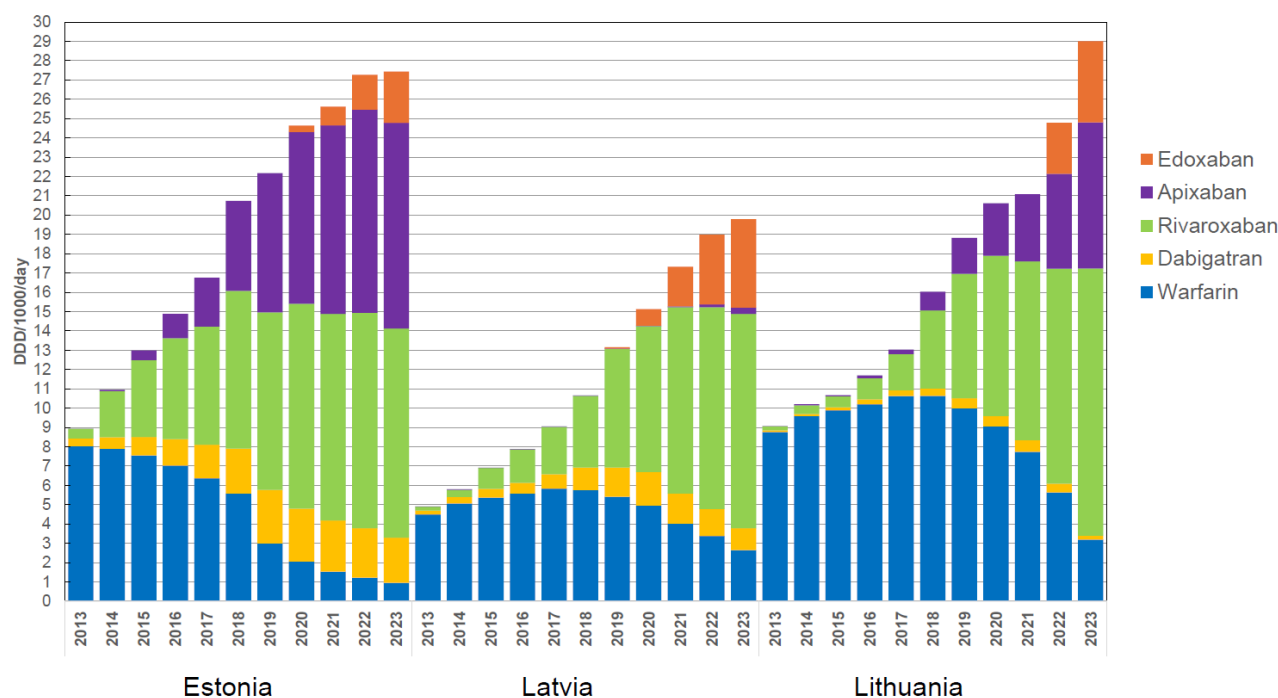


Fig. 1. Usage of DOACs in Baltic countries from 2013 to 2023. Data from Estonia [2], Latvia [3] and Lithuania [4]
1 pav. TVGA vartojimas Baltijos šalyse 2013–2023 m. Estijos [2], Latvijos [3] ir Lietuvos [4] duomenys

Although routine laboratory monitoring of DOACs is generally not recommended, assessing their anticoagulant effects may be beneficial in specific clinical scenarios [5]. In this review, we outline the development of a standard operating procedure for the laboratory assessment of DOACs based on the currently available DOAC assays in Estonia.

MATERIALS AND METHODS

Laboratory monitoring and assay methods

In Estonia, the anticoagulant effects of DOACs can be evaluated qualitatively in plasma using an anti-Xa activity assay of low molecular weight heparin to exclude the presence of anti-Xa DOACs, and thrombin time (TT) to rule out the presence of DBTN. Although quantitative measurements are performed using chromogenic assays with DOAC-specific calibrators and controls for APBN, EDBN, DBTN, and RXN, these assays are not universally available in Estonian laboratories. Currently, a similar limitation exists across all Baltic countries [6]. Moreover, whereas DOACs influence prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT) values, these effects are inconsistent, making these assessments unreliable in emergencies and other critical clinical situations [5, 7]. Additionally, viscoelastic testing methods, such as rotational thromboelastometry (ROTEM) and SEER method by Quantra, are not yet validated for use in patients treated with DOACs in Estonia.

In addition to plasma assays, the clinically relevant effects of DOACs can also be evaluated based on urine analysis using the DOAC Dipstick (DOASENSE GmbH, Germany), an innovative point-of-care test designed for

the qualitative assessment of anti-Xa DOACs and DBTN in urine [8, 9], which is currently available in Estonia. A preclinical study conducted at the North Estonia Medical Centre in 2019 demonstrated that the DOAC Dipstick yields results in 10 minutes, and negative results can reliably exclude the presence of clinically relevant DOAC concentrations in plasma (<30 ng/mL) [10, 11]. However, as the diagnostic performance of this test depends on renal function and may be influenced by the time elapsed since the last urination, results should be interpreted with caution, as DOACs may accumulate in urine over time due to their gradual elimination from the bloodstream [5]. Additionally, visual interpretation of DOAC Dipstick results is observer-dependent and may be influenced by differences in color vision among observers or the effect of artificial light sources [10]. Nevertheless, such inter-observer variability can be mitigated by using the DOASENSE Reader (DOASENSE GmbH, Germany), specifically for patients in emergency medicine care. Other potential causes of false-positive results have previously been documented [12].

To facilitate the incorporation of the DOAC Dipstick into clinical practice, an international working group published an algorithm in 2024 for the rapid exclusion of clinically relevant plasma levels of DOACs using the DOAC Dipstick [12]. This algorithm has been adopted for routine use in Estonia (Fig. 2). The potential benefits of utilizing the DOAC Dipstick in clinical practice are further highlighted in the 2024 guidelines on the reversal of DOACs in patients with life-threatening bleeding, published by the European Society of Anesthesiology and Intensive Care, which recommend that in the absence of specific coagulation testing, DOAC Dipstick testing can be employed to detect the presence of DOACs [13].

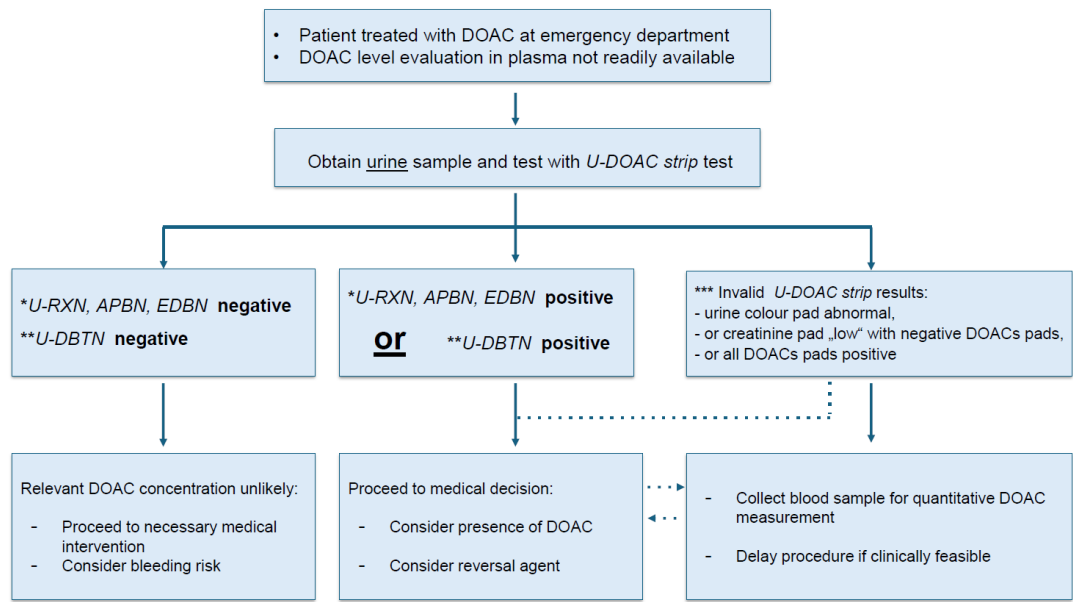


Fig. 2. Practical algorithm for DOAC Dipstick (U-DOAC test strip) utilization (modified from [12]).

* – DOASENSE Reader results for factor Xa inhibitors correspond to LIS request for rivaroxaban, apixaban and edoxaban in urine (U-RXN, APBN, EDBN); ** – DOASENSE Reader results for thrombin inhibitors correspond to LIS request for dabigatran in urine (U-DBTN); *** – Results are not issued; a comment stating ‘Test result is unreliable’ is added; LIS – Laboratory Information System

2 pav. Praktinis „DOAC Dipstick“ (U-DOAC juostelės) naudojimo algoritmas (modifikuota pagal [12]).

* – DOASENSE skaitytuvo rezultatai Xa faktoriaus inhibitorių atveju atitinka LIS užklausą dėl rivaroksabano, apiksabano ir edoksabano tyrimo šlapime (U-RXN, APBN, EDBN); ** – DOASENSE skaitytuvo rezultatai trombino inhibitorių atveju atitinka LIS užklausą dėl dabigatrano tyrimo šlapime (U-DBTN); *** – rezultatai nėra pateikiami, vietoje jų pridedamas komentaras „Tyrimo rezultatas yra nepatikimas“; LIS – laboratorijos informacinė sistema

Standard operating protocol

Given the increasing need for accurate laboratory evaluation and interpretation of DOAC levels, establishing a standard operating protocol is recommended to ensure optimal patient management tailored to the clinical requirements and laboratory facilities of each healthcare institution [14]. Consequently, a recommended standard operating protocol for the laboratory-based assessment of DOAC therapy in Estonia

has been developed based on currently available laboratory methods (Fig. 3). These laboratory methods, detailed in Table and incorporated into the algorithm shown in Fig. 3, are also referenced in the Estonian Society of Anesthesiologists’ guidelines for antithrombotic medication in both elective and emergency surgery, which form part of the Estonian Transfusion Guidelines (Part 1) [15]. Furthermore, the guidelines propose a clinical approach to different scenarios associated with DOAC therapy.

Table. Haemostasis laboratory tests cut-offs for excluding the presence of DOACs in plasma
Lentelē. Kraujo krešėjimo tyrimų ribinės vertės TVGA buvimui plazmoje atmesti

Medicine	LIS test	Relevant DOAC concentration in plasma unlikely	Unconscious patient or DOAC level evaluation in plasma not readily available	Important notice
Dabigatran	P-DBTN	<30 µg/L*	P-TT <21 s or U-DBTN** negative test result excludes the presence of DBTN in plasma	OACs impact PT/INR and aPTT values, however, these effects are inconsistent, rendering the assays unreliable in emergencies
Apixaban	P-APBN	<30 µg/L*	P-LMWH (anti-Xa) <0.1 kU/L or U-RXN, APBN, EDBN*** negative test result excludes the presence of APBN, EDBN, and RXN in plasma	
Edoxaban	P-EDBN	<30 µg/L*		
Rivaroxaban	P-RXN	<30 µg/L*		

* – µg/L corresponds to the ng/mL units used elsewhere; ** – U-DBTN performed with U-DOAC strip test; *** – U-RXN, APBN, EDBN performed with U-DOAC strip test; LIS – Laboratory Information System; P – plasma; U – urine; DBTN – dabigatran; APBN – apixaban; EDBN – edoxaban; RXN – rivaroxaban; TT – thrombin time; LMWH – low molecular weight heparin; PT/INR – prothrombin time / international normalized ratio; aPTT – activated partial thromboplastin time; DOACs – direct oral anticoagulants
* – µg/l atitinka ng/ml vienetus, naudojame kituose šaltiniuose; ** – U-DBTN atliekamas su U-DOAC juostele; *** – U-RXN, APBN, EDBN atliekamas su U-DOAC juostele; LIS – laboratorijos informacinė sistema; P – plazma; U – šlapimas; DBTN – dabigatranas; APBN – apiksabanas; EDBN – edoksabanas; RXN – rivaroksabanas; TT – trombino laikas; LMWH – mažos molekulinės masės heparinas; PT/INR – protrombino laikas / tarptautinis normalizuotas santykis; aPTT – aktyvinto dalinio tromboplastino laikas; DOACs – tiesiogiai veikiantys geriamieji antikoagulantai

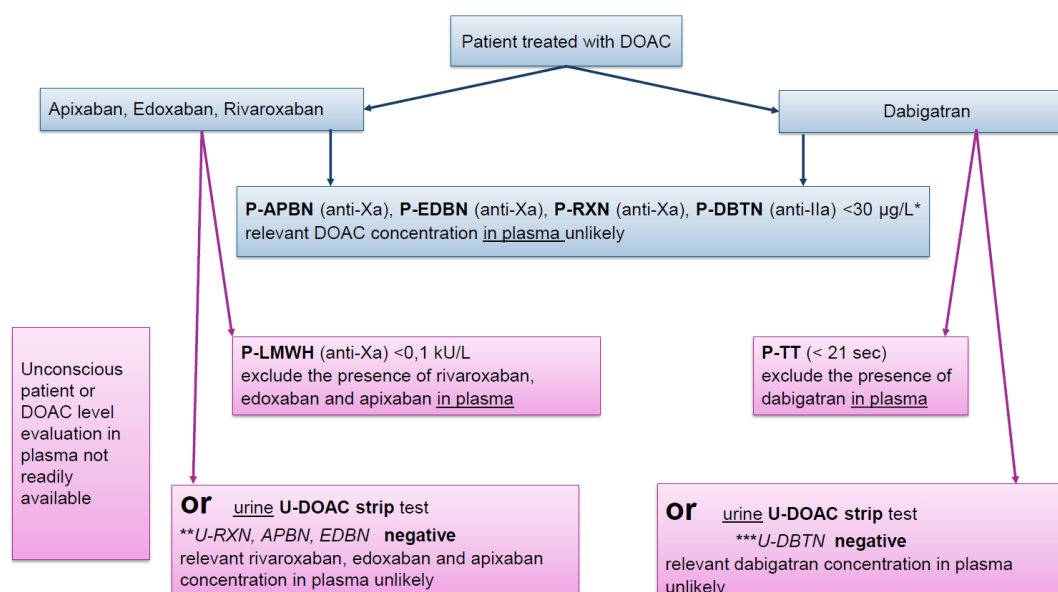


Fig. 3. Recommended standard protocol for laboratory assessment of DOAC therapy. * – µg/L corresponds to ng/mL units used elsewhere; ** – DOASENSE Reader results for factor Xa inhibitors correspond to LIS request for rivaroxaban, apixaban and edoxaban in urine (U-RXN, APBN, EDBN); *** – DOASENSE Reader results for thrombin inhibitors correspond to LIS request for dabigatran in urine (U-DBTN); LIS – Laboratory Information System

3 pav. Rekomenduojamas standartinis TVGA terapijos laboratorinio vertinimo protokolas. * – µg/l atitinka ng/ml vienetus, naudojame kituose šaltiniuose; * – DOASENSE skaitytuvo rezultatai Xa faktoriaus inhibitorių atveju atitinka LIS užklausą dėl rivaroksabano, apiksabano ir edoksabano tyrimo šlapime (U-RXN, APBN, EDBN); *** – DOASENSE skaitytuvo rezultatai trombino inhibitorių atveju atitinka LIS užklausą dėl dabigatrano tyrimo šlapime (U-DBTN); LIS – laboratorijos informacinė sistema

DISCUSSION

In assessing DOAC trough and peak levels, where the trough level is measured immediately before the next drug intake according to the treatment regimen, and the peak level is measured 1.5 to 4 hours after the last dose [16], accurate information regarding the last intake should be included in the laboratory analysis order. This protocol has been implemented at the North Estonia Medical Centre Laboratory, where recording the date and time of the last dose is mandatory for DOAC measurements. Additionally, documenting the dose taken by the patient is required for order confirmation. However, only expected plasma concentrations after therapeutic doses are currently available for DOACs, as detailed in the 2021 Update of the International Council for Standardization in Haematology Recommendations for Laboratory Measurement of Direct Oral Anticoagulants [17]. Nevertheless, these expected therapeutic values should be interpreted cautiously, as they are based on clinical trials whose inclusion and exclusion criteria may not fully reflect real-world patient conditions [18]. Accordingly, at present, it is not possible to adjust DOAC doses based on current measurements [19].

In clinical practice, the ability to interpret DOAC levels is essential for predicting bleeding or thrombotic events, particularly in patients with renal or hepatic impairment, extreme body weight, older age, recurrent thrombosis despite adequate DOAC intake, or significant drug interactions [20–22]. However, high plasma DOAC levels do not necessarily correlate with increased bleeding risk (unpublished data). The

pharmacokinetic and pharmacodynamic variability of DOACs among different patient groups remains insufficiently studied [23]. Further research assessing DOAC levels in specific patient populations may provide valuable insights into clinical decision-making and improved outcomes [24].

Furthermore, DOAC administration can influence clot-based assays, potentially resulting in false-negative or false-positive results [25]. However, in Estonia, DOAC-Stop (Haematex, Hornsby, NSW, Australia), which facilitates the in vitro adsorption of DOAC from plasma prior to performing the requisite laboratory assays [26, 27], can be used in rare but clinically challenging cases, such as for patients with hemophilia and atrial fibrillation undergoing DOAC therapy.

CONCLUSIONS

In Estonia, although different laboratory methods are available for assessing clinically relevant DOAC levels in plasma and urine, the selection of the appropriate method depends on various factors, including the clinical indication, urgency, and availability of the required equipment. Laboratory results should be interpreted within the clinical context, and medical decisions should not rely solely on these values. This review outlines two algorithms to support clinical decision-making: one for interpreting DOAC Dipstick results and another for understanding the available laboratory assays for DOAC measurement in Estonia. However, the unanswered questions remain, underscoring the need for further research.

Conflicts of Interests

The authors declare no conflicts of interest.

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Santrauka

LABORATORINĖS GALIMYBĖS ESTIJOJE VERTINANT TIESIOGIAI VEIKIANČIŲ GERIAMŲJŲ ANTIKOAGULIANTŲ POVEIKĮ

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Įvadas. Tiesiogiai veikiantys geriamieji antikoagulantai (TVGA) yra plačiai vartojami trombinės embolijos sutrikimų gydymui, ypač venų trombinės embolijos ir insulto prevencijai bei pacientų, sergančių prieširdžių virpėjimu, gydymui. Nors įprastinė TVGA laboratorinė stebėseną paprastai nerekomenduojama, tam tikrose klinikinėse situacijose jų vertinimas yra būtinas. Estijoje didėja laboratorinių tyrimų poreikis siekiant įvertinti TVGA koncentraciją ir padėti priimti kliniskus sprendimus. Šio darbo tikslas – sukurti standartizuotą TVGA laboratorinio vertinimo protokolą, remiantis šiuo metu prieinamais tyrimo metodais.

Medžiaga ir metodai. Atlikta išsami laboratorinių TVGA vertinimo metodų analizė Estijoje, atsižvelgiant į kokybinius ir kiekybinius tyrimus, įskaitant anti-Xa aktyvumą, trombino laiką ir chromogeninius metodus. Taip pat įvertintas „DOAC Dipstick“ (DO-ASENSE GmbH, Vokietija) kaip greitas šlapimo kokybinis tyrimas. Siekiant sukurti standartizuotą laboratorinį vertinimo protokolą remtasi tarptautinėmis gairėmis ir ekspertų rekomendacijomis.

Rezultatai. TVGA vertinimo metodų prieinamumas ir tikslumas Estijos laboratorijose skiriasi. Plazmos tyrimai užtikrina tikslus kiekybinius duomenis, tačiau nėra visuotinai prieinami, o šlapimo „DOAC Dipstick“ testas yra greita alternatyva klinikinio požiūriu reikšmingoms TVGA koncentracijoms atmeti. Autoriai siūlo šiuos metodus integruojantį standartizuotą protokolą, kad būtų pagerintas TVGA vertinimas klinikinėje praktikoje.

Išvados. TVGA laboratorinio vertinimo standartizavimas Estijoje gali pagerinti kliniskus sprendimus, užtikrindamas patikimus ir prieinamus tyrimo

metodus. Plazmos ir šlapimo tyrimų integracija leidžia visapusiškai įvertinti TVGA terapiją, tačiau reikalingi papildomi tyrimai, kad būtų galima optimizuoti jų taikymą ir pacientų gydymo rezultatus.

Reikšminiai žodžiai: tiesiogiai veikiantys geriamieji antikoagulantai, laboratorija, stebėseną, skubioji pagalba.

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