

Comparison of the sensitivity and specificity of rivaroxaban, apixaban and dabigatran concentrations measured in urine samples by the DOAC Dipstick with the cut-off plasma concentration of 30 ng/mL



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INTRODUCTION

The qualitative determination of direct oral anticoagulants (DOACs) has been shown to be sensitive and specific when managing stroke and when deciding on treatment for acute hip fracture in relatively small clinical studies. Treatment of major haemorrhage, thrombolysis or ischemic stroke, and the timing of acute hip fracture repair in patients on DOAC therapy has been guided by a cut-off plasma DOAC level of \geq 30 ng/mL.

The aim of the current study was to determine whether DOAC Dipstick test in urine can be used to exclude clinically relevant plasma concentrations. To do this, we compared direct oral factor Xa inhibitors (DXI) and thrombin inhibitor (DTI) in urine by the qualitative DOAC Dipstick test with the plasma concentrations of DOACs at a threshold of \geq 30 ng/mL from patients taking DOACs.

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CONCLUSIONS

- ▶ The DOAC Dipstick determines the presence and absence of rivaroxaban, apixaban and dabigatran in urine with at least >95% correctness when compared with the cut-off value of ≥ 30 ng/mL in plasma.
- The assessment of DXI and DTI concentrations at this cut-off value by visually inspecting the DOAC Dipstick pads and by using the DOASENSE Reader were close to 100% agreement.
 Further studies are currently evaluating these findings in additional patient groups.
- REFERENCE RESULTS **Plasma concentration** Dipstick Dipstick ng/mL. mean. SD positive negative • The DOAC concentrations in plasma – separated according adjudication of Table 1: Thromb Haemost. 2022 Jan 27. Plasma concentrations of DOACs according colours of pads of DOAC Dipstick for presence versus absence of DOACs Rivaroxaban 44.4 ± 14.0 18.8 ± 7.1 doi: 10.1055/a-1753-2748. to positive and negative results of DOAC in urine – were 44.4 ± 14.0 ng/mL and 18.8 ± 7.1 ng/mL for rivaroxaban, Online ahead of print. 50.5 ± 18.3 23.8 ± 8.8 Apixaban Dipstick from urine samples of patients 50,5 ± 18,3 ng/mL and 23,8 ± 8,8 ng/mL for apixaban, and 48,4 ± 14,0 ng/mL Dabigatran 48.4 ± 14.0 25.7 ± 3.7 and $25,7 \pm 3,7$ ng/mL for dabigatran (mean, SD), respectively (**Table 1**). Table 2: • Sensitivity, specificity, accuracy, negative and positive predictive values in p-value Sensitivity % Area under the curve (AUC) Threshold AUC ROC **Specificity %** PPV % NPV % DOAC . 30 vs 14 urine compared with a threshold of \geq 30 ng/mL plasma are shown for DXI according to the receiver operating (95 % CI) (95 % CÍ) (95 % CI) (95 % CI) (ng/mL) (95 % CĪ) ng/mL curve (ROC) analysis and statistical and DTI in Table 2. parameters for DXI (n=84) and DTI 21.4 71.8 100 100 • The best fitting threshold of plasma levels was \geq 14 ng/mL for DXI and DXI 0.859 (n=44) at thresholds of ≥ 30 ng /mL (93.6 - 100)(8.3 - 41.0)(60.5 - 81.4)(54.1 - 100) \geq 19 ng/mL for DTI. The specificity, positive and negative predictive values ≥ 30 and thresholds of \geq 14 ng/mL and 100 5.9 62.8 100 DTI 0.814 for FXA and DTI pads were substantially higher compared to \geq 30 ng/mL \geq 19 ng/mL in plasma (87.2 - 100) (0.2 – 28.7) (46.7 - 77.0)(2.5 - 100)AUC = area under the curve, threshold (Table 2). 0.994 100 85.7 98.7 100 ROC = receiver operating curve, DXI ≥14 < 0.001 • The kappa values between observers for visual inspection pads of DOAC (0.981 - 1.0)(95.3 – 100) (42.1 – 99.6) (93.1 - 100) (54.1 - 100)CI = confidence interval, 100 100 100 100 Dipstick of DXI and DTI and analysis between observers and DOASENSE PPV = positive predictive value. DTI ≥19 n.a. (2.5 - 100)(91.8 - 100)(91.8 - 100)(2.5 - 100)NPV = negative predictive value Reader were all 1.0.

METHODS

- We evaluated 131 of 132 plasma and urine samples taken from patients with neurologic and cardiovascular diseases and who were taking DOACs at Sestre Milosrdnice University Hospital Center at Zagreb. Participants were treated with rivaroxaban (n=53), apixaban (n=34) and dabigatran (n=44). Plasma and urine samples were taken before intake of DOAC to determine trough DOAC concentrations.
- The colours of DOAC Dipstick pads were visually evaluated to determine the presence or absence of DOACs by two trained medical professionals and by a DOASENSE reader. DOAC concentrations in plasma were measured by specific chromogenic substrate assays.
- Logistic regression analyses with the binary outcome DOAC present or absent was performed together with receiver operating curve (ROC) analyses in order to find best fitting thresholds for plasma concentrations for FXA and THR pads. A ROC analysis determines specified thresholds by the maximum value of the sum of sensitivity and specificity.