



A. Martini¹, R. Bauersachs², J. Beyer Westendorf³, M. Crowther⁴, J. Douxfils⁵, I. Elalamy⁶, <u>J. Harenberg⁷</u>, S. Hetjens¹, C. Weiss¹ 1 Heidelberg University, Medical Faculty Mannheim, Mannheim, Germany, 3 University Hospital, Dresden, Germany, 4 McMaster University, Hamilton, Canada, 5 University of Namur, and Qualiblood sa, Namur, Belgium, 6 Hôpitaux Universitaires Est Parisien, Paris, France, 7 Heidelberg University, and DOASENSE GmbH, Heidelberg, Germany

INTRODUCTION

The DOAC Dipstick accurately determines the presence or absence of oral direct factor Xa (DXI) or oral direct thrombin inhibitors (DTI) in urine samples from patients treated with these classes of direct oral anticoagulants (DOACs). Several studies have investigated the performance of prototype and commercial dipsticks.

AIM

To compare the performance of prototype and commercial dipsticks in a systematic review and meta-analysis to analyze the robustness and consistency of the data collected in these different studies.

METHOD

The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement

The sensitivity is defined as the proportion of true positive results in relation to the population treated with a DOAC (factor Xa or thrombin inhibitor) and the specificity as the proportion of true negative results in relation to the population of untreated controls (not treated with a factor Xa or thrombin inhibitor). Sensitivity and specificity of individual and pooled studies were analysed using MetaDiSc. The sensitivities and specificities of prototype and commercial test strips were compared using Chi-squared test.

If the presumptions of the Chi-squared test were not fulfilled, Fisher's exact test was used alternatively. Test results were considered as statistically significant at p-values below 0.05.

Heterogeneity between studies was calculated using chi-squared heterogeneity test and the I² index at a p-value of < 0.05. An I² index value gauges heterogeneity - between 0 to 25 % indicates insignificant heterogeneity; > 25 % to 50 % low heterogeneity; > 50 % to 75 % moderate heterogeneity; and > 75 % high heterogeneity.

The random effects model according to DerSimonian and Laird was used to analyse pooled data – this technique takes any heterogeneity between the studies into account. Forest plots were created for sensitivity and specificity of studies showing weight by size of points and in percent, values with 95% CI, I² index and p-values for differences.

Based on the sensitivity and specificity analyses, the accuracy, negative predictive value (NPV) and positive predictive value (PPV) of test strips results were calculated for the simulated prevalences of 1%, 10%, 30% and 60% based on Bayes' rule. The simulated prevalence represents the simulated proportion of a population who take DOACs in a given period of time.

A systematic review and meta-analysis of performances of prototype and commercial DOAC Dipstick tests for detecting direct oral anticoagulants in patient urine samples – Increasing confidence for testing in emergency care

RESULTS

Four of 1081 publications were considered eligible for inclusion; three reported results on prototype dipsticks (DXI n=658, DTI n=586) and one on commercial dipsticks (DXI n=451, DTI n=429) (Fig. 1).

There were no significant differences in sensitivity and specificity of DXI and DTI detection between prototype and commercial dipsticks (Fig. 2A and 2B).

The pooled sensitivity and specificity was 0.968 (95%CI 0.956-0.978, p=0.1290, I² 47.1%) and 0.979 (95%CI 0.968-0.992, p=0.1965, l² 35.9%) respectively for detecting DXIs and 0.993 (95%CI 0.986-0.997, p=0.1870, I² 37.5%) and 0.993 (95%CI 0.986-0.997, p=0.7380, I² 0%) respectively for detecting DTIs.

Simulation down to 1% prevalence showed a very high negative predictive value of 0.999, indicating that the dipstick test may remain valid for detecting DOACs in patients' urine with acute medical conditions, and a still high positive predictive value between 0.238 and 0.590 for type of DOAC probably depending upon population and renal function.

CONCLUSIONS

Detection of DXI and DTI in patient urine samples was not significantly different between prototype and commercial DOAC dipsticks.

This should increase confidence to use of the DOAC Dipstick in emergency patient care and other medical indications.

The simulation of the prevalence showed the very high NPV that is important in a general population and in patients when intake of DOACs in unknown.



REFERENCES

Harenberg J, et al R. Concept of a point of care test to detect new oral anticoagulants in urine samples. *Thromb J 2013 Aug 1;11(1):15.* Harenberg J, et al. Measurement of dabigatran, rivaroxaban and apixaban in samples of plasma, serum and urine, under real life conditions. An international study. *Clin Chem Lab Med 2016;54(2):275-83* Harenberg J, et al. Performance characteristics of DOAC Dipstick in determining direct oral anticoagulants in urine. Clin Appl Thromb Hemost. 2021 Jan-Dec;27:1076029621993550. doi:10.1177/1076029621993550.

Harenberg J, et al. Accuracy of a Rapid Diagnostic Test for the Presence of Direct Oral Factor Xa or Thrombin Inhibitors in Urine-A Multicenter Trial. *Thromb Haemost. 2020;120(1):132-140.*

CONFLICT OF INTEREST

No authors reported a COI for this investigation







		value (95% CI)	weight (%)
study 1	0	1.000 (0.992 - 1.000)	41.00
study 2	-0	0.987 (0.930 - 1.000)	13.74
study 3	0	1.000 (0.881 - 1.000)	6.05
study 4	•	0.995 (0.985 - 0.999)	39.21
pooled	4.	0.993 (0.986 - 0.997)	.997) 100.00
0.1 0.2 0.3 0.4 0.5 0.6 0.	7 0.8 0.9 1.0	Chi-Square = 4.80; df = 1.1 Inconsistency (I-Square	=3 (p = 0.1870) e) = 37.5%
Sensitivity			
		value (95% CI)	weight (%)
	db.	0.992 (0.979 - 0.998)	47.34
study 1		(/	
study 1 study 2		1.000 (0.932 - 1.000)	5.22
study 1 study 2 study 3		1.000 (0.932 - 1.000) 1.000 (0.881 - 1.000)	5.22 2.95
study 1 study 2 study 3 study 4		1.000 (0.932 - 1.000) 1.000 (0.881 - 1.000) 0.993 (0.981 - 0.999)	5.22 2.95 44.49
study 1 study 2 study 3 study 4 pooled		1.000 (0.932 - 1.000) 1.000 (0.881 - 1.000) 0.993 (0.981 - 0.999) 0.993 (0.986 - 0.997)	5.22 2.95 44.49 100.00

CONTACT INFORMATION

j.harenberg@doasense.de

http://www.doasense.de