ORIGINAL ARTICLE
UDC: 616.151.5:615.273
DOI: https://doi.org/10.2298/VSP210217101K

Influence of DOACS and DOAC-REMOVE® on coagulation assays during thrombophilia testing in DOAC-treated patients

Uticaj DOAK i DOAC-REMOVE® na testove koagulacije u toku testiranja trombofilije kod bolesnika lečenih primenom DOAK

Mirjana Kovač*†, Dušica Basarić†, Branko Tomić‡, Maja Gvozdenov‡, Dragana Backović§, Sanja Lalić-Ćosić§

University of Belgrade, *Faculty of Medicine, †Institute of Molecular Genetics and Genetic Engineering, §Faculty of Pharmacy, Belgrade, Serbia; ‡Blood Transfusion Institute of Serbia, Hemostasis Department, Belgrade, Serbia

Abstract

Background/Aim. Direct oral anticoagulants (DOACs) administration significantly interferes with coagulation assays. The aim of the study was to evaluate the effect of DOACs and DOAC-Remove® on coagulation assays during thrombophilia testing. **Methods.** The study was carried out from January 2019 to the end of June 2020. It included 30 DOAC-treated patients, 14 females and 16 males aged 23 to 63 (median age 47.6 years), tested for thrombophilia due to venous thromboembolism (VTE). Thrombophilia testing was performed using DOAC-Remove® tablets (activated charcoal). The results before and after DOAC-Remove® were compared. **Results.** Positive lupus anticoagulant (LA) results were observed in 20% apixaban, 100% dabigatran, and 70% rivaroxaban-treated patients, while in samples after DOAC-Remove®, the LA positivity was observed only in one from the apixaban group. Before DOAC-Remove®, the activated protein C (APC) resistance (APC-R) was measurable in 40% dabigatran and 80% rivaroxaban-treated patients, while, after using DOAC-Remove®, the APC-R was measurable in all cases. Comparing the results obtained from the samples before and after DOAC-Remove®, a difference was noted in relation to all dilute Russell's viper venom time (dRVVT) coagulation tests, except for the dRVVT ratio in the apixaban group. Clot-based methods for detecting the APC resistance were significantly affected by dabigatran and less by rivaroxaban. **Conclusion.** DOACs were practically inactivated after the addition of the DOAC-Remove®, which made it possible to perform analyses for the LA and APC-R testing freely and obtain relevant results.

Key words:
anticoagulants; blood coagulation tests; evaluation study; thrombophilia.

Apstrakt

Uvod/Cilj. Primena direktnih oralnih antikoagulansa (DOAK) značajno utiče na testove koagulacije. Cilj rada bio je da se proceni uticaj DOAK i DOAC-Remove® tableta (aktivni ugalj) na testove koagulacije tokom ispitivanja trombofilije. **Metode**. Istraživanjem, sprovedenim od januara 2019. do juna 2020. godine, obuhvaćeno je 30 bolesnika lečenih DOAK-om i testiranih na trombofiliju zbog venskog tromboembolzma (VTE). Bilo je 14 žena i 16 muškaraca, starosti od 23 do 63 godine (medijana 47,6 godina). Ispitivanje trombofilije izvršeno je upotrebom DOAC-Remove® tableta (aktivni ugalj). Upoređivani su rezultati pre i posle primene DOAC-Remove®. **Rezultati**. Pozitivni rezultati za lupus antikoagulantni (LA) test dobijeni su kod 20% bolesnika lečenih apiksabanom, kod 100% bolesnika lečenih dabigatranom i kod 70% lečenih rivaroksabanom, a u uzorcima posle DOAC-Remove® pozitivnost na LA dobijena je samo kod jednog bolesnika iz grupe lečnih apiksabanom. Pre primene DOAC-Remove®, rezistencija na aktivisani protein C (*activated protein C resistance* – APC-R) bila je merljiva kod 40% i 80% bolesnika lečenih dabigatranom, odnosno rivaroksabanom, dok je posle primene DOAC-Remove®, APC-R bila merljiva u svim slučajevima. Upoređivanjem rezultata dobijenih iz uzoraka pre i posle primene DOAC-Remove®, primećena je razlika u odnosu na sve testove vremena koagulacije izvršene razblaženim Russell-ovim zmijskim otrovom (*dilute Russell's viper venom time* – dRVVT), osim dRVVT u grupi bolesnika lečenih apiksabanom. Na koagulacionu metodu za otkrivanje APC-R značajno je uticao dabigatran, a manje rivaroksaban. **Zaključak**. Nakon primene DOAC-Remove® tableta, DOAK su praktično inaktivisani što je omogućilo izvođenje analiza za LA i APC-R i dobijanje relevantnih rezultata testova.

Ključne reči:
antikoagulansi; krv, testovi koagulacije; procena, istraživanja; trombofilija.

Correspondence to: Mirjana Kovač, Blood Transfusion Institute of Serbia, Belgrade, Serbia, Sv. Save 39, 11 000 Belgrade, Serbia.
E-mail: mkovac008@gmail.com

Introduction

The new class of anticoagulants has been referred to as novel oral anticoagulants (NOACs). With regard to the mechanism of action, they are target-specific oral anticoagulant agents and are, as such, aimed at inhibiting a specific coagulation factor. Hence, dabigatran is a direct inhibitor of thrombin, while rivaroxaban, apixaban, and edoxaban are direct inhibitors of activated factor X (FXa). For the control of anticoagulation, the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH) recommends the term direct oral anticoagulants (DOACs) [1]. DOACs are increasingly being used as an alternative to warfarin in the treatment of venous thromboembolism (VTE). However, the introduction of DOACs brought new challenges for all those involved in laboratory testing and assessing thrombophilia presence. These challenges include DOACs interference on coagulation (clot-based) assays, which can lead to false-positive or false-negative results (depending on drug concentration) [2–5]. Particularly problematic thrombophilia tests include clotting assays for proteins C and S, lupus anticoagulant (LA), and activated protein C resistance (APC-R) [6–9]. The most recent guidance from the Clinical and Laboratory Standards Institute (CLSI), published in 2014, gave a firm conclusion that LA testing was not recommended in DOAC-treated patients [10]. Concerning the results of the recently published study, all DOACs led to a prolongation in both dilute Russel's Viper Venom Time (dRVVT) based screen and confirm assays used for LA detection [11]. As a result of the extent prolongation of the dRVVT screen influenced by DOACs, mixing studies (ratio 1:1) recommended by the guidelines could not remove this interference, as it can do with vitamin K antagonist (VKA). Therefore, inhibition from the DOACs would still be present [12].

Despite this interference in coagulation assays, clinicians continue to request thrombophilia testing for DOAC-treated patients. The correct interpretation of thrombophilia testing results obtained in DOAC-treated patients is mandatory to prevent misclassification and subsequent clinical consequences [6].

The aim of the study was to evaluate the effect of DOACs and DOAC-Remove® tablets (activated charcoal) on coagulation assays during thrombophilia testing among our DOAC-treated patients.

Methods

Patients

The study included 30 DOAC-treated patients, 14 females and 16 males aged 23 to 63 years (median age 47.6 years), tested for thrombophilia due to VTE. The study was conducted from January 2019 to the end of June 2020. In all patients, thrombophilia testing was performed from a sample before and after the addition of DOAC-Remove® tablets. The results obtained before and after DOAC-Remove® tablets were compared. One of the DOAC-treated patients from the apixaban group was known to be LA-positive. The LA-positive test was diagnosed in this case upon low molecular weight heparin during the first VTE event.

Patient samples treated with DOAC-Remove®

In all subjects, whole blood was collected 2–12 hrs after DOACs intake into buffered sodium citrate tubes (containing 1/10 volume sodium citrate stock solution at 0.129 mmol/L; Vacutest, Kima) by sterile, atraumatic venipuncture. Two samples were taken for each patient. One was prepared by a standard method to obtain platelet-poor plasma for coagulation assays used in the thrombophilia testing and denoted as a sample before DOAC-Remove®. The second sample was prepared using DOAC-Remove® tablets. According to the instruction, 1 mL of previously prepared plasma sample was mixed gently for 5 min with a DOAC-Remove® tablet and then centrifuged for two min at 2,000 g. The supernatant obtained after centrifugation, denoted as a sample after DOAC-Remove®, was used for coagulation assays.

Thrombophilia testing included the following: screening tests, activated partial thromboplastin time (APTT), and prothrombin time (PT); determination of antithrombin (AT), protein C (PC), and protein S (PS) activity; presence of LA and APC-R. All assays were performed using Siemens Healthcare Diagnostics reagents on a BCS XP system (Siemens, Marburg, Germany) according to the manufacturer's instructions. Pathromptin SL and Thromborel S were used for APTT and PT testing, respectively. The activity of natural inhibitors was measured using Berichrom ATIII (anti-IIa based) and Innovance Antithrombin (anti-Xa based) for AT, Berichrom Protein C for PC, and Innovance Free Protein S Ag for PS. The presence of LA was evaluated using an integrated assay based on dilute Russel's viper venom time (dRVVT) tests that utilize dRVVT LA screen reagent (LA1) and dRVVT LA confirm reagent (LA2). Results for LA1, LA2, and LA ratio were expressed following CLSI recommendations published in 2014 [10] as normalized ratios, and a value of 1.2 was used as the cut-off value. APC-R was determined using the Russell Viper Venom Time (RVVT)-based functional clotting test (ProC Ac R assay). APC-R lower than 1.8 was considered pathological. Additionally, genotyping of FV Leiden and FII G20210A mutations was carried out in all study participants. The mutations were detected by polymerase chain reaction (PCR) followed by digestion with specific restriction enzymes (MnlI for FV Leiden and HindIII for FII G20210A, NEBiolabs). Normal and mutated alleles were distinguished by the size of the restriction fragments using electrophoresis on polyacrylamide gels. For one AT deficient patient revealed in routine thrombophilia testing, the PCR analysis for SERPINC 1 gene was performed afterward. In order to minimize the effect of acute thrombosis on thrombophilia testing, the blood samples were collected 6–8 weeks after the acute thrombosis. Concerning the defined indication for the thrombophilia testing, patients who developed their first thrombosis before the age of 50 were included in the study.

Institutional approval for the study was granted by the Local Research Ethics Committee (No 1101/2, from September 17, 2020) following internationally accepted ethical standards. Each patient signed the informed consent form.

Statistical analysis

The distribution of analyzed data was tested. Description of data was done using median and interquartile range (IQR). Differences between groups' data were evaluated using the Mann-Whitney *U* test and Fisher's exact test. A *p*-value less than 0.05 was considered statistically significant.

The Statistical Package for Social Sciences 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA) was used for statistical analyses.

Results

The clinical data of the study participants (age, sex, thrombotic manifestation, comorbid condition, and DOACs doses) are presented in Table 1.

Analysis of the results obtained among 30 DOAC-treated patients, denoted as samples before DOAC-Remove® and after DOAC-Remove®, are shown in Figures 1−3. Positive LA results were observed in 20% apixaban, 100% dabigatran, and 70% rivaroxaban-treated patients. In samples after DOAC-Remove®, the LA positivity was observed only in one from the apixaban group. Before DOAC-Remove®, the APC-R ratio was measurable in 40% of dabigatran and 80% of rivaroxaban-treated patients, while, after using DOAC-Remove®, the APC-R was measurable in all cases.

Table 1

Patient characteristics

Parameter	Apixaban	Rivaroxaban	Dabigatran
Current age (years), range (median)	43–63 (48.3)	23–63 (43.4)	40–61 (51.2)
Sex (m/f), n	6/4	7/3	3/7
Thrombosis localization, n			
DVT/PE	4**	7***	4*
PE	3*	2	4*
DVT	3*	1*	2*
Age of the first VTE (years), range (median)	41–49 (45.6)	19–50 (37.8)	40–49 (45.8)
Risk factors for the first VTE, n			
surgery	2	2	–
hormonal therapy	2	1	3
CA			1
Concomitant diseases, n			
CA	2	1	1
hypertension	1		
arrhythmia	1		
DOACs doses, mg	2 pts, 2 × 5 8 pts, 2 × 8	20	2 ×150

m – male; f – female; n – number of patients (pts); DVT – deep venous thrombosis; PE – pulmonary embolism; VTE – venous thromboembolism; * – patient with recurrent thrombosis, the number of stars refers to the number of pts in some groups; CA – breast cancer; DOACs – direct oral anticoagulants.

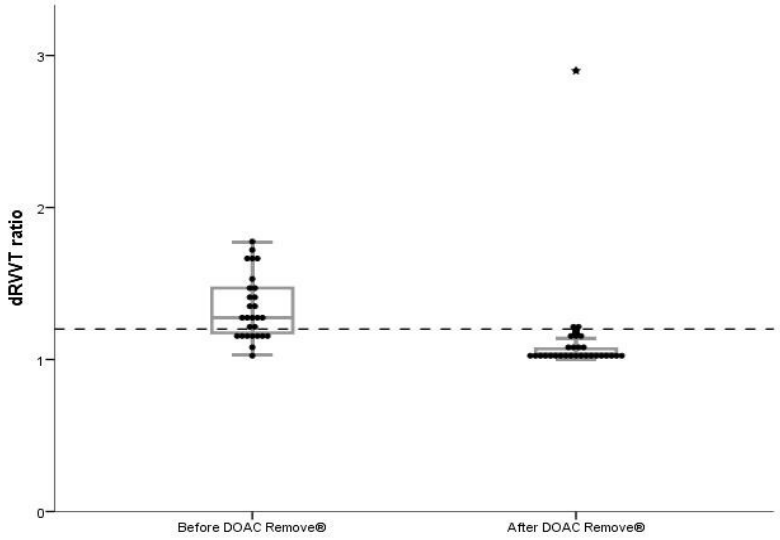

Fig. 1 – Results for dilute Russel's viper venom time (dRVVT) ratio of tested patients. Data are shown as individual dot plots with median and interquartile range (IQR) ratios for dRVVT ratio (y-axis). The samples are denoted as before and after DOAC-Remove® (x-axis).

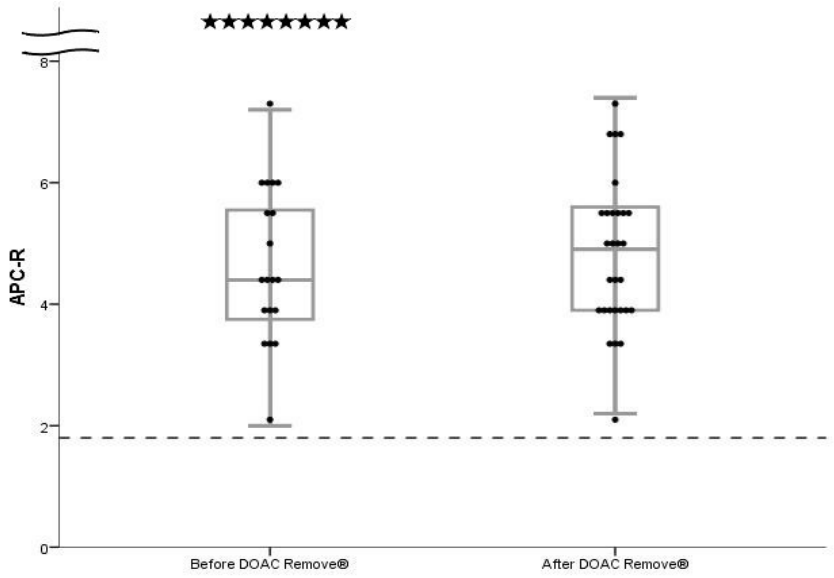

Fig. 2 – Results for activated protein C resistance (APC-R) of tested patients. Data are shown as individual dot plots with median and interquartile range (IQR) ratios for APC-R (y-axis). The samples are denoted as before and after DOAC-Remove® (x-axis). The dashed horizontal line presents a cut-off for APC-R (1.8) to define negative vs. positive test results. ★– immeasurable data.

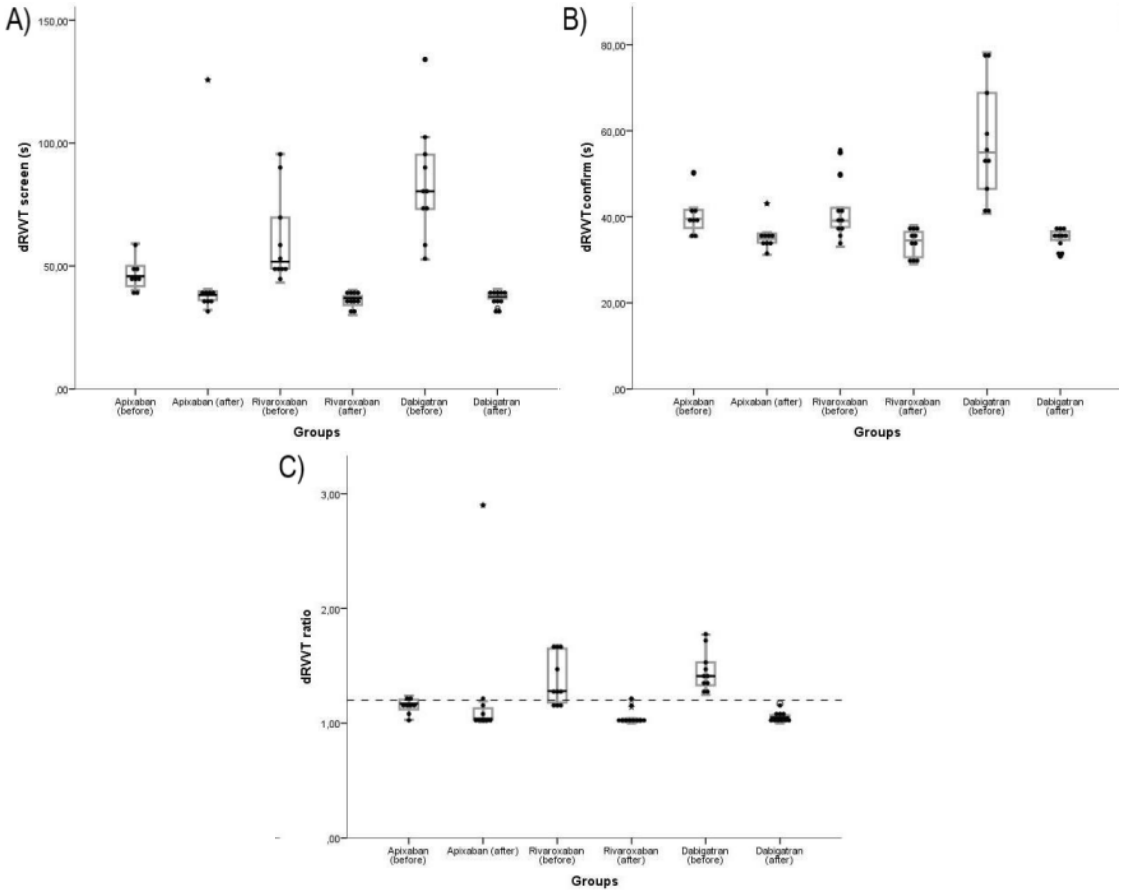

Fig. 3 – Results for: a) dilute Russel's viper venom time (dRVVT) screen; b) dRVVT confirm; c) dRVVT ratio of tested patients.

Data are shown as individual dot plots with median and interquartile range (IQR) ratios for dRVVT screen (A), dRVVT confirm (B), and dRVVT ratio (C) (y-axis). The patient groups are presented in relation to DOACs drugs (apixaban, rivaroxaban, dabigatran) before and after DOAC-Remove® (x-axis). The dashed horizontal line presents a cut-off for the dRVVT ratio (1.2) to define negative vs. positive test results.

Regarding the APC-R test results, PCR tests confirmed the obtained APC-R findings – the patients tested did not have the FV Leiden mutation.

A comparison of the coagulation assays results obtained before and after applying DOAC-Remove® showed a significant difference concerning the APTT only in the dabigatran group. A significant difference was observed in all DOAC-treated groups in relation to the dRVVT screen ($p = 0.012$, $p < 0.001$, $p < 0.001$) and dRVVT confirm ($p = 0.016$, $p = 0.005$, $p < 0.001$). In contrast, the difference in the dRVVT ratio was observed among rivaroxaban and dabigatran-treated patients ($p < 0.001$). In relation to the evaluation of the biological activity of natural inhibitors, there were no differences between samples before and after the addition of DOAC-Remove® tablets (Table 2).

One patient from the apixaban group, after treatment of the sample with DOAC-Remove®, was confirmed as an AT-deficient patient. Using an anti-IIa assay before applying DOAC-Remove®, AT activity of 73% was obtained, while after applying DOAC-Remove®, it was 61%. Using anti-factor Xa (anti-Xa) assay before applying DOAC-Remove®, AT activity of 106% was obtained, while after applying DOAC-Remove®, it was 54%. Repeated analyses of a new sample taken after one month showed similar results. Genetic analyses have confirmed the presence of AT deficiency type I.

Table 2

Coagulation assays obtained from plasma samples before and after the addition of DOAC-Remove® tablets

Coagulation assay	Apixaban*		Rivaroxaban**		Dabigatran	
	(median)	IQR	(median)	IQR	(median)	IQR
APTT (s)						
BDR	31.2	5.15	31.85	8.875	41.15	5.5
ADR	28.5	2.6	29.7	3.5	30.05	3.5
p	0.101		0.054		**< 0.001**	
PT (%)						
BDR	108	13	104.5	18.25	95.5	19.25
ADR	120	14	110.5	12.25	105	20.5
p	0.477		0.173		0.054	
Fibrinogen						
BDR	3.7	1.55	3.6	0.95	3.55	0.725
ADR	3.35	1.275	3.05	1.1	3.4	0.7
p	0.343		0.172		0.544	
dRVVT screen (s)						
BDR	45.8	9.125	51.75	26.575	80.4	27.7
ADR	38.2	4.75	36.95	4.833	37.5	3.275
p	**0.012**		**< 0.001**		**< 0.001**	
dRVVTconfirm (s)						
BDR	39.55	5	39.05	6.85	54.95	25.625
ADR	35	2.65	34.55	6.15	35.6	3.025
p	**0.016**		**0.005**		**< 0.001**	
dRVVT ratio						
BDR	1.17	0.108	1.28	0.478	1.41	0.255
ADR	**1.04	0.135	1.025	0.057	1.05	0.043
p	0.112		**< 0.001**		**< 0.001**	
AT (%)						
BDR	99	19	99.5	19.75	100	17.25
ADR	#93	30.5	93	11.75	99.5	19.75
p	0.132		0.161		0.762	
PC (%)						
BDR	124	47	91	29.5	118.5	33.75
ADR	120	44.5	92.5	31.25	118	32
p	0.536		0.97		0.97	
PS (%)						
BDR	94	16.5	84.5	36.75	109	35
ADR	93	13.5	82.5	37.75	108	33.5
p	0.965		0.91		0.97	
APC-R						
BDR	5.300	1.3	4.1	1.3	4	2.95
ADR	5.600	0.9	4.2	1.175	4.7	3
p	0.873		0.657		0.62	

***One patient with positive lupus anticoagulant (LA) and one with AT deficiency were diagnosed in the apixaban group;**PCR tests confirmed that one patient treated with rivaroxaban was a carrier of the *FII G20210A* mutation.**

BDR – before DOAC-Remove®; ADR – after DOAC-Remove®; APTT – activated partial thromboplastin time; APC-R – activated protein C resistance; AT – antithrombin; dRVVT – dilute Russel's viper venom time; PC – protein C; PS – protein S; PT – prothrombin time; IQR – interquartile range.

***p* – Mann-Whitney *U* test (significant values are bolded).**

Discussion

The results obtained from the samples denoted before DOAC-Remove® showed that the reliability of the tests used in the detection of LA and APC-R was uncertain. Most patients on dabigatran (100%), rivaroxaban (70%), and apixaban (20%) appeared to be LA positive, while in half of those on dabigatran and up to 20% on rivaroxaban, the APC-R test was not measurable. The results obtained from the samples before DOAC-Remove® confirmed that DOACs administration has a significant interference on coagulation assays, mostly to those based on the APTT principle. The analysis of the standard coagulation tests showed that APTT is most responsive to dabigatran. With regard to the specific assays, all DOACs interfere with most APTT-based assays that were used in the detection of LA, while clot-based methods for detecting the APC resistance are significantly affected by dabigatran and less by rivaroxaban.

Comparing the results obtained from the samples before and after DOAC-Remove®, a difference was noted in relation to all dRVVT tests, except for the dRVVT ratio in the apixaban group. Favaloro et al. [11] explained the difference between DOACs in LA testing, which was also confirmed in our study. They showed that rivaroxaban affected the screen more than the confirm, leading to higher RVVT ratios, while apixaban affected the confirm more than the screen, leading to lower RVVT ratios.

We have to note that in the apixaban group, one patient was diagnosed as an AT-deficient patient. In this particular case, in the sample before DOAC-Remove®, we found a discrepancy in the level of measured AT activity since that anti-Xa assay provided a normal AT level, while after DOAC-Remove®, both assays showed reduced AT activity. Ząbczyk et al. [13] showed that treatment with rivaroxaban and apixaban overestimates AT activity measured by FXa- but not FIIa-based assay in AT-deficient individuals. Due to the mechanism of inhibition (via FIIa or FXa), DOACs may interfere with AT activity tests based on the same principles. Therefore, the FIIa-based assay is preferred in patients treated with rivaroxaban or apixaban [14].

On the other hand, the analysis of PCR results confirmed the obtained findings of the APC-R test, obtained from samples denoted as after DOAC-Remove®. We have to emphasize that in relation to the uncertain findings of the APC-R test, we can always instruct the patient to perform PCR in order to confirm or exclude the FV Leiden mutation. However, in the detection of LA, we do not have such a possibility. It should be noted that the findings of the tests used in evaluating the LA presence are very significant, given its impact on the recurrent thrombosis risk, which is important for clinicians in assessing the anticoagulant therapy duration. Therefore, the use of *in vitro* drug adsorption with activated charcoal (DOAC-Remove® or DOAC-Stop®) is a useful tool for DOACs neutralization and subsequent LA diagnosis in patients treated with DOACs. That is supported by recently published studies showing that activated charcoal effectively reduced plasma DOACs concentrations leading to appropriate dRVVT results in up to 97% of VTE patients [15, 16]. The authors of the second-mentioned study suggest the use of DOAC-Remove® for every rivaroxaban sample and in positive apixaban and dabigatran samples [16]. Likewise, Favresse et al. [17] suggested the use of the DOAC-Stop® treatment in clinical practice to avoid potential misclassifications and clinical consequences.

One of the limitations of our study worth discussing is the missing data on DOACs concentration in plasma before and after DOACs removal. However, less than 1% of laboratories that perform routine coagulation screening tests, PT or APTT, could measure DOACs plasma concentrations [5]. It is known that DOACs have predictable pharmacokinetic and stable pharmacodynamics profiles, so their administration does not require coagulation monitoring or measurement of concentration and dose adjustment. Peak plasma levels for DOACs are reached 2–5 hrs after administration, and their half-life is between 7–14 hrs, while the minimum effect is observed directly before the next drug administration at least 18–24 hrs after the last dose [4, 6, 15]. Recent studies reported that the addition of activated charcoal tablet has been able to neutralize the highest likely clinical concentrations of apixaban, dabigatran, rivaroxaban, and edoxaban and provide measurable and appropriate results for routine screening and specialty coagulation tests in patients taking DOACs. At the same time, these products showed minimal influence on non-DOACs plasmas [16, 18]. Kopytek et al. [9] demonstrated that DOAC-Remove® reduced DOACs concentrations of apixaban (< 3–7 ng/mL, $p < 0.0001$) and dabigatran (all < 5 ng/mL, $p < 0.0001$), while rivaroxaban concentrations were abolished at almost 100% (all < 3 ng/mL, $p < 0.0001$). Moreover, Slavik et al. [19], using reference HPLC-MS/MS method, reported that half a tablet of DOAC-Stop® added to each 0.5 mL of plasma removed apixaban from 97.1%, dabigatran from 99.5%, and rivaroxaban from 97.9% of participants' plasmas, leaving in some samples residual concentrations of DOACs that do not affect coagulation. In another study by Favresse et al. [17], DOAC-Stop® treatment was efficacious in neutralizing DOACs in patient samples removing DOACs to residual levels lower than the limit of quantification of the corresponding DOACs assays.

Conclusion

DOACs were practically inactivated after the addition of the DOAC-Remove® tablets in the prepared plasma samples, which made it possible to perform analyses for the LA and APC-R testing freely and obtain relevant results. Since DOACs laboratory monitoring is not routinely performed in most clinical laboratories, using activated charcoal tablets to neutralize DOACs in samples collected immediately prior to re-dosing may be an optimal approach to enable the coagulation testing and the correct interpretation of results in patients taking DOACs.

Acknowledgement

This study was supported by grant No. 173008 from the Ministry of Education, Science and Technological Development of the Republic of Serbia.

Conflict of interest statement

The authors declare no conflict of interest.

R E F E R E N C E S

1. *Barnes GD, Ageno W, Ansell J, Kaatz S*. Subcommittee on the Control of Anticoagulation of the International Society on Thrombosis and Haemostasis. Recommendation on the nomenclature for oral anticoagulants: communication from the SSC of the ISTH. J Thromb Haemost 2015; 13(6): 1154–6.
2. *Douxfils J, Chatelain C, Chatelain B, Dogné JM, Mullier F*. Impact of apixaban on routine and specific coagulation assays: a practical laboratory guide. Thromb Haemost. 2013; 110(2): 283–94.
3. *Bonar R, Favaloro EJ, Mohammed S, Ahuja M, Pasalic L, Sioufi J,* et al. The effect of the direct factor Xa inhibitors apixaban and rivaroxaban on haemostasis tests: a comprehensive assessment using in vitro and ex vivo samples. Pathology 2016; 48(1): 60–71.
4. *Mani H, Hesse C, Stratmann G, Lindhoff-Last E*. Rivaroxaban differentially influences ex vivo global coagulation assays based on the administration time. Thromb Haemost 2011; 106(1): 156–64.
5. *Gosselin R, Grant RP, Adcock DM*. Comparison of the effect of the anti-Xa direct oral anticoagulants apixaban, edoxaban, and rivaroxaban on coagulation assays. Int J Lab Hematol 2016; 38(5): 505–13.
6. *Hoxha A, Banzato A, Ruffatti A, Pengo V*. Detection of lupus anticoagulant in the era of direct oral anticoagulants. Autoimmun Rev 2017; 16(2): 173–8.
7. *Lippi G, Mattiuzzi C, Favaloro EJ*. Thrombophilia testing in patients taking direct oral anticoagulants. Handle with care. Diagnosis (Berl) 2014; 1(4): 311–2.
8. *Goodwin AJ, Adcock DM*. Thrombophilia testing and venous thrombosis. N Engl J Med 2017; 377(23): 2297–8.
9. *Kopytek M, Ząbczyk M, Malinowski KP, Undas A, Natorska J*. DOAC-Remove abolishes the effect of direct oral anticoagulants on activated protein C resistance testing in real-life venous thromboembolism patients. Clin Chem Lab Med 2020; 58(3): 430–7.
10. *Clinical and Laboratory Standards Institute (CLSI)*. Laboratory testing for the lupus anticoagulant; approved guideline. CLSI document H60-A. Wayne, PA: Clinical and Laboratory Standards Institute; 2014.
11. *Favaloro EJ, Mohamed S, Curnow J, Pasalic L*. Laboratory testing for lupus anticoagulant (LA) in patients taking direct oral anticoagulants (DOACs): potential for false positives and false negatives. Pathology 2019; 51(3): 292–300.
12. *Pengo, V, Tripodi A, Reber G, Rand JH, Ortel TL, Galli M,* et al. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. Update of the guidelines for lupus anticoagulant detection. J Thromb Haemost 2009; 7(10): 1737–40.
13. *Ząbczyk M, Natorska J, Kopytek M, Malinowski KP, Undas A*. The Effect of Direct Oral Anticoagulants on Antithrombin Activity Testing Is Abolished by DOAC-Stop in Venous Thromboembolism Patients. Arch Pathol Lab Med 2021; 145(1): 99–104.
14. *Ruhl H, Reda S, Muller J, Oldenburg J, Potzsch B*. Activated Factor X-Based versus Thrombin-Based Antithrombin Testing in Thrombophilia Workup in the DOAC Era. Thromb Haemost 2018; 118(2): 381–7.
15. *Ząbczyk M, Kopytek M, Natorska J, Undas A*. The effect of DOAC-Stop on lupus anticoagulant testing in plasma samples of venous thromboembolism patients receiving direct oral anticoagulants. Clin Chem Lab Med 2019; 57(9): 1374–81.
16. *Jourdi G, Delrue M, Stepanian A, Valaize J, Foulon-Pinto G, Demagny J,* et al. Potential usefulness of activated charcoal (DOAC-Remove®) for dRVVT testing in patients receiving Direct Oral AntiCoagulants. Thromb Res 2019; 184: 86–91.
17. *Favresse J, Lardinois B, Sabor L, Devalet B, Vandepapeliere J, Braibant M, et al*. Evaluation of the DOAC-Stop® Procedure to Overcome the Effect of DOACs on Several Thrombophilia Screening Tests. TH Open 2018; 2(2): e202–e9.
18. *Cox-Morton S, MacDonald S, Thomas W*. A diagnostic solution for haemostasis laboratories for patients taking direct oral anticoagulants using DOAC-Remove. Br J Haematol 2019; 187(3): 377–85.
19. *Slavik L, Jacova J, Friedecky D, Ulehlova J, Tauber Z, Prochazkova J,* et al. Evaluation of the DOAC-Stop Procedure by LC-MS/MS Assays for Determining the Residual Activity of Dabigatran, Rivaroxaban, and Apixaban. Clin Appl Thromb Hemost 2019; 25: 1076029619872556.

Received on February 17, 2021
Revised on November 22, 2021
Accepted on November 23, 2021
Online First December 2021