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Full Length Article

Potential usefulness of activated charcoal (DOAC remove®) for dRVVT testing in patients receiving Direct Oral AntiCoagulants

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ABSTRACT

Introduction: Lupus Anticoagulant testing using dilute Russell Viper Venom Time (dRVVT) is challenging in patients receiving Direct Oral AntiCoagulants (DOAC) due to potential false positive results. In a multicenter study, we evaluated the *in vitro* removal of DOAC by activated charcoal (DOAC remove®), allowing reliable dRVVT testing.

Materials and methods: Patient samples were analyzed before and after treatment with DOAC remove®: 49 apixaban, 48 rivaroxaban, 24 dabigatran and 30 none. DOAC plasma concentrations were measured using anti-Xa or diluted thrombin time assays. In a subset of 28 samples, DOAC concentrations were also measured using HPLC-MS/MS following treatment with DOAC remove®. DRVVT was performed using STA-Staclot dRVVT Screen®/Confirm® (Stago) or LAC-Screening®/Confirmation® (Siemens).

Results: Baseline median [min-max] concentrations were 94 [< 20–479] for apixaban, 107 [< 20–501] for rivaroxaban and 135 ng/mL [< 20–792] for dabigatran; dRVVT screen ratio/confirm ratio was positive in 47, 90 and 42% of apixaban, rivaroxaban and dabigatran samples. Treatment with DOAC remove® did not affect dRVVT results in non-DOAC patients while it resulted in DOAC concentrations < 20 ng/mL in 82, 98 and 100% of samples, respectively. Concentrations were < 5 ng/mL with HPLC-MS/MS in 5 out of 10, 8 out of 10 and 7 out of 8 samples, respectively. DOAC remove® corrected DOAC interference with dRVVT assays in 76, 85 and 95% of the patients, respectively.

Conclusion: For dRVVT testing in DOAC patients, we suggest the use of DOAC remove® for every rivaroxaban sample, whereas it might only be used in positive apixaban and dabigatran samples. A residual DOAC interference cannot be ruled out in case of persisting dRVVT positive results after treatment with DOAC remove®.

Abbreviations: APS, Antiphospholipid syndrome; DOAC, Direct Oral AntiCoagulants; dRVVT, Dilute Russell viper venom time; dTT, Diluted thrombin time; F, Factor; HPLC-MS/MS, High-performance liquid chromatography coupled with electrospray ionization tandem mass spectrometry; LA, Lupus anticoagulant; LLOQ, Lower limit of quantification; LMWH, Low molecular weight heparin; PPP, Platelet-poor plasma; TE, Thromboembolic events; VKA, Vitamin K antagonists

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1. Introduction

Direct oral anticoagulants (DOAC), including factor (F) Xa (xabans) and thrombin (dabigatran) inhibitors, are increasingly prescribed for treatment and prevention of arterial and venous thromboembolic events (TE). Although the majority of patients with TE should not be tested for thrombophilia during the anticoagulation period [1], screening assays including lupus anticoagulant (LA) testing may be useful in selected patients while they are still anticoagulated. Indeed, LA results might affect the choice of the anticoagulant drug and the treatment duration [1–3]. However, rivaroxaban, apixaban and dabigatran may interfere with LA testing [4–6]. Their effect may vary according to the DOAC and the assays [7] making therefore the LA diagnosis challenging.

Dilute Russell viper venom time (dRVVT) is one of the recommended tests for LA detection [8–10]. Previous studies have shown false positive results in dRVVT assays performed in DOAC spiked plasma samples or in *ex vivo* samples drawn from DOAC patients [2,4,11–13] while Favaloro et al. have recently shown a potential for false negative dRVVT results in apixaban samples [6]. *In vitro* extraction of DOAC from *ex vivo* anticoagulated patient samples prior to plasma testing could be an option for a reliable LA diagnosis. Many options have already been described such as *in vitro* neutralization of DOAC with specific antidotes [6,14,15], *in vitro* drug adsorption using activated charcoal (DOAC remove®, DOAC stop™), or sample filtration on DOAC filter (Stago) or Hemofilter® (Hemosafe) [6,16–18]. The potential usefulness of these devices for DOAC neutralization and subsequent LA diagnosis in treated patients is currently under investigation.

LA testing remains therefore problematic in DOAC patients with no clear guidance about how and when to conduct testing in such patients. In a multicenter study, we hence sought to investigate 1) the extent of interference of dabigatran, rivaroxaban, or apixaban with dRVVT in plasmas from anticoagulated patients referred to us for LA detection and 2) whether a neutralizing agent, DOAC remove®, could reduce the proportion of false positive results. Finally, based on our study results, we propose a diagnosis algorithm for dRVVT testing in DOAC patients.

2. Materials and methods

2.1. Plasma samples

This non-interventional study was conducted in three university hospitals: Cochin (AP-HP, Paris, France), Lariboisière (AP-HP, Paris, France) and Pontchaillou (Rennes, France). In each center, blood samples were collected into 0.109 M buffered trisodium citrate (9:1 v/v) tubes (Greiner Bio One, Courtabœuf, France) and referred to the hospital hematology laboratory for locally LA testing including dRVVT. A double centrifugation at 2500*g* for 15 min at room temperature with plasma decantation in a second tube in between led to platelet-poor plasma (PPP) which was frozen at −80 °C until use. Just prior to experiments, PPP was thawed at 37 °C then processed within 2 h. Overall, 154 samples were analyzed in the present study: 121 from patients receiving DOAC, 30 from patients not receiving DOAC known as dRVVT negative or positive, which were used as controls and 3 from patients with a known positive dRVVT for years receiving DOAC. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

2.2. DRVVT assays

Two different reagents were used: STA-Staclot dRVVT Screen® and Confirm® (Stago, Asnières-sur-Seine, France) in one center, and LAC Screening® and Confirmation® (Siemens Diagnostics, Saint-Denis, France) in two centers. They consist in a direct activation of coagulation FX by a protease extracted from the venom of the Russell's viper in the presence of calcium ions and phospholipids added at low (screen assay) or high (confirm assay) concentration. Pool Norm Plasma (Stago) or CryoCheck® (Cryopep, Montpellier, France) were used as reference plasma and run in each series. Both are integrated tests with similar performances having screen/confirm results in the same order of magnitude in external quality control reports. Forty-eight samples were analyzed using LAC Screening® and Confirmation® and Pool Norm Plasma on STAR-Evolution analyzer (Stago), 44 using LAC Screening® and Confirmation® and CryoCheck® on CS-5100 (Siemens) and 29 using STA-Staclot dRVVT Screen® and Confirm® and Pool Norm Plasma on STAR-Evolution (Stago). Patient screen and confirm results were normalized *i.e.* expressed as ratios against reference plasma results. Final results were expressed as screen ratio/confirm ratio. Cut-off value was 1.20 for both screen ratio and screen ratio/confirm ratio with both reagents as stated by the manufacturers and locally validated [8,9].

2.3. Direct oral anticoagulant measurement

Xabans and dabigatran concentrations were measured in plasma before and after treatment with DOAC remove® (see below) using specific anti-Xa (STA-Liquid anti-Xa) or diluted thrombin time (dTT) assays (Hemoclot Thrombin Inhibitor, Hyphen Biomed, Neuville-sur-Oise, France), respectively. The lower limit of quantification (LLOQ) was locally determined and was equal to 20 ng/mL for both assays in each center. In order to precisely measure the concentration below 20 ng/mL following treatment with activated charcoal, drug concentrations were additionally measured in a subset of samples (see *infra*) using a validated high-performance liquid chromatography coupled with electrospray ionization tandem mass spectrometry (HPLC-MS/MS). The LLOQ of HPLC-MS/MS was 5 ng/mL [19].

2.4. Treatment with activated charcoal

Treatment with DOAC remove® (5-Diagnostics, Heuberg, Switzerland) was performed according to the manufacturer instructions. Briefly, one tablet of activated charcoal was added to 1 mL of plasma sample. Sample was gently mixed for 10 min at room temperature, then centrifuged for 2 min at 2500*g*, 20 °C. Supernatant was thereafter spun for 1 min at 2500*g*, 20 °C to remove any residual activated charcoal particulate and supernatant plasma was tested again using dRVVT and specific anti-Xa or dTT assay.

2.5. Study design

dRVVT screen was performed in all patient samples. No additional assay was performed in samples tested negative while those tested positive (*i.e.* with LA screen ratio ≥ 1.20) were subsequently analyzed using confirm assay, and in parallel, were treated with DOAC remove® as previously described. Screen assays were repeated on charcoal treated samples along with the confirm assays if screen ratio remained above the cut-off value (≥1.20). The same samples were used for all steps of pre- and post-DOAC remove® treatment testing.

2.6. Statistical analysis

DOAC plasma concentrations were expressed as median [min - max]. A paired *t*-test was used to compare anticoagulant concentrations, screen and confirm ratios as well as screen ratio/confirm ratio before and after treatment with DOAC remove®. A p-value < 0.05 was considered statistically significant. All statistical analysis and graph representation were computed using the GraphPad Prizm 3.0 software.

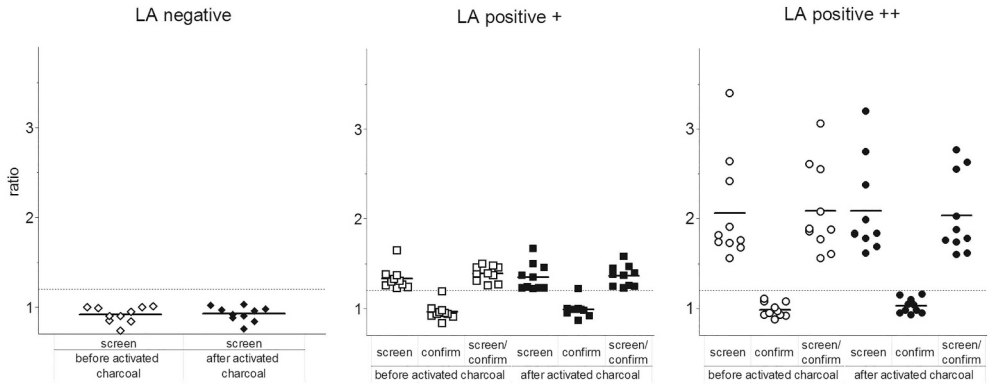

Fig. 1. Effect of DOAC remove® (activated charcoal) on dRVVT in the absence of DOAC. Non-DOAC patients' samples were tested using dRVVT screen and confirm before (open symbols) and after (closed symbols) treatment with DOAC remove®. Dashed line corresponds to the cut-off value of 1.20. LA positive + samples correspond to those having a screen ratio/confirm ratio ranged between 1.20 and 1.50 while LA positive + + samples correspond to those with a screen ratio/confirm ratio > 1.50. No significant effect of DOAC remove® on either screen or confirm assays was observed.

3. Results

3.1. Neutrality of DOAC remove® with regard to dRVVT in the absence of DOAC

Thirty samples from non-DOAC treated patients were tested before and after treatment with activated charcoal. Before treatment with DOAC remove®, 10 were LA negative (*i.e.* screen ratio < 1.20), 10 were low LA positive with a screen ratio/confirm ratio between 1.20 and 1.50, and 10 were high LA positive with a screen ratio/confirm ratio above 1.50. DOAC remove® did not affect dRVVT results in either negative ($p = 0.8$), low ($p = 0.4$) or high ($p = 0.2$) positive LA samples (Fig. 1) confirming therefore the neutrality of activated charcoal with regard to dRVVT screen and confirm assays in the absence of DOAC. Moreover, we also checked three additional rivaroxaban patients with a known positive LA for years before starting DOAC treatment. They still had LA positive results after charcoal treatment.

3.2. Impact of DOAC on dRVVT assays

dRVVT screen was performed in plasma samples from 121 DOAC patients referred for LA testing. Forty-nine patients received apixaban, 48 rivaroxaban and 24 dabigatran. DOAC plasma concentrations ranged from < 20 to 479, < 20 to 501 and < 20 to 792 ng/mL, respectively (Table 1). Screen ratio increased in a concentration-dependent manner in the presence of DOAC. Rivaroxaban and dabigatran appeared to have a more pronounced effect on the dRVVT screen than apixaban (Fig. 2). Screen ratio was positive (*i.e.* ≥ 1.20) in 80% of apixaban, 98% of rivaroxaban and 100% of dabigatran samples (Fig. 3). Samples with positive screen results were further tested using confirm assay: confirm ratio was increased to a less extent compared to screen ratio with all the three DOAC ($p \leq 0.005$; Fig. 2). Screen ratio/confirm ratio was positive in 47% of apixaban, 90% of rivaroxaban and 42% of dabigatran samples (Fig. 3).

3.3. Effect of DOAC remove® on DOAC plasma concentrations

Activated charcoal significantly reduced the plasma concentration of apixaban ($p < 0.0001$), rivaroxaban ($p < 0.0001$) and dabigatran ($p = 0.0001$). Overall, 82% of apixaban, 98% of rivaroxaban and 100% of dabigatran samples had DOAC plasma concentrations below the LLOQ as assessed by specific anti-Xa or dTT assays (*i.e.* < 20 ng/mL; Table 1, Supplementary Fig. 1) following treatment with DOAC remove®.

We wondered whether DOAC remove® completely adsorbed anticoagulant drugs from plasma samples or it only decreased their plasma concentrations below the LLOQ. Therefore, in a randomly selected subset of 28 samples (apixaban with median [min - max] initial concentrations of 144 [49–370] ($n = 10$), rivaroxaban 140 [42–501] (n = 10) and dabigatran 74 ng/mL [51–196]) ($n = 8$), DOAC plasma concentrations were additionally measured with HPLC-MS/MS following treatment with DOAC remove®. Nine out of 10 rivaroxaban samples and all dabigatran samples had residual DOAC concentration < 20 ng/mL as assessed by specific anti-Xa or dTT assays, respectively; HPLC-MS/MS revealed residual DOAC concentration < LLOQ (*i.e.* 5 ng/mL) in 8 out of 10 rivaroxaban samples and 7 out of 8 dabigatran samples. Results were different for apixaban samples. While 9 out of 10 samples had residual concentration < 20 ng/mL (specific anti-Xa assay), only 5 out of 10 samples had a plasma concentration below 5 ng/mL with HPLC-MS/MS. Results are detailed in the Supplementary Table 1.

3.4. Effect of DOAC remove® on dRVVT in DOAC samples

Following treatment with activated charcoal, drug interference with dRVVT screen was corrected in 61, 69 and 67% of apixaban, rivaroxaban and dabigatran samples (Fig. 3). Following dRVVT confirm, DOAC interference was corrected in 76, 85 and 95% of patients, respectively (Fig. 3). Consequently, DOAC interference with dRVVT could not be ruled out in 24, 15 and 5% of apixaban ($n = 49$), rivaroxaban ($n = 48$) and dabigatran ($n = 24$) patients. Comparable results were obtained independently of the reagent/analyzer system used.

4. Discussion

This real-life multicenter study provided evidence on the extent of interference of DOAC at different concentrations with LA testing using dRVVT in plasmas of anticoagulated patients and showed that DOAC

Table 1
DOAC plasma concentrations before and after treatment with DOAC remove®.

	Before DOAC remove® Median concentration[a] [min-max] (ng/mL)	After DOAC remove® Median concentration[a] [min-max] (ng/mL)	% of total neutralization (DOAC < LLOQ)
Apixaban ($n = 49$)	94 [< 20–479]	< 20 [< 20–85]	82%
Rivaroxaban ($n = 48$)	107 [< 20–501]	< 20 [< 20–45]	98%
Dabigatran ($n = 24$)	135 [< 20–792]	< 20	100%

[a] DOAC concentrations measured using specific anti-Xa or dTT assays. LLOQ: lower limit of quantification (20 ng/mL).

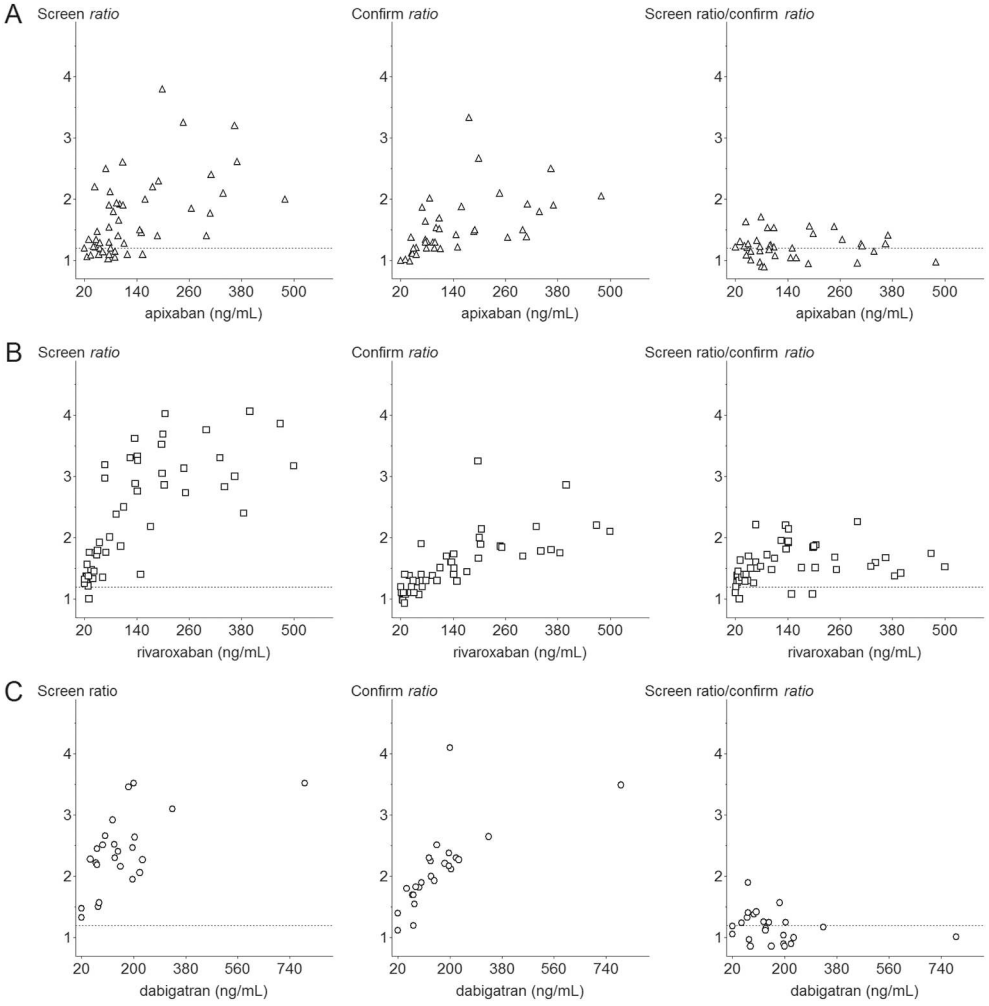

Fig. 2. Impact of DOAC on dRVVT ratios. Samples from DOAC patients were tested using dRVVT screen and confirm. Screen and confirm ratios are plotted as a function of apixaban (A), rivaroxaban (B) or dabigatran (C) plasma concentration. Dashed line corresponds to the cut-off value of 1.20.

remove® allowed reducing this interference from around 50% for apixaban and dabigatran and 90% for rivaroxaban samples before DOAC remove® to 24, 5 and 15% after DOAC remove®, respectively.

International experts suggest that dRVVT in samples from DOAC patients should be performed just before the next intake of the drug since it would less likely lead to false positive results [20]. Nevertheless, DOAC even at concentrations below the trough levels [21] or even below the LLOQ of specific anti-Xa and dTT assays widely used in clinical laboratories may induce false positive results [7,22,23]. Owing to the high inter-individual variability of DOAC plasma level, a temporary interruption of DOAC treatment for 24 to 48 h or even longer could be required to ensure undetectable DOAC concentrations thus preventing false positive results [4,19,24–26]. However, this might be clinically unacceptable: patients with potential antiphospholipid syndrome are at high risk of thrombotic events on one hand, and in the day-to-day practice they may choose not to stop or forget to stop anticoagulant treatment on the other hand [27]. Our results from real-life DOAC patients confirmed that dabigatran as well as both xabans are likely to induce false positive dRVVT results even at low plasma concentrations.

A temporarily switch from DOAC to low molecular weight heparin (LMWH) might be suggested to avoid DOAC interference with dRVVT:

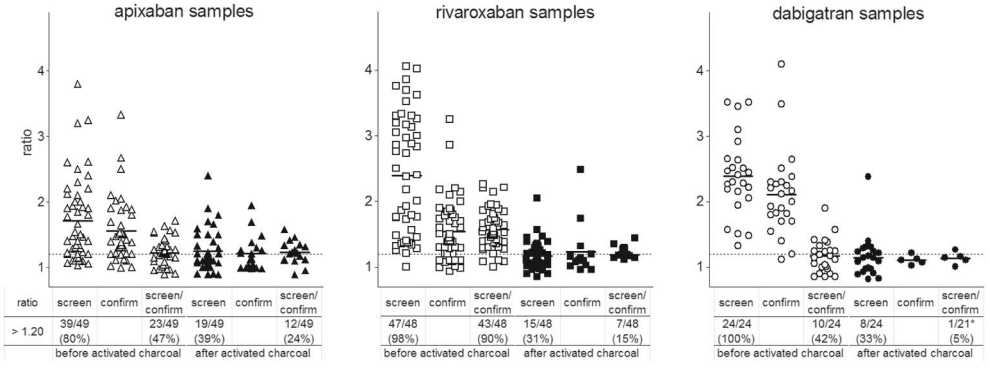

Fig. 3. Effect of DOAC remove® (activated charcoal) on LA testing using dRVVT in DOAC patients' samples. dRVVT screen and confirm ratios of plasma samples from DOAC patients were calculated before (open symbols) and after (closed symbols) treatment with DOAC remove®. Dashed line corresponds to the cut-off value of 1.20. * 3 dabigatran samples could not be tested with confirm assay following treatment with DOAC remove® due to insufficient sample volume.

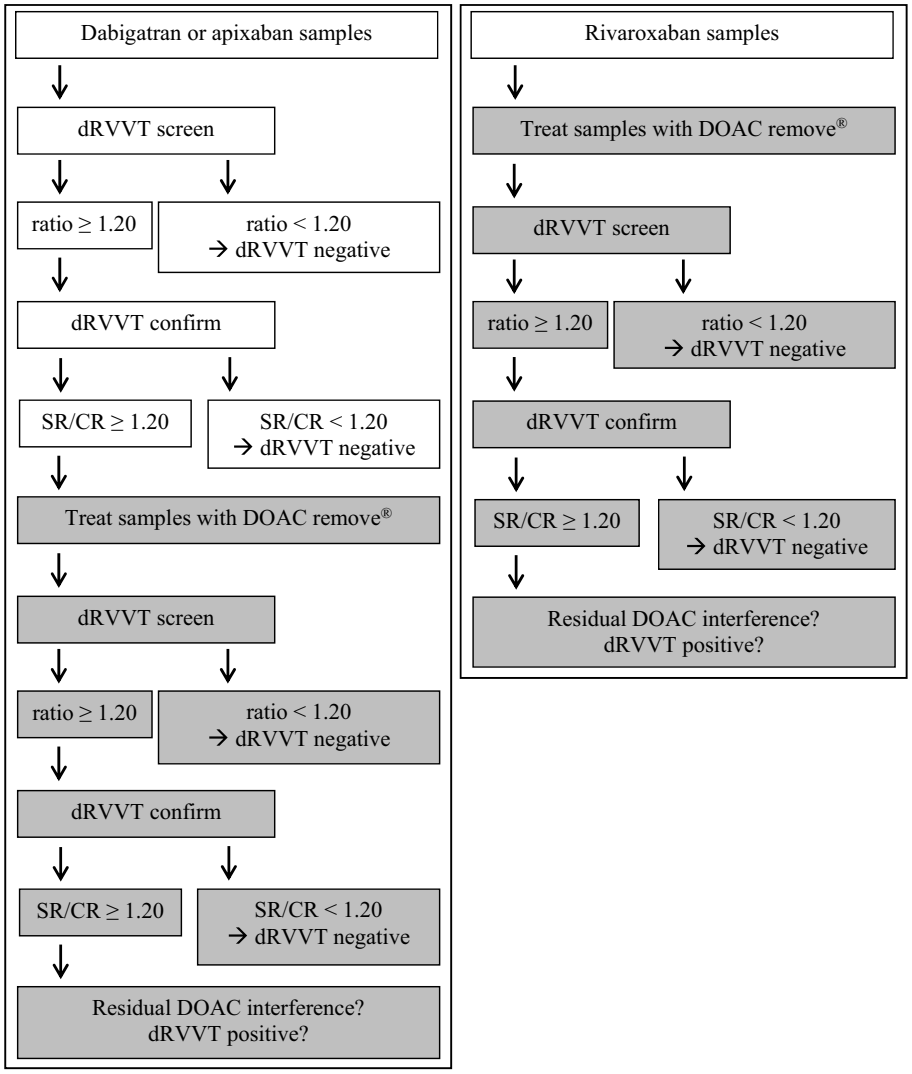

Fig. 4. Proposed algorithm for dRVVT testing in DOAC patients' samples. SR/CR corresponds to screen ratio/confirm ratio.

nevertheless, it might be challenging to manage, all the more since a repeat of the assays is required in 12 weeks-time following a first positive dRVVT in order to establish the diagnosis of anti-phospholipid syndrome [28]. Some studies also recommend Taipan snake venom time, ecarin and textarin clotting times in DOAC patients, however these tests are neither widely available nor standardized in clinical practice [5,29,30].

Based on our results, we propose a diagnosis algorithm for LA testing using dRVVT in DOAC patients (Fig. 4). Since at least 90% of the screen ratio/confirm ratio were positive before treatment with activated charcoal, rivaroxaban samples should be readily treated with DOAC remove® before assay performance. If dRVVT screen ratio is ≥1.20, dRVVT confirm should be performed and screen ratio/confirm ratio calculated. In our study, this strategy resulted in negative dRVVT results in 85% of rivaroxaban samples. As sample treatment with DOAC remove® requires manual input and is time consuming, dRVVT could be performed before treating apixaban and dabigatran samples with DOAC remove® as it resulted in negative dRVVT in around 50% of the cases, irrespectively of the initial DOAC plasma concentration. Remaining samples tested positive could afterwards be treated with DOAC remove® and dRVVT assays repeated. This algorithm prevented the DOAC interference with dRVVT in 76 and 95% of apixaban and dabigatran samples in our study. Of note, it remains at the discretion of the clinical pathologist to readily treat apixaban and dabigatran samples as for rivaroxaban before any dRVVT testing. Whenever screen ratio/confirm ratio is ≥1.20 after treatment with DOAC remove®, a residual DOAC interference cannot be ruled out, and a switch from DOAC to LMWH would be mandatory for a reliable LA diagnosis using dRVVT.

Our study has some limitations. First, we solely evaluated the sensitivity of two commercially available dRVVT reagents to DOAC before and after treatment with DOAC remove®. Therefore caution should be made on the generalization of our results to other dRVVT reagents without local validation of the process. It is to mention that the cut-off of 1.20 cannot be generalized and should be validated in each laboratory. Moreover, LA diagnosis requires the association of a sensitive aPTT-based assay with dRVVT. DOAC interference with the former depends on the reagent used, therefore on phospholipid type and concentration. DOAC interference with dRVVT is less reagent-dependent than with aPTT: this is the reason why we focused on evaluating dRVVT sensitivity to DOAC molecules and DOAC remove® in this study [13,31]. Second, the potential interference of DOAC concentrations comprised between 5 and 20 ng/mL on dRVVT results after DOAC remove® treatment requires further confirmation since only a limited number of samples had DOAC concentration measured using HPLC-MS/MS: nevertheless, apixaban seems less susceptible to adsorption by activated charcoal compared to rivaroxaban and dabigatran. A potentially longer adsorption time might be required for a total neutralization of apixaban compared to other DOAC as recently suggested with DOAC-

Stop™ [16]. Third, fewer data were obtained with dabigatran in comparison to xabans, therefore limiting conclusions regarding this DOAC, although the observed effects are consistent with previously reported trends [32]. Fourth, no mixing studies were performed with dRVVT screen and confirm since no correction of dRVVT in the presence of active DOAC molecules in mixed samples is expected [13].

In conclusion, it is mandatory to interpret dRVVT results in DOAC patients with great caution in order to prevent false positive diagnosis and subsequent clinical consequences. DOAC remove® is a valuable tool that limits DOAC interference with this key assay as it was the case in 76, 85 and 95% of apixaban, rivaroxaban and dabigatran samples included in our study. Nevertheless, complete adsorption of DOAC molecules did not occur in all samples, thus a residual DOAC interference cannot be ruled out in case of persisting dRVVT positive results after treatment with DOAC remove®.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.11.001.

Declaration of competing interest

I.G.-T. P.G. and V.S. received honoraria for participating in expert meetings on apixaban (Bristol-Myers Squibb/Pfizer), rivaroxaban (Bayer Healthcare AG) and dabigatran (Boehringer Ingelheim). The other authors declare no conflicts of interest.

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