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BRIEF REPORT

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The effect of unfractionated heparin, enoxaparin, and danaparoid on lupus anticoagulant testing: Can activated carbon eliminate false-positive results?

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Abstract

Background: Heparins and heparinoids interfere with functional clotting assays used for lupus anticoagulant (LAC) detection. However, current guidelines for LAC testing do not provide clear guidance on this matter.

Objectives: We aimed to assess to effect of unfractionated heparin (UFH), enoxaparin, and danaparoid on LAC assays over broad anti-Xa activity ranges and to evaluate whether activated carbon (AC) is able to neutralize these effects.

Methods: UFH (0.1-3.0 IU/mL), enoxaparin (0.2-2.9 IU/mL), and danaparoid (0.6-2.2 IU/mL) were spiked to normal pooled plasma. AC was added at multiple activity levels. Anti-Xa assays and LAC tests were performed on all samples using Stago analyzers and reagents.

Results: Abnormal activated partial thromboplastin time (APTT) screening and mixing tests were obtained at the lowest levels for all compounds. Abnormal APTT confirmation tests were seen from 2.5 and 1.9 anti-Xa IU/mL for enoxaparin and danaparoid, respectively. Abnormal dilute Russell's viper venom test (dRVVT) screening tests were obtained from 1.6, 1.4, and 1.1 anti-Xa IU/mL for UFH, enoxaparin, and danaparoid, respectively. Mixing tests were abnormal from 2.5 and 1.3 anti-Xa IU/mL for enoxaparin and danaparoid, respectively. Abnormal dRVVT confirmation results were seen for danaparoid only from 1.9 anti-Xa IU/mL. AC was unable to neutralize anti-Xa activity in plasma and overcome the effect of the tested anticoagulants on LAC assays but may cause prolongation of APTT clotting times.

Conclusions: UFH, enoxaparin, and danaparoid clearly affected LA tests; however, false-positive LAC conclusions were obtained at supratherapeutic enoxaparin and danaparoid levels only. AC may prolong APTT screen clotting times, requiring 3-step testing to avoid potential misdiagnosis of LAC.

KEYWORDS

carbon, danaparoid, enoxaparin, heparin, lupus coagulation inhibitor

Essentials

- Heparins/heparinoids may interfere with laboratory tests for lupus anticoagulant (LAC) detection.
- We evaluated effects of unfractionated heparin, enoxaparin, and danaparoid on LAC assays.
- False-positive LAC conclusions were obtained at supratherapeutic enoxaparin and danaparoid levels.
- Activated carbon was unable to eliminate the effects but prolonged the activated partial thromboplastin time clotting times.

1 | INTRODUCTION

Detection of lupus anticoagulant (LAC), as part of the laboratory criteria for classification of antiphospholipid syndrome (APS), is performed using dilute Russell's viper venom test (dRVVT) and activated partial thromboplastin time (APTT), being phospholipid-dependent functional clotting assays.[1–3] Interference of anticoagulants is a well-known issue in LAC testing and has been widely addressed in the literature, especially for vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs).[4–8] Unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs), and heparinoids also carry the intrinsic potential of interfering with both APTT and dRVVT, as their anticoagulant activity mainly originates from catalyzation of the antithrombin-mediated inhibition of factors IIa and Xa.[9]

Administration of LMWH and UFH to patients with APS is recommended in specific cases only, for example, as secondary thromboprophylaxis in patients with APS with recurrent venous thrombosis treated with VKA, in pregnant women with a history of obstetric APS, or as first-line treatment in catastrophic APS.[10] However, presence of heparins in samples admitted to the clinical laboratory for LAC testing is a common finding.[8,11] The latter is often the result of prompt initiation of anticoagulant therapy after clinical diagnosis of thromboembolism and subsequent LAC testing as part of thrombophilia screening. This carries the risk of physicians or laboratory professionals being unaware of the heparinized state of the patient when interpreting LAC results, especially if additional tests, such as thrombin time or anti-Xa activity measurement, are not routinely performed. The ability of UFH to prolong functional clotting assays and thereby cause false-positive LAC results is well known. On the other hand, studies investigating the effect of LMWH on LAC detection showed conflicting results. While some found a high prevalence of false-positive LAC results in patients treated with LMWH,[7] others could not identify such an effect when comparing LMWH-containing to nonanticoagulated samples.[5]

Current guidelines for laboratory detection of LAC issued by the International Society on Thrombosis and Haemostasis (ISTH),[2] the Clinical and Laboratory Standards Institute,[12] and the British Committee for Standards in Haematology (BCSH)[13] recommend caution when interpreting LAC tests in patients on heparins because of the risk of false-positive conclusions. The ISTH guideline recommends performing LAC testing more than 12 hours after the last LMWH dose. The BCSH guideline states that LAC testing should not be performed in patients receiving therapeutic doses of UFH, while prophylactic UFH or LMWH doses should have less effect. A recent survey questionnaire performed by the Scientific and Standardization committee for Lupus Anticoagulant/Antiphospholipid Antibodies of the ISTH showed that there were a variety of opinions about whether and when to test patients on LMWH or UFH.[14]

For LAC detection in samples from patients on VKA treatment, the ISTH guideline provides International Normalized Ratio (INR) ranges at which LAC testing can still be performed (INR < 1.5) or could be done after mixing samples 1:1 with normal pooled plasma (1.5 ≤ INR <3.0). Similar guidance, for instance, based on anti-Xa activity, is not available for heparinized samples. Therefore, the first aim of this study was to assess the effect of UFH, an LMWH (enoxaparin), and a heparinoid (danaparoid) on LAC assays over broad anti-Xa activity ranges and to establish their potential for causing false-positive results. In addition, it should be noted that many commercial reagents used for LAC detection already contain inhibitors that neutralize heparin effects up to specified anti-Xa activity levels. Recently, an interesting approach to overcome the influence of DOAC on coagulation assays has been introduced. This method, DOAC-Stop, is based on incubating plasma with an adsorbent material, consisting of activated carbon (AC), prior to further testing.[15] Several studies confirmed that this approach is able to remove DOAC from plasma.[16–21] In this light, the second aim of our study was to evaluate whether AC is able to adsorb heparins and heparinoids and neutralize their effect on LAC assays.

2 | MATERIALS AND METHODS

2.1 | Spiking experiment

Citrated whole blood (BD Vacutainer citrate 3.2%, 2.7 mL; BD, Erembodegem, Belgium) was collected from 15 healthy volunteers after informed consent. Normal pooled plasma (NPP) was obtained following double centrifugation at 2230 *g* for 15 minutes, stored at −80°C and thawed at 37°C for 5 minutes before analysis. UFH (Heparine Leo 100 IU/mL solution for injection) was purchased from LEO Pharma (Ballerup, Denmark), enoxaparin (Clexane 2000 IU [20 mg]/0.2 mL solution for injection) from Sanofi (Diegem, Belgium), and danaparoid (Orgaran 750 IU/0.6 mL solution for injection) from Aspen Pharma (Dublin, Ireland). Starting from these solutions, working solutions at 20 anti-Xa IU/mL were prepared in demineralized water for all 3 anticoagulants and added to NPP to obtain broad anti-Xa activity ranges. Anti-Xa activity measurement and LAC testing was performed in neat and spiked NPP as described below.

2.2 | LAC testing and interpretation

According to current ISTH guidelines,[2] 3-step LAC testing was carried out in a dRVVT-based and an APTT-based test system. All tests were carried out on a STA-R Evolution analyzer (Stago, Asnières, France). Lupus anticoagulant–sensitive partial thromboplastin time (PTT-LA) and STA-Staclot dRVV Screen reagents with low phospolipid content (both Stago) were used for LAC screening tests. Mixing tests were performed on patient plasma diluted 1:1 with NPP, prepared in-house by mixing citrated plasma from 75 healthy volunteers, using screen reagents. APTT confirmation tests were carried out using hexagonal phase phosphatidylethanolamine (HPE) (Staclot LA, Stago) and differences between clotting times measured in the absence and presence of HPE were calculated. For dRVVT confirmation tests, phospholipid-rich STA-Staclot DRVV Confirm reagent (Stago) was used. Mixing tests were also performed using this reagent. dRVVT screen/confirm ratios were used as confirmation tests. When dRVVT confirm results exceeded the local cutoff values, screen mix/confirm mix ratios were applied.[4] Analysis of NPP in each sample batch allowed normalization of clotting times and calculation of normalized clotting time ratios (NCRs) for screening, mixing, and confirmation assays. For individual test interpretation, NCRs were compared with local cutoffs calculated as 99th percentiles on 120 healthy donors.[2,22,23] Cutoff values, expressed as NCRs except for Staclot LA, were 1.48 for dRVV screen, 1.19 for dRVV screen mix, 1.21 for dRVV confirm, 1.10 for dRVV confirm mix, 1.21 for dRVV screen/confirm ratio, 1.10 for dRVV screen mix/confirm mix ratio, 1.35 for PTT-LA screen, 1.13 for PTT-LA screen mix, and 8.00 seconds for Staclot LA. For the dRVVT system, mixing and confirmation tests were performed simultaneously if NCRs of screening tests exceeded cutoffs. For the APTT system, mixing tests were performed first when screening tests were prolonged. Confirmation testing was performed only if both screening and mixing tests exceeded cutoffs, as this is a partly manual procedure. LAC was considered positive if screening, mixing, and confirmation steps all exceeded cutoff values in at least 1 of both test systems.

2.3 | Anti-Xa activity measurement

Anti-Xa activity was measured using calibrated, chromogenic anti-Xa assays (STA-Liquid anti-Xa, Stago). For UFH and enoxaparin, STA-Multi Hep Calibrator plasma (Stago) was used. Biophen Orgaran calibration plasma (Hyphen BioMed, Neuville-sur-Oise, France) was used for danaparoid. All analyses were performed on STA analyzers (Stago).

2.4 | Sample pretreatment with AC

Norit Carbomix (Norit Pharmaceuticals, Klazienaveen, The Netherlands), an AC granulate intended for suspension in water and subsequent oral administration as reversal agent in acute intoxications, was used. This AC formulation allows homogenous and rapid suspension of AC in plasma samples. To determine the optimal AC concentration, increasing concentrations (0, 40, 80, and 120 mg/mL) were added to NPP spiked with UFH (1.4 anti-Xa IU/mL), enoxaparin (1.5 anti-Xa IU/mL), and danaparoid (1.3 anti-Xa IU/mL). After addition of AC, samples were mixed for 5 minutes and centrifuged for 15 minutes at 2230 *g*. The supernatant was collected for further analysis. Anti-Xa activities were measured in all samples.

An AC concentration of 40 mg/mL was selected for further experiments. At multiple anti-Xa activity levels, aliquots of spiked NPP were pretreated with 40 mg/mL AC. Anti-Xa activity measurement, and LAC testing was performed on AC-treated and untreated plasmas.

3 | RESULTS AND DISCUSSION

3.1 | In vitro effect of UFH, enoxaparin, and danaparoid on lupus anticoagulant assays

3.1.1 | General findings

For UFH and enoxaparin, 12-point anti-Xa activity levels ranged from 0.1 to 3.0 IU/mL and from 0.2 to 2.9 IU/mL, respectively. Six-point anti-Xa activity levels for danaparoid ranged from 0.6 to 2.2 IU/mL. These broad activity ranges allowed to evaluate the impact of the tested anticoagulants on LAC assays from sub- to supratherapeutic levels.[9,24,25] In Figure 1, dRVVT and APTT screening, mixing and confirmation results are depicted in function of measured anti-Xa activity in NPP spiked with UFH, enoxaparin, and danaparoid. It is clear that all 3 anticoagulants prolong both APTT and dRVVT results, with APTT being affected most. UFH exerted the highest effect on both assays, while the influence of enoxaparin and danaparoid was comparable. These general findings are in agreement with previous observations.[5,7] Anti-Xa activity levels at which LAC test results exceeded the local cutoffs are summarized in Table 1.

3.1.2 | APTT test system

Abnormal APTT screening and mixing results were obtained at the lowest anti-Xa activity levels (0.1, 0.2, and 0.6 anti-Xa IU/mL for UFH, enoxaparin, and danaparoid, respectively). It should be noted that the PTT-LA screen reagent used in these assays does not contain a heparin-neutralizing agent, which results, for example, in screening results outside the measurement range of the assay starting from 1.0 anti-Xa IU/mL UFH. The Staclot LA reagent used for APTT confirmation testing does contain a heparin inhibitor, with the manufacturer stating that heparin levels up to 1.0 anti-Xa IU/mL do not interfere with the assay. Indeed, abnormal results were obtained at high enoxaparin (starting from 2.5 anti-Xa IU/mL) and danaparoid (starting from 1.9 anti-Xa IU/mL) levels. Interestingly, prolongation of Staclot LA clotting times by UFH seems to be phospholipid dependent as high UFH levels (starting from 1.6 anti-Xa IU/mL) prolonged clotting times in the presence of hexagonal phase phospholipids to a higher extent than clotting times in the absence of phospholipids. This resulted in APTT confirmation results never exceeding the cutoff.

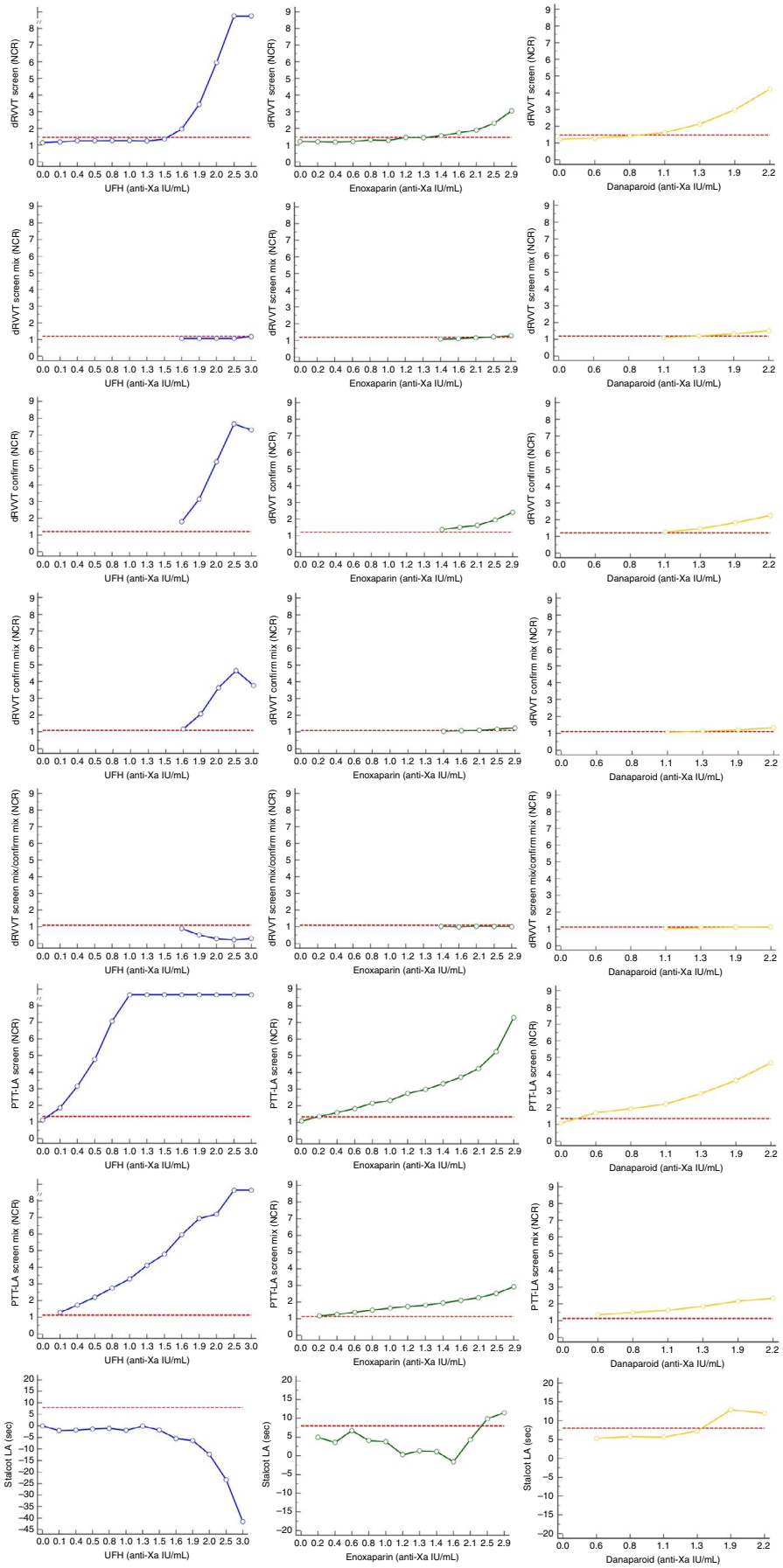

FIGURE 1 Dilute Russell's viper venom test (dRVVT)- and activated partial thromboplastin time (APTT)-based lupus anticoagulant screening, mixing and confirmation clotting times in function of measured anti-Xa activity (IU/mL) in normal pooled plasma spiked with unfractionated heparin (UFH), enoxaparin, and danaparoid. Red dotted lines indicate in-house cutoff values

TABLE 1 Anti-Xa activity levels in normal pooled plasma spiked with unfractionated heparin, enoxaparin, and danaparoid at which lupus anticoagulant tests, performed using dilute Russell's viper venom test– and activated partial thromboplastin time–based clotting assays, were false positive

	UFH (anti-Xa IU/mL)	Enoxaparin (anti-Xa IU/mL)	Danaparoid (anti-Xa IU/mL)
(A) dRVVT system			
Screening	≥1.6	≥1.4	≥1.1
Mixing	…	≥2.5	≥1.3
Confirmation	…	…	≥1.9
Conclusion	…	…	≥1.9
(B) APTT system			
Screening	≥0.1	≥0.2	≥0.6
Mixing	≥0.1	≥0.2	≥0.6
Confirmation	…	≥2.5	≥1.9
Conclusion	…	≥2.5	≥1.9
(C) LAC conclusion	…	≥2.5	≥1.9

Abbreviations: APTT, activated partial thromboplastin time; dRVVT, dilute Russell's viper venom test; LAC, lupus anticoagulant; UFH, unfractionated heparin.

Altogether, false-positive LAC conclusions in the APTT-based test system were obtained at supratherapeutic enoxaparin and danaparoid levels, starting from 2.5 and 1.9 anti-Xa IU/mL, respectively.

3.1.3 | dRVVT test system

As previously mentioned, dRVVT assays were less impacted compared to APTT-based tests. According to the manufacturer, a heparin-neutralizing agent is contained in dRVV reagents, quenching heparin up to 0.8 anti-Xa IU/mL. For UFH and enoxaparin, dRVVT screen NCRs started to prolong at anti-Xa activity levels higher than the level stated by the manufacturer, with abnormal results obtained from 1.6 IU/mL and 1.4 IU/mL anti-Xa activity on, respectively. dRVVT screen NCRs in danaparoid-spiked samples prolonged from 0.8 anti-Xa IU/mL on and exceeded the cutoff from 1.1 anti-Xa IU/mL on. For UFH, mixing test results using the screen reagent never exceeded the cutoff. For enoxaparin and danaparoid, abnormal mixing tests were obtained starting from 2.5 and 1.3 anti-Xa IU/mL, respectively. Although prolongation of mixing tests was minimal in the latter 2 cases, results above the cutoff values were considered relevant as they exceeded the analytical variability of the assay. For dRVVT confirmation testing, screen mix/confirm mix ratios were applied as confirm clotting times were clearly prolonged at the anti-Xa activity levels where screen clotting times were prolonged as well. The effects of UFH and enoxaparin on dRVVT tests seem to be independent from phospholipid content, as screen and confirm results were affected to a similar extent. This resulted in screen mix/confirm mix ratios never exceeding the cutoff. For danaparoid, abnormal ratios were seen from 1.9 anti-Xa IU/mL, although differences between obtained NCRs and cutoff values were within the assay's analytical variability and, therefore, seem to be less relevant.

3.1.4 | Summary

UFH, enoxaparin, and danaparoid clearly affected LAC assays, especially APTT-based tests, with abnormal screening and mixing tests in this test system already seen at low anti-Xa activity levels. However, applying the 3-step procedure including results of confirmation tests, UFH did not result in false-positive LAC, while enoxaparin as well as danaparoid caused false-positive

TABLE 2 Dilute Russell's viper venom test screen and activated partial thromboplastin time screen clotting times measured in neat normal pooled plasma and normal pooled plasma spiked with unfractionated heparin, enoxaparin, and danaparoid at different anti-Xa activity levels before and after incubation of plasma with activated carbon

		dRVVT screen (s)		APTT screen(s)	
	Anti-Xa IU/mL	Before AC	After AC	Before AC	After AC
Neat NPP	…	32.5	31.5	35.6	35.3
UFH	0.1	41.1	40.4	64.5	78.3
	0.4	43.7	42.1	109.8	140.5
	0.8	44.0	44.6	245.2	298.0
	1.3	43.0	43.7	>300.0	>300.0
	2.0	204.1	254.1	>300.0	>300.0
Enoxaparin	0.2	39.3	43.7	47.8	49.6
	0.4	38.6	39.6	54.8	59.8
	0.8	43.1	39.8	74.2	79.2
	1.2	48.0	43.4	93.9	101.1
	2.1	62.0	67.9	145.1	191.5
Danaparoid	0.6	42.2	40.5	58.2	59.1
	1.1	53.3	51.1	76.3	76.4
	1.9	97.3	89.9	124.6	132.6

Abbreviations: AC, activated carbon; APTT, activated partial thromboplastin time; dRVVT, dilute Russell's viper venom test; NPP, normal pooled plasma; UFH, unfractionated heparin.

APTT-based LAC conclusions at supratherapeutic anti-Xa activity levels starting from 2.5 and 1.9 anti-Xa IU/mL, respectively.[9,24,25] dRVVT screening and mixing tests were influenced as well, albeit at higher anti-Xa activity levels compared to APTT. Abnormal dRVVT confirmation tests and, consequently, false-positive dRVVT-based LAC conclusions were observed for danaparoid only, at high anti-Xa activity levels (from 1.9 anti-Xa IU/mL on). Anti-Xa activity levels at which false-positive LAC results were obtained exceeded those mentioned in the package inserts of the evaluated reagents up to where included inhibitors should neutralize heparin effects.

3.2 | Impact of AC on anti-Xa activity and LAC assays

3.2.1 | AC concentration

Initial anti-Xa activities in untreated spiked NPP were 1.4, 1.5, and 1.3 anti-Xa IU/mL for UFH, enoxaparin, and danaparoid, respectively. Identical results were obtained for samples to which 40 and 80 mg/mL AC was added. When 120 mg/mL AC was added, slightly higher anti-Xa activities were measured (1.6, 1.7, and 1.4 anti-Xa IU/mL for UFH, enoxaparin, and danaparoid, respectively). The latter may be attributed to incomplete removal of high AC concentrations after centrifugation and subsequent interference with the chromogenic anti-Xa assay or to adsorption of water by AC, resulting in increased anticoagulant plasma concentrations. As there was no benefit from using higher AC concentrations, the lowest tested concentration (40 mg/mL) was selected for further experiments. AC concentrations <40 mg/mL were not tested, as it was previously described by others that lower AC concentrations, being 5 mg/mL[26] and 20 mg/mL,[27] are unable to eliminate the effect of heparins and heparinoids on routine clotting assays. As routine clotting tests (APTT, STA-PTTA, Stago; prothrombin time, STA-NeoPTimal, Stago; thrombin time, STA-Thrombin, Stago; data not shown) and LAC screening tests (PTT-LA screen and dRVVT screen, Table 2) performed on NPP were not affected by 40 mg/mL AC, this AC concentration could be used safely. By using the same AC product as in our study, Frans et al[27] also showed that AC concentrations up to 80 mg/mL did not significantly interfere with routine clotting assays in neat plasma from healthy volunteers.

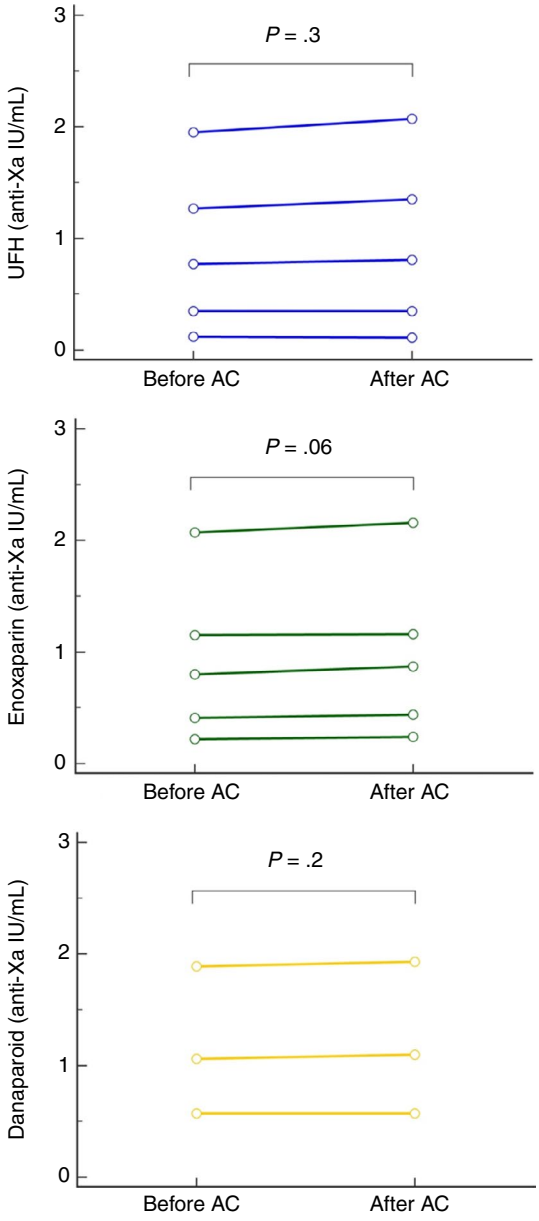

FIGURE 2 Anti-Xa activity obtained before and after adding activated carbon (AC) at 40 mg/mL to normal pooled plasma spiked with unfractionated heparin (UFH), enoxaparin and danaparoid. *P* values result from Wilcoxon signed-rank tests

3.2.2 | Anti-Xa activity

Anti-Xa activity values for UFH, enoxaparin, and danaparoid obtained before and after incubating spiked NPP with AC (40 mg/mL) are shown in Figure 2. Wilcoxon signed-rank tests revealed no significant differences between results before and after AC. These results indicate that AC does not adsorb the 3 tested anticoagulants from plasma. Similar findings were recently described by Exner et al[26] using DOAC-Stop.

3.2.3 | LAC assays

Table 2 summarizes dRVVT screen and PTT-LA screen clotting times measured in neat NPP and NPP spiked with UFH, enoxaparin, and danaparoid at different anti-Xa activity levels. Although incubation of plasma with AC did not alter interpretation of LAC results, changes in APTT screen clotting times were noticed. Consistently longer clotting times after AC were seen in UFH- and enoxaparin-spiked samples. Differences ranged from 13.8 to 52.8 seconds for UFH (mean difference, 23.6 ± 3.8%) and from 1.8 to 46.4 seconds for enoxaparin (mean difference, 13.1 ± 18.7%). The more pronounced prolongation in UFH-containing samples might potentially originate from the adsorption of water and some enoxaparin by AC, while UFH is excluded from AC due to its higher molecular size. Prolongation of APTT mixing test results (using the same PTT-LA screen reagent) and confirmation tests (using Staclot

LA reagent containing HPE) was noticed as well, but differences were limited compared to screening tests (mean differences before and after AC for UFH and enoxaparin, respectively, 14.8 ± 6.9% and 3.2 ± 2.4% for mixing tests and 6.4 ± 6.4% and 2.9 ± 5.1% for confirmation tests). It should be noted that sample sizes are small and that the differences observed for PTT-LA screen were statistically insignificant based on Wilcoxon signed-rank tests. Moreover, these findings obtained using 1 type of AC and 1 APTT reagent probably may not be generalized for other AC products or APTT reagents. Although not explicitly mentioned by the authors, a similar pattern was seen in the study by Exner et al[26] for NPP spiked with enoxaparin and treated with DOAC-Stop. Prolongation of APTT results after applying DOAC-Stop was previously reported as well.[15,16] Differences between APTT results for danaparoid and between dRVVT results for all 3 anticoagulants were limited and statistically insignificant.

3.2.4 | Summary

AC proved unable to neutralize anti-Xa activity of UFH, enoxaparin, and danaparoid in plasma and overcome their effect on LAC testing. Furthermore, incubating samples with the AC product used in this study may cause prolongation of APTT screening clotting times in UFH- and enoxaparin-containing samples starting from low anti-Xa levels, requiring 3-step LAC testing to avoid potential misdiagnosis of LAC.

4 | CONCLUSIONS

Applying the 3-step procedure for LAC testing, including a screening, mixing, and confirmation step, avoids misclassification for LAC in the APTT test system caused by prolongation of APTT by UFH. For LMWH (enoxaparin) and danaparoid, false-positive LAC results in the APTT test system are observed, although at supratherapeutic anti-Xa activity levels. In the dRVVT test system, only false-positive LAC results for danaparoid were observed, again at high anti-Xa levels. In contrast to DOACs, heparins/heparinoids are not adsorbed by AC, and thus is not suited to avoid interference of heparin therapy in LAC testing.

RELATIONSHIP DISCLOSURE

The authors report nothing to disclose. No external funding was received to perform the study.

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AUTHOR CONTRIBUTIONS

KD and PDK designed the study. PDK performed the experiments in collaboration with the staff of the coagulation laboratory of Ghent University Hospital mentioned in the Acknowledgments section and under the supervision of KD. PDK and KD interpreted the data and wrote the manuscript.

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