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ORIGINAL ARTICLE

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DOAC-stop can remove direct oral anticoagulants and allow analysis by global coagulation assays

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Abstract

Introduction: Activated charcoal based compounds such as DOAC-stop™ (DS) have been developed to remove direct oral anticoagulant (DOAC) interference in-vitro. However, few studies have used this approach with global coagulation assays (GCAs), such as thrombin generation assays, which are sensitive to the effect of DOACs.

Methods: Thrombin generation with and without thrombomodulin (TM) via the automated ST-Genesia system, and the overall haemostatic potential (OHP) assay, a spectrophotometric fibrin generation assay in which fibrin formation (triggered by small amounts of thrombin (overall coagulation potential, OCP)) and fibrinolysis (by the addition of thrombin and tissue plasminogen activator) were measured on (i) pooled normal plasma (PNP) spiked with varying amounts of rivaroxaban, apixaban, and dabigatran, and (ii) platelet poor plasma (PPP) from 21 non-anticoagulated adults, before and after DS addition.

Results: Following the addition of DS to spiked PNP without thrombomodulin, thrombin and velocity index increased by 21.9% and 42.6%, respectively, while ETP increased by 6.93%. A decrease in OCP (−10.6%) and OHP (−12.7%) was observed following DS. Similar changes were seen post-DS to plasma from non-anticoagulated patients. Also in this group, pre- and post-DS thrombin generation parameters showed high correlation, with the strongest observed for ETP ($R^2 = 0.94$). There was a strong correlation for OHP parameters, with the closest seen with OCP ($R^2 = 0.96$) and OHP ($R^2 = 0.95$).

Conclusion: DS causes some changes to the ETP and OHP assay, however, strong correlations were seen pre- and post-DS in all GCA parameters. These findings support the use of DS to facilitate GCA testing in anticoagulated individuals for evaluation of the underlying thrombotic state.

KEYWORDS
DOAC-stop, global coagulation assays, overall haemostatic assay, ST-Genesia, thrombin generation

1 | INTRODUCTION

Anticoagulation with direct oral anticoagulants (DOACs) is the mainstay of treatment for many cardiovascular and thrombotic conditions. However, their presence interferes with coagulation tests, including those for lupus anticoagulants and clot-based thrombophilia testing.[1] Activated charcoal-based compounds like DOAC-stop™ (Haematex, Sydney, Australia) have been developed to eliminate DOAC interference in the laboratory.[2,3] However, few studies have examined the effect of DOAC-stop compounds and their effects on global coagulation tests.[4,5]

Global coagulation assays (GCAs), such as thrombin generation assays and global fibrinolytic assays, are increasingly being used in the study of haemorrhagic and prothrombotic states.[6,7] However, the anticoagulant effect of DOACs has a direct impact on these assays,[8] limiting their ability to assess underlying thrombotic risk in patients receiving anticoagulation. This has necessitated the measurement of these assays after the patients have ceased or withheld anticoagulation, which may put patients at risk of further thrombosis complications. The ability to neutralise the anticoagulant effect in-vitro allows for the analysis of thrombotic states without requiring treatment cessation and would facilitate more inclusive study designs, and consequently more accurate insights into venous thromboembolism (VTE) and cardiovascular disease.

DOAC-stop™ and DOAC-remove™ (5-Diagnostics, Basel, Switzerland) are activated charcoal compounds that may be useful for reversing the anticoagulant effect of DOACs in vitro. One limitation is that these compounds can have a direct effect on some coagulation proteins, with previous research showing decreased tissue factor pathway inhibitor (TFPI) in post-DS plasma, and consequently an increased thrombin generation profile, particularly the peak thrombin and velocity index parameters.[4,5] Understanding the magnitude and pattern of these changes is critical for interpreting GCA results following the addition of DOAC-stop (DS).

The purpose of this study was to investigate how DOAC-stop affected two GCAs: thrombin generation with and without thrombomodulin (TM) and the overall haemostatic potential (OHP) assay. We wanted to describe in detail the changes in GCA parameters after DS in: (A) pooled normal plasma (PNP) and PNP spiked with DOACs and (B) non-anticoagulated patient plasma samples.

2 | METHODS

2.1 | Part one: Effect of DS on DOAC spiked pooled normal plasma (PNP)

The aim of the first part of the study was to understand the effects of DS on DOAC spiked PNP. Ethics approval and patient consent was not required, as this project was considered a laboratory quality improvement verification study to incorporate the use of DS into laboratory assays. Commercially available frozen pooled normal plasma PNP (CRYOcheck™, Precision BioLogic Inc, Dartmouth, Canada) was thawed at 37°C and spiked with known varying concentrations of apixaban, rivaroxaban, or dabigatran to achieve three levels of concentration up to 600 ng/ml. Apixaban and rivaroxaban were dissolved in dimethyl sulfoxide (DMSO), then diluted in PNP to reach the desired concentration while dabigatran was dissolved in hydrochloric acid and water, then diluted with PNP to reach an end pH of 7.

Thrombin and fibrin generation assays (described below in detail) were measured on the DOAC-spiked PNP prior to the addition of DS. One millilitre of DOAC-spiked PNP was then incubated with one tablet of DOAC-stop™ (Haematex Research, Sydney, Australia) for 10 min at room temperature. These were then centrifuged for 5 min at 2500*g* and supernatants collected and stored at −80°C for subsequent testing with thrombin generation assay and OHP assay.

2.1.1 | Coagulation assays

Fibrinogen, active partial thromboplastin time (APTT), prothrombin time (PT) and DOAC drug levels were measured on the PNP samples before and after the addition of DS. Rivaroxaban and apixaban anti-Xa levels were assessed with the STA®-Liquid Anti-Xa assay that is calibrated with STA®-Rivaroxaban and STA®-Apixaban calibrator and controls. Dabigatran levels were determined using the Haemoclot™ assay (Hyphen BioMed, Neuville-sur-Oise, France), in which diluted test plasma is mixed with pooled normal plasma, then clotting triggered by adding a constant concentration of human thrombin in the presence of calcium. The obtained clotting time is related to the concentration of dabigatran in the test plasma. APTT and PT were performed using standard accredited laboratory protocol on the STA-Max 2 analyser. The STA® fibrinogen kit was used to measure the fibrinogen levels by the Clauss method.

2.2 | Part two: Effect of DS on non-anticoagulated platelet poor plasma from patients

The second part of the study was designed to understand the effects of DS on platelet poor plasma taken from different non-anticoagulated individuals. This was so the effect of DS by itself could be isolated, without the additional interference of anticoagulation. Frozen platelet poor plasma (PPP) from 21 non-anticoagulated adult patients with multiple myeloma and monoclonal gammopathy of uncertain significance (MGUS) were used.[9] The PPP was obtained from citrated plasma double centrifuged for 10 min at 2500*g* and stored at −80°C. In this part of the study, thrombin and fibrin generation were batch-tested and measured prior to and after the addition of DS to the thawed samples. Ethics approval was given by the Human Research Ethics Committee of Austin Health (H2013/04977) and Northern Health (P5/13).

Sample size estimation was derived based on previous thrombin generation data from the study by Lim et al.,[9] from which the 21 non-anticoagulated individuals were sampled. Considering a significance level of 0.05% and 80% power, a sample size of 11 would be required to accept the hypothesis that the pre- and post-DS thrombin generation and OHP values would be correlated by at least 0.7. To detect a pre- and post-DS difference of 10% and reject the null hypothesis (no difference),

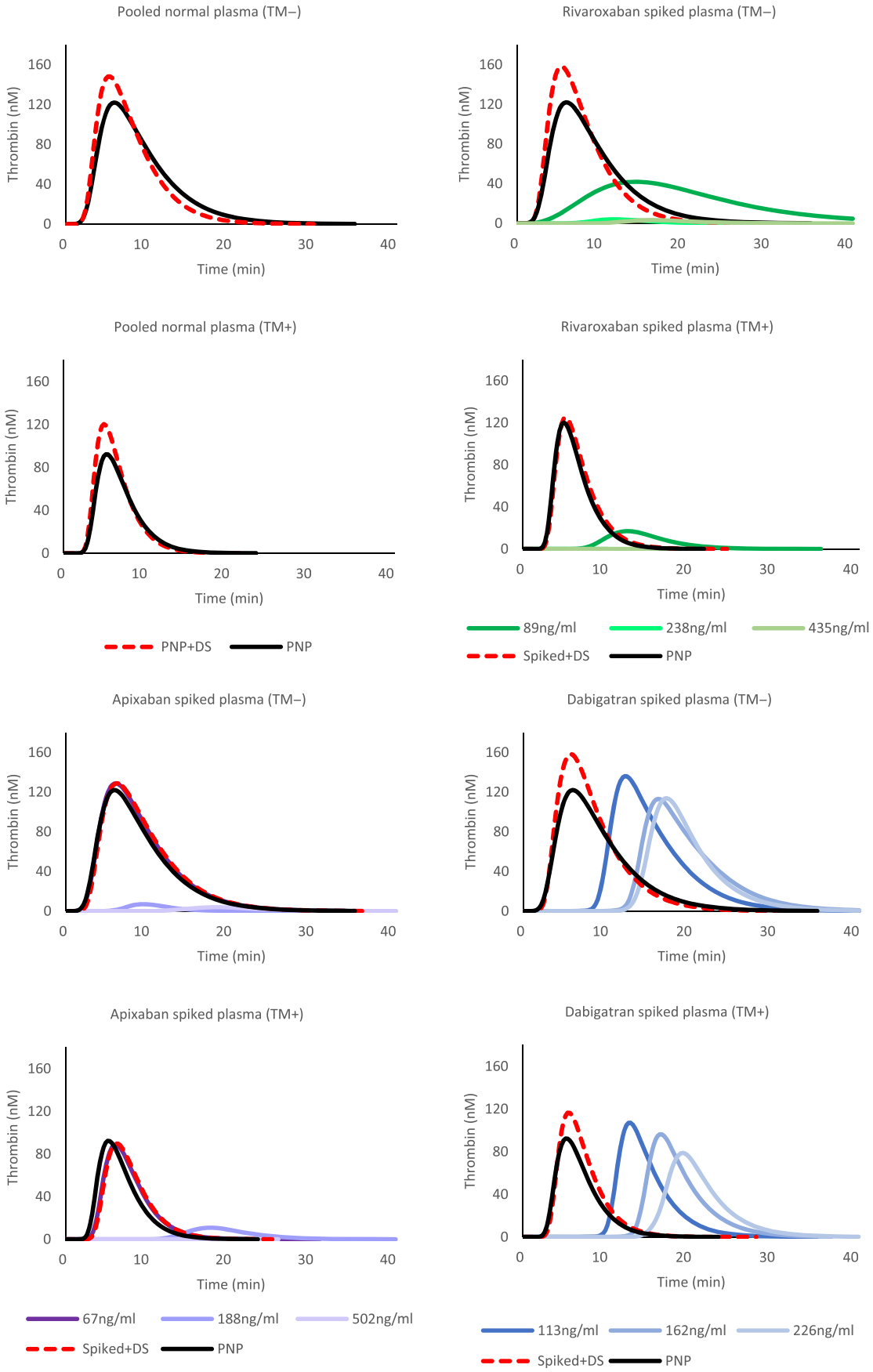

FIGURE 1 Thrombin generation curves from DOAC-spiked pooled normal plasma, with and without TM. The red dashed line shows the average of the three spiked plasma samples after the addition of DS. DOAC, direct oral anticoagulant; DS, DOAC-stop; TM, thrombomodulin

a sample size of 12 was needed for ETP and 21 for peak thrombin. Correlation between pre- and post-DS results was determined by performing simple linear regression. Statistical significance was set at 0.05.

2.2.1 | Global coagulation assays

Thrombin generation was measured using the ST Genesia (Stago, Asniere-sur-Seine, France), an automated thrombin generation system based on the calibrated automated thrombogram (CAT).[10] The STG-ThromboScreen, which has phospholipids and a moderate picomolar amount of human tissue factor in the presence or absence of TM, was used. The assay was triggered by the addition of $CaCl_2$ and a fluorogenic substrate. The assay included a reference plasma for parameter calibration along with three quality controls for low, normal, and high TM resistance. The resulting parameters were measured: lag time, peak height, time to peak, endogenous thrombin potential (ETP), and velocity index (Figure S1a).

The OHP assay is derived from a fibrin aggregation curve formed from repeated spectrophotometric measurements of platelet-poor plasma (Figure S1b). Seventy-five microliter of thawed PPP was added to wells with 75 μl of buffer containing either (i) Tris, NaCl, $CaCl_2$ (final concentration 66 nM Tris, 130 mM NaCl, 35 ml $CaCl_2$; pH 7.0) and thrombin (0.006 IU/ml) to generate the overall coagulation potential (OCP) or (ii) Tris, NaCl, $CaCl_2$, thrombin and tissue plasminogen activator (tPA) (600 ng/ml) to generate the OHP. The two fibrin-aggregation curves (OCP and OHP) are cumulatively calculated from the FLUOstar Optima (BMG Labtech) plate reader at 405 nM. The difference between the area underneath the two curves gives the overall fibrinolytic potential (OFP%). All samples were performed in duplicate.

3 | RESULTS

3.1 | Part one: Effect of DS on DOAC spiked pooled normal plasma (PNP)

PNP samples were spiked with the respective DOACs to the concentrations of (i) apixaban anti-Xa levels 67, 188, and 502 ng/ml; (ii) Rivaroxaban anti-Xa levels 89, 238, and 435 ng/ml; and (iii) Dabigatran levels 113, 162, and 226 ng/ml. After the addition of DS, drug levels in all samples of PNP spiked with DOAC were reduced to ≤1 ng/ml, except for the sample containing 502 ng/ml of apixaban, which had 6 ng/ml of apixaban.

The addition of DS to spiked PNP restored coagulation parameters. For thrombin generation with thrombomodulin (TM+) and without thrombomodulin (TM−) (Figure 1 and Table 1), the addition of DS to spiked PNP, compared to PNP, showed increases in the lag time, peak height, ETP, and velocity index. The parameters with the smallest increases following addition of DS were lag time and ETP without thrombomodulin, where there were mean increases of 6.23% (95% CI 1.79%, 10.67%) and 6.93% (95% CI 5.10%, 8.75%), respectively. Peak height and velocity index showed the greatest magnitude of change regardless of thrombomodulin presence (>20% for both).

TABLE 1 Summary of changes following the addition of DS in DOAC-spiked pooled normal plasma

	PNP	Spiked plasma[a] +DS, mean (SD)	Mean difference % between spiked plasma[a] +DS and PNP (95% CI)
APTT (s)	28.2	29.67 (0.49)	5.20 (4.06, 6.34)
PT (s)	12.7	13.24 (1.30)	0.79 (0.42, 1.15)
Fibrinogen (g/L)	3.29	2.94 (0.05)	−10.64 (−11.55, −9.72)
Thrombin generation (TM−)			
Lag time (min)	2.55	2.71 (0.17)	6.23 (1.79, 10.67)
Peak height (nM)	122.04	148.80 (15.43)	21.92 (13.67, 30.18)
ETP (nM)	1033.34	1104.91 (28.92)	6.93 (5.10, 8.75)
Velocity index	49.88	71.11 (12.31)	42.57 (26.44, 58.70)
Thrombin generation (TM+)			
Lag time (min)	2.91	3.30 (0.34)	13.55 (5.86, 21.25)
Peak height (nM)	92.42	110.96 (16.48)	20.06 (8.41, 31.71)
ETP (nM)	477.70	557.77 (51.99)	16.76 (9.65, 23.87)
Velocity index	54.87	68.31 (15.37)	24.49 (6.20, 42.79)
OHP assay			
OCP (units)	31.31	28.07 (1.70)	−10.58 (−14.12, −7.04)
OHP (units)	5.99	5.25 (0.24)	−12.70 (−15.29, −10.11)
OFP (%)	80.85	81.25 (1.38)	0.50 (−0.62, 1.62)

Abbreviations: DOAC, direct oral anticoagulant; DS, DOAC-stop; ETP, endogenous thrombin potential; OCP, overall coagulation potential; OFP, overall fibrinolytic potential; OHP, overall haemostatic potential; PNP, pooled normal plasma.
[a]Spiked plasma = PNP+ relevant additional DOACs.

For the OHP assay, the addition of DS to spiked PNP resulted in a slight decrease in OCP with mean difference −10.58% (95% CI −14.12%, −7.04%) and OHP with mean difference −12.70% (95% CI −15.29%, −10.11%) (Figure 2 and Table 1). See Supplementary Table 1 for the individual GCA results for each spiked PNP sample.

3.2 | Part two: Effect of DS on non-anticoagulated platelet poor plasma from patients

The mean differences seen in thrombin generation and OHP assay parameters after the addition of DS to 21 non-anticoagulated patients is shown in Table 2. The most noticeable difference following the addition of DS was a significant increase in velocity index. ETP did not change significantly in the absence of TM and increased slightly in the presence of TM (8.55%, 95% CI [0.39, 16.71]). The pre- and post-DS thrombin generation results consistently showed strong correlation (Figure 3) with the closest correlation seen with respect to ETP ($R^2 = 0.94$ without TM and 0.92 with TM). After DS, OCP and OHP showed a slight decrease, whereas OFP% was unaffected. High correlation was observed in OHP parameters before and after DS (Supplementary Figure 2), with the closest correlation seen with OCP ($R^2 = 0.96$) and OHP ($R^2 = 0.95$).

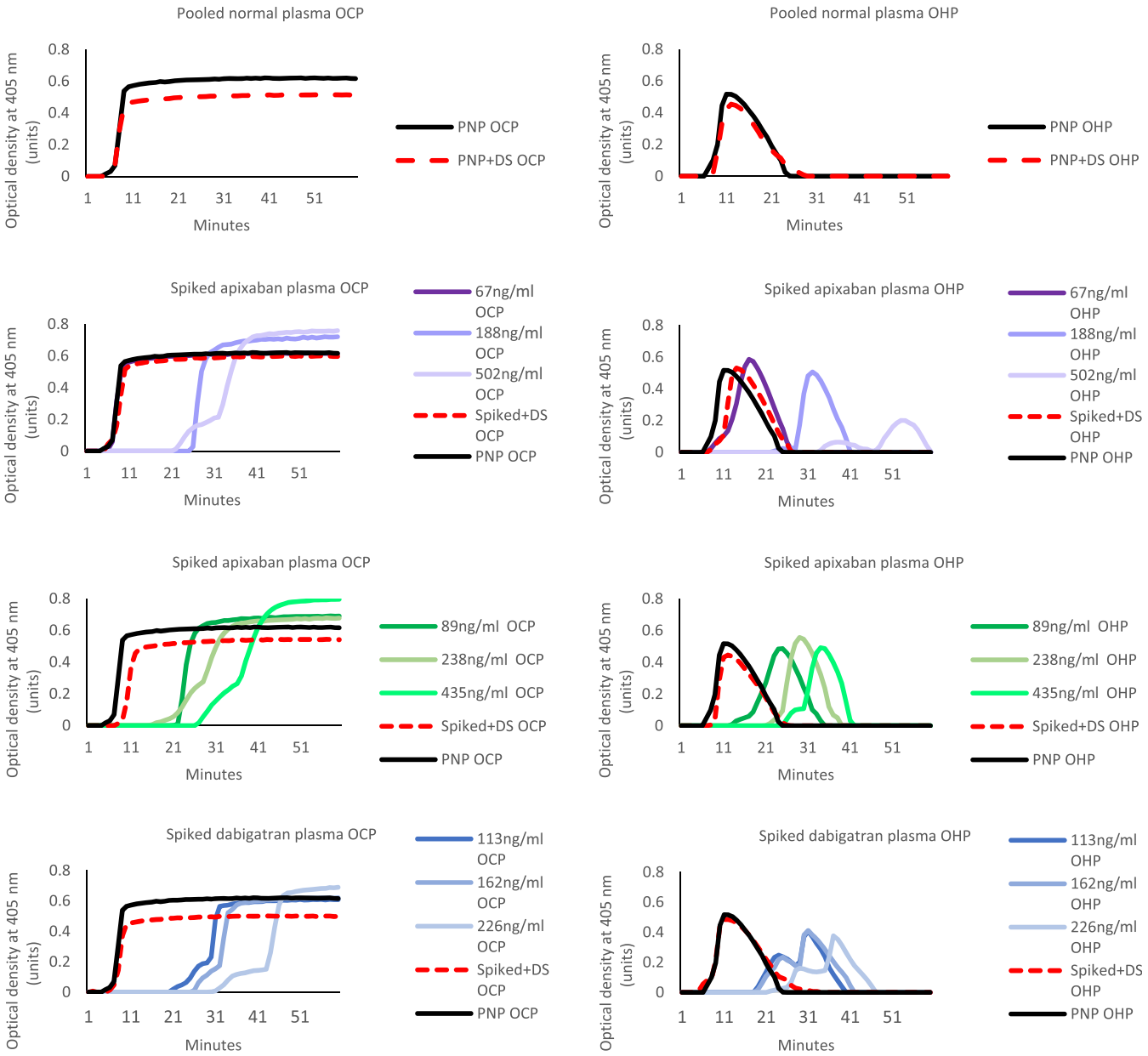

FIGURE 2 OHP curves from DOAC-spiked pooled normal plasma. The red dashed line shows the average of the three spiked plasma samples after the addition of DS. DOAC, direct oral anticoagulant; DS, DOAC-stop; OCP, overall coagulation potential; OHP, overall haemostatic potential; PNP, pooled normal plasma

4 | DISCUSSION

In this study, we demonstrated that the addition of DS restores global coagulation parameters in anticoagulated samples with some additional changes in both thrombin generation and fibrin generation parameters attributable directly to the addition of DS. Despite these effects, there was strong linear correlation between GCA parameters pre- and post-DS in non-anticoagulated patient samples suggesting that DS can be reliably applied to plasma to measure GCA whilst maintaining its clinical relevance. Additionally, the effects of DOAC-stop on thrombin generation in the presence of TM have been reported for the first time, and we are also the first to investigate the effect of the DOAC-stop on a fibrin based global coagulation assay, the OHP.

The addition of DS to spiked PNP largely restored all parameters in the thrombin generation assay, but caused an additional increase especially in peak height and the resultant derived velocity index (peak thrombin/(time to peak-lag time)). The additional increase was also seen post-DS in the non-anticoagulated patients with regards to peak thrombin and velocity index, but ETP in TM-patients was not significantly different (Table 2). Of note, velocity index has previously been reported to show high coefficients of variability (CV).[11] A similar finding was made in the studies by Kopatz[4] and Monteyne,[5] with the exception that in the Monteyne study, lag time was reduced following DS addition, which was observed only in non-anticoagulated patients in our study. Both studies found a reduction in TFPI after DS addition, which could explain the increases in peak height and velocity index, but relatively preserved ETP. We add to this body of evidence by demonstrating for the first time that these changes persist in the presence of thrombomodulin.

While subtle changes (generally <10% difference) were seen in most of the thrombin and fibrin generation parameters following the addition of DS to non-anticoagulated patient plasma (Table 2), it is important to note that there was a strong correlation between the pre- and post-DS GCA parameters, with all parameters demonstrating $R^2 > 0.80$. Importantly, the strongest correlation was shown with ETP ($R^2 = 0.94$). This is beneficial because ETP has consistently been linked to increased thrombotic tendency after VTE[6,12,13] and suggests this may be the key thrombin generation parameter for assessment of the underlying thrombotic state. Our findings suggest that ETP, or total amount of thrombin generated, remains relatively unchanged after the addition of DS, and that it may be the most reliable marker of thrombin generation. Similarly, strong correlation was demonstrated between other thrombin generation parameters in the non-anticoagulated patients, with and without TM. The preservation of a strong linear correlation in results before and after DS even in different individuals supports the practical use of adding DS to patient plasma in a real-world setting.

On the other hand, DS addition to spiked PNP and non-anticoagulated patient samples resulted in a small decrease in OCP and OHP, which was most likely caused by a small decrease in fibrinogen of around 10%. Interestingly, despite using the same Clauss method for determining fibrinogen, the reduction in fibrinogen has only been demonstrated in the Monteyne[5] study but not in the Kopatz[4] study. There was no difference in OFP% after the addition of DS, indicating that the fibrinolytic pathway was unaffected by the addition of DS. Importantly, and similar to thrombin generation results, OHP, the key parameter for this assay, showed strong correlation between pre- and post-DS samples ($R^2 = 0.95$). While we have previously shown that OHP performed on anticoagulated samples can be useful in predicting VTE recurrence,[14] the ability to remove any DOAC effect may provide a more accurate assessment of thrombotic risk. Similarly, it may further extend the use of OHP assays which has been shown to reflect a prothrombotic state in long-term survivors of

TABLE 2 Summary of changes following the addition of DS in 21 non-anticoagulated patients

	Pre-DS, mean (SD)	Post-DS, mean (SD)	Mean difference % between pre and post DS (95% CI)
Thrombin generation (TM−)			
Lag time (min)	2.65 (0.86)	2.53 (0.74)	−3.53 (−6.11, −0.96)
Peak height (nM)	206.40 (56.18)	226.60 (60.86)	10.37 (5.47, 15.27)
ETP (nM)	1285.53 (224.51)	1270.10 (236.13)	−1.34 (−3.34, 0.66)
Velocity index	94.29 (44.48)	118.98 (57.85)	27.40 (17.61, 37.20)
Thrombin generation (TM+)			
Lag time (min)	2.87 (1.17)	2.82 (1.02)	−0.66 (−4.12, 2.79)
Peak height (nM)	114.78 (60.91)	130.08 (68.21)	13.80 (3.76, 23.84)
ETP (nM)	509.53 (256.48)	549.18 (263.22)	8.55 (0.39, 16.71)
Velocity index	73.12 (50.34)	90.21 (61.87)	26.42 (10.10, 42.74)
OHP assay			
OCP (units)	47.09 (17.27)	43.02 (17.94)	−9.30 (−12.29, −6.32)
OHP (units)	10.68 (4.88)	9.71 (4.44)	−8.67 (−11.76, −5.57)
OFP (%)	77.42 (6.00)	77.54 (4.04)	0.44 (−1.55, 2.43)

Abbreviations: DS, DOAC-stop; ETP, endogenous thrombin potential; OCP, overall coagulation potential; OHP, overall haemostatic potential; OFP, overall fibrinolytic potential.

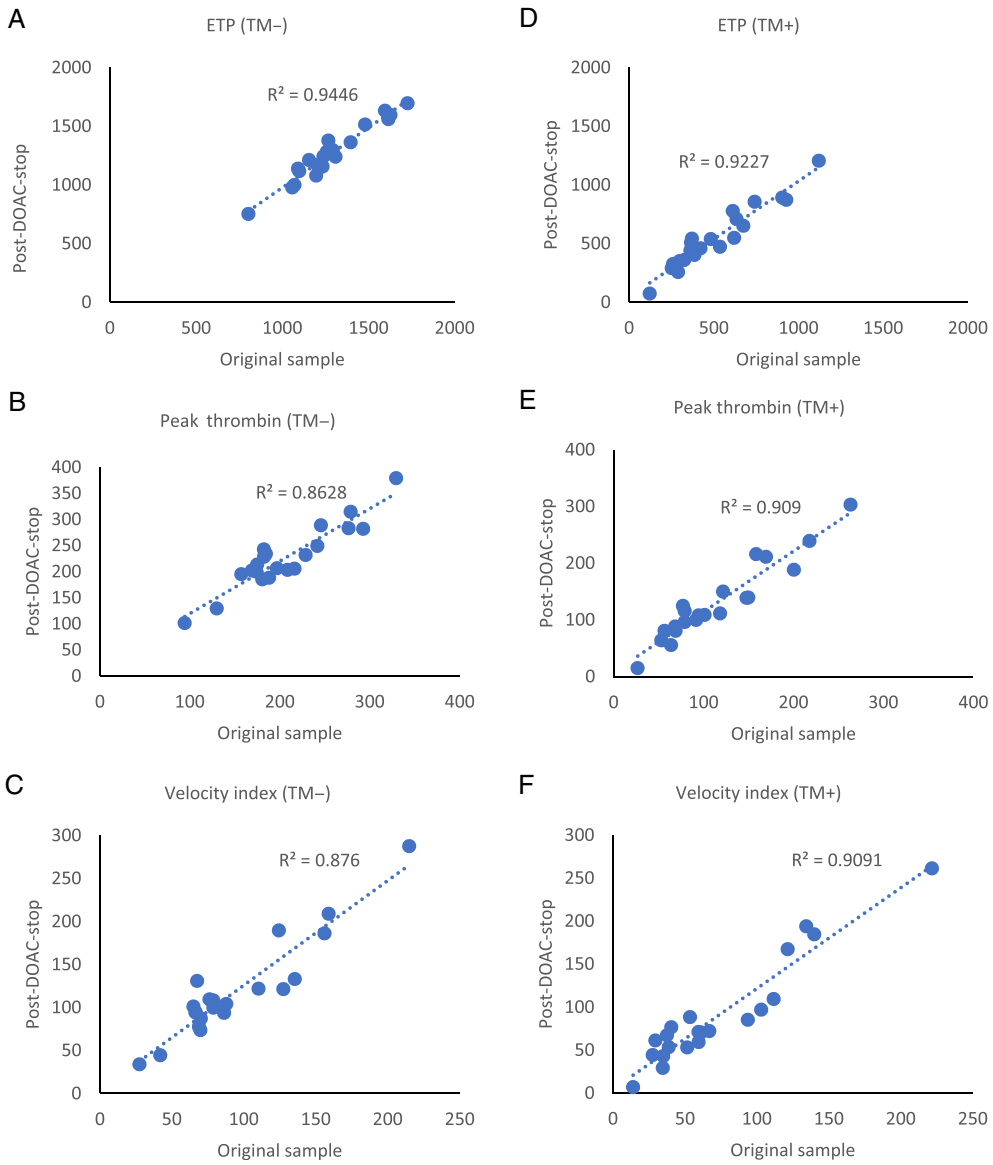

FIGURE 3 Correlation of thrombin generation parameters before and after DS in 21 non-anticoagulated patient samples. (A–C)—without TM. (D–F)—with TM. DS, DOAC-stop; ETP, endogenous thrombin potential; TM−, without thrombomodulin; TM+, with thrombomodulin

pulmonary embolism,[15] in antiphospholipid syndrome[16] and diabetes.[7]

The addition of DS to patient plasma may allow the assessment of an individual's underlying thrombotic potential using thrombin generation and the OHP assay despite anticoagulation. This was previously not possible, and necessitated the discontinuation or temporary withholding of anticoagulation, which may not be practical for many patients as it could increase the risk of thrombotic complications. This is especially pertinent for patients with impaired renal function as all DOACs rely significantly on renal elimination and may require long periods to fully clear the anticoagulant effect. While the clinical likelihood of bleeding complications in patients with low level of residual anticoagulation is small, this may have a significant impact on global coagulation assays which are highly sensitive to small amounts of anticoagulation.[8] Additionally, there is significant inter-individual variability with previous studies showing non-linear relationships between all thrombin generation parameters and DOAC drug levels with marked variability seen in drug levels as would be seen with trough measurements (e.g., <50 ng/L).[17,18] Removal of DOAC interference by DS in-vitro thus does not rely on these patient factors.

One limitation of this study is that plasma from patients with active myeloma or paraprotein was used. However, none of these patients were anticoagulated and all had a normal coagulation profile with a wide range of thrombin generation result. There is no evidence that paraproteins interfere with the function of DS or global coagulation assays and was shown to be discriminatory of the underlying thrombotic states in previous studies.[9] Their inclusion aided our study's aim of examining the inter-individual variations of DS by providing a wide range of thrombin and fibrin generation results. Our study focused on the effects of DS on normal plasma, and patients with normal coagulation parameters. It would be important to study any potential influence of DS on patients with prothrombotic or coagulopathic states, and these experiments have been planned for the future. Furthermore, we did not specifically measure levels of TFPI or other coagulation factors before and after DS, but the reduction in TFPI has been confirmed

by two separate studies and the pattern of our results are consistent with those previously reported.

5 | CONCLUSIONS

This study supports the use of DS in global coagulation assays, such as thrombin generation and overall haemostatic potential, to remove the interference caused by direct oral anticoagulants. Importantly, this study demonstrated that the effect of DS on coagulation in plasma from healthy donors measured by thrombin generation and OHP was marginal, and showed strong correlation pre- and post-DS. Our findings suggest that the results obtained following the use of DS are reliable, and may help to reveal an individual's underlying thrombotic tendency without the need to stop anticoagulation. The findings of this study may allow for more inclusive study designs enabling anticoagulated individuals to participate in studies of cardiovascular disease and VTE.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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