Anticoagulated patients exhibit intact endogenous thrombin potential using ST Genesia unlike the Calibrated Automated Thrombogram

Tuukka A. Helin MD, PhD1 | Marja Lemponen BSC1 | Riitta Lassila MD, PhD2 | Lotta Joutsi-Korhonen MD, PhD1

Abstract

Background: The thrombin generation (TG) assay is a feasible but labor-intensive method for detecting global coagulation. It enables comprehensive assessment of anticoagulation, while drug-specific assays assess only exposure. Traditionally, the Calibrated Automated Thrombogram (CAT) has been used, however the ST Genesia (Diagnostica Stago) allows automated evaluation.

Objective: We aimed to observe coagulation using the ST Genesia and compare the data with those of CAT in anticoagulated patients.

Patients and methods: In total, 43 frozen-thawed samples were studied using DrugScreen to assess direct oral anticoagulants (DOACs), warfarin, and low-molecular-weight heparin. Twenty samples (nine rivaroxaban, five apixaban, three warfarin, and three heparin) were also compared using CAT (5 pM tissue factor).

Results: TG reduction in DrugScreen depended on the specific drug and modestly correlated with DOAC levels (lag time $R^2 = 0.36$; peak $R^2 = 0.50$). The best correlation was observed with peak thrombin and rivaroxaban-specified anti–activated factor X (anti-Xa) activity ($R^2 = 0.60$). When comparing ST Genesia with CAT, only the results for apixaban concorded ($R^2 = 0.97$). Unlike CAT, ST Genesia yielded a normal endogenous thrombin potential (ETP) in 77% (24/31) activated factor X inhibitor cases, and it failed to give readouts at international normalized ratio (INR) $\geq 4.5$ and at anti-Xa $\geq 1.0$ IU/mL.

Conclusion: The ST Genesia data did not correlate with CAT, but it was independently associated with INR, anti-Xa, and DOAC concentrations. The lag time and peak responses were similar; the major differences were that ST Genesia showed no ETP effect of DOACs and failed to give readout at high INR or anti-Xa activity.

KEYWORDS: anticoagulants, calibration, heparin, thrombin/analysis, warfarin
The thrombin generation (TG) assay is often used to assess coagulation in research settings. It can be used to monitor anticoagulant response, as well as to identify coagulation deficiencies and prothrombotic tendencies. The semi-automated Calibrated Automated Thrombogram (CAT; Thrombinoscope, Diagnostica Stago, Asnières, France) method has been available to evaluate the TG for more than 2 decades. Although the CAT has proven useful in several clinical settings, such as when using hemophilia bypassing agents and emicizumab, the method is labor intensive and poorly standardized. For this reason, it has mainly been restricted to research use. The ex vivo capacity of citrated recalculated plasma to generate thrombin is measured by adding phospholipids and tissue factor (TF).

A new device, ST Genesia (Diagnostica Stago), enables automated TG measurement, which would make the assay more useful in clinical settings. However, the method is still being validated in patients, particularly those using anticoagulants. Currently, ST Genesia has three available test reagents: BleedScreen, ThromboScreen, and DrugScreen, which have low, intermediate, and high TF content, respectively. The exact TF concentrations are not publicly available. DrugScreen is recommended for measuring anticoagulant effects. The TF component is associated with the sensitivity of the assay to anticoagulants; the TG curve is negligible if TF is used at too low a concentration. Recently, the validation results and reference intervals of ST Genesia were reported in healthy volunteers.

The ST Genesia and CAT assays have both practical and methodological differences (Table 1). Both are fluorogenic methods that use a substrate split by thrombin after initiation, with supplementation of varying amounts of TF and phospholipids into the plasma. In ST Genesia, TG is measured in single cuvettes that require a higher plasma sample volume, while microtiter plates are used in CAT. ST Genesia is calibrated using buffered human thrombin without patient plasma, unlike CAT, which uses alpha-2-macroglobulin. ST Genesia is calibrated daily. To this end, the individual plasma properties are compared using the FluoSet reagent. In CAT, each patient sample is run in parallel with an alpha-2-macroglobulin calibrant. Due to this difference, dabigatran likely has less influence on ST Genesia than on CAT.

Few studies have compared CAT with ST Genesia. Recently, the plasma levels of direct oral anticoagulants (DOACs) were shown to correlate with the lag time and peak height of the DrugScreen test. However, no studies have compared the DrugScreen test with the CAT assay in anticoagulated patient samples. In the present study, we aimed to verify the ST Genesia DrugScreen test in patients using different anticoagulants at different plasma concentrations. We also compared ST Genesia with the more established CAT method. DOACs, low-molecular-weight heparin (LMWH), and warfarin plasma samples were included in this comparison.

Blood samples were collected and assays performed at the Department of Clinical Chemistry of the Helsinki University Hospital (HUSLAB Laboratory Services, Finland). The samples comprised surplus plasma from clinical thrombophilia panels or DOAC concentration assessments. Citrated plasma (3.2% sodium citrate) was collected, centrifuged at 2500 g for 10 minutes, aliquoted within 2 hours of collection, and frozen at −80°C. All requested routine coagulation test analyses were freshly performed using ACL TOP coagulation analyzers (Instrumentation Laboratory, Werfen, Columbia, MD, USA), including international normalized ratio (INR), anti–activated factor Xa (anti-Xa), diluted thrombin time calibrated with dabigatran, and the anti-Xa method calibrated using either rivaroxaban or apixaban. For all the anti-Xa assays, we used the HemosIL Liquid anti-Xa (Instrumentation Laboratory, Werfen), which contains dextran sulfate (may affect heparin measurement) but no added exogenous antithrombin. The TG analyses were performed within 1-2 weeks of sample collection. No corn trypsin inhibitors were added. All samples were anonymously analyzed, and thus the specific indications for anticoagulation were not available. The study received institutional approval from Helsinki University Hospital (HUS/211/2020; § 34, 30.9.2020). We compared the response of the CAT 5 pM TF reagent (Thrombinoscope, Diagnostica Stago) with those of the ST Genesia ThromboScreen and DrugScreen reagents (Diagnostica Stago).

### 2.1 DOAC plasmas

We collected 31 samples from patients using DOACs: 4 using dabigatran, 17 using rivaroxaban, and 10 using apixaban. Six patient samples were used in the pilot study: three using rivaroxaban, two using apixaban, and one using edoxaban.
2.2 | Pooled warfarin and LMWH plasmas

We also prepared a series of pooled plasmas from samples in which treatment with warfarin or the LMWH effect was measured. There were five patient samples per pool, except in the high INR (>9.9) pool, where two samples were used. Different warfarin samples (n = 38) were pooled to obtain a series of plasma samples covering INR levels ranging from 1.0 to >9.9 (Table 2). Different LMWH samples (n = 31) were pooled to obtain plasma samples with wide anti-Xa levels, from <0.1 to 1.2 IU/mL (Table 2).

2.3 | ST Genesia DrugScreen anticoagulant response and comparison with CAT assay

The following TG parameters were recorded: lag time (minutes), time to peak (minutes), peak height (nM), and endogenous thrombin potential (ETP) (nM × min). The methods were compared with consideration for the different TF concentrations of the reagents. For comparison, the same pooled samples or patient samples (different frozen aliquots) were used in parallel to assay DrugScreen and CAT. The TG assays were analyzed without adding thrombomodulin.
2.4 | Statistical analysis

Both devices have specific software programs: ST Genesia uses a software of the same name, while CAT uses ThromboScope. Pearson correlations or Bland-Altman plots were used as appropriate. Statistical analyses were performed using SPSS Statistics version 25 (IBM, Armonk, NY, USA).

3 | RESULTS

3.1 | Pilot study for ST Genesia

A pilot was conducted using ST Genesia ThromboScreen to analyze six DOAC and five warfarin plasma samples. We assumed that the intermediate TF concentration would best represent the concentration of 5 pM in the CAT assay. Because the TG curves were flat and INR levels >4.5 could not be analyzed, we selected the DrugScreen with its higher TF content for the subsequent studies.

3.2 | ST Genesia DrugScreen in samples with anticoagulation

After the pilot, 43 samples were assessed in 31 individual DOAC samples, 7 INR pooled samples, and 5 LMWH pooled samples.

For reference, we analyzed the normal plasma pool sample (n = 10 healthy donors) 13 times in parallel. In this pooled analysis, the mean lag time was 1.19 minutes, the time to peak 2.34 minutes, the peak height 453 nM, and the ETP 1610 nM × min, with the intra-assay coefficients of variation (CVs) between 1.9% and 2.8%. These values correspond well with those reported in the literature. The normal reference values for ST Genesia DrugScreen are: lag time, 0.82-1.00 minutes; peak, 380-539 nM; time to peak, 1.87-2.17 min; and ETP, 1122-1851 nM × min, with a good precision and stability (CV <3% for all variables). These reported reference values were used to interpret our own results.

The ST Genesia results correlated with increasing concentrations of each anticoagulant, that is, with increasing DOAC concentrations, INRs, and anti-Xa values (Figure 1, Table 2, Figure 2). The lag time and time to peak were prolonged in all anticoagulated samples (Figure 1A–B, Table 2). Peak height was lowered in all warfarin and LMWH samples, and in most DOAC samples (Figure 1 and 2). The peak at an INR level: two LMWH samples (anti-Xa ≥0.5 IU/mL), three warfarin samples (INR ≥4.5), and two dabigatran (187 and 195 ng/mL) samples. The lag time and time to peak were prolonged at high DOAC levels, while the peak values were lower. However, the ETP remained essentially unchanged, even at anticoagulant levels high above the target range; that is, DOAC concentrations >400 ng/mL or apixaban concentrations of 428 ng/mL and 795 ng/mL, respectively.

3.3 | Comparing ST Genesia DrugScreen with the CAT assay

To compare the CAT assay with ST Genesia, we studied 24 samples using the CAT 5 pM TF assay. ST Genesia failed to provide results in three samples with high anticoagulant concentration (Table 2), while CAT failed in one case involving dabigatran due to a calibration error that may have been related to the alpha-2-macroglobulin concentration. Ultimately, 20 samples were available for both assays: 14 activated factor X (FXa) inhibitor samples (nine rivaroxaban, five apixaban), four warfarin samples, and two LMWH samples (Figure 3).

The sensitivity of lag time, time to peak, peak height, and ETP raw values differed among the assays, with ST Genesia showing higher ETP and peak and shorter lag time than CAT (Figure 3). In ST Genesia, only 6 of 21 samples (29%) had diminished ETP: two rivaroxaban samples, a heparin pooled sample, and three warfarin pooled samples (Figure 3D). In contrast, ETP was normal in only 2 of 21 samples analyzed using CAT (10%), both of which were rivaroxaban samples. These samples also showed normal ETP in ST Genesia (Figure 3D).

Lag time was the most sensitive variable, regardless of the TG method used; it was prolonged in all samples analyzed using CAT and in 20 of 21 samples (95%) analyzed using ST Genesia (Table 2, Figure 3A). All samples showed prolonged time to peak when analyzed using ST Genesia; 19 of 21 (90%) did so when analyzed using CAT (Figure 3B). The peak value was normal in 1 of 21 samples (5%) analyzed using ST Genesia, while 3 of 21 (14%) were normal with CAT (Figure 3C).

The overall correlations between ST Genesia and CAT methods were poor, as follows: lag time, R² = 0.19; time to peak, R² = 0.20; peak height, R² = 0.20; ETP, R² = 0.20. Such poor correlation reflects the mode of action of individual anticoagulants, which were correlated with drug concentrations in a drug-specific manner. For rivaroxaban, the lag time showed an R² value of 0.43, time to peak
an $R^2$ value of 0.27, peak height an $R^2$ value of 0.001, and ETP an $R^2$ value of 0.11; as such, no correlations were detected. In contrast, for apixaban, lag time showed an $R^2$ value of 0.65, time to peak an $R^2$ value of 0.92, peak height an $R^2$ value of 0.97, and ETP an $R^2$ value of 0.76, delineating previous discrepancies with these two factor Xa inhibitors.11

The differences in responses were calculated by plotting each result variation against the mean of the results (Bland-Altman). Based on lag time change, CAT seemed more sensitive to all the studied anticoagulants, especially rivaroxaban, which was the DOAC with the highest observed concentrations. In all, ST Genesia yielded more prolonged lag time and time to peak than CAT, while peak height and ETP were higher, indicating a slower initiation phase but more capacity to generate thrombin.

**DISCUSSION**

To our knowledge, this was the first study to compare the new ST Genesia DrugScreen thrombin generation method with the established CAT assay in plasma samples of anticoagulated patients. Since the DrugScreen is the preferred assay for assessing anticoagulant activity according to Stago, we chose this reagent to compare with CAT 5 pM TF concentration, which is commonly used to assess anticoagulated samples.11,12 When 5 pM TF is used, also factors VIII and IX contribute to TG.13 In addition, our small pilot study tested the Stago ThromboScreen reagent, which is close in TF concentration to the CAT 5 pM assay. The results showed very modest responses in some strongly anticoagulated patients. Overall, the results differ between the assays. CAT seemed more robust and provided results even when anticoagulation levels exceeded their clinical or assumed targets.

The ST Genesia Drugscreen results correlated with the concentrations of DOACs, especially when the FXa inhibitor apixaban was used, the peak was decreased, or the lag time was prolonged. This is in concordance with a recent study.7 The level of anticoagulation impacted the findings; the difference between the methods grew at anticoagulant levels that were higher than the target (Table 2). The peak values for rivaroxaban—approximately 100 nM with a rivaroxaban concentration of 200 ng/mL—were comparable to the data previously reported using the ThromboScreen reagent.14 Indeed, in LMWH and warfarin samples, the DrugScreen was oversensitive to the anticoagulant levels exceeding the usual clinical targets (anti-Xa of ≥1.0; INR of ≥4.5), while CAT still provided readouts at these levels. In addition, in two high samples containing high dabigatran levels (187 and 195 ng/mL), DrugScreen did not provide readouts. In the case of rivaroxaban and apixaban, DrugScreen seemed to provide results at higher concentrations than with dabigatran, even at FXa inhibitor
concentrations of 330 and 795 ng/mL, respectively. In only one apixaban sample, the drug level was supratherapeutic, so distinctions at levels of overanticoagulation remain to be elucidated in the future. Because the curves are flat, the DrugScreen reagent cannot be used to diagnose high warfarin, LMWH, or dabigatran levels, which is a clinical problem. Bleeding risks with warfarin increase by 8- to 10-fold at INRs >4.5 and at anti-Xa levels >0.7 IU/mL, which are considered supratherapeutic in patients with trough levels of LMWH.15,16 These differences are highly clinically relevant after incidents such as a severe bleeding episode, impaired renal function, or thrombolysis, as well as during unfractionated heparin therapy and warfarin overdose assessment.

ST Genesia has been proposed as a tool to exclude the presence of DOACs, because it can detect levels <30–50 ng/mL.7 We were unable to confirm this finding because only two samples had low DOAC levels (<50 ng/mL). However, we did find that lag time was prolonged in all DOAC samples using DrugScreen. The peak value was also diminished in >95% of the samples studied. In accordance with a previous study, the ETP of DrugScreen was insensitive to DOAC effects,7 exhibiting mostly normal values. In contrast, the CAT ETP was decreased in most of the samples (86%). It is not possible to compare the two methods directly because the formula for calculating ETP in ST Genesia is not publicly available. Recently, ST Genesia was used to assess TG in patients with coronavirus disease 2019, but the effects of anticoagulation were eliminated in vitro before testing.17

Unlike previous TG methods, in which chromogenic reactions determine the readout,18 ST Genesia is based on a fluorogenic measurement similar to that of CAT. This likely leads to similar results between the two methods. Again, in a comparison between ST Genesia and the CAT assay using 12 normal samples, BleedScreen correlated with both 1 and 5 pM TF-triggered CAT results in terms of both lag time and peak, whereas ETP correlated poorly.19 In the present study, the overall correlations between the methods were poor because the different anticoagulants had different modes of action. In contrast, the apixaban concentrations correlated well, with $R^2$ values >0.90 for both lag time and peak height. Regardless of the anticoagulant, the ETP failed to correlate between the methods. Differing TF concentrations between the methods likely explain some of the quantitative differences in the TG results. That is, ST Genesia DrugScreen has higher ETP and shorter lag time than CAT. Previous studies have shown that a TF concentration of 1 pM in CAT is sensitive to hypocoagulable conditions such as hemophilia,20 while 5 pM TF generates more thrombin at baseline under hypercoagulable states. The difference in ETP between baseline and hypercoagulability is also enhanced at lower TF concentrations (1 pM).21 Based on these previous findings, we assume that the DrugScreen reagents contain TF levels >5 pM, but the actual concentration is not publicly available (Table 1).

The present study had several limitations. For example, no clinical information, such as indication for anticoagulation, were available.
because the samples were collected and analyzed anonymously. Furthermore, the DOAC intake was unknown, and no other coagulation laboratory tests were carried out. Since some of the samples were obtained as surplus plasma from a thrombophilia panel, patients undergoing acute thrombosis may have been included, potentially confounding the results. The strength of the present study was that it used actual, real-life patient samples with a range of exposure to specific anticoagulants. Since INR and anti-Xa samples were pooled, individual differences in response to TG were dampened, enabling more accurate comparison of the methods. While the different TG capacities of the reagents impact quantitative TG variables, the use of reference intervals of the ST Genesia and CAT methods enabled the two methods to be compared.

Few studies have compared ST Genesia with the CAT assay. In a small study involving six patients who had undergone liver transplant with repeated sampling, the ThromboScreen and BleedScreen reagents exhibited lower ETP and peak values than 5 pM CAT. We detected opposite results using the DrugScreen, which showed higher peak and ETP values, perhaps because it has a high TF concentration and low factor VII levels, which are common in liver disease. The lag time was shortest using the ThromboScreen reagent, while BleedScreen and CAT exhibited similar results. In the present study, DrugScreen exhibited a shorter lag time than CAT, as well as higher ETP and peak values. Another study by Roullet et al. involving 85 patients with liver cirrhosis reported similar results. The main difference was reagent-specificity: The ThromboScreen reagent of CAT showed similar results to ST Genesia. A practical difference between these assays is the higher sample volume required by the ST Genesia (800 µL; Table 1). Finally, in our study, while the absolute ST Genesia results displayed stronger TG (shorter lag time, higher peak and ETP), the CAT assay performed more robustly when patients were overly anticoagulated. Thus, the sensitivity differences between the reagents seemed nonlinear.

**5 | CONCLUSIONS**

Both the ST Genesia DrugScreen and CAT methods correlated with anticoagulation intensity; ST Genesia and CAT showed similar lag time.
and peak thrombin alterations, while the respective readouts did not correlate well. ST Genesia DrugScreen exhibited weaker ETP response, possibly because of differences in the sensitivity of the reagents. As the ETP remained normal in most DOAC samples using DrugScreen, it should not be used to assess ETP in patients prescribed DOACs. However, the lag time and peak values behave as expected when using DrugScreen, offering better markers. At high INR and anti-Xa levels, the CAT method seemed more robust and provided readouts, unlike ST Genesia DrugScreen. Overall, ST Genesia DrugScreen remains limited in its practical use, failing to measure overanticoagulation using warfarin and heparin, as well as showing normal ETP with DOACs.

ACKNOWLEDGMENTS
Diagnostica Stago (France) is acknowledged for allowing access to use the ST Genesia device for this study. J. Perholehto, K. Karjalainen, J. Toikka, K. Salonen, and L. Tulikallio of the HUSLAB Coagulation Laboratory are thanked for their contribution in collecting the patient samples for this study.

AUTHOR CONTRIBUTIONS
TH, RL, and LJ-K were involved in the planning of the study, in analyzing the data, and in formulating and finalizing the manuscript. ML collected patient samples from the study and ran the analyses (CAT, ST Genesia, and DOAC concentrations). All authors approved the final version of the manuscript.

RELATIONSHIP DISCLOSURE
The authors declare that nonfinancial support was received from Diagnostica Stago (use of the ST Genesia device). The authors have no other disclosures to declare.

ORCID
Tuukka A. Helin https://orcid.org/0000-0002-5273-8088

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