

Fully automated thrombin generation assays: current characteristics, advances, and clinical relevance

Ensayos automatizados de generación de trombina: características actuales, avances y relevancia clínica

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Abstract

The thrombin generation assay (TGA) is a diagnostic tool that enables a global assessment of hemostasis. In recent years, technical advances have been made to achieve full automation of these assays, with the aim of ensuring standardization and consistency across studies. Currently, two fully automated devices are available: ST-Genesia® (Diagnostica Stago, Asnières-sur-Seine, France) and Ceveron® alpha TGA (Technoclone, Vienna, Austria). This is a highly versatile tool that has demonstrated clinical applicability both in the field of bleeding disorders – by assessing patients' bleeding phenotypes and monitoring their hemostatic treatment – and in thrombotic disorders, as it can identify thrombotic risk profiles not only for venous thrombosis but also for cardiovascular risk and cancer-associated thrombosis. Its role is also being investigated in the monitoring of anticoagulant therapy and the hemostatic status of patients with liver cirrhosis.

Keywords: Thrombin generation assay. Global assay. Automatization.

Resumen

El test de generación de trombina es una herramienta diagnóstica que permite evaluar de forma global la hemostasia. En los últimos años se ha avanzado técnicamente para lograr automatizar completamente dichos estudios con el fin de lograr su estandarización y homogeneidad. En la actualidad están disponibles dos dispositivos, ST-Genesia® (Diagnostica Stago, Asnières-sur-Seine, France) y Ceveron® alpha TGA (Technoclone, Vienna, Austria) completamente automatizados. Se trata de una herramienta muy versátil que ha demostrado su aplicabilidad clínica tanto en el campo de la diátesis hemorrágica evaluando el fenotipo hemorrágico de los pacientes y la monitorización del tratamiento hemostático, como en el campo de la diátesis trombótica siendo capaz de identificar el perfil de riesgo trombótico no solo en trombosis venosa sino también en riesgo cardiovascular y trombosis asociada a cáncer. También se está evaluando su papel en la monitorización del tratamiento anticoagulante y el estado hemostático de pacientes con cirrosis hepática.

Palabras clave: Test de generación de trombina. Test global. Automatización.

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Introduction

The thrombin generation assay (TGA) is an advanced diagnostic tool designed to evaluate the entire coagulation process, particularly focusing on the thrombin generation (TG) phase. Thrombin, a critical enzyme in the coagulation cascade, plays a pivotal role in blood clot formation. TGA is especially useful in identifying and assessing the functionality of the hemostatic system in various clinical situations, ranging from bleeding disorders to thrombophilia.

Historical development

TGA has evolved over several decades from manual methods to automated techniques, since its first development in 1952 by McFarlane and Bigg¹. Initially, the method involved measuring TG in whole blood or plasma using triggers such as tissue factor (TF) or cephalin, with clotting times used to construct a dose-response curve². This method was highly manual, requiring subsampling and discontinuous measurement, which required skilled operators and a considerable amount of time to carry out the experiments^{3,4}.

Between 1970 and 1990, the understanding of coagulation began to shift toward a more dynamic approach. Automated methods, such as the amidolytic assay, were introduced, utilizing chromogenic substrates to measure TG, its total production, and rate. This advancement provided greater precision and efficiency compared to manual methods⁵. Moreover, in 1986, Hemker introduced significant improvements, such as replacing fibrinogen with synthetic chromogenic substrates and incorporating computer software for automated analysis¹. Over the following decades, the assay evolved further, transitioning to fluorogenic substrates, which eliminated the need for defibrination and enabled its application in platelet-rich plasma².

In the early 2000s, a growing interest in TG appeared with the development of calibrated automated thrombography (CAT), which marked a significant milestone. CAT employs fluorogenic substrates for continuous and calibrated measurement of TG, offering a comprehensive assessment of hemostasis by capturing initiation, propagation, and termination phases of coagulation with new parameters such as lag time, peak thrombin, and thrombin potential^{4,6,7}.

In recent decades, the advent of fully automated TGA methods (which are the subject of this review) has led to a significant improvement and increased interest in this technique. Today, TGA continues to evolve, and new

methods are being explored, including TG in whole blood, CAT with lower volume, or technologies such as electrochemistry and fluorescence for real-time monitoring⁴.

Fundamentals of TG: biochemical mechanisms and differences from conventional techniques

Thrombin formation is the central event in the coagulation process. It involves several steps from its initiation, following the interaction of TF and factor VIIa, to the formation of the prothrombinase complex and the subsequent conversion of prothrombin to thrombin. In addition, thrombin is involved not only in the conversion of fibrinogen to fibrin and platelet activation, but also in the activation of inhibitory pathways, such as protein C activation⁸. What makes the TGA interesting, compared to classical hemostatic tests, is that it allows visualizing the dynamics of this process in a global way, reflecting not only the production of thrombin but also its degradation. Traditional coagulation tests assess only the initiation phase of coagulation, and they do not reflect the entire hemostatic balance⁹.

TGA is able to represent this process after thrombin formation triggered by small amounts of TF and phospholipids. The resulting TG, balanced by thrombin inhibition occurring simultaneously as soon as traces of thrombin appear in the reaction medium, is continuously monitored using a thrombin-specific chromogenic or fluorogenic substrates⁴.

The kinetics of the TG reaction comprises three stages: Initiation, amplification, and resolution phase. First, the trigger allows reactions to reflect the initiation phase, which can be inhibited by the TF pathway inhibitor. The time taken to complete this phase in the TGA corresponds to the time to initial fibrin formation, or clotting time, in routine tests such as prothrombin time (PT) or activated partial thromboplastin time (APTT), which requires only trace amounts ($\approx 5\%$ of total thrombin formed) and is designed to measure events up to, but not beyond, initial clot formation. Second, the amplification/propagation phase, in which prothrombin conversion occurs more rapidly than thrombin inhibition. Finally, in the resolution phase, prothrombin conversion is overcome by the action of various inhibitors present in the plasma sample, such as activated protein C (APC), antithrombin (AT), and alpha-2-macroglobulin. From the initial raw optical signal measured in relative fluorescence units (RFU), the first derivative is calculated to present an initial TG curve in terms of RFU/min over time. Specialized software then compares the

thrombin activity to a thrombin standard, plots the TG curve, and determines key parameters that describe the thrombogram expressing the amount of thrombin generated in nM over time (Fig. 1)^{2,4}.

The meaning of the different parameters that characterize a thrombogram is as follows:

- Lag time: time until the formation of the first traces of thrombin.
- Time to peak: time required to reach the maximum thrombin peak.
- Peak height: maximum amount of thrombin generated.
- Endogenous thrombin potential (ETP): net amount of thrombin that can be generated by the plasma, which depends on both procoagulant and anticoagulant factors, represented by the area under the curve.
- Start tail: point at which TG has come to an end, and all generated thrombin has been inhibited.
- Velocity index: the slope of TG between the lag time and the time to peak, which corresponds to the first derivative of this part of the curve.

Advantages of fully-automated versus semi-automated TGA

Semi-automated TG systems typically require manual preparation steps, such as reagent mixing, sample handling, and initiation of the assay, followed by measurement using a fluorometer or similar detection system. This approach offers flexibility in assay customization, allowing researchers to tailor reagents and protocols to specific study needs. However, semi-automated TGA are more prone to variability due to operator handling, have longer turnaround times, and require trained personnel to ensure consistency and accuracy¹⁰.

In contrast, fully automated TG analyzers integrate sample preparation, reagent handling, assay initiation, and detection into a streamlined workflow. These systems minimize human intervention, reducing the risk of pipetting errors and inter-operator variability, which significantly enhances reproducibility and throughput. Fully automated TG platforms also provide standardized assay conditions and data analysis, facilitating comparability between runs and across laboratories. Moreover, they often feature user-friendly interfaces and faster processing times, making them suitable for routine clinical use and large-scale studies. While the upfront cost of fully-automated systems is higher, their advantages in consistency, efficiency, and scalability position them as the preferred choice for clinical

diagnostics and research environments demanding high precision and reliability¹⁰.

What fully-automated TGA brings to semi-automated TGA is the implementation of temperature control, the addition of reference plasma to normalize data, and control over reagents to avoid inconsistencies, ensuring that laboratories can compare results without discrepancies¹¹.

Regarding the mentioned lack of standardization, efforts have been made by several groups to homogenize and standardize this technique. In this context, the ISTH SCC Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibodies published their recommendations for the measurement of TG. They provided indications for controlling pre-analytical, analytical, and post-analytical factors¹².

Citrate tubes at a concentration of 0.109 M are recommended. As for the sample, platelet-poor plasma, containing $< 10 \times 10^9$ platelets/L, is most commonly used. After centrifugation, the sample should be processed within 4 h or stored at either -80°C or -20°C ¹². For clinical purposes, standardized commercial reagents should be used^{4,12}.

TGA should always be performed at 37°C . In addition, it is recommended to pre-heat samples, triggers, and substrates for at least 10 min¹². Some devices, such as ST-Genesis®, incorporate this pre-heating and perform it automatically¹¹.

Fully-automated devices perform triplicates for each sample, whereas, for manual/semi-automated methods, it is recommended that samples should be analyzed at least in duplicate and preferably in triplicate^{11,12}. Finally, it is strongly recommended to use a control plasma sample to normalize results, to improve comparability^{12,13}.

To date, several studies on TGA reference ranges based on the ST-Genesis® method have been published. Whereas the studies by Ninivaggi et al., Calzavarini et al., Carlo et al., and Kristensen et al. established reference ranges in adult individuals¹⁴⁻¹⁷, other works have focused on ranges in the pediatric population^{18,19}.

Available fully automated TGA

There are two fully-automated TGA platforms currently available: ST-Genesis® (Diagnostica Stago, Asnières-sur-Seine, France) and Ceveron® alpha TGA (Technoclone, Vienna, Austria). Their differences are summarized in table 1. Both platforms offer walk-away automation, including reagent dispensing, calibration,

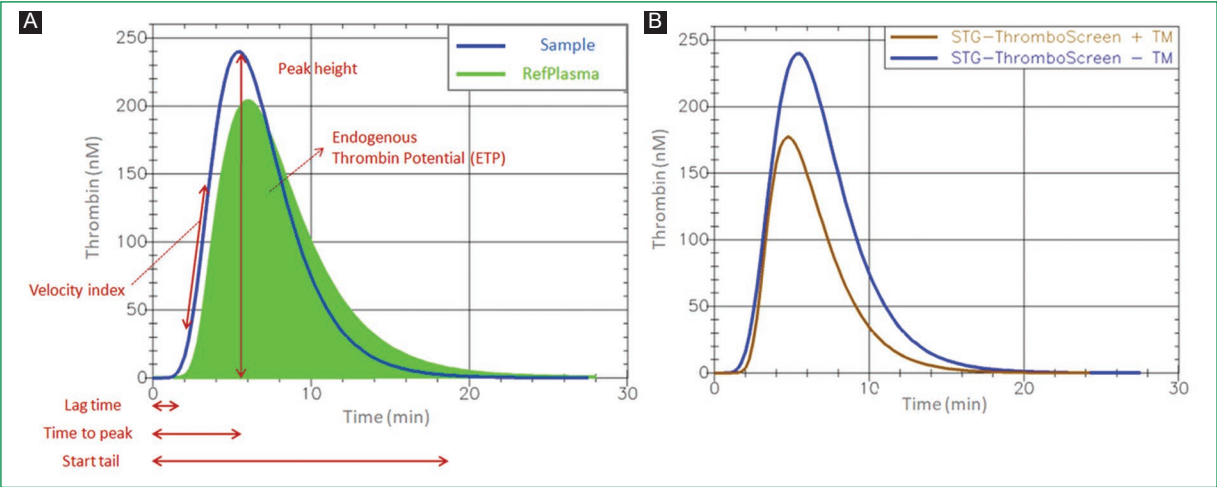


Figure 1. Representative thrombin generation (TG) curves obtained from the ST-Genesis analyzer. **A:** TG curve showing key kinetic parameters: lag time, time to peak, peak height, velocity index, start tail, and endogenous thrombin potential (ETP), which is represented by the area under the curve. Blue line represents the sample compared to a reference plasma (green area). **B:** the blue curve represents TG in the absence of thrombomodulin (TM), whereas the brown curve shows the inhibitory effect of TM on thrombin formation, as evidenced by a lower peak and reduced ETP.

Table 1. Comparison of the two fully automated TGA platforms currently available

Parameters	ST-Genesis®	Ceveron® alpha TGA
Detection method	Fluorogenic	Chromogenic
Excitation/emission	360/460 nm	Absorbance at ~405 nm
Scan time	~60 min	~30-60 min
Calibration	Internal (per well)	External calibrator
Filter required	Yes	No
Plasma volume	~20 µL	~60-80 µL

TGA: thrombin generation assay.

alpha TGA uses a chromogenic substrate, making it conceptually different from fluorogenic CAT-based assays.

Regarding internal filter requirements, ST-Genesis® requires optical filters for fluorescence excitation and emission, whereas Ceveron® relies on absorbance photometry, and no special filters beyond standard ones are required.

Finally, in terms of the volume of plasma required, ST-Genesis® uses a low sample volume, compatible with small pediatric samples; in contrast, Ceveron® requires more plasma, which may be a limitation in neonates or small volume studies.

and data analysis. However, ST-Genesis® is designed only for TGA, whereas Ceveron® Alpha is a multiparameter analyzer that also handles other coagulation tests.

Technoclone's approach integrates seamlessly with its Ceveron t100/s100 coagulation analyzers by adding a fluorescence-based TGA module, which allows routine and TGA measurements from the same plasma sample, with minimal handling and robust traceability. Both systems record the full TG curve over time, but the exact scanning time can vary depending on the protocol and triggering reagent used.

Whereas ST-Genesis® uses the CAT principle with a fluorogenic substrate, similar to manual CAT, Ceveron®

Clinical applications

As mentioned above, TGA can be useful in detecting situations of hypo- or hypercoagulability. For example, in situations of hypocoagulability, patients will have a prolonged lag time and time to peak and lower peak height, velocity index, and ETP².

The applications of TGA have expanded since its development, particularly in personalized medicine. This technology has been evaluated across multiple fields, including hemostasis research, clinical diagnostics, and personalized medicine.

The current review will be focused on evidence on fully-automated TGA.

Hemostasis and coagulation disorders

One of the primary applications of TGA was the assessment of bleeding risk in patients with coagulopathy.

HEMOPHILIA

TGA has been shown to be useful in identifying, among hemophilic patients with the same factor level, those with an increased hemorrhagic phenotype²⁰. In addition, this technology helps to personalize supplementation therapy in hemophilic patients, as it reflects an increase in TG after treatment²¹. Therefore, it allows guiding factor replacement in surgical and non-surgical settings²².

Another complex scenario in which conventional hemostasis tests are ineffective, and in which TGA has proven effective, is in monitoring treatment in hemophilia patients who have developed an inhibitor. These patients exhibit an increased bleeding risk, which is not adequately identified by classical coagulation tests. Moreover, in many cases, these patients require combination therapy with bypass agents and emicizumab, which exposes them to increased thrombotic risk. TGA can detect these changes in coagulation status and serve as a valuable tool to monitor the appropriate therapeutic regimen to be administered²².

COAGULATION FACTOR DEFICIENCIES

Four different TGA, 2 semi- and 2 fully-automated, proved effective in differentiating single coagulation factor-deficient samples from healthy controls, with modest discrepancies observed between the platforms¹⁰.

UNDIAGNOSED BLEEDING DISORDERS

A recent study compared ST-Genesia® and CAT in patients with mild bleeding tendency not diagnosed with traditional laboratory analysis. Lower ETP was detected in 62.7% and 69.5%, respectively, so the authors conclude that the addition of TGA to traditional clot-based testing could reduce the number of undiagnosed patients²³.

Thrombophilia and hypercoagulability disorders

ST-Genesia® has also been evaluated in patients at risk for thrombophilia and other hypercoagulability disorders. These conditions are characterized by an increased tendency to form abnormal blood clots, leading to deep

vein thrombosis, pulmonary embolism, or stroke. Quantifying TG helps to identify the hypercoagulable state in these patients, offering a more nuanced view of their coagulation status beyond traditional tests such as PT or APTT². Several studies have addressed the ability of TGA to identify patients at risk of first and recurrent venous thromboembolism (VTE), showing that an increased ETP was associated with VTE development; however, cutoff values have not been identified²⁴.

INHERITED THROMBOPHILIA

Patients with inherited AT, protein C, or Protein S deficiencies, APC resistance, factor V Leiden, or G20210A prothrombin gene mutations, present an increased TG represented by higher ETP and peak height²².

ANTIPHOSPHOLIPID SYNDROME (APS)

APS patients often show prolonged lag time and time to peak, indicating delayed thrombin formation, whereas their ETP may be either lower, similar, or slightly higher than that of healthy individuals. In addition, increased resistance to APC has been consistently observed in APS subjects. Lupus anticoagulant (LA) subjects without clinical manifestations of APS also presented TG alterations described in APS patients. A high LA potency and a triple-positive antiphospholipid profile enhance differences in lag time, time to peak, and, especially, increase APC resistance, but no effect in ETP is seen under any of these circumstances²⁵.

Anticoagulation therapy monitoring

TGA parameters are affected by all anticoagulant treatments; thus, this technique represents a powerful tool to assess their effect and to help tailor treatment, and to optimize antithrombotic treatment, but limiting hemorrhagic risk². Regarding Vitamin K antagonists (VKA), Brocal et al. reported that ETP, peak height, and lagtime showed high correlation with international normalized ratio (INR)²⁶. In addition, VKA patients admitted to emergency units because of bleeding had lower ETP values than those admitted to the emergency department for other reasons with a similar INR²⁴. Regarding direct oral anticoagulants (DOAC), Metze et al. demonstrated that TG remains reduced 12 h after DOAC intake²⁷. In addition, TGA has been evaluated for the determination of residual anticoagulant effect at low drug levels²⁸. Whereas dabigatran increased lag time, apixaban and rivaroxaban decreased peak height and ETP. Furthermore, DOAC plasma levels

did not correlate with TGA parameters²⁴. Finally, in patients treated with heparin, TGA showed lower ETP values after heparin administration compared to baseline values²⁴. However, TGA seems insufficiently sensitive for low concentrations of low molecular weight heparin²⁹.

Cardiovascular disease

Thrombin plays a key role in cardiovascular pathophysiology, and its generation can be influenced by various factors such as atherosclerosis and other cardiovascular conditions. Berntorp and Salvagno demonstrated that patients with acute myocardial infarction generate more thrombin, earlier and faster, reflecting hypercoagulability. Moreover, they propose that TGA could be useful for guiding therapy, increasing treatment in those with persistence of elevated peak height over time⁹.

Cancer research

Cancer patients frequently face an elevated risk of thrombotic events, partly due to the procoagulant tumor activity. The overall risk of VTE is variable and changes dynamically throughout the course of the disease. TG has been investigated as a potential biomarker for cancer-associated thrombosis and as a prognostic indicator of disease progression^{22,30}.

In relation to cancer-related thrombosis, the Vienna Cancer and Thrombosis study showed that those who developed a VTE presented elevated peak height levels, a greater area under the curve, a higher velocity index, and shorter time to peak and lag time. Comparing thrombin peak quartiles, those in the upper quartile had an increased risk of thrombosis during follow-up. At 6 months, the probability of developing a VTE was 11% in the upper quartile compared to 4% in those with lower peak height³¹. Similarly, Norris et al. developed and validated the thrombogyn score, which can predict the occurrence of VTE in patients with gynecological cancer within 24 months of cancer staging. The performance of this score was improved by extending it to include both ETP and D-dimer³².

Among hematologic malignancies, studies in multiple myeloma (MM) and acute lymphoblastic leukemia (ALL) have been published³³⁻³⁶. Recently, a Spanish group has demonstrated that newly diagnosed MM patients show an enhanced TG compared to healthy controls³³. They generate a higher peak of thrombin, it takes less time to produce it, and they exhibit resistance to TM inhibition. Moreover, a significant decrease was observed in velocity index (after one cycle) and peak height (after four cycles), and alongside increased

sensitivity to TM (after four cycles), indicating a reduction in hypercoagulability post-treatment³⁴. Children with ALL are known to be at increased risk of VTE during induction therapy, with these events not being predictable by conventional coagulation assays. Remarkably, in those who developed thrombotic complications, Betticher et al. demonstrated significantly higher ETP very early (as early as days 8-12), well before clinical manifestation³⁵. After pegylated asparaginase administration, an even higher ETP and lower inhibition of TG with TM have been described in these patients³⁶.

Liver cirrhosis

In a study published by Talon et al., ST-Genesia[®] detected that, overall, patients with cirrhosis had a hypercoagulable phenotype (higher ETP) in the presence of TM³⁷. In addition, Brodard et al. found that higher liver stiffness measurements correlated with increased TG and TM resistance³⁸. Notably, ST-Genesia[®] parameters showed a stronger correlation with liver stiffness compared to CAT assays, suggesting that ST-Genesia[®] could more effectively identify a procoagulant state in cirrhotic patients³⁸.

Finally, another study reported that TM-mediated inhibition of TG was significantly decreased in patients with liver cirrhosis compared with healthy donors, and also in Child-Pugh B and C patients compared with Child-Pugh A patients³⁹.

Research in thromboinflammation

Emerging research has highlighted the complex interaction between thrombosis and inflammation, known as thromboinflammation. Regarding COVID-19 patients, studies evaluating TGA have yielded discrepant results. While some of them demonstrated a hypercoagulable TG, which was even more pronounced in the most severely affected patients⁴⁰, others reported that TGA could predict neither survival nor thrombotic events in hospitalized COVID-19 patients⁴¹. Finally, lower ETP inhibition with TM has been described in patients with post-COVID syndrome compared to healthy controls⁴².

Advantages and limitations of this new technology

Advantages

TGA provides a more holistic view of the coagulation process compared to standard tests, reflecting both

pro- and anticoagulant activities as a consequence of an imbalanced hemostasis state, making it useful in the diagnosis of a number of disorders. It represents *in vivo* hemostasis better than traditional techniques²².

Automation ensures that results are comparable across different centers and facilitates the standardization of techniques. Nowadays, TGAs are user-friendly and easily accessible, requiring minimal skills. In addition, it makes these methods more accessible to routine laboratories, no longer limiting them to research settings⁴.

When incorporated into routine laboratories, it may help in personalizing treatments both for hemorrhagic and thrombotic disorders.

Limitations

To date, there is a lack of standardization not only on reagents and protocols but also in pre-analytical variability, although ISTH and manufacturers are making high efforts in solving this issue^{4,10,12}. Moreover, variations in techniques and reagents may hinder result interpretation, as the presence of coagulation inhibitors or activators can differ¹².

Conclusion

TGA is a powerful tool for assessing coagulation function in a more comprehensive manner. It offers valuable insights, especially for patients with complex coagulation disorders or those undergoing anticoagulant treatment. While it has clear advantages in terms of sensitivity and depth of information, its complexity, cost, and the need for specialized knowledge can limit its widespread use. As the technology and standardization improve, TGA is expected to become more integrated into clinical practice, enhancing diagnostic and therapeutic approaches to coagulation disorders in the upcoming years.

Summary

A. Clinical applications

A.1- TGA detects coagulation abnormalities not evident on standard tests; guides individualized treatment, especially in patients requiring bypass agents or emicizumab. Recommendation: TGA can be used in bleeding risk assessment in hemophilia, including patients with inhibitors

A.2- TGA can reveal abnormalities of thrombin potential not detected by conventional tests, improving diagnostic yield. Recommendation: TGA can be used in the evaluation of diagnosed and undiagnosed bleeding disorders.

A.3- TGA provides detailed information on thrombin dynamics, e.g., increased ETP and APC resistance, which aids in establishing risk stratification. Recommendation: TGA can be employed for the assessment of hypercoagulable conditions in thrombophilia, aiding in risk stratification.

A.4- TGA with thrombomodulin (TM) has a greater correlation with liver stiffness and can detect TM resistance, a marker of prothrombotic risk. Recommendation: TGA can be used to assess the coagulation status in liver cirrhosis, with special regard to TM.

B. Automation and standardization

B.1- Such systems reduce human error, increase reproducibility, and enable standardized data interpretation. Recommendation: employ with preference fully automated TGA devices for clinical use.

B.2- Standardized conditions enable between-center comparison. Recommendation: employ prewarming, duplicate/triplicate testing, and control plasmas to increase assay robustness.

B.3- Standardized sample processing and preparation reduce intra-laboratory variability and increase data reliability. Recommendation: follow ISTH guidelines for pre-analytical and analytical quality control, including PPP and citrate tubes.

C. Global consideration

C.1- TGA monitors both pro- and anticoagulant activity, providing a comprehensive view of hemostatic balance.

Recommendation: TGA can be considered a new global coagulation assay in clinical laboratory practice for hemostasis evaluation

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Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

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Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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