Update on Tissue Factor Detection in Blood in 2024: A Narrative Review

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Hamostaseologie 2024;44:368–376.

Abstract

Tissue factor (TF) is a transmembrane protein essential for hemostasis. Different forms of active TF circulate in the blood, either as a component of blood cells and extracellular vesicles (EVs) or as a soluble plasma protein. Accumulating experimental and clinical evidence suggests that TF plays an important role in thrombosis. Many in-house and commercially available assays have been developed to measure TF-dependent procoagulant activity or antigen in blood and have shown promising results for the prediction of disease outcomes or the occurrence of thrombosis events in diseases such as cancer or infectious coagulopathies. This review addresses the different assays that have been published for measuring circulating TF antigen and/or activity in whole blood, cell-free plasma, and EVs and discusses the main preanalytical and analytical parameters that impact results and their interpretation, highlighting their strengths and limitations. In the recent decade, EVTF assays have been significantly developed. Among them, functional assays that use a blocking anti-TF antibody or immunocapture to measure EVTF activity have higher specificity and sensitivity than antigen assays. However, there is still a high variability between assays. Standardization and automatization are prerequisites for the measurement of EVTF in clinical laboratories.

Keywords

- tissue factor
- extracellular vesicles
- functional assays
- antigenic assays
- flow cytometry

Introduction

Tissue factor (TF) is the primary factor responsible for initiating the coagulation cascade by forming a complex with factor (F) VII and FVIIa, which can activate FX and FIX, subsequently generating thrombin. Besides, TF is also involved in other cellular processes, including cell survival,[1] angiogenesis,[2] metastasis formation, and tumor growth.

Different forms of TF circulate in blood either as a component of blood cells or soluble plasma protein or associated with extracellular vesicles (EVs) which are membrane-enclosed submicronic vesicles released by all types of cells that carry molecular cargo from their parental cells. Elevated levels of these circulating forms have been detected in various pathological conditions, such as cancer,[3,4] infectious disorders,[5,6] heparin-induced thrombocytopenia,[7] sickle cell disease,[8–10] acute myocardial infarction,[11] and preeclampsia.[12] Interestingly, a link has been found between increased EVTF activity in a large spectrum of pathological contexts and the disease severity, such as the stage of cancer,[4,13] or patient mortality,[14–19] as recently reviewed.[20] In addition, increased EVTF activity was also correlated with the occurrence of disseminated intravascular coagulation (DIC)[21–23] or thrombotic events, including venous thrombosis, in patients suffering from cancer[24–27] or COVID-19.[5,28]

In the present review, after a brief overview of the different forms of TF detected in circulating blood and their mechanisms of biogenesis, we address the available methodologies, including in-house and commercial assays that have been published to measure TF in clinical samples, highlighting their main preanalytical and analytical characteristics, strengths, and

received
June 1, 2024
accepted after revision
August 6, 2024

DOI https://doi.org/10.1055/a-2381-6854.
ISSN 0720-9355.

limitations. Finally, we will discuss potential next steps toward the application of TF measurement in clinical laboratories.

Different Forms of Circulating TF

TF is a transmembrane protein composed of three domains: an extracellular domain of 219 amino acids that can bind to factor VII, a transmembrane domain of 23 amino acids, and a cytosolic domain of 21 amino acids that is involved in signal transduction.[29] Different forms of TF circulate in the blood, either as a component of blood cells and EVs or as a soluble plasma protein. Under physiological conditions, most of the TF associated with the cell or EV membrane is detectable in an encrypted nonactive form. This encryption is related to posttranslational suppression of TF procoagulant activity by the absence of a disulfide bond in the C-terminal region between unpaired cysteine residues 186 and 209, which changes the conformation of the TF to a nonfunctional form.[30] The TF procoagulant activity became detectable after decryption, which implied both the formation of a disulfide bond between unpaired cysteine residues by protein disulfide isomerase[31] and the exposure of anionic phospholipids on the membrane surface,[32] which involved an increase in the intracytoplasmic concentration of calcium in cells. This negatively charged phospholipid surface is required for maximum TF activity.[33]

TF is largely expressed in several organs, including the brain, lung, kidney, and placenta.[34] To ensure a hemostatic barrier in the case of vessel injury,[35] TF is constitutively expressed by cells covering vessels such as fibroblasts of the adventitia and vascular smooth muscle in the subendothelium. Moreover, monocytes and endothelial cells can express TF after stimulation by lipopolysaccharide[36] or by proinflammatory cytokines.[37] The presence of TF on neutrophils[38–41] and platelets[42–44] is controversial. Several studies have suggested that it could result from contamination or molecular exchange with monocytes.[45]

The initial concept of TF serving predominantly as a hemostatic envelope encapsulating the vascular bed has been challenged by the observation that the human plasma may form TF-induced thrombi, corroborating the notion of "blood-borne TF."[46] Indeed, in addition to the tissue- and cell-associated compartments, TF is also mainly detectable in two forms, one associated with EV and the other as a soluble form generated by alternative splicing (asTF) containing only the extracellular domain. This soluble form of TF is able to slowly bind to factor VIIa, but the amidolytic properties of the asTF–FVIIa complex are substantially reduced because of the absence of a plasma membrane with anionic phospholipids to facilitate the spatial accumulation of coagulation factors.[47] Indeed, endothelial cells can release asTF after stimulation with tumor necrosis factor-α and interleukin-6. This soluble form of TF becomes a procoagulant only in the presence of phospholipids.[48] Besides, EVs could be another source of "blood-borne TF." Several EV subsets, such as monocytes,[49] endothelial cells,[37,50] and tumor-derived EVs,[51] have been reported to carry functional TF.[52] In addition to the origin of cells triggering their formation, the composition of EVs can be modulated by stimuli that induce their biogenesis. Accordingly, the expression of TF on EVs increases due to factors such as proinflammatory cytokines[37] and individual habits such as smoking.[53] Conversely, the EVTF decreases by pharmacological intervention such as inhibitors of the protein convertase subtilisin/kexin type 9[54] and the direct oral anticoagulant apixaban.[55]

However, since the first demonstration of the blood-borne TF,[46] several controversies have been highlighted in the literature. First, an increase in EVTF activity was not consistently observed within the same pathophysiological context.[15,17] Second, the presence[56] or absence[57,58] of EVTF in healthy individuals has been an active matter of debate. However, it is increasingly accepted in the scientific community that circulating TF is present in low quantities in healthy individuals. Most of these discrepancies are probably due to methodological heterogeneity. Indeed, the preanalytical and analytical conditions largely differ among the numerous methods used to measure circulating TF.

Methods to Measure TF

Based on the different forms detectable in clinical samples, the following sections will review the main in-house and commercially available assays to measure TF detectable in whole blood (red section), in platelet-poor plasma (yellow section), or in EVs (blue section; ►Table 1). This article will discuss the main preanalytical and analytical parameters that impact the results and assay interpretation, highlighting their strengths and limitations. Within each section, methods have been divided into two categories: TF antigenic assays (A) and TF functional assays (F). For each assay, the principle of the assay, the preanalytical step, an estimation of the duration, and the commercialized or in-house version of the test are listed in ►Table 1. Given the multitude of assays that have been developed, only the most representative references were selected for each assay.

Whole Blood

More than 20 years ago, different functional assays have been developed to measure TF activity in whole blood. Among them, thromboelastography[59–61] measures clot formation around a thin wire probe used as a sensor. The system is commercialized by various manufacturers: for example, ROTEM (TEM International GmbH, Munich, Germany), TEG (Haemonetics, Boston, Massachusetts, United States), and Sonoclot (Sienco, Inc., Morrison, Colorado, United States). All these assays are Food Drug Administration (FDA) approved to assess hypercoagulable tendencies but not yet CE-IVDR (European In Vitro Diagnostic Medical Devices Regulation) labeled. Among several parameters deduced from the thrombus formation curve, the lag time has been shown to be correlated with the amount of TF present in the samples.[60] However, the absence of a TF-blocking antibody limits the specificity of these assays. Indeed, procoagulant activity can be either TF dependent or independent. Consequently, the use of a TF-blocking antibody enables the determination of the activity specifically dependent on TF, usually after

Table 1 Main methods used to measure TF

Method	Reference	Preanalytical step	Sample preparation duration (min)		Reagent incubation duration (min)	Sensitivity	Specificity	In-house or commercialized assay
Whole blood								
F	Thromboelastography	[59–61]	NA	NA	<30	Unknown	No aTF	ROTEM,[a,b] TEG,[a,b] Sonoclot[a,b]
	Clotting assay	[10]	NA	NA	<30	Unknown	aTF	In-house
	TiFaCT	[62]	NA	NA	20	70 fM	aTF	In-house
Platelet-poor plasma								
F	FXa generation	[64]	Centrifugation	30	45	2,000 fM	No aTF	ACTICHROME TF[c]
	FIIa generation	[65]	Centrifugation	20	<30	Unknown	No aTF	CT[c]
A	ELISA	[67]	Centrifugation	10	≈180	Imubind: 1,400 fM[§] Quantikine: 20 fM Hum SimpleStep: 103 fM	NA	IMUBIND TF,[c] Quantikine,[c] Human SimpleStep[c]
		[4,91]	Centrifugation	15	≈180	1,400 fM	NA	In-house
Extracellular vesicles								
F	FXa generation	[72]	Centrifugation	120	160	3 ± 1 fM	aTF	CY-QUANT MV-TF Activity[c]
		[4,92]	Centrifugation	90	105	12 ± 1 fM	aTF	In-house
		[93]	Centrifugation	60	105	Unknown	No aTF	In-house
		[94]	Immunocapture	Overnight	240	28 fM	aTF	ZYMUPHEN MP-TF ACTIVITY[c]
		[69]	Immunocapture	60	150	Unknown	aTF	In-house
	FIIa generation	[71]	Centrifugation	30	20	15 fM	HFVIIai	In-house
		[70]	Centrifugation	60	30	Unknown	aTF	In-house
		[95]	Centrifugation	30	NA	Unknown	No aTF	In-house
		[55]	Centrifugation	30	NA	Unknown	No aTF	In-house
	Fibrin generation	[96]	Centrifugation	30	30	Unknown	aTF	In-house
A	Single EV flow cytometry	[81,97]	Centrifugation	60	≈30–150	*	*	In-house
		[98]	NA	NA	≈30	*	*	In-house
	Beads-based flow cytometry	[76]	Immunocapture or centrifugation	NA	Overnight	*	*	MACSPlex EV[c]

Abbreviations: aTF, tissue factor–blocking antibody; HFVIIai: Human Factor VIIa Inactivated; NA, not applicable.
Notes: The column entitled "sensitivity" lists the limit of detection of each assay when this characteristic is known. This needs to be interpreted with caution in the absence of a universal TF or EV-TF standard.
When endpoint of the calibration curve was used to estimate the sensitivity of the assay, the symbol "§" was added.
When the multicenter study demonstrates a lower specificity and sensitivity of antigenic assays compared with functional assays, the symbol "*" was added.
[a]Food and Drug Administration (FDA) approval.
[b]European Conformity (CE) approval.
[c]Research use only.

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subtraction of the activity of the control condition obtained by performing the same assay with an isotype antibody. This is incorporated in the tissue factor clotting time (TiFaCT) assay which measures the time of whole blood clot formation after recalcification in the presence or absence of a TF-blocking antibody.[62] Similarly, another clot formation assay including a TF-blocking antibody recommends carrying out a freeze–thawing cycle during the preanalytical step, to lyse all cellular components and decrypt any TF in the cell membrane.[10] In summary, the main advantage of these whole blood methods is the almost complete absence of a preanalytical step, while it implies that the assays must be done quickly to avoid any artifactual activation of the cells without the possibility of storage. Moreover, the sensitivity of these assays can be limited because of the presence of TF inhibitors such as tissue factor pathway inhibitors (TFPIs). Indeed, TFPI is known to be one of the main physiological inhibitors of TF by forming a complex with TF, FVIIa, and FXa. The choice to have an assay not sensitive to TFPI and/or to increase the sensitivity by blocking TFPI is a matter of discussion. On one side, the use of an anti-TFPI antibody was shown to increase the TF activity[63] and therefore the sensitivity of the assay. On the other side when blocking TFPI, the assay will no more integrate the impact of the main TF physiological inhibitor.

Platelet-Poor Plasma

TF can also be measured in platelet-poor plasma (PPP). Several commercial and in-house assays including both antigenic and functional methods have been developed (►Table 1, yellow section). Regarding functional methods, ACTICHROME[64] (BioMedica Diagnostics, Windsor, Canada) is a commercial plasma TF activity assay in which FVIIa, FX, and a chromogenic substrate for FXa are added to the plasma. Importantly, no TF-blocking antibody was used to confirm the specificity of the assay. In addition, an automated thrombin generation assay has been developed called calibrated automated thrombinogram[65] which can be performed on a commercialized instrument like ST Genesia (Stago, Asnières-sur-Seine, France). This method assesses the dynamics of thrombin generation. According to a standard curve, thrombin generation is detected by the cleavage of a fluorogenic substrate in the sample, and the lag time can be used to monitor the levels of circulating TF in plasma.[60]

These assays can be performed quite rapidly ($<$ 1 hour). However, several concerns were raised regarding a limited sensitivity probably due to the presence of TF inhibitors such as TFPI in the plasma and a limited specificity especially when these assays are performed without TF-blocking antibodies and a high concentration of FVIIa.

Regarding antigenic tests, several commercial assays including Imubind (BioMedica Diagnostics), Quantikine (R&D Systems, Minneapolis, Minnesota, United States), and Human SimpleStep (Abcam, Cambridge, United Kingdom) or in-house enzyme-linked immunosorbent assays (ELISAs) have been developed to quantify the TF antigen in the PPP (►Table 1). They most commonly used an anti-TF monoclonal antibody as a capture antibody and either a monoclonal or polyclonal anti-TF antibody as a detection antibody, which should increase the specificity of the method. The choice of the antibody clone is a key point that directly impacts the specificity of the ELISAs. Indeed, one previous study attributes false-positive TF detection to the cross-reactivity of the antibody with non-TF proteins.[66] Moreover, another issue is that most ELISAs detect both active and nonactive forms of TF such as the asTF, which has little or no procoagulant activity. Consequently, a large variation of the plasma TF concentration has been reported in healthy subjects between in-house methods[66] and commercial ELISA,[67] with variations ranging from picomolar to nanomolar levels.

Overall, despite the ease of the preanalytical step to obtain PPP, plasma-based assays present limited analytical performances.

Moreover, it is important to note that all the previously commercialized assays are for research use only and do not yet have FDA approval or CE-IVDR labeling.

Extracellular Vesicles

Given that active circulating TF in plasma is primarily found on EVs,[68] various methods (functional and antigenic) have been developed to measure EVTF.

Regarding the functional assays, FXa, FIIa, and fibrin generation assays have been developed, as illustrated in ►Fig. 1. Briefly, EVs contained in a sample are purified by either high-speed centrifugation or immunocapture. Then, their specific procoagulant activity is measured by incubation with a reaction mixture that contains coagulation factors and calcium, with or without a TF-blocking antibody. Next, the reaction is blocked by a calcium chelator such as EDTA, and a specific fluorogenic or colorimetric substrate of FXa or FIIa is used to reveal the reaction. For fibrin generation assays, turbidimetry allows monitoring the clot formation. A large spectrum of assays has been published,[4,69–72] and the most representative are illustrated in ►Table 1. Among them, several differences in the protocol were observed regarding the preanalytical or analytical steps.

EV purification has been identified as one of the major sources of variability, and ultracentrifugation is the most likely cause of intra-assay variability. Previous studies have shown that ultracentrifugation can be influenced by the rotor type, centrifugation speed (*g* force), temperature, brake use, and centrifugation duration.[72] For example, one study indicated that increasing the centrifugation force from 20,000 *g* to 100,000 *g* does not result in an increase in EVTF activity in plasma issued from whole blood stimulated with LPS.[73] Conversely, another study recommended applying a centrifugation force of 100,000 *g*[74] after demonstrating that both large and small EVs exhibit TF-dependent procoagulant activity in a proportion that varies according to the pathophysiological context. Additionally, ultracentrifugation steps are time-consuming and not available in most laboratories. Therefore, providing access to an EV preparation strategy independent of ultracentrifugation is a major challenge for measuring EVTF activity in routine biological laboratories. Already, more than 20 years ago, a hybrid assay was developed combining the capture of EVs on a plate by a TF antibody that does not interfere with its activity and the measurement of FXa generation. This

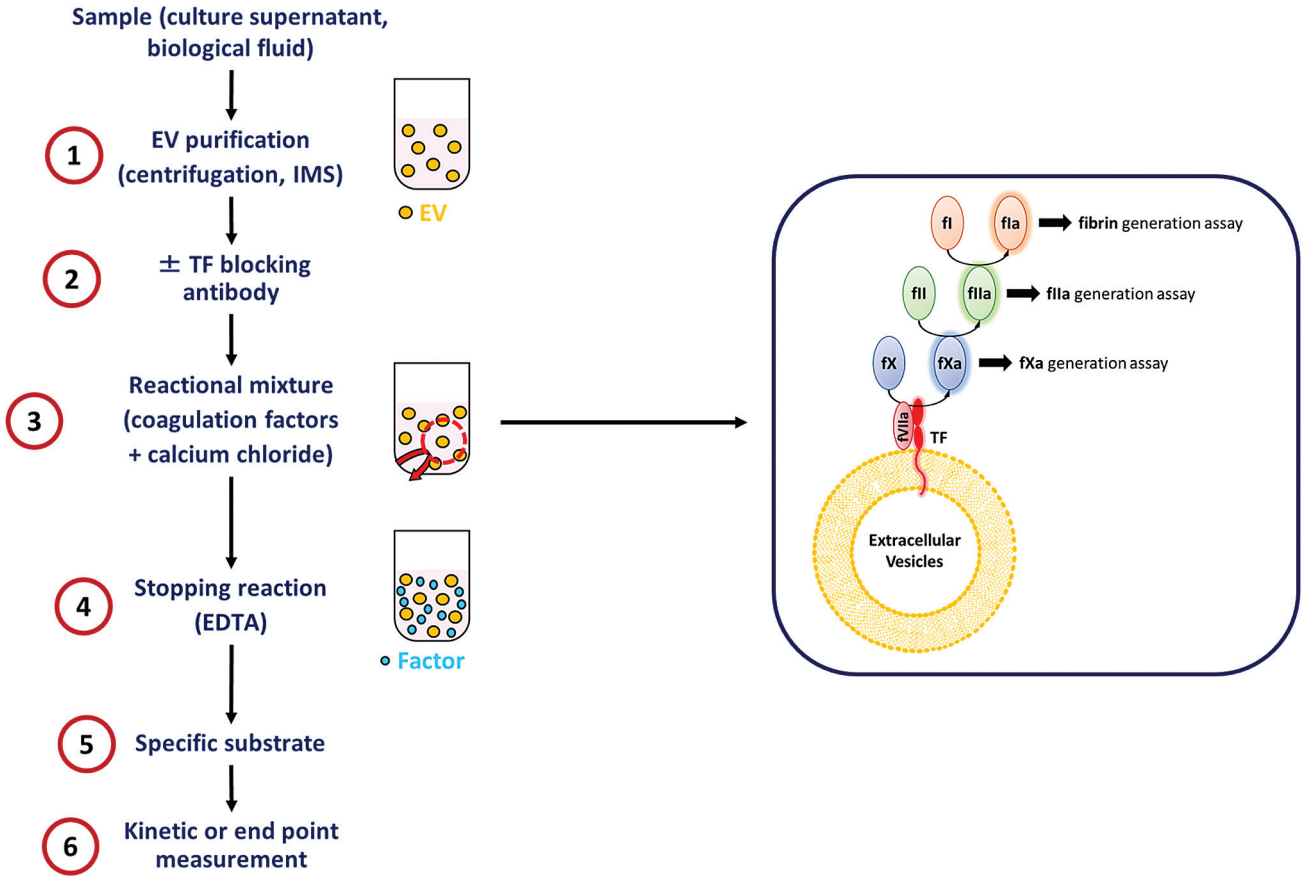

Fig. 1 Global method for measuring the TF-dependent procoagulant activity of EVs. a, activated; EDTA, ethylenediaminetetraacetic acid; EVs: extracellular vesicles; f, factor; TF, tissue factor.

test was commercialized as the Zymuphen MP-TF (Hyphen Biomed, Neuville-sur-Oise, France). The overnight incubation needed to capture EVs is a limitation of using this assay in clinical practice. More recently, an immunocapture strategy based on immunomagnetic separation using beads coated with CD29 and CD59 antibodies was proposed to enhance the repeatability of the assay.[69]

Other differences among EVTF functional assays rely on the concentration of the coagulation factors and the choice of the TF-blocking antibody which can be a source of variability. Indeed, in one study, the SBTF1 antibody displayed a better performance than the HTF1 antibody.[72] The SBTF1 antibody has been incorporated in the recent commercial assay as CY-QUANT MV-TF Activity (Stago). The assays also differ in their duration which is largely influenced by the EV preparation steps and the incubation time ranging from less than 1 hour to more than 4 hours. One recent study proposed shortening the assay duration by performing a single centrifugation of the plasma to obtain the EV pellet, without the need for additional washing steps.[71]

Regarding the antigenic assays, the most commonly employed method to detect TF on EVs is flow cytometry (FCM) by either single-EV FCM[75] or bead-based FCM.[76] Besides TF measurement, FCM remains the most commonly used method to enumerate EV subsets in patients. This technology is available in many research and clinical laboratories and theoretically has a high potential for EV analysis. FCM detection relies on the combination of a scatter light profile and the expression of specific antigens detected by fluorescence. The main advantage of this method is that single-particle analysis allows the detection of different EV subsets on a quantitative basis. Moreover, unlike functional tests, the FCM technique allows analysis without purification of the EVs, which saves a significant amount of time. Despite these strengths, the current flow cytometer lacks performances to reliably measure EVTF. This can be explained because a large proportion of EVs has a small size below the detection limit of the instrument and a low antigen density with only a few molecules of TF present on each EV. Alternatively, bead-based FCM assays were developed to capture EVs with tetraspanin antibodies (CD9, CD63, and CD81), which allow to catch small EVs and increase the fluorescence signal. This method is commercialized as MACSPlex EV Kit IO (Miltenyi Biotec, Bergisch Gladbach, Germany). However, an overnight incubation is needed to capture EVs which compromises the use of this technique in clinical laboratories. Another recent development to improve the performance of FCM to detect EVTF in plasma samples highlights the importance of the fluorochrome-to-protein ratio as a key parameter in addition to the antibody clone.[77]

As for the plasma assays, the commercialized EV-based assays are for research use only so far and do not yet have FDA approval or CE-IVDR labeling.

Besides FCM, other antigenic assays, such as Western blot,[76] superresolution,[78] or confocal[79] microscopy, are available, but they are labor intensive and not amenable to large-scale use in clinical studies.

Assay Comparison

First of all, to our knowledge, there are no studies that compare whole blood, plasma, and EVs methods to detect circulating TF simultaneously. Besides, there are only a few monocentric studies that compare the analytical performances of TF detection from PPP or EVs. One of them evaluates the performances of four commercial ELISAs in PPP compared with an FXa generation assay on EVs.[80] They conclude that ELISA methods are not able to detect TF in plasma obtained from LPS-stimulated whole blood compared with the functional assay performed on EVs, showing a poor sensitivity of the ELISAs methods. The other studies also show that functional assays performed on EVs have the best analytical performance in terms of specificity and sensitivity compared with antigenic assays such as commercial ELISA[23,73,80,81] and bead-based FCM.[82]

Additionally, several monocentric studies compare the performances of functional assays. Two studies compared an in-house FXa and a thrombin-generation assay to a commercial TF immunocapture assay and reported a lower specificity and sensitivity of the commercial assay.[83,84] Recently, a study compared the thrombin-generation assay published by Østerud et al[71] to the FXa-generation assay developed by the Mackman team. These two assays allow the measurement of EV-TF in a specific and reproducible manner.[85]

Recently, a multicentric study allowed for the first time to compare the analytical performances of 27 EVTF assays (18 functional and 9 FCM assays).[86] The aim of this study was to compare the specificity, the sensitivity, and the repeatability of the assays. The specificity was assessed by using EV-derived HAP-1 cell lines, wild type or knockout for TF. The sensitivity was evaluated using three different models of EVs: (1) two levels of EVs derived from wild-type HAP-1 cell, (2) PPP obtained from whole blood with or without LPS stimulation,[37] and (3) two levels of EVs derived from human milk.[87] The repeatability was estimated by the coefficient of variation since each type of sample was measured in triplicate. The results of this study demonstrate that the evaluated FCM methods have less specificity than most functional assays because they were not able to distinguish samples that contained EVs with or without TF expression. Regarding the comparison of the functional assays, the use of a TF-blocking antibody or specific immunocapture improved the specificity and sensitivity of the assays, regardless of the principle (FXa, FIIa, or fibrin generation assays), in agreement with the recommendations previously established by expert teams.[88] Moreover, it appears that the preanalytical method used to purify EVs affects the intra-assay reproducibility. Indeed, the assays that use immunocapture instead of classical centrifugation have a lower coefficient of variation. Finally, this recent study demonstrated that despite the use of a common recombinant TF as a calibrant, which should have prevented a significant impact of variables affecting the analytical step, considerable variation in TF activity measurement remains between the different functional assays. This encourages the continuation of the efforts to improve the standardization of these assays with the aim of transposing the measurement of EVTF in clinical practice.

Conclusion and Perspectives

As addressed in the previous section, each assay has advantages and limitations. In particular, serious concerns have been raised in terms of sensitivity, specificity, and reproducibility regarding the measurement of TF activity in whole blood and plasma to ensure robust and reproducible data between laboratories. These limitations may explain why EVTF measurement methods have been significantly developed over the past decade. Additionally, substantial evidence has accumulated in recent years demonstrating the correlation between EVTF levels and patient outcomes in various diseases.[20] However, there is currently no ideal assay.

Future directions for progress are based on different strategies that are not exclusive:

1. Better define the impact of preanalytical variables on data reproducibility and whether the measurement of TF is hampered by freeze–thawing deserves more attention. As a correlate, this variability can be overcome by developing a preanalytical step independent of centrifugation.
2. Standardize reagents and harmonize protocols that emerge from multicentric assays with the best analytical performance in terms of specificity and sensitivity.
3. Move toward an automated version of these assays.
4. Improve the FCM performance, in terms of sensitivity and calibration strategies, to adapt FCM analysis to reliable EVTF measurements.
5. Develop an international standard of TF adapted to EV, either for functional or antigenic assays.
6. Compare simultaneously several assays not only for their analytical performances but also their clinical performances.
7. Combine circulating TF with other biomarkers of coagulation, such as D-dimer, in scoring systems, as proposed, for example, to diagnose DIC in patients with solid cancer[23] and acute leukemia.[89]

The development of these assays aims ultimately to provide new tools for patient management. For this, several characteristics related to the assays must be evaluated, including analytical and clinical performances. Several studies have evaluated the analytical performance of the tests,[69,71,72] and a recent multicenter study allowed for the first time to compare them.[86] Additionally, the clinical performance of some of these tests has also been evaluated in various conditions[20] such as COVID-19[5,90] which show an association between the EVTF activity level and the occurrence of thrombosis. However, for hospital use, it is necessary to proceed with the evaluation of the performance of an industrial test. These data are required to compile a dossier for FDA approval and/or a CE-IVD label for a specific clinical application.

In conclusion, the measurement of TF-dependent procoagulant activity, especially from EVs, is a promising biomarker for predicting the occurrence of thrombosis and stratifying disease severity in different contexts, such as cancer and infectious diseases, to personalize anticoagulation treatment and improve patient care. However, efforts must be made to standardize and automate functional assays to measure EVTF in clinical practice.

Conflict of Interest

F.D.-G. and R.L. received grants from Stago.

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