An eBook on
Biomedical Sciences

Chapter 1

Viscoelastic Point-of-Care Tests for Diagnosis of Fibrinogen Deficiency and Guidance of Fibrinogen Administration in Bleeding Patients

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1. Introduction

Thrombelastography (TEG; Haemonetics Corporation, Haemoscope Division, Nile, Illinois, USA) and rotational thromboelastometry (ROTEM; Tem Innovations GmbH, Munich, Germany succeeded by Instrumentation Laboratory, Bedford, Massachusetts, USA) are two point-of-care systems for hemostatic tests in whole blood [1,2]. Both provide a global measure of hemostasis by quantitatively measuring the elasticity of blood from the beginning of coagulation to the ending with fibrinolysis. This includes the onset of clot formation, its progress, maximum clot strength, and clot stability, which provides important information about coagulation, fibrinolysis, and platelet function [3]. TEG and ROTEM can also identify the relative contributions of clotting factors, such as fibrinogen and platelets, to the overall coagulation process [1].

Moreover, TEG and ROTEM measures two aspects of patient coagulation: the prothrombotic (hypercoagulability) [4] and the hemorrhagic state (hypocoagulability). Both aspects of hemostasis play an essential role in bleeding patients e.g., trauma patients [5]. In addition, TEG and ROTEM can provide rapid and accurate detection of systemic fibrinolysis and prediction for mortality in trauma [6-9]. In contrast, standard laboratory tests (SLT, e.g., prothrombin time (PT), activated Partial Thromboplastin Time (PTT), thrombin clotting time (TCT), and Clauss fibrinogen assay) are mainly concerned with isolated components of the

coagulation and fibrinolysis system, such as thrombus formation and platelet function, and thus cannot show overall effects and take into account the interactions of the clotting cascade and platelets in whole blood. For example, PT and TCT focus only on the initiation of the coagulation cascade [10]. Because platelets are critical to both amplification and propagation of the thrombin signal, assays performed in the absence of platelets would appear to completely miss these events. It is, therefore, difficult to relate isolated findings from such tests to the overall effects in whole blood systems, as occurs in clinical settings. This may explain the inability of the PT and PTT to detect coagulation abnormalities and transfusion requirements in surgical and severely injured patients [11-13] and the clinical effects of therapeutic agents, such as recombinant Factor VIIa in hemophilia population [14].

Alternatively, specific evaluation of a particular coagulation process can also be illustrated by modified TEG and ROTEM methods using partial blood components, e.g., plasma or coagulation factor-deficient blood [3,15]. Moreover, TEG and ROTEM would provide faster testing results than the SLT as early TEG and ROTEM parameters are available within 10-20 min [16], compared to the turnaround time for laboratory PT results with a median of 78 [62–103] min [17] and the turnaround time of approximately 40 min for the Clauss fibrinogen assay [18].

A retrospective study has concluded that TEG can replace SLTs, e.g., PT/International Normalized Ratio [INR] for predicting transfusion requirements in trauma [19]. A recent meta-analysis has found that TEG- or ROTEM-guided coagulation management is superior to that based on the current standard of care as evidenced by decreased risk of allogeneic blood product exposure, lower re-exploration rate, decreased incidence of postoperative acute kidney injury and thromboembolic events in cardiac surgery patients [20]. Compared to the SLTs (INR, PTT, fibrinogen, platelet count, D-dimer), TEG was better to identify coagulopathy prevalence in traumatic brain injury in a retrospective study [21] and predict functional outcomes (degree of disability on hospital discharge) after moderate-to-severe subarachnoid hemorrhage in a prospective observational study [22]. Furthermore, a randomized controlled trial (RCT) has concluded that TEG-guided massive transfusion protocol for severe trauma improved survival compared with that guided by SLTs (i.e., PT/INR, fibrinogen and D-dimer) and utilized less plasma and platelet transfusion during the early phase of resuscitation [23]. A similar RCT has shown that ROTEM-directed hemostatic therapy reduced patient exposure to allogenic blood products and provided significant benefits with respect to clinical outcomes in comparison with SLTs [24]. ROTEM was validated against SLTs for detection of acute traumatic coagulopathy and massive transfusion requirements [25]. When compared to laboratory prothrombin time ratio, ROTEM clot amplitude at 5 min could identify acute traumatic coagulopathy and predict the need for massive transfusion faster and more accurately [17].

As a results, TEG and ROTEM have been applied to assess blood coagulation and

fibrinolysis, diagnose coagulopathy, predict massive transfusion [26] and mortality [27], and guide hemostatic resuscitation in the emergency and perioperative settings [28-33].

In addition to clinical utilization, TEG and ROTEM have found applications in the studies on the hemostatic effects of biomedical materials and devices [34], physiological and psychological stress [35], pharmacological agents [36], vasoactive agents [37], coagulation factors [38,39] and resuscitation fluids [40].

Fibrinogen is perhaps the most important protein in hemostasis, as the final stage of the coagulation cascade, being converted to fibrin by thrombin and crosslinked by factor XIII [41]. It also induces platelet activation and aggregation via binding to glycoprotein GPIIb/IIIa receptors on the surface of platelets, acting as the bridge for stable clot formation. During major bleeding, fibrinogen is the first clotting factor to reach critically low levels below the normal physiological level of around 2 to 4 g/L, earlier than those of other routine coagulation parameters and before patients meet the criteria for massive blood transfusion [3]. Low fibrinogen levels are associated with increased bleeding, coagulopathy, and in turn worsened clinical outcomes [42-45]. Fibrinogen level is an independent predictor of mortality in major trauma patients [46] and the requriemment for massive transfusion in patients with pelvic fractures [47].

There is increasing evidence for clinical benefits of fibrinogen replacement through intravenous injection of Fibrinogen Concentrate (FC) reconstituted in sterile water or transfusion of cryoprecipitate in trauma [48] and perioperative patients with severe bleeding, especially in cardiac surgery [49]. Several retrospective studies and case series have reported improved outcomes using FC in trauma [48,50]. For example, Wafaisade et al. reported improved survival at 6 h after hospital admission, but not at discharge in exsanguinating trauma patients who received FC between hospital arrival and intensive care unit admission compared to matched patients who had not received FC [51]. On the other hand, questions about its efficacy and safety for bleeding patients have been raised [52,53]. There were some debates about its clinical benefits [54,55] and its use as a universal hemostatic agent [56]. RCTs have been reported in cardiac surgery that showed reduced bleeding and transfusions [57], however this is conflicting with a more recent multicentre RCT, suggesting that more allogeneic blood products were given to the patients who received a single dose of FC at the end of their cardiopulmonary bypass than those who received placebo [58]. In addition, randomized, placebo-controlled trials failed to show any impact of pre-emptive administration of FC on transfusion requirements in liver transplantation [59], and patients with severe postpartum hemorrhage [60], but was safe and effective in reducing blood loss after adjusting operation time in total hip arthroplasty [61]. Recently, there are a few RCTs of fibrinogen as a pre-emptive first-line treatment for trauma hemorrhage in pre-hospital [62] and early hospital settings [63,64]. As these studies were focused on the feasibility and safety with a

small number of patients they may not show any clinical benefits.

A review of 21 major RCTs assessing FC use in perioperative settings found that approximately 60% of the studies in which FC was used to treat clinically relevant bleeding showed decreased bleeding tendency and decreased transfusion requirements versus comparative treatment [65]. In contrast, a systematic review and meta-analysis of the use of FC for trauma-related bleeding found no statistically significant difference in mortality between the groups, with 22% and 23.4% in the FC and comparator arms, respectively: Risk Ratio 1.00 [95% Confidence Interval (CI) 0.39 to 2.56], p=0.99. Additionally, there was no statistical difference between FC and control in transfusion requirements and thromboembolic events [66].

Further prospective studies of fibrinogen replacement in acquired bleeding are needed to accurately assess the range of clinical settings in which this management strategy is appropriate, the most effective method of replacement and a comprehensive safety profile of FC used for such an approach [41].

Both TEG and ROTEM have been increasingly used as a diagnostic and treatment tool in various clinical settings involving bleeding patients to diagnose fibrinogen deficiency [67], predict risk of bleeding and mortality, and guide fibrinogen transfusion in trauma 68], cardiac surgery [69], liver transplantation [70] and postpartum bleeding [71]. They have also been used to study *in vitro* effects of different sources of fibrinogen supplementation on coagulation and fibrinolysis in an model of dilutional coagulopathy [72] and hypothermic coagulopathy [73] as well as in patient blood [74].

TEG- and ROTEM-based algorithms have been widely used to direct fibrinogen administration in different settings (trauma surgery, visceral and transplant surgery, cardiovascular surgery and general and surgical intensive care medicine), leading to reduction in transfusion needs, costs, adverse outcomes and even mortality [31,75-79]. However, a recent review indicated that the benefit of reduced blood products (red blood cells, fresh frozen plasma and platelet) and improved morbidity in patients with bleeding from the application of TEG- or ROTEM-guided transfusion strategies were primarily based on trials of elective cardiac surgery involving cardiopulmonary bypass, with low-quality evidence [80].

Retrospective observational studies showed that incorporation of TEG functional fibriongen (FF) into TEG-based administration of FC reduced the need for transfusion in patients undergoing liver transplantation, but had no impact on survival [81], and ROTEM FIBTEM-guided administration of FC represented a rapid and feasible method of fibrinogen replacement in severe traumatic haemorrhage [82].

On the other hand, studies have shown that TEG and ROTEM provided different results

for diagnosing coagulopathy and guiding transfusion [29]. For example, different transfusion algorithms have been developed for each system [83]. ROTEM-guided transfusion tended to recommend FC [84] or cryoprecipitate [85] while TEG-based algorithms appeared to recommend plasma [86], but both recommendations have resulted in decreased blood transfusion compared to standard laboratory measures of blood coagulation. The difference may be more due to the assays as opposed to the instrument *per se,* because most ROTEM-guided transfusion involved FIBTEM which is a specific assay for fibrinogen level and function [78]. In contrast, TEG FF assay was less recognized and included for TEG-guided blood product transfusions [87] and FC administration [76,88].

The existing guidelines suggest applying viscoelastic fibrinogen tests (TEG FF, ROTEM FIBTEM) for a fast determination of (functional) fibrinogen levels [89]. Furthermore, Society of Cardiovascular Anesthesiologists suggests fibrinogen supplementation in cardiac surgery patients at cut-off values of TEG FF MA<8 mm and ROTEM FIBTEM A10<10 mm [90]. Alternatively, cut-off values of kaolin TEG K> 2.4 min, angle<60.6° and MA<51.2 mm for diagnosis of hypofibrinogenemia [91].

This review is focused on clinical studies on the use of TEG and ROTEM in particular the FF tests: TEG FF and ROTEM FIBTEM for the diagnosis of fibrinogen deficiency, the prediction of transfusion requirements, and the guidance for fibrinogen replacement in bleeding patients. The two systems are also compared.

The chapter is structured into five major sections. The first section describes the principles of the two systems and various commercially available tests in terms of reagents, parameter values and clinical performance with an emphasis on the FF tests. The second section reviews the use of TEG and ROTEM for the measurement of fibrinogen levels in relation to fibrinogen concentration assays and the hemostatic effect of fibrinogen replacement. The third section discusses the diagnosis of fibrinogen related coagulopathy and prediction of transfusion requirements in different clinical settings. The fourth section summarizes TEG- and ROTEM-guided fibrinogen replacement in different clinical settings. The last section is devoted to the discussion of their similarities and differences of the two systems for fibrinogen detection and transfusion.

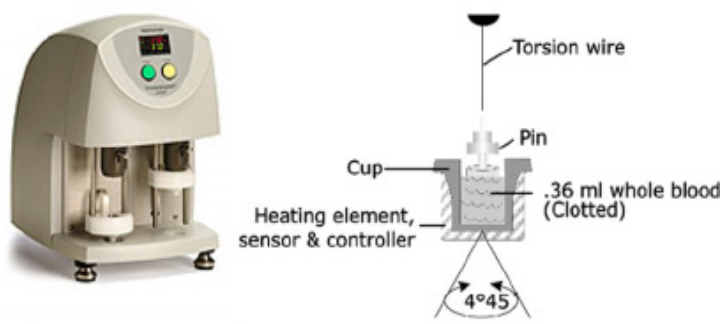
2. Principles of TEG And ROTEM Functional Fibrinogen Tests

Figure 1(a) shows the TEG 5000 hemostasis analyzer (Haemonetics Corporation, Haemoscope Division, Niles, IL, USA) and schematic principals of TEG 2-channel measurement of the viscoelastic properties of blood as it clots under low shear stress. For each channel, a pin suspended by a torsion wire is immersed in 360-μL whole blood or plasma in a plastic cup made of acrylic polymer with a smooth interior surface. The cup transversely oscillates back and forth through an arc of 4.75° every 5 sec while the pin is deflected by the torque pressure of the

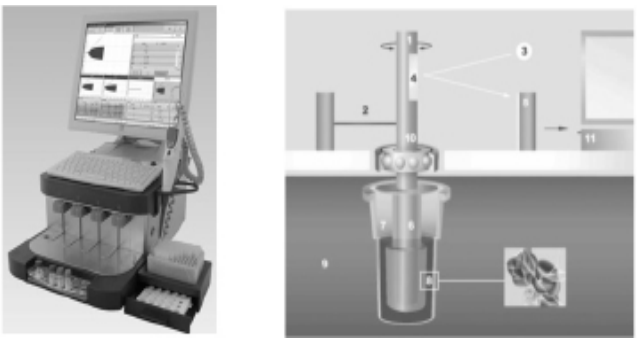
viscoelastic properties of blood during modifications of fibrin strands and platelet aggregates as coagulation proceeds. Torque pressure is transmitted to the torsion wire, which is converted by a mechanical-electrical transducer to an electrical signal, monitored by computer [92].
Figure 1(b) shows the ROTEM delta system (Tem Innovations GmbH, Munich, Germany succeeded by Instrumentation Laboratory, Bedford, MA, USA) and schematic principals of ROTEM 4-channel measurement of the viscoelastic properties of blood as it clots under low shear stress. For each channel, a pin suspended on a ball bearing mechanism transversely oscillates back and forth through 4.75° every 6 sec with a constant force in a fixed cup made of polymethylmethacrylate with a ridged interior surface into which 300-µL whole blood and 40-µL reagents are electronically pipetted and mixed. As the blood clots the impedance to pin rotation is transmitted via an optical detector system, and recorded by computer [85].

The measurement of both instruments is graphically represented as a characteristic shape profile over time **(Figure 1(c))**, from which the following parameters can be derived for TEG: 1) reaction time R, which is related to plasma clotting factors and circulating inhibitory activity; 2) coagulation time K, which is associated with the activity of the clotting factors, fibrinogen and platelets; 3) rate of clot polymerization, α angle, which is a main function of platelets, fibrinogen and plasma components residing on the platelet surface; 4) maximum amplitude or maximum clot strength, MA, which is a direct function of the maximum dynamic properties of fibrin and platelet number and functions; and 5) fibrinolysis at 30 min or the rate of amplitude reduction 30 min after MA, LY30/CL30, which is related to plasma levels and activities of tissue plasminogen activator. For rapid TEG where both intrinsic and extrinsic activators are used, activated clotting time (ACT) is calculated through a transformation of the R value by the TEG software and may provide a better measure of initial clot formation than R [93]. For the TEG FF, MA can be transformed in the analytical software into FLEV, which is functional fibrinogen level in mg/dL or g/L [94, 95]. Similar parameters to TEG as shown in **Figure 1(c)** [e.g., coagulation time (CT), clot formation time (CFT), α angle, maximum clot firmness (MCF), clot lysis index LI30] can be derived from ROTEM which are commonly used in Europe [96]. In addition, the clot firmness at 5 and 10 min after CT (A5 and A10) have been well reported. **Table 1** further describes the key TEG and ROTEM parameters and their associated impact factors.

(a)



(b)



1. Oscillating axis (~ 4.75 °)
2. Spring
3. Light source
4. Reflector
5. Detector (electric camera)
6. Sensor pin
7. Cup filled with blood
8. Fibrin thread and thrombocyte aggregate
9. Heated cup holder
10. Ball bearings
11. Data processing

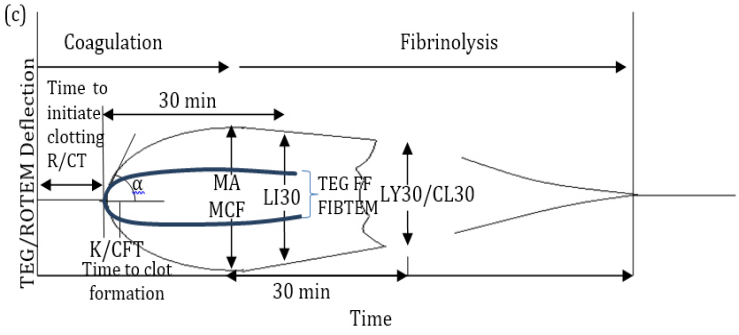


Figure 1: Schematic illustration of a) TEG mechanism and machine, b) ROTEM mechanism and machine, and c) a representative TEG/ROTEM tracing showing the relationship between the qualitative tracing and the quantitative parameters. R, K, α, MA, LY30/CL30 are TEG parameters and represent reaction time, kinetic time, angle, maximum amplitude, lysis (reduced clot strength) 30 min after MA, respectively. CT, CFT, α, MCF, LI30 are ROTEM parameters and represent coagulation time, clot formation time, angle, maximum clot firmness and lysis index (residual clot firmness) at 30 min after CT, respectively. Courtesy of Haemonetics Corporation and TEM Systems, Inc. for the use of **Figure 1(a) and (b).**

All the TEG and ROTEM parameters are derived in the same way for each assay, except the one for fibrinolysis. The TEG system provides LY30 and CL30. LY30 is computed as the percentage reduction of the area under a TEG tracing from the time MA is measured until 30 min after the MA. CL30 represents the value of the amplitude of a TEG tracing at 30 min after the MA relative to MA. The ROTEM system provides LI30 as a measure of fibrinolysis. It is

calculated as the ratio between clot firmness (in mm amplitude) at CT+30 min and maximum clot firmness (MCF). There are no same fibrinolytic parameters between TEG and ROTEM. CL30 is a fibrinolytic parameter in TEG most similar to LI30 in ROTEM.

Table 1: Summary of the key parameters measured by TEG and ROTEM and their associated impact factors [1, 34, 35, 97-99].

TEG	ROTEM	Definition	Impact factors
Reaction time R	Coagulation time CT	Time from test start to an amplitude of 2 mm	Plasma clotting factors and circulating anticoagulants
Kinetics time K	Clot formation time CFT	Time from R/CT to an amplitude of 20 mm	Activities of the intrinsic clotting factors, fibrinogen, platelets and anticoagulants
The rate of clot development Alpha	α-Angle	Slope between R/CT and K/CFT	Main functions of fibrinogen, platelets and plasma components
Maximum amplitude MA	Maximum clot firmness MCF	Maximum amplitude reached during test	Direct function of the maximum dynamic properties of fibrin and platelet number and function
Fibrinolysis at 30 min LY30 after MA	Fibrinolysis at 30 min after CT	The rate of amplitude reduction at a given time	Plasma levels of tissue plasminogen activator

In addition to the differences in instrument, the two viscoelastic point-of-care systems use different reagents and procedures as summarized in **Table 2**. Specifically, the FF reagent for TEG is composed of lyophilized tissue factor and a platelet inhibitor (abciximab) that binds to glycoprotein-IIb/IIIa receptors to inhibit platelet aggregation and exclude the platelet contribution to clot strength [100]. However, it could contain kaolin instead of tissue factor [101]. To perform TEG FF assay, 0.5 mL of citrated or native blood was activated with a mixture of tissue factor and a monoclonal glycoprotein IIb/IIIa receptor antagonist and then 340 µL of the activated blood was added to a TEG cup preloaded with 20 µL 0.2 M $CaCl_2$ [101].

ROTEM FF assay (FIBTEM) was performed by directly mixing 20 µL ex-tem, 20 µL fib-tem and 300 µL citrated blood in a ROTEM cup [100]. The ex-tem solution contains a combination of recombinant tissue factor and phospholipids that activates the extrinsic pathway of the coagulation system, while the fib-tem solution contains $CaCl_2$ as a recalcification reagent and a platelet inhibitor (cytochalasin D) that inhibits actin/myosin-system.

A new reagent called fib-TEM plus contains 2 platelet inhibitors, cytochalasin D which inhibits platelet cytoskeletal reorganization, and tirofiban, a glycoprotein IIb/IIIa inhibitor similar to abciximab which prevents fibrin(ogen) from binding to glycoprotein IIb/IIIa receptors on the surface of platelets and platelet aggregation [102]. A recent study showed that the addition of a synthetic IIb/IIIa receptor antagonist alone or in combination with acetylsalicylic acid could reduce platelet aggregation and its contribution to clot strength in both EXTEM and FIBTEM tests [103]. Furthermore, single portion reagents composed of all lyophilized reagents required for each ROTEM test have been developed [43].

In contrast with TEG Platelet Mapping test, ROTEM does not provide a specific test for platelets. Instead, it can be connected to ROTEM platelet to measure platelet aggregation in whole blood samples for platelet function analysis [104]. On the other hand, unlike ROTEM AP-TEM, there is no commercially available TEG test specifically for fibrinolysis. Standard TEG tests (rapid TEG, kaolin TEG and TEG FF) have been used to detect tissue plasminogen activator-induced fibrinolysis in whole blood [105].

Table 2: Summary of activators and inhibitors and corresponding tests from TEG and ROTEM manufacturers [1, 33, 93,106]

Type of reagents	TEG			ROTEM		
	Constituents	**Tests**	**Applications**	**Constituents**	**Tests**	**Applications**
Calibration reagents	Lyophilized animal citrated plasma with stabilizers and buffers	Level 1 for normal and level 2 for abnormal control	Quality control	Lyophilized human citrated plasma with stabilizers and buffers	ROTROL N for normal control and ROTROL P for abnormal control	Quality control
Re-calcification	0.2 M calcium chloride queous solution	Native TEG	Not well used given long runtime and high variability	star-tem: 0.2 M calcium chloride and 0.1% sodium azide in pH 7.4 buffer	NATEM	Not well used given long runtime and high variability
Surface activator	Kaolin suspension in buffered stabilizers and a blend of phospholipids	Kaolin TEG	Information similar to that of aPTT; thrombin generation as indicated by R	in-tem: Ellagic acid and partial thromboplastin phospholipid and preservatives in buffer	INTEM	Information similar to that of aPTT for intrinsic coagulation pathway; thrombin generation as indicated by CT
Extrinsic activator	Consisting of 8% kaolin, human recombinant tissue factor, phospholipids, buffers and stabilizers	Rapid TEG	Both intrinsic and extrinsic pathway activated to more rapidly assess coagulation properties	ex-tem: a combination of recombinant tissue factor and phospholipids	EXTEM	Information similar to that of the PT for extrinsic coagulation pathway, indication for FFP/PCC administration
Platelet inhibitor	Lyophilized tissue factor and abciximab	TEG FF	Used in conjunction with kaolin TEG can assess relative contribution of platelets and fibrin to overall clot strength	fib-tem: a combination of platelet inhibitor (cytochalasin D) and ex-tem	FIBTEM	Measurement of fibrinogen and platelet contribution (in conjunction with EXTEM) to clot strength, indication for cryoprecipitate or fibrinogen and platelets administration

Heparin inhibitor	Lyophilized heparinase I from flavobactrium heparinum of 2 international units in a TEG cup enough to reverse 6 IU of heparin/ml of blood	HTEG	Compared to kaolin TEG to assess heparin effects	hep-tem: lyophilized heprinase I from flavobacteria, preservatives and buffer and calcium-containing diluent nd start reagent with sodium azide (<0.1%) and preservatives and in-TEM	HEPTEM	Assessment of heparin effect in conjunction with INTEM
Platelet activator	Arachidonic acid (AA) Adenosine 5'-diphosphate (ADP)	Platelet Mapping TEG	Access coagulopathy, plate dysfunction, hyperfibrinolysis and suggest interventions	Adenosine 5'-diphosphate (ADP) or thrombin receptor – activating peptide 6, buffers and stabilizers with ROTEM platelet odule	ADPTEM TRAPTEM	Assessment of platelet function by activating either the ADP or thrombin receptor pathways
Fibrinolysis inhibitor	Not available			ap-tem: Aprotinin, 0.2 M calcium chloride and 0.1% sodium azide in pH 7.4 buffer and ex-tem	APTEM	Assessment of fibrinolysis in conjunction with EXTEM, indication for tranexamic acid administration

APTT: Activated Partial Thromboplastin Time; PT: Prothrombin Time; FFP: Fresh Frozen Plasma; PCC: Prothrombin Complex Concentrate.

Table 3 summarizes the normal and trigger values of commonly employed TEG and ROTEM parameters for hemostatic therapy in bleeding patients [9,23,31,107-109]. Although multiple parameters can be measured for blood coagulation and fibrinolysis, maximum clot strength as indicated by MA in TEG and MCF in ROTEM has been mostly used as a direct measure of fibrinogen levels. According to each manufacturer, the normal range of MA as measured by TEG FF assay using citrated blood is 11-24 mm (Guide to functional fibrinogen). The normal range of MCF as measured by ROTEM FIBTEM assay is 7-24 mm (Instructions for use of fib-tem). Alternatively, different reference ranges have been reported in the literature: 14-27 mm TEG FF MA [107] and 9-25 mm for ROTEM FIBTEM MCF [96]. It should be noted that the discrepancy can be ascribed to the differences in both instrument itself and activation reagents used to perform the assays, leading to the differences between TEG FF and ROTEM FIBTEM for guided fibrinogen replacement and assessment of its hemostatic effect.

It should be noted that new and fully automated (no pipetting) TEG and ROTEM systems (TEG 6s and ROTEM Sigma) are now commercially available. Both work with 4-channel cartridges based on different mechanisms. TEG 6s uses a new technology called coagulation resonance analysis and works with two types of cartridges. One is a global hemostasis cartridge to perform four tests (kaolin TEG, kaolin TEG with heparinase, RapidTEG and TEG FF) simultaneously and the other is a PlateletMapping cartridge to perform the TEG PlateMapping test (kaolin TEG, Activator F (ActF), Adenosine Diphosphate (ADP), and arachidonic acid (AA) [110,111]. ROTEM sigma operates on the proven pin and cup technology as ROTEM delta, but uses two types of cartridges containing lyophilized beads reagents instead of liquid reagents for four tests per cartridge (cartridge 1: FIBTEM, EXTEM, INTEM, APTEM; cartridge 2: FIBTEM, EXTEM, INTEM, HEPTEM) [104].

Studies have demonstrated the high reliability of TEG 6s, the results derived from which have a close correlation to those derived from TEG 5000 (linear correlation estimates > 0.9) [67]. The high precision of ROTEM sigma has also been demonstrated, with the results derived from it being strongly correlated with those derived from ROTEM delta (Pearson correlation coefficients ≥ 0.8) [68]. However, some of the absolute values and reference ranges for TEG 6s and ROTEM sigma can be significantly different. Furthermore, when compared for their use in trauma patients, strong to very strong correlations (Spearman correlation coefficients > 0.6) were observed between corresponding TEG 6s and ROTEM sigma parameters, albeit there were significant differences in absolute values for most measurements [69].

Furthermore, other viscoelastic hemostatic testing systems are available and emerging [112]. Sonoclot is a legacy device developed by Sienco. The Sonoclot device differs from TEG and ROTEM in that it is not a rotational-based system, but a linear motion system [2] Quantra hemostasis analyzer is a relatively new product developed by HemoSonics based on a proprietary technology that uses ultrasound to measure clot time and clot stiffness from changes in viscoelastic properties of whole blood during coagulation [113]. Multicenter evaluation of the Quantra system in adult patients undergoing major surgical procedures consisting primarily of cardiac and major orthopedic surgeries was conducted, showing that the correlation between ROTEM and Quantra was very strong with correlation coefficients ranging between 0.84 and 0.89 [114]. Additional receiver operating characteristics analysis indicated sensitivities and specificities in the 80%–90% range when Quantra parameters were used to discriminate ROTEM threshold values currently used in goal-directed treatment algorithms. Several emerging technologies are currently in development for point-of-care viscoelastic hemostatic testing, including microfluidics, fluorescent microscopy, electrochemical sensing, photoacoustic detection, and micro/nano electromechanical systems (MEMS/NEMS) [115].

Table 3: Normal and trigger values of commonly employed TEG and ROTEM parameters for diagnosis of coagulopathy and guidance of hemostatic therapy in bleeding patients [31,107]

TEG	Reference ranges*	Patient values	ROTEM	References ranges*	Patient values	Coagulopathy	Therapy
Kaolin TEG R	300-600 sec	≥600 sec	INTEM CT	122-208 sec	>200 sec	Coagulation factors deficiency	Fresh frozen plasma (FFP)
Kaolin TEG Alpha	53-72°	<52°	INTEM Alpha	70-81°	N/A	Fibrinogen deficiency	FFP, Cryoprecipitate or fibrinogen concentrate
Kaolin TEG MA	50-70 mm	<45 mm	INTEM MCF	51-72 mm	N/A	Platelets deficiency if TEG FF MA normal	Platelets
Kaolin TEG LY30	-2.3-5.77% [108]	>4%	INTEM ML	0-12% [96]	>15%	Hyperfibrinolysis	Tranexamic acid
Rapid TEG ACT	86-118 sec	>140 [23]	N/A	N/A	N/A	Coagulation factors and platelets deficiency	FFP, Cryoprecipitate and platelets
Rapid TEG R	22-44 sec	>66 sec	EXTEM CT	43-82 sec	>80 sec	Coagulation factors deficiency	FFP
Rapid TEG K	30-118 sec	>150 sec	EXTEM CFT	48-127 sec	N/A	Fibrinogen deficiency	FFP, Cryoprecipitate or fibrinogen concentrate
Rapid TEG Angle	66-82°	<56°	EXTEM Angle	65-80°	N/A	Fibrinogen deficiency	FFP, Cryoprecipitate or fibrinogen concentrate
Rapid TEG MA	52-71 mm	<55 mm	EXTEM MCF	52-70 mm	<50 mm	Platelets deficiency if TEG FF MA of FIBTEM normal	Platelets
Rapid TEG LY30	0.0-7.5% [109]	>7.5% [109]	EXTEM ML	0-18% [96]	>15% [9]	Hyperfibrinolysis	Tranexamic acid
			EXTEM LI30	95-100% [96]	<94% [31]		
TEG FF MA	11-24 mm	<14 mm	FIBTEM MCF	7-24 mm	<9 mm	Fibrinogen deficiency	Cryoprecipitate or fibrinogen concentrate
Kaolin/heparinase TEG R	300-600 sec	Delta^{+}>180 sec	HEPTEM CT	122-208 sec	Ratio^{+}>1.25	Heparinization	Protamine or FFP

*Unless specified, the reference ranges are according to the manufacturers of TEG and ROTEM for citrated and recalcified blood samples. $^{+}$Difference in R between kaolin/heparinase TEG and kaolin TEG, and ratio between INTEM CT and HEPTEM CT.

3. Evaluation of Functional Fibrinogen Levels and Hemostatic Effects of Fibrinogen Replacement

Clinical studies showed variable correlations between maximum clot strength/firmness and fibrinogen levels as summarized in **Table 4.** The correlation coefficients range from 0 (no significant correlation) [95] to 0.9 (strong correlation) [116] for TEG FF and 0.27 [43] to

0.94 [117] for ROTEM FIBTEM. The correlations between A5, A10 or A15 and fibrinogen levels have also been reported [118-124]. These early values of clot firmness can provide fast and reliable prediction of MCF to guide haemostatic therapy in severe bleeding [16]. Other ROTEM tests (e.g., EXTEM) showed certain degrees of correlations with plasma fibrinogen concentrations as well [125,126]. Both TEG FF and ROTEM FITBEM have been used in clinical settings of trauma [101,118,127-129], cardiac surgery [94,95,130-132], liver transplantation [116,133] and pregnancy [124,134] with different popularities. In addition, ROTEM FIBTEM has been used for assessment of fibrinogen function in neurosurgery [135], burn injury [136] and cirrhosis [137]. The variations in the correlations could be due to the differences in study population and range of fibrinogen concentrations as most TEG and ROTEM tests were performed using TEG 5000 and ROTEM delta with the same reagents and procedures as recommended by their manufacturers. For example, one study reported no significant correlations between either TEG FF level (FLEV) or MA and Clauss fibrinogen level at baseline or 10 min post protamine in cardiac surgery patients [95]. The different correlations were also reported for children at different ages [138,139].

Figure 2(a) shows the correlation between plasma fibrinogen concentration measured by the Clauss method and TEG FF MA based on the data extracted from several studies [116, 127, 134, 140]. Overall correlation from pooled literature data was strong. Similarly, **Figure 2(b)** shows an overall strong correlation between the Clauss fibrinogen and FIBTEM MCF from pooled data extracted from literature [102,127,132,140,141].

The Clauss assay is considered a standard functional test for fibrinogen concentration by determination of the time in sec to clot formation following addition of excess thrombin [142]. Other methods such as prothrombin time-derived method [141] and Enzyme-Linked Immunosorbent Assay (ELISA) [142] are also used. ELISA does not discriminate between functional and non-functional immunoreactive fibrinogen protein, and even some degraded forms of fibrinogen [143].

The Clauss method is limited to only small concentrations of heparin (which inactivates thrombin through anti-thrombin III), which is a serious limitation in cardiac surgery. It may be affected by fibrin degradation products, polymerization inhibitors as other inhibitors of fibrin formation [144]. Its turnaround time is approximately 40 min [18]. In comparison, TEG and ROTEM FF assays can be completed in 15 min and can provide rapid and accurate detection of hyperfibrinolysis [145]. Another advantage of TEG and ROTEM is that they can be used for fully heparinized patients, e.g. when on cardiopulmonary bypass, with the use of a heparinase TEG cup or heparinase. *In vitro* studies showed that TEG FF MA was unaffected by heparin levels up to 2.8 IU/mL, but was reduced at 5.6 IU/mL of heparin in blood even performed in heparinase TEG cups [100], while ROTEM FIBTEM MCF was insensitive to heparin up to a concentration of 4 IU/mL in whole blood, but then declined to values less than 50% of baseline

at 8 IU/ml [146]. A clinical study in pediatric cardiac surgery validated the use of FIBTEM in the presence of very high heparin concentrations (400 IU/kg body weight) [147].

The correlations between Clauss fibrinogen concentration and TEG FF MA or ROTEM FIBTEM MCF could be affected by a number of factors in addition to heparin concentration. As elucidated in **Table 4**, different reagents and instruments produced by Stago, Siemens and Instrumentation Laboratory are used to quantify fibrinogen concentration. It is known that there can be systematic differences between the fibrinogen concentrations obtained with various commercial kits [148]. The different detections used in the Clauss method and resuscitation fluids administered may affect the correlation [149, 150]. This is likely due to the fact that FIBTEM test is more affected than fibrinogen concentration assays by the fluids [151]. Solomon et al. examined correlations between ROTEM FIBTEM MCF and Clauss fibrinogen concentration as determined using photo-optical, mechanical and electromechanical detections in cardiac surgery patients [149]. The correlations obtained from the photo-optical and electromechanical methods (r=0.82 and 0.81) were greater than the mechanical method (r=0.73 and 0.71). Fenger-Eriksen et al. assessed fibrinogen levels in plasma diluted *in vitro* with different fluids (isotonic saline, hydroxyethyl starch, human albumin) using an antigen determination, three photo-optical Clauss methods, one mechanical Clauss method, a prothrombin-derived method, and viscoelastic measurement through ROTEM [150]. The fibrinogen levels were overestimated using the photo-optical Clauss methods as a result of the dilution with hydroxyethyl starch, whereas ROTEM FIBTEM MCF was reduced by the dilution and to a lesser extent by human albumin. The former was ascribed to an unexplained interference with the optical source by hydroxyethyl starch and latter was due to impairment of fibrin polymerization induced by the fluid. Mittermayr et al. reported that the magnitude of clot firmness reduction was determined by the type of fluid used in major orthopedic surgery [40]. FIBTEM MCF was mostly impaired by hydroxyethyl starch, followed by gelatin solution and Ringer lactate solution. In addition, the fibrinogen measurement by the Clauss method for the same set of plasma samples can vary within and between laboratories [152].

Table 4: Summary of correlations between TEG FF/ROTEM FIBTEM and fibrinogen levels.

Clinical settings	Study population and blood sample	TEG and ROTEM methods	Results	Ref.
TEG FF				
Trauma	A randomized controlled trial of trauma patients at risk of significant hemorrhage (n=45, ISS=18-29) receiving either 6 g fibrinogen concentrate (RiaSTAP™) or placebo (normal saline).Citrated whole blood was collected from the randomized trauma patients at admission, 1-, 3-, 11-, 23- and 47-h post-infusion time.	Standard TEG FF was performed on a computerized TEG Hemostasis System 5000 according to manufacturer's protocol. Specifically, 500 µL of the blood sample was pipetted into a FF vial which contains lyophilized tissue factor with platelet inhibitor (abciximab) and gently mixed by inversion five times, and then 340 µL of the mixture from the FF vial was added into a TEG cup pre-warmed to 37ºC containing 20 µL of 0.2 M calcium chloride. Plasma fibrinogen levels were measured by the standard von Clauss method.	TEG FF MA strongly correlated with Clauss fibrinogen concentration determined by Spearman's correlation (ρ=0.75, p<0.001).TEG FF K, Alpha showed moderate correlations with fibrinogen concentration (ρ=-0.46 and 0.40, p<0.001), while TEG FF CL30 only showed week correlations with fibrinogen concentration (ρ=0.21, p=0.004).	[63, 27]
	A prospective observational study of trauma patients (n = 68), with a median ISS of 23.5. Citrated whole-blood samples were obtained from the patients on arrival to the emergency department and within the first 5 days of admission to the surgicalintensive care unit.	The FF and kaolin TEG assays were performed on the TEG 5000 device (Haemonetics Corporation, Niles, IL) in the trauma research laboratory. The FF assay measures the FF level (FLEV), which is extrapolated from the MA fibrinogen value. Plasma fibrinogen levels were measured by the standard von Clauss method.	Significant correlations between TEG FLEV and Clauss fibrinogen levels (R^2=0.87, p<0.0001) and between TEG FF MA and Clauss fibrinogen levels (R^2=0.75, p<0.0001). Moderate inverse correlation between FLEV and K (R^2=0.35, p<0.0001), between FLEV and alpha (R^2=0.70, p<0.0001).	[101]
	A prospective observational study of 251 critically injured trauma patients with a median ISS of 9 (1-19) at a single Level 1 trauma center. Citrated whole blood was collected from the patients on arrival and at 2, 3, 4, 6, 12, 24, 48, 72, 96, and 120 h after admission.	For the kaolin TEG, 340 µL kaolin-activated blood was transferred to the TEG cup, pre-warmed to 37°C and containing 20 µL of 0.2 M $CaCl_2$. For the TEG FF, 500 µL of citrated blood was added to the FF vial (kaolin + glycoprotein IIb/IIIa antagonist) and mixed; 340 µL was then transferred to the TEG cup. Plasma fibrinogen concentration was assayed by the von Clauss method.	FLEV calculated by analytical software through a transformation of the FF MA to approximate the concentration of functional fibrinogen correlates with standard Clauss fibrinogen (R^2= 0.57, p<0.001), similar to MA (R^2=0.44-0.64, p<0.001) better than the kaolin TEG measures of fibrinogen function (kinetic time and angle) (R^2=0.01, p=0.095; and R^2=0.03, p=0.004)	[128]
	A prospective observational study of 182 trauma patients with a median ISS of 17 (9-26). Citrated blood was sampled immediately upon arrival.	The TEG FF with tissue factor activator and a platelet inhibitor (ReoPro, a GPIIb/IIIa inhibitor) was performed by a TEG 5000 Hemostasis Analyzer System using TEG Analytical Software version 4.2.3 (Haemonetics Corp., Braintree, MA), according to the manufacturer's recommendations.	TEG FF MA, A5, A10 had moderate correlations with fibrinogen concentration determined by Spearman's correlation (ρ=0.64, 0.68, 0.68, p<0.01).	[118, 140]

Cardiac surgery	A prospective observational study of 117 patients operated for ischemic heart disease. Blood was collected before cardiopulmonary bypass	TEG FF test was conducted usinglyophilized tissue factor with platelet inhibitor-glycoprotein-IIb/IIIa receptor blocker.Analytical software calculated the FF level (FLEV) through the transformation of the MA value. Fibrinogen levels were assessed by the von Clauss method.	A moderate correlation was found between fibrinogen level and TEG FF FLEV with a Spearman correlation coefficient of 0.476 ($p<0.0001$).	[94]
	A prospective study of 160 cardiac surgery patients. Blood was collected at baseline, prior to heparinisation and 10 min post protamine administration	TEG FF test was conducted with native blood using lyophilized tissue factor with platelet inhibitor- glycoprotein IIb/IIIa receptor blocker. Analytical software calculates the FF level (FLEV) through the transformation of the MA value. Fibrinogen levels were assessed with citrated blood by the von Clauss method using Fibrinogen-C XL (HemosIL; Instrumentation Laboratory, Bedford, MA, USA) performed on the ACL TOP 300 CTS analyser (Instrumentation Laboratory, Bedford, MA, USA).	No significant correlation between the TEG FLEV and the Clauss fibrinogen level at the baseline (R^2=0.106) and 10 min post protamine (R^2=0.025) and between the TEG FF MA and the Clauss fibrinogen concentration at the baseline (R^2=0.061) and 10 min post protamine (R^2=0.26)	[95]
	A prospective study of 60 elective patients operated for ischemic heart disease with CPB and randomly assigned to a group with a heparin-coated CPB system or a group with a conventional (non-coated) circuit. Blood was collected from right after induction of general anesthesia, 2-h post operation, and second postoperative day.	TEG FF test was conducted by modified TEG with platelet inhibition (Haemoscope Corporation, Niles, IL, USA). Plasma fibrinogen levels were determined by the Clauss method.	Spearman's correlation analysis showed a moderately positive correlation between perioperative Clauss fibrinogen level and TEG FF MA (n=60, r=0.408, p=0.002)	[153]
	A prospective non-randomized study of 51 cardiac surgery patients. Citrated (3.2%) blood collection tubes were used for all samples 3 time points: (1) baseline; (2) rewarming on cardiopulmonary bypass; (3) post bypass.	FLEV assays were determined by TEG 5000 Hemostasis Analyzers in accordance with company's protocol utilizing the provided FF reagent vials (heparinase cups were used for all bypass samples). Plasma fibrinogen levels were measured using the Clauss method (TriniCLOT Fibrinogen Kit with Destiny Max Coagulation Analyzer; Tcoag, Bray, Ireland).	A simple linear regression model showed a strong correlation between the standard laboratory assay (Clauss) and the FF level (FLEV) assay (r=0.76; $p<0.0001$) of the fibrinogen values at the baseline.Similar correlation was seen at the rewarming and post bypass. FLEV values were consistently higher than the standard laboratory assay.	[130]
	A prospective observational study of 105 children less than 5 years of age undergoing congenital heart surgery with CPB. Citrated blood was collected before and after bypass.	TEG FF was performed on the TEG5000 with FF reagent vial and heparinase TEG cup (Hemonetics, Niles, IL) by a single technician, within 20 min of collection of the samples. Fibrinogen levels were determined by the Clauss method on platelet-poor, centrifuged blood samples (STA Fibrinogen, Diagnostica Stago).	Linear correlation coefficients between TEG FF MA and fibrinogen levels were 0.36 ($p<0.001$) before and 0.52 after bypass (p=0.02).	[138]
	A retrospective and observational study of 119 children younger than 10 years old undergoing congenital cardiac surgery with CPB. Blood was collected twice during surgery, after anesthesia induction and CPB.	ROTEM FIBTEM was performed according to manufacturer's procedure. Fibrinogen concentration was measured by a fully automated device (Diagnostica Stago, Asnières, France).	Post-CPB fibrinogen levels were not correlated with post-CPB FIBTEM MCF in infants (r=0.155, p=0.197, 0.155), whereas they were correlated with FIBTEM MCF in children older than 12 months (r=0.311, p=0.031).	[139]
Liver transplantation (LT)	A prospective study of 27 consecutive adult LT patients. Blood sample was taken from an arterial line at the time of the skin incision (the baseline) and 30 min after graft reperfusion	The whole blood was analyzed with TEG Hemostasis System 5000 analyzer, Haemonetics Corp., Niles, IL) according to the manufacturer's instructions. Plasma fibrinogen level were measured with a modified Clauss method using a coagulation analyzer (STA-R Evolution Expert series hemostasis system, Diagnostica Stago, Parsippany, NJ, USA)	TEG FF MA correlated strongly with the plasma fibrinogen level at the baseline (Spearman's correlation coefficient ρ=0.90, $p<0.01$); however, the correlation reduced after the graft reperfusion (ρ=0.58, $p<0.01$). The same correlation was seen between TEG FF FLEV and the plasma fibrinogen level.	[116]

Pregnancy	A prospective study of 21 healthy, term parturients scheduled for elective cesarean delivery. Fresh whole blood was drawn from each patient.	Modified TEG was performed with 360 mL of 1% celite-activated whole blood and with 5 mL of (2 mg/mL) ReoPro (platelet aggregation inhibitor) added to 355 mL of 1% celite-activated whole blood within 4 min of blood collection. The plasma fibrinogen concentration was measured by the Clauss quantitative fibrinogen assay using thrombin derived from bovine plasma (Ortho Diagnostic System Inc., Raritan, NJ).	Linear regression analysis revealed TEG MA as a significant predictor of the plasma fibrinogen level, with an adjusted R^2 of 0.49, and a slope of fibrinogen level= 9.56×MA + 150.68	[134]
	A prospective observational study of three groups: healthy women (32); non-pathological pregnant patients (34); and pregnant patients who went on to develop postpartum hemorrhage blood loss>1000 mL (32).	Blood samples were collected into a blood tube containing citrate (0.13 M) and analyzed using a TEG 5000 hemostasis analyzer (Haemoscope Corporation,Niles, IL, USA). The corresponding plasma samples were analysed for fibrinogen concentration by the Clauss assaysimultaneously.	Bland-Altman plots showed a significant overestimation with the FLEV method in all three patient groups. Regression analyses detected a linear correlation between FLEV and Clauss fibrinogen concentration for healthy volunteers, healthy pregnant patients, and hemorrhagic pregnant patients (R^2=0.27, p=0.002; R^2=0.31, p= 0.001; R^2=0.35, p=0.001, respectively). There was a significant difference (p<0.001) in Clauss fibrinogen concentration between all three patients groups, but no difference in FLEV between the two pregnant patients groups.	[154]
ROTEM FIBTEM				
Trauma	Randomized controlled trial of trauma patients at risk of significant hemorrhage (n=45, ISS=18-29) receiving either 6 g fibrinogen concentrate (RiaSTAP™) or placebo (normal saline). Citrated whole blood was collected from the randomized trauma patients at admission, 1-, 3-, 11-, 23- and 47-h post-infusion time.	Standard ROTEM FIBTEM was performed on a ROTEM delta system (Tem Innovations GmbH, Munich, Germany) according to manufacturer's protocol. Specifically, analyses were performed using 300 µL of citrated whole blood and 20 µL of ex-tem together with 20 µL of fib-tem following the procedure as recommended by the company. Plasma fibrinogen levels were measured by the standard von Clauss method.	ROTEM FIBTEM MCF strongly correlated with Clauss fibrinogen concentration determined by Spearman's correlation (ρ=0.87, p<0.001). ROTEM FIBTEM CFT, Alpha showed moderate correlations with fibrinogen concentration (ρ=-0.41 and 0.54, p<0.001), while CT and LI30 weekly correlated with fibrinogen concentration (ρ=-0.29, p<0.001 and 0.20, p=0.003).	[63, 127]
	A prospective study of 517 adult trauma patients with a systolic blood pressure (SBP) of < 90 mmHg and a median ISS of 14 (8–27). Citrated blood was collected within 20 min of arrival in the emergency department (ED).	Blood samples were analyzed within 2 h of blood draw, with a ROTEM delta instrument (TEM International, Munich, Germany), at 37°C. Two separate ROTEM assays were performed for each patient, the EXTEM, measuring tissue factor-initiated clotting, and the FIBTEM, with the addition of cytochalasin D, a platelet inhibitor as per manufacturer's protocols. Fibrinogen levels were determined with the Clauss method using STA Fibrinogen (Stago, Asnières sur Seine, France) and Siemens Thrombin (Sysmex UK, Milton Keynes, UK) reagents.	EXTEM and FIBTEM measures ofA5 and maximal clot formation (MCF) were significantly correlated with Clauss fibrinogen levels, and the correlations between FIBTEM A5 and MCF were slightly stronger than EXTEM (r^2 = 0.44 vs. 0.35 and 0.27 vs. 0.26).EXTEM and FIBTEM A5 gave a receiveroperating characteristic curve area of 0.8 (95% CI 0.7–0.9, p<0.001) for discriminating patients with admission fibrinogen levels below 1.5 g/L.	[43]
	A retrospective study of 358 trauma patients with a median ISS of 26 (17–34). Citrated blood was collected at admission and during the first 12-h care.	EXTEM and FIBTEM were performed in a standardized fashion within 30 min of blood collection. Fibrinogen concentration was measured by the Clauss technique, STA-Fibrinogen.	Correlations between fibrinogen concentration and FIBTEM A5 at admission (Spearman coefficient ρ=0.858 and during care (ρ=0.824), no blood product group (ρ=0.772) and blood product group (ρ=0.823).	[120]
	A prospective observational cohort study of 182 trauma patients with a median ISS of 17 (9 to 26). Blood was sampled immediately upon arrival at hospital and kept at room temperature.	EXTEM, INTEM and FIBTEM assays were performed with citrated blood according to the manufacturer's recommendations 1 h after sampling.	Fibrinogen concentration had moderate correlations with A5, A10 and MCF of EXTEM (ρ=0.65-0.68), INTEM (ρ=0.62-0.68) and FIBTEM (ρ=0.68).	[118]
	A prospective observational study of 88 trauma patients with an ISS of 22 (12-34). Blood samples were collected immediately after the patient's arrival to the trauma room and at 6, 12 and 24 h after admission	EXTEM, INTEM and FIBTEM were performed at 37°C in parallel with the citrated blood within 2 h and after 15 min of collection in a standardized way. Fibrinogen levels were assayed according to Clauss technique using Fibriquick® reagent (Biomérieux).	A significant correlation was found between fibrinogen levels and EXTEM CT (r = 0.40, p<0.001), A15 (r=0.69, p<0.001), between fibrinogen levels and INTEM A15 (r=0.66, p<0.001), and between fibrinogen levels and FIBTEM A10 (r=0.85, p<0.001)	[119]

	A prospective cohort study of 334 blunt trauma patients (ISS≥15 or Glasgow Coma Score ≤14). Citrated blood was collected at hospital admission.	ROTEM EXTEM and FIBTEM tests were performed according to manufacturer's guides. Plasma fibrinogen concentration was measured using test kits from Siemens Healthcare AG, Erlangen, Germany.	EXTEM and FIBTEM MCF showed strong correlations with fibrinogen concentration (ρ=0.79 and 0.81, respectively, p<0.001).	[129]
Cardiac surgery	A prospective, observational pilot study of 35 patients undergoing elective cardiac surgery on cardiopulmonary bypass for cyanotic congenital heart disease. Blood samples were collected after induction of anesthesia.	EXTEM, INTEM and FIBTEM were performed with citrated blood after recalcification with 20 μL $CaCl_2$. Fibrinogen concentration assay was not provided.	Fibrinogen concentration showed a significant correlation with ROTEM FIBTEM MCF (Pearson coefficient r=0.94, p< 0.001), but not with EXTEM MCF (r=0.077, p=0.67) and INTEM MCF (r=0.162, p=0.37).	[117]
	A prospective observational study of 30 patients undergoing cardiac surgery with cardiopulmonary bypass (CPB). Citrated blood was drawn at the beginning of surgery (pre-CPB), 20 min before weaning from CPB and 5 min after heparin neutralization.	TEG with the FF reagent (TEG FF), ROTEM with fib-tem (FIBTEM) and fib-tem plus containing two platelet inhibitors: cytochalasin D and tirofiban (FIBTEM PLUS) were run for a minimum of 30 min. Fibrinogen concentration was measured using the Clauss method and photo-optical determination on the ACL Top 700 and QFA thrombin reagent (Instrumentation Laboratory, Milan, Italy).	Significant positive correlations were found between MCF or MA and fibrinogen concentration (all p<0.001); the highest correlation was with FIBTEM PLUS MCF (Spearman coefficient ρ=0.70), followed by FIBTEM (ρ=0.66) and TEG FF (ρ=0.56).	[102]
	A prospective study of 157 patients undergoing cardiac surgery with CPB. Citrated blood were collected at baseline (before induction of anaesthesia) and at the end of CPB (after protamine administration).	Whole blood FIBTEM was performed using a ROTEM® device according to the manufacturer's instructions at each time point. Plasma fibrinogen concentration was measured using the Clauss method and whole blood fibrinogen concentration was calculated as plasma fibrinogen concentration × (100 − haematocrit)/100.	The Spearman correlation coefficient between FIBTEM MCF and plasma fibrinogen concentration was 0.68 at baseline and 0.70 after protamine, while that between FIBTEM MCF and whole blood fibrinogen concentration was 0.74 at baseline and 0.72 after protamine (all p<0.001).	[131]
	A prospective observational study of 35 patients undergoing elective cardiac surgery with CPB. Citrated blood was collected from at three different time points: preoperatively (immediately before anesthesia induction), and at 1- and 24-h post operation.	Kaolin TEG and ROTEM EXTEM, INTEM, FIBTEM were conducted with the citrated blood within 1 h after the collection, according to the manufacturer's instructions. Fibrinogen concentration was measured by a standard method (not specified).	Correlations between fibrinogen concentration and EXTEM MCF (Pearson coefficient r=0.71, p<0.0005), INTEM MCF (r=0.53, p=0.001), FIBTEM MCF (r=0.79, p<0.0005) were found at 1-h post operation and correlations between fibrinogen concentration and TEG K (r=-0.52, p=0.002), Alpha (r=0.53, p=0.001), TEG MA (r=0.63, p<0.0005), EXTEM MCF (r=0.58, p=0.001), INTEM MCF (r=0.63, p<0.0005), FIBTEM (r=0.50, p=0.003) at 24-h post operation.	[125]
	A retrospective observational study of 1077 patients undergoing cardiac surgery with CPB. Citrated blood was collected during the rewarming phase (≥36°C).	EXTEM and FIBTEM were conducted at 37°C as per manufacturer's reagents and procedures (TEM innovations, GmbH, Munich, Germany). Fibrinogen concentration was measured by the Clauss method using STAR Evolution (Stago, Paris, France).	Clauss fibrinogen concentration was correlated strongly with EXTEM MCF and A10 (Spearman coefficient ρ=0.68 and 0.70; p<0.01) and FIBTEM MCF and A10 (ρ=0.78 and 0.78; p<0.01). The correlation was related inversely to hemoglobin concentration (p< 0.01).	[121]
	A randomized controlled trial of 116 high-risk patients undergoing cardiac surgery with CPB.Blood was collected at 20 min before removal of the aortic cross-clamp (baseline) and after placebo or fibrinogen administration.	FIBTEM test was conducted. Fibrinogen concentrations were measured according to a photo-optical Clauss method, with a coagulation analyser (ACL TOP 700), a calibrator (HemosIL Normal Control), and a thrombin reagent (HemosIL QFA thrombin).	Linear regression analyses showed a good association between FIBTEM MCF and Clauss fibrinogen concentration at the baseline population (R^2=0.66, p=0.001), which reduced to R^2=0.16 (p=0.003) in fibrinogen-supplemented subjects.	[132]
	A prospective observational study of 110 patients undergoing cardiac surgery with CPB.Citrated whole blood was sampled from a central venous line or from the extracorporeal circuit at pre-CPB, on-CPB, post-CPB.	ROTEM assays of INTEM, EXTEM, FIBTEM and HEPTEM were performed at 37°C by certified bioanalytical technicians. Plasma levels of fibrinogen were measured using the Clauss technique on a coagulation analyzer (BCS, Dade Behring Inc., Germany) using the Multifibren U-Reagent according to manufacturer's specifications.	The fibrinogen level and FIBTEM A10 were significantly correlated for all data points (Pearson coefficient r=0.81; p<0.05). Their correlation was stronger on-CPB at a mean hemoglobin of 83 g/L (r= 0.87) and post-CPB (mean hemoglobin 88 g/L; r=0.74) than pre-CPB (mean Hemoglobin 105 g/L; r 0.66).	[122]

Liver transplantation (LT)	A retrospective observational study of 282 patients receiving liver transplantation. Citrated blood was collected at 1 h after induction of general anesthesia, 1 h after the first surgical incision, 30 min after hepatectomy, 30 min after graft reperfusion, and after hepatic artery anastomosis.	ROTEM tests (EXTEM, INTEM and FIBTEM) were routinely performed according to the manufacturer's instructions (Tem International GmbH, Munich, Germany). Fibrinogen concentration was measured using the Dade thrombin reagent (Siemens Healthcare Diagnostics, Erlangen, Germany) and an automatic coagulation analyzer (Sysmex CA-7000, Siemens Healthcare Diagnostics, Erlangen, Germany).	Fibrinogen was the primary determinant of FIBTEM MCF, accounting for 73% of the variability. However, in severe hypofibrinogenemia (fibrinogen <100 mg/dL), fibrinogen accounted only 22% of FIBTEM MCF variability. Spearman's correlations between fibrinogen concentration and EXTEM MCF (ρ=0.66, p<0.001), INTEM MCF (ρ=0.65, p<0.001), FIBTEM MCF (ρ=0.83, p<0.001).	[133]

CI=Confidence Interval; CPB=Cardiopulmonary Bypass; ISS=Injury Severity Score; LCC=Lin Concordance Coefficient; LT=Liver Transplantation.

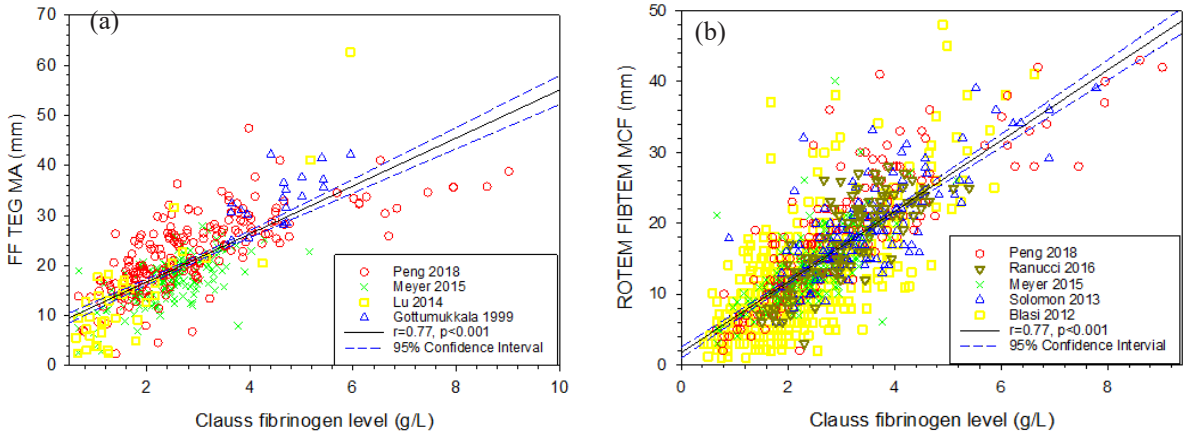


Figure 2: Correlations of Clauss fibrinogen level with TEG FF MA (a) and with ROTEM FIBTEM MCF (b). The correlation coefficients were obtained through linear regression of all data extracted from literature. The data were pooled from different clinical studies involving a total of 275 patients for the correlation between Clauss fibrinogen level and TEG FF MA [116, 127, 134, 140] and a total of 626 patients for the correlation between Clauss fibrinogen level and ROTEM FIBTEM MCF [102, 127, 132, 140, 141]. The means ± standard deviations of TEG FF MA and Clauss fibrinogen level in **Figure 2(a)** are 20.14±8.28 mm and 2.71±1.32 g/L. The means ± standard deviations of ROTEM FIBTEM MCF and Clauss fibrinogen level in **Figure 2(b)** are 15.40±7.86 mm and 2.74±1.22 g/L.

On the other hand, it was found that plasma fibrinogen level (FLEV) estimated by TEG FF was on average 1.0 g/L higher than that determined by the Clauss method in both surgical patients and healthy controls [158]. This is consistent with other report of higher TEG FLEV values than the Clauss values in cardiac surgery [130], and obstetric patients [154] and overestimation of plasma fibrinogen level in liver transplantation when the plasma fibrinogen level became less than 1 g/L [116].

In our subgroup analysis of trauma patients who received FC versus placebo (i.e., normal saline), the correlation coefficients were not significantly altered between the two groups (0.68 versus 0.67 for TEG FF and 0.88 versus 0.82 for ROTEM FIBTEM) [159]. This is in contrast with the patients undergoing liver transplantation [116, 133] and cardiac surgery [132, 149] where the correlation was impaired by severe hypofibrinogenemia and FC administration. Specifically, the correlations between FIBTEM MCF and Clauss fibrinogen concentration decreased from r=0.71-0.82 to 0.33-0.59 after administration of FC in patient undergoing complex cardiovascular surgery [149]. In addition, hyperfibrinogenemia (>4 g/L) could impair the correlation between ROTEM FIBTEM MCF and fibrinogen levels as reported in major

upper gastrointestinal surgery [160]. Herefore, the discrepancy may be due to the differences in the range of plasma fibrinogen concentrations among these studies (e.g., interquartile range of 1.88-3.63 g/L in our study vs. 0.77-1.38 g/L in the liver transplantation study). Similar correlations were reported between FIBTEM clot amplitude and fibrinogen concentration (r=0.86) at admission and then decreased correlations (r=0.43 and 0.63) after admission in the trauma patients receiving FC [120].

It should be noted that the concentration measurements by the Clauss and other plasma fibrinogen assays cannot be the same as the clot strength of whole blood measured by TEG and ROTEM. Apparently, fibrinogen is not the only contributor to clot amplitude in these TEG FF and ROTEM FIBTEM assays, which may impose some limitations on TEG FF and ROTEM FIBTEM for the assessment of fibrinogen deficiency. Activated Factor XIII and hematocrit could have an impact on clot firmness as well and affect the correlations [131, 160-163]. Postoperative Factor XIII levels correlated to FIBTEM MCF more significantly than fibrinogen levels in patients undergoing major upper gastrointestinal surgery [160]. However, the same study also showed a significant correlation between platelet count and ROTEM FIBTEM MCF ($r=0.55$, $p<0.01$) which implied that the test might be profoundly impaired by incomplete inhibition of the platelet contribution to the clot strength. Furthermore, Factor XIII levels might affect TEG FF as well [138,162].

In addition, Ogawa et al. reported a higher correlation between ROTEM FIBTEM MCF and Clauss plasma fibrinogen at lower hematocrit (<25%) than at higher hematocrit (>30%) (r =0.88 and 0.67, respectively) in cardiac surgery (163). In contrast, Solomon et al. found no significant differences between the lowest haematocrit group (<25%) and the higher haematocrit groups (25-27.9%, 28-29.9% and >30%) for FIBTEM MCF or fibrinogen concentrations in whole blood and plasma, and thus the hematocrit effect appeared to be negligible [131]. TEG FF has shown hypocoagulable states in patients with cyanotic congenital heart disease mainly due to impaired fibrinogen function negatively affected by elevated haematocrit [164]. The correlation between FIBTEM A10 and Clauss fibrinogen level became weaker as hemoglobin concentration increased, suggesting hemoglobin concentration could influence the measurement of fibrinogen by the FIBTEM assay as well [121]. The correlation could also be impaired by fibrinogen replacement in trauma patients [120].

In addition to MA, other TEG parameters, e.g. estimated FF level (FLEV) and kinetic time K and Alpha, kaolin TEG K and Alpha, have shown different extents of correlations with fibrinogen concentration [101, 117, 128]. Kornblith et al. confirmed a significant correlation between TEG FF FLEV and the Clauss fibrinogen assay in trauma patients in agreement with the published finding from Harr et al., but the correlation as assessed by linear regression was weaker (R^2=0.57 vs. 0.87) [101, 128]. In addition, different correlations of FLEV with kaolin TEG MA (R^2= 0.44-0.64 vs. 0.80), K (R^2=0.01 vs. 0.35) and Alpha (R^2=0.03 vs. 0.70)

were reported in their studies likely due to different statistical methods (linear vs. polynomial regression). The correlations were affected by fibrinogen concentration, decreasing at low and high ranges [101], respectively. TEG FF FLEV was diminished and negatively correlated to haematocrit [164].

We observed moderate correlations of Clauss fibrinogen concentration with TEG FF K and Alpha (Spearman's correlation ρ=-0.46 and 0.40) and with ROTEM FIBTEM CFT and Alpha (ρ=-0.41 and 0.54) in trauma patients [159]. Furthermore, there were weak correlations of fibrinogen concentration with ROTEM FIBTEM CT (ρ=-0.29), and with TEG FF CL30 and ROTEM FIBTEM LI30 (ρ=0.21 and 0.20). The correlations between K/CFT, Alpha and fibrinogen concentration are consistent with their measurement of the activity of clotting factors, in particular fibrinogen [35], and are comparable with or stronger than reported correlations between TEG FF K/Alpha and fibrinogen concentration [101,128]. A linear correlation was observed between the clot shear elasticity G calculated from TEG FF MA and FF levels measured by the Clauss method in both whole blood (R^2=0.605) and platelet-poor plasma (R^2=0.94) [165]. Like other TEG and ROTEM tests, the correlations with platelet count and hemoglobin concentration are generally in agreement with the reported associations between TEG/ROTEM parameters and platelet count [166-168] and hematocrit [165, 167, 169]. Bhardwaj et al. reported that fibrinogen concentrations also correlated with kaolin TEG Alpha angle (r = 0.47, p=0.006) and TEG MA (r=0.49, p=0.004) in acyanotic patients [117]. Espinosa et al. also found a correlation between fibrinogen concentration and kaolin TEG K (r=-0.52, p=0.002), Alpha (r=0.48, p=0.004) after cardiac surgery [125].

Among all the parameters, the strongest correlations between TEG FF MA/ROTEM FIBTEM MCF and plasma fibrinogen concentration have been reported [101,128,159,170], suggesting these parameters are most useful for monitoring the role of fibrinogen in hemostasis of bleeding patients.

Together with kaolin TEG, TEG FF has been used to characterize functional fibrinogen to platelet ratio and found useful in preoperatively identifying thrombotic complication in patients undergoing microvascular free tissue transfer in head and neck surgery [171]. TEG FF MA correlated with a number of biomarkers of endothelial activation and damages such as syndecan-1, thrombomodulin and protein C, and plasminogen activator inhibitor-1 (r=-0.37, p<0.001) in patients with severe sepsis [172].

In addition to clinical applications, TEG has been used to study *in vitro* effects of fibrinogen on coagulation of plasma deficient in coagulation factors and diluted by colloids [15, 173]. It has also been used to monitor the effect of a cardiopulmonary bypass system with biocompatible coating on fibrinogen levels [153]. ROTEM has been used to determine the usefulness of fibrinogen substitution to reverse dilutional coagulopathy in *in vitro* [174],

animal [175] and *ex vivo* models [176]. *In vitro* study showed dose-dependent increases in ROTEM MCF with the amount (0-3 mg/mL) of FC (Haemocomplettan P, CSL Behring GmbH, Marburg, Germany) added to normal human plasma pool, fibrinogen-deficient plasma pool, and individual plasma samples from 17 patients with fibrinogen deficiency [142]. All these studies showed that to various extents, fibrinogen improved clot strength (MA or MCF), clot formation (R or CT), and clot propagation (Alpha) as measured by TEG or ROTEM.

Furthermore, *ex vivo* ROTEM studies indicated that administration of 6 g FC to samples of coagulopathic trauma patients could correct FIBTEM A5 and MCF to the level of patients with minor injury [43]. In contrast, the *ex vivo* addition of cryoprecipitate at a standard dose of cryoprecipitate (equivalent to 2.6 g fibrinogen) was unable to reverse the coagulopathy until a high dose (equivalent to 7.8 g).

As summarized in **Table 5**, there are a number of clinical studies involving TEG and ROTEM tests especially ROTEM FIBTEM to assess hemostatic effects of FC administration in major trauma [43, 84, 159, 177-181] including early cryoprecipitate transfusion [182], cardiovascular surgery with cardiopulmonary bypass [58, 132, 183], liver transplantation [59, 156], and orthopedic surgery [40]. Unless specified, the TEG and ROTEM tests were performed using TEG 5000 and ROTEM delta with the reagents and procedures as recommended by their manufacturers.

Most clinical studies are randomized controlled, while a few are prospective observational and retrospective. Fibrinogen replacement was administered pre-emptively or guided by ROTEM or TEG. Among various clinical settings, ROTEM FIBTEM has been mostly used in trauma, cardiac surgery and liver transplantation, showing a dose-dependent increase in MCF immediatly after fibrinogen administration. For example, it was found that one gram of FC raised FIBTEM clot amplitude by about 1 mm in severe trauma [82]. The dosage study of fibrinogen supplementation after cardiac surgery showed that FIBTEM MCF increased linearly with FC dose (range 1-11 g) administered in high-risk patients undergoing cardiac surgery with cardiopulmonary bypass with a correlation coefficient of 0.7 [132]. The hemostatic effect could last for 4 h [60] and up to 48 h [159]. Furthermore, several studies have also shown that the TEG FF and ROTEM FIBTEM-measured hemostatic effect mirrored plasma fibrinogen profiles in response to fibrinogen replacement [182,183]. On the other hand, although there was a decrease in plasma fibrinogen in the placebo group at post administration of FC this was not detected by FIBTEM, while the increase in plasma fibrinogen in the treatment group after fibrinogen administration corresponded to increased FIBTEM MCF [156].

Some of these studies also used ROTEM to guide administration of FC [84,132,177-180, 183, 184]. In contrast, fewer studies on the effects of FC administration on TEG FF have been reported [159], although a number of studies have shown correlations between TEG FF

MA and Clauss fibrinogen concentration [101, 128]. Alternatively, TEG FF has been used to measure the effect of fibrinogen levels on heparin resistance/thromboprophylactic treatment in trauma [185].

As aforementioned, fibrinogen is not the only contributor to clot amplitude in TEG FF and ROTEM FIBTEM assays, which may impose some limitations on their applications for assessing the hemostatic effects of fibrinogen replacement.

Table 5: Hemostatic effects of fibrinogen replacement as measured by TEG and ROTEM.

Clinical settings	Study design	Fibrinogen replacement and ROTEM/ TEG tests	Findings	References
Pre-emptive fibrinogen replacement				
Trauma	A single centre, randomized-controlled, double-blinded, feasibility trial of adult trauma patients requiring blood transfusion randomly treated with FC (n=21) or normal saline (placebo, n=24) for pre-emptive use at hospital	Within 1 h hospital arrival, 95% of patients received a single dose of 6 g FC (RiaSTAP, CSL Behring GmbH, King of Prussia, PA, USA). TEG FF and ROTEM FIBTEM were performed at hospital admission and 2, 4, 12, 24 and 48 h after the admission.	TEG FF MA and ROTEM FIBTEM MCF mirrored plasma fibrinogen profiles, reached a maximum difference between the two groups 1–3 h after fibrinogen administration, TEG FF MA for the placebo patients was significantly lower than that for the FC patients at all time points ($p \leq 0.019$) during the 48-h hospitalization except at admission ($p=0.11$). ROTEM FIBTEM CT and MCF showed the between-group differences in the period 2–24 h after admission ($p \leq 0.028$ for CT and $p \leq 0.002$ for MCF).	Nascimento et al. (2016) [63] and Peng et al. (2019) [159]
	A randomized, placebo-controlled, double-blinded trial of adult trauma patients treated with FC (n=28) or placebo (25) before hospital arrival	FC (Clottafact, LFB France) at a dose of 50 mg/kg bodyweight or an equivalent amount of placebo was administered at the scene or during transportation to the study centre. ROTEM FIBTEM at baseline (at the scene, prior to study drug administration), and on arrival at ED, 3, 9, 24 and 48 h, and 7 days after ED admission.	Median FIBTEM MCF decreased in the placebo group between the baseline and admission to the ED, from 12.5 (interquartile range: 10.5–14) mm to 11 (9.5–13) mm, $p=0.0226$, but increased in the FC group from 13 (11–15) mm to 15 (13.5–17) mm, $p=0.0062$. The median between-group difference in the change in FIBTEM MCF was 5 (3–7) mm, $p<0.0001$.	Ziegler et al. (2019) [181]
	A blinded, randomized, placebo-controlled trial of adult trauma patients requiring MHP randomly treated with FC (n=24) or 0.9% saline (n=24)	An infusion of 6 g of FC (RiaSTAP; CSL Behring, King of Prussia, PA, USA) was administered as soon as possible upon hospital arrival.	The median time to delivery of FC was 37.5 min (IQR, 31.0–43.5 min). It was not feasible to deliver study intervention within 45 min of hospital admission, and the pre-defined target of 90% compliance was not met. Fibrinogen levels in the FC arm rose by a mean of 0.9 g/L compared with a reduction of 0.2 g/L in the placebo arm and were significantly higher in the FC arm ($p < 0.0001$) at 2 h. Fibrinogen levels were not different at day 7.	[186]

	A randomized controlled trial of adult trauma patients with ISS≥15 who received 10 units of cryoprecipitate and major hemorrhage therapy (MHT) or MHT alone	85% participants received cryoprecipitate (CYRO) within 90 min after hospital admission. Blood samples were drawn for ROTEM tests, immediately upon admission, during active bleeding (immediately after transfusion of 4, 8 and 12 units RBC) and at 24 and 72 h from randomisation.	FIBTEM data mirrored the changes seen in Clauss fibrinogen levels, with higher FIBTEM A5 and MCF levels in the CRYO arm during active bleeding.A significant rise in A5 and MCF values for both FIBTEM and EXTEM measurements was seen between 24 and 72 h in both study arms ($p < 0.0001$), with a greater increase in the CYRO group.	Curry et al. (2015) [182]
Postpartum hemorrhage (PPH)	A randomized controlled trial of patients with severe PPH and with normo-fibrinogenemia randomly treated with 2 g FC (n=123) or isotonic saline (n=121)	A single IV dose of 2 g FC (RiaSTAP, CSL Behring GmbH, Marburg, Germany) dispensed in 100 mL sterile water was administered using syringe pump infusion over 20 min by the anaesthetist on arrival in the operating theatre	There were differences in fibrinogen levels 15 min and 4 h after FC administration, and no difference at 24 h between the two groups	Wikkelsø et al. (2015) [60]
Total hip arthroplasty	A randomized trial of total hip arthroplasty surgery patients randomly received FC (n=15) or normal saline (n=15)	After induction of general anesthesia, 30 mg/kg FC (Haemocomplettan P; CSL Behring, Germany) dissolved in distilled water and reached 100 mL then was infused within 10 min	There were no differences in pre and postoperative fibrinogen levels, no differences in transfused blood products and blood loss	[61]
Guided fibrinogen replacement				
Trauma	A single-centre, parallel group, open-label, randomised study of patients with an ISS>15, bleeding signs, and FIBTEM A10<9 mm or EXTEM CT>90 s, randomly treated with FFP (n=48) or CFC (primarily FC, n=52)	ROTEM analyses were conducted at ED, ICU, and at 24 and 48 h after admission. Patients were randomized to receive FC (CSL Behring, Marburg, Germany) at 50 mg/kg of body weight or placebo when FIBTEM A10<9 mm or EXTEM CT>90 s.	EXTEM CT was shorter in the CFC group.EXTEM Alpha and EXTEM A10 worsened after FFP treatment, whereas they normalised quickly in patients receiving CFC. FIBTEM A10 increased insufficiently with FFP, whereas values well above the thresholds for transfusion were achieved with CFC. Most of these differences persisted until 24 h after admission, except EXTEM Alpha which was comparable between the two groups at 24 h after admission.	Innerhofer et al. (2017) [180]
	A retrospective observational study of 96 trauma patients with a median ISS of 34.0 (25.0–44.5) treated by three different interventions: FC only (FC group); FC and PCC (FC + PCC group) and PCC only (PCC group)	Blood samples for ROTEM tests (EXTEM, FIBTEM and INTEM) were collected as soon as possible following ED admission, during initial operative treatment and ICU stay. For patients with severe coagulopathy upon admission, immediate treatment with both FC (Haemocomplettan P, CSL Behring, Marburg, Germany) (6 to 8 g) and PCC (20 to 30 IU/kg body weight) was administered. Additional fibrinogen treatment for a FIBTEM A10<7 mm (target FIBTEM A10: 10 to 12 mm). If EXTEM CT remained prolonged (>80 s) following FC treatment, PCC (Baxter, Vienna, Austria) was administered.	Administration of FC resulted in a reduction of EXTEM and FIBTEM CT, and an increase of FIBTEM A10, but had no effect on INTEM CT, A10 and EXTEM A10. The combined administration of FC and PCC increased FIBTEM MCF and normalized EXTEM CT, but did not change either INTEM or FIBTEM CT. PCC therapy normalized EXTEM and FIBTEM CT; decreased A10 in EXTEM, INTEM and FIBTEM.	Ponschabet al. (2015) [177]
	A retrospective study of 157 trauma patients with a median ISS of 29 treated with FC alone (FC group), FC and PCC (FC–PCC group) or FC with PCC and FFP (FC–PCC–FFP group)	Blood samples were drawn following ER admission, ICU admission and at 24 h for EXTEM and FIBTEM tests. FC (Haemocomplettan P; CSL Behring GmbH, Marburg, Germany) was administered, at a dose of 2–6 g (2–4 g if initial FIBTEM A10=4–6 mm; 6 g if FIBTEM A10=0–3 mm).	Prolonged EXTEM CT and CFT in the FC–PCC–FFP group upon ICU admission, as well as low MCF and reduced Alpha in the FC–PCC–FFP group at the same time point. Between-group differences in all EXTEM parameters reached statistical significance upon ER and ICU admission but not at 24 h. FIBTEM A10 increased between ER and ICU admission in the FC–PCC group, but not in either of the other groups. FIBTEM A10 was lower in the FC–PCC–FFP group than in the other two groups at ICU admission. No between-group differences were observed in either of these parameters at 24 h with all in the normal range.	Schlimpet al. (2013) [178]

	A prospective study of 144 patients with major blunt trauma (ISS>15,), who received FC and/or PCC alone (CF Group, n=66) were compared with those additionally receiving FFP transfusions (CF+FFP group, n=78)	ROTEM was conducted with blood samples collected at ED admission and 4, 6, and 24 h thereafter. FC (Haemocomplettan P, CSL Behring GmbH, Marburg, Germany) was administered at dosages of 25–50 mg/kg body weight when fibrinogen concentration < 1.5–2.0 g/L which equals FIBTEM MCF<7 mm.	The CF + FFP patients showed increased FIBTEM MCF at 4, 6 and 24 h compared to ER admission. The group also showed higher FIBTEM MCF at 4 and 6 h than the CF group.	Innerhofer et al. (2013) [179]
	A retrospective analysis of 131 trauma patients with a mean ISS of 38 ± 15 who received ≥ 5 units of RBC concentrate within 24 h	Blood was drawn immediately after admission to ER and ICU. ROTEM tests were performed according to the manufacturer's recommendations, within five min of blood sampling. When FIBTEM MCF<10 mm, 2 to 4 g of FC (Haemocomplettan P, CSL Behring, Marburg, Germany) was administered. Patients showing prolonged EXTEM CT (>1.5 times normal) received an additional 1000 to 1500 IU of PCC.	On admission to the ER, the mean EXTEM MCF was 50 mm, the median FIBTEM MCF was 6 mm, lower than the normal range (9 to 25 mm). The median EXTEM CT was 78 sec within the normal range (35 to 80 sec). On admission to the ICU, the ROTEM parameters were comparable with the preoperative parameters. Mean plasma fibrinogen was 1.26 g/L on admission to the ER and 1.50 g/L on arrival at the ICU. The mean fibrinogen level only reached low-normal values 24 h after admission to the ER (2.28 g/L, normal range 2 to 4.5 g/L).	Schöchlet al. (2010) [84]
	A retrospective observational study of 36 adult trauma patients with an ISS≥15	ROTEM analysis was collected at various time points at ED admission, pre- and post-FC transfusion, post-bleeding episode, 24 to 48 h after admission. Median of 22 min (IQR, 17–30 min) from time of a FIBTEM A5 analysis to FC administration. If FIBTEM A5≤6 mm, an initial dose of 4 g FC was transfused	FIBTEM A5 and Clauss fibrinogen concentration were correlated (coefficients 0.7-0.8) and both increased significantly ($P < 0.05$) by 24 and 48 h after admission. One gram of FC raised FIBTEM clot amplitude by about 1 mm.	Seebold et al. (2019) Seeboldet al. (2019) [82]
Cardiovascular surgery	A multi-centre, randomized, double-blind, placebo-controlled study of patients with a 5 min bleeding mass of 60–250 g after separation from bypass and surgical haemostasis who randomly received FC (n=78) or saline (n=74).	FC (CSL Behring GmbH, Marburg, Germany) was intravenously infused during 1–2 min within 13±9 min after the first 5-min bleeding mass assessment. The dose was based on FIBTEM MCF at the end of CPB, targeting a FIBTEM MCF of 22 mm.	FIBTEM MCF was increased at the end of FC administration, the difference between FC and saline group researched maximum at the second bleeding mass assessment, and then decreased as time passed.	Rahe-Meyeret al. (2016) [58]
	A retrospective study of patients undergoing cardiac surgery with CPB who received FC due to FIBTEM MCF≤6 mm (n=73) matched with 73 patients who did not receive FC	A single dose of 1-2 g fibrinogen was only given when FIBTEM MCF≤6 mm after the protamine administration and once the clinical bleeding was no more under control despite the transfusion of FFP and PC.	The FIBTEM MCF values before and after fibrinogen administration were 6 (5–7) mm and 12 (11–14) mm, respectively.	Lupuet al. (2018) [187]
	A randomized controlled study of 116 patients undergoing cardiac surgery with CPB treated with placebo or FC	FIBTEM MCF was obtained at 20 min before removal of the aortic cross-clamp, and after fibrinogen replacement. The treatment arm received FC at the end of CPB based on the value of FIBTEM MCF according to the following equation: $\frac{22\ (mm) - \text{FIBTEM MCF}\ (mm)}{140} \times \text{body weight}\ (kg)$ to reach a target value of FIBTEM MCF of 22 mm.	FIBTEM MCF increased linearly with FC dose, with a correlation coefficient that explains 49% of the variance. A target value of FIBTEM MCF of 14 mm might be sufficient to prevent bleeding in cardiac surgery.	Ranucci and Baryshnikova (2016) [132]

	A placebo-controlled randomized trial of patients undergoing aortic replacement surgery involving CPB treated with either FC (n=14) or FFP alone (n=32) or FC followed by FFP (n=15).	ROTEM was performed at pre-study medication (before induction of anaesthesia, 20 min before removal of CPB, and after removal from CPB/ administration of protamine) and post-study medication (after last suture, at 24 and 48 h, and 8–12 days after surgery). FC (Haemocomplettan P, RiaSTAP; CSL Behring, Marburg, Germany) dose (g) = (target FIBTEM MCF − actual FIBTEM MCF) (mm) × (bodyweight [kg] / 70) × 0.5 g/mm, targeting FIBTEM MCF of 22 mm and actual FIBTEM MCF at the end of CPB	Fibrin clot measurements mirrored plasma fibrinogen profiles. In all groups, FIBTEM MCF decreased by 50% by the time of CPB removal and protamine administration. Although FIBTEM MCF was higher in the FC group than the FC+FFP group 20 min before CPB removal, this difference disappeared by the time study medication was administered. At last suture, FIBTEM MCF was higher in the FC and FC+FFP groups than in the FFP group. Between-group differences in plasma fibrinogen and FIBTEM MCF at last suture were short-lived; all groups were comparable by 24 h post-surgery. By postoperative day 10, plasma fibrinogen and FIBTEM MCF reached 150–200% of preoperative levels in all groups.	Solomon et al. (2013) [183]
	A randomized, placebo-controlled, double-blind clinical trial of cardiac surgery patients with a 5-min blood loss between 60 and 250 ml after CPB whorandomly received FC (n=60) or 2 g albumin (200 g/L, Sanquin CLB) diluted with 50 ml 0.9% of sodium chloride (n=60).	After cardiopulmonary bypass was completed and intraoperative bleeding was established, FC (Haemocomplettan P) was administered at a dose calculated based on plasma fibrinogen levels at the end of CPB measured with the Clauss method, targeting plasma fibrinogen concentration of 2.5 g/L.	There were no significant differences in the amount of intraoperative blood loss and plasma fibrinogen level between the two groups.	
Liver transplantation	A randomized, double-blind, placebo-controlled trial of 86 adult patients with a preoperative plasma fibrinogen level ≤2.9 g/L who received a median of 3.54 g FC or saline before the induction of anesthesia.	FC was administered once a patient's plasma fibrinogen level was known. The dose was estimated as 1 g FC expecting to obtain a mean plasma fibrinogen value increase of 0.29 g/L to reach the target value of 2.9 g/L.	FIBTEM A10 and MCF were higher in the FC group than in the saline group (11 (9–14) vs 8 (7–11; 11 (10–15) vs 9 (7–12)) after FC intervention. No significant difference in FIBTEM A10 and MCF between the two groups before the intervention was observed.	Sabate et al. (2016) [59] and Blasi et al. (2017) [156]
	A retrospective, single-centre, observational study of 243 adult liver transplant patients whose coagulation management was based on ROTEM-guided factor concentrate treatment.	EXTEM and FIBTEM were performed immediately upon admission to the ICU. If EXTEM MCF was reduced and FIBTEM MCF≤9 mm, 2 g FC (Haemocomplettan P; CSL Behring GmbH, Marburg, Germany) was infused; if FIBTEM MCF≤6 mm, 4 g FC was infused. If FIBTEM MCF≥9 mm and EXTEM MCF<40 mm, 1 apheresis or pooled unit PC was transfused.	FIBTEM A10 was significantly lower in the bleeding group compared with the non-bleeding group (9 vs 11mm, p=0.042). In addition, FIBTEM MCF was also significantly lower in the bleeding group (10 vs 12mm, p=0.05). All other ROTEM parameters were not significantly different between the groups.	Dötschet al. (2017) [184]
Orthopedic surgery	A prospective study of 66 orthopedic patients randomly received modified gelatin solution, hydroxyethyl starch 130/0.4, or exclusively Ringer lactate solution	FIBTEM MCF<7 mm, 30 mg/kg FC (Haemocomplettan P, CSL Behring GmbH, Marburg, Germany) was administered to maintain a serum fibrinogen of about 150 g/L.	FIBTEM MCF decreased most significantly in the patients receiving hydroxyethyl starch, followed by gelatin solution and Ringer lactate solution. The dilutional coagulopathy can be reversed by administering FC, even during continuing blood loss and intravascular volume replacement.	Mittermayr et al. (2007) [40]

CFC: Coagulation Factor Concentrates, CPB:Cardiopulmonary Bypass, ED: Emergency Department; ER: Emergency Room; FC: Fibrinogen Concentrate, FFP: Fresh Frozen Plasma, IQR: Interquartile Range; PCC: Prothrombin Complex concentrate, ICU: Intensive Care Unit, ISS=Injury Severity Score; PC: Platelet Concentrate; RBC: Red Blood Cell.

4. Diagnosis of Hypofibrinogenemia and Prediction of Blood Transfusion

Table 6 summarizes the predictive accuracy of TEG FF and ROTEM FIBTEM in various clinical settings. MA and MCF are the main parameters used for the predictions of hypofibrinogenemia and blood transfusions. The prediction accuracy was evaluated by sensitivity, specificity and area under the receiver operating characteristic curve (AUC) and

variate regression analyses. Different cut-off values of fibrinogen concentrations ranging from 1 to 1.8 g/L were used to define hypofibrinogenemia. Traditionally, a plasma fibrinogen level of 1 g/L was established for fibrinogen replacement in patients with congenital fibrinogen deficiency, whereas the threshold varied from 0.8 to 2.0 g/L in patients with acquired fibrinogen deficiency [76]. In contrast, a critical fibrinogen concentration of 2.29 g/L was identified in trauma below which a significant increase in mortality occurred [188]. The discrepancy implies that the negative impact of fibrinogen deficiency in trauma may have been underestimated. It should also be noted that hypofibrinogenemia prevalence in major bleeding varies across clinical contexts [189].

Most clinical studies are prospective observational, while a few are retrospective and randomized controlled. Sample size ranged from 23 to 1077 patients. In contrast with ROTEM, TEG FF has been used less to detect hypofibrinogenemia and predict blood transfusion requirements with a focus on trauma patients. Among various clinical settings, ROTEM FIBTEM has been mostly used in trauma, cardiac surgery and liver transplantation, with the best predictive power for hypofibrinogenemia (fibrinogen <1.5 g/L) (AUC=0.99) in cardiac surgery [117]. Furthermore, several studies have shown that TEG FF and ROTEM FIBTEM could predict bleeding and transfusion requirements in trauma [79, 190], cardiac surgery [132] and liver transplantation [155, 184] with various accuracies. It appeared that ROTEM would have better predictive accuracy than TEG because it has greater specificity for some common coagulopathies in cardiacsurgery, such as fibrinogen deficiency. The averaged likelihood ratio of TEG FF MA for diagnosis of hypofibrinogenemia is 4.71±2.18 based on a number of studies [127, 138, 140], while the corresponding value of ROTEM FIBTEM MCF is 9.24±2.64 calculated from the literature [126,127,140].

Two studies evaluated ROTEM devices in patients with postpartum hemorrhage (PPH). One study provided data on the ability of ROTEM FIBTEM to predict hypofibrinogenemia (<1.5 g/L) [124]; the other evaluated the predictive power of ROTEM FIBTEM and Clauss fibrinogen for PPH and found no associations between the prepartum coagulation parameters and severe PPH defined as blood loss ≥ 500 mL [191]. Alternatively, one study showed that TEG FF MA with a cut-off value of 12.1 mm could predict obstetric complications in non-pregnant dysfibrinogenemia patients with a sensitivity of 100%, specificity of 69.2% and AUC of 0.923, but could not distinguish patients with bleeding and non-bleeding symptoms [192].

Only a few studies demonstrated that ROTEM FIBTEM provided faster and better prediction than plasma fibrinogen concentration for massive transfusion [190] and bleeding [184], respectively. ROTEM FIBTEM provided early prediction of massive transfusion in trauma similar to the most predictive laboratory parameters (e.g., fibrinogen and hemoglobin concentrations) [190]. A separate study comparing standard fibrinogen measurement methods (i.e. Clauss method and thrombin clotting time) with ROTEM FIBTEM in patients with cirrhosis

suggested FIBTEM as a promising alternative to standard plasma fibrinogen measurement in cirrhotic patients, especially in evaluating fibrin polymerization disorders in these patients [137].

There is insufficient evidence or low-quality evidence for the benefits of TEG and ROTEM for the prediction of bleeding and adverse outcomes beyond that achieved using routinely measured baseline factors or SLTs except for rapidity. ROTEM EXTEM and FIBTEM were no better than routine laboratory tests for detecting differences between surviving and nonsurviving critically ill patients [193]. ROTEM FIBTEM was unable to predict PPH and not superior to SLTs in a prospective observational study of 217 healthy pregnant women [191]. On the other hand, ROTEM FIBTEM was not a good test to predict the presence of acute coagulopathy of trauma defined by INR>1.3 or a fibrinogen level < 1.5 g/L unless combined with EXTEM, and either of the tests could predict the need for emergent blood product transfusions (defined as ≥5 units of RBC and ≥3 units of plasma within the first 24 h of care) [194]. The use of SLTs such as INR in trauma has been severely criticized due to the lack of association with bleeding and blood transfusion. It has been reported that INR overestimated coagulopathy and should not be used to guide blood transfusion in stable trauma and surgical patients [195].

Finally, if fibrinogen deficiency has a causal relationship with bleeding and adverse clinical outcomes, it is sensible to suggest that TEG and ROTEM FF tests that improve clinical prediction for fibrinogen-related bleeding may also have the potential to predict adverse clinical outcomes. However, randomized trials are needed to provide high-quality evidence for the role of TEG and ROTEM in diagnosis, management and monitoring of fibrinogen function and replacement in bleeding patients.

Table 6: Clinical evaluation of TEG and ROTEM functional fibrinogen tests for diagnosis of coagulopathy (hypofibrinogenemia), prediction of transfusion requirements and mortality.

Clinical settings	Study design and patients	Blood collection and analysis	Findings	Ref.
TEG FF				
Trauma	Randomized controlled trial of trauma patients at risk of significant hemorrhage (n=45, ISS=18-29) receiving either 6 g FC (RiaSTAP™) or placebo (normal saline)	Citrated whole blood was collected from the randomized trauma patients at admission, 1-, 3-, 11-, 23- and 47-h post-infusion time.Standard TEG FF was performed on a computerized TEG Hemostasis System 5000 (Haemonetics Corporation, Haemoscope Division, Niles, IL, USA) according to the manufacturer's protocol.	TEG FF MA predicted hypofibrinogenemia (fibrinogen concentration < 1 g/L) and massive transfusion (≥10 RBC units) with high accuracies (AUC=0.95, p=0.002 and 0.95, p=0.034) and 24-h plasma transfusion (AUC=0.70, p=0.042).	[63, 127]
	A prospective study of 182 adult trauma patients with a median ISS of 17 (9-26)	Blood was sampled immediately upon arrival to trauma centre and evaluated in tissue factor-activated and platelet inhibited TEG (i.e. TEG FF) precisely 1 h after sampling by a hemostasis analyzer system (TEG 5000, Haemonetics Corp., Braintree, MA) according to the manufacturer's recommendations. All analyses were conducted at 37°C.	Sensitivity, specificity and AUC of TEG FF MA for detection of fibrinogen < 1.5 g/L were 77%, 81% and 0.869, respectively. TEG FF MA was also a univariate predictors of massive transfusion (>10 units of RBCs) at 6 and 24 h with odd ratios of 0.79, 0.82 and mortality at 28 days with a hazard ratio of 0.84.	[79, 140]

Cardiac surgery	A prospective observational study of 105 children less than 5 years of age undergoing congenital heart surgery with CPB	Whole blood samples were collected via indwelling arterial catheters before and after CPB. TEG FF and kaolin heparinase TEG were performed on the TEG 5000 with company's reagents (Hemonetics, Niles, IL) by a single technician, within 20 min of collection of the samples. Plasma fibrinogen levels were determined by the Clauss method using the commercial reagents and instrument (STA Fibrinogen, Diagnostica Stago).	TEG FF MA predicted hypofibrinogenemia (fibrinogen concentration < 2 g/L) with AUC of 0.71 (95% CI 0.59-0.83)	[138]
ROTEM FIBTEM				
Trauma	Randomized controlled trial of trauma patients at risk of significant hemorrhage (n=45, ISS=18-29) receiving either 6 g fibrinogen concentrate (RiaSTAP) or placebo (normal saline)	Citrated whole blood was collected from the trauma patients at admission, 1-, 3-, 11-, 23- and 47-h post-infusion time. Standard ROTEM FIBTEM was performed on a ROTEM delta system (Tem Innovations GmbH, Munich, Germany) according to the manufacturer's protocol.	ROTEM FIBTEM MCF predicted hypofibrinogenemia (fibrinogen concentration < 1 g/L) with high accuracies (AUC=0.96, p<0.001) and 24-h plasma transfusion (AUC=0.70, p=0.042 and 0.72, p=0.023).	[63, 127]
	A prospective observational study of 88 trauma patients an median ISS score of 22 (12-34)	Blood samples were collected immediately after the patient's arrival to the trauma room (H0) and at 6 h (H6), 12 h (H12) and 24 h (H24) after admission, representing a total of 270 samples. The ROTEM measurements and standard coagulation tests were performed within 2 h of collection of blood samples.	Sensitivity, specificity and AUC of FIBTEM A10 for detection of fibrinogen < 1 g/L were 91%, 85% and 0.96, respectively.	[119]
	A retrospective analysis of data from 323 patients with an injury severity score (ISS) ≥16 (20-50)	Blood samples were taken immediately upon admission to ER. ROTEM analyses (EXTEM, INTEM, FIBTEM) were typically performed at the bedside within minutes of sample collection. Fibrinogen concentration was measured by the Claussmethod (STA-Fib assay (Roche Diagnostics GmbH); optical read-out), using a STA-Compact machine (Roche Diagnostics GmbH, Vienna, Austria).	Sensitivity, specificity and AUC of FIBTEM A10/MCF for prediction of massive transfusion (≥10 units RBC transfused in 24 h) 63.3/77.5%, 83.2/74.9%, 0.83/0.84 (95% CI 0.78-0.87/0.79-0.88), similar to fibrinogen concentration	[190]
	A prospective cohort study of 517 trauma patients with a median ISS of 14 (8-27)	Blood was drawn from either the femoral vein or antecubital fossa into a 2.7-mL citrated vacutainer within 20 min of arrival in the emergency department (ED). ROTEM tests were performed within 2 h of blood draw with a ROTEM delta instrument (TEM International, Munich, Germany), at 37°C.	Sensitivity, specificity and AUC of FIBTEM A5 for detection of fibrinogen <1.5 g/L 87%, 70% and 0.8 (95% CI 0.7-0.9)	[43]
	A prospective, single-center, non-interventional, non-controlled, open clinical study of 50 trauma patients with a median ISS of 13 (4-66)	Blood was collected at hospital admission, 3- and 24-h after admission and analyzed by ROTEM assays (EXTEM and FIBTEM). EXTEM was considered positive if one of the four principle parameters (CT, CFT, MCF, and Maximum Lysis) greater than 20% of the expected highest or lowest normal value of the manufacturer normal value ranges (CT≥94 sec, CFT≥190 sec, MCF≤40 mm, ML≤12%). FIBTEM was considered positive if MCF was at least 20% smaller than the expected mean normal value (MCF≤7 mm).	Sensitivity, specificity and AUC of FIBTEM MCF < 7 mm within normal EXTEM patients are 100%, 90.2%, 0.951 and 0%, 87.5%, 0.563 for predictions of coagulopathy (INR≥1.3) and mortality at 30 days	[194]
	A prospective study of 182 adult trauma patients with a median ISS of 17 (9-26)	Blood was sampled immediately on hospital arrival. FIBTEM assays were performed with citrated blood precisely 1 h after sampling according to the manufacturer's recommendations. Fibrinogen level was determined by Clauss method.	Sensitivity, specificity and AUC of FIBTEM MCF < 10 mm were 80%, 89% and 0.889 for detection of fibrinogen <1.5 g/L.	[140]
	A prospective cohort study of 334 blunt trauma patients (ISS≥15 or Glasgow Coma Score ≤14).	Citrated blood was collected at hospital admission. ROTEM tests were performed according to the manufacturer's instructions, using equipment and test reagents provided by Tem International GmbH. Logistic regression models were used to evaluate ROTEM tests for prediction of 24-h death and 6-h transfusions.	FIBTEM MCF with a cut-off of 7 mm predicted the need for RBC transfusion with an odd ratio of 0.92 (95% CI 0.87–0.98)	[129]
Cardiac surgery	A prospective, observational pilot study of 35 patients undergoing elective cardiac surgery on cardiopulmonary bypass (CPB) for cyanotic congenital heart disease	Citrated blood was collected after induction of anesthesia and analyzed by ROTEM. No details were provided. Fibrinogen concentration assay was not provided.	ROTEM FIBTEM MCF is highly predictive of hypofibrinogenemia (fibrinogen <1.5 g/L) (AUC=0.99).	[117]
	A randomized, placebo-controlled trail of 116 high-risk patients undergoing cardiac surgery with CPB	ROTEM FIBTEM was performed 20 min before removal of the aortic cross-clamp, after fibrinogen supplementation. Fibrinogen concentrations were measured upon arrival in ICU according to a photo-optical Clauss method.	FIBTEM MCF with the best cut-off value of 14 mm yielded a good discriminative power for severe bleeding with an AUC of 0.721, sensitivity of 80%, specificity of 72%	[132]
	A retrospective observational study of 1077 patients undergoing cardiac surgery with CPB.	Citrated blood was collected during the rewarming phase (≥36°C). EXTEM and FIBTEM were conducted at 37°C as per manufacturer's reagents and procedures (TEM innovations, GmbH, Munich, Germany). Fibrinogen concentration was measured by the Clauss method using STAR Evolution (Stago, Paris, France).	The optimal FIBTEM A10 cut-off for diagnosis of a fibrinogen concentration <1.5 g/L was ≤8 mm with an AUC of 0.95.	[121]

	A prospective observational study of 110 patients undergoing cardiac surgery with CPB.	Citrated whole blood was sampled from a central venous line or from the extracorporeal circuit at pre-CPB, on-CPB, post-CPB. ROTEM assays of INTEM, EXTEM, FIBTEM and HEPTEM were performed at 37°C by certified bioanalytical technicians. Plasma levels of fibrinogen were measured using the Clauss technique on a coagulation analyzer (BCS, Dade Behring Inc., Germany) using the Multifibren U-Reagent according to manufacturer's specifications.	An on-CPB FIBTEM A10≤10 mm identified patients with a post-CPB Clauss fibrinogen of ≤1.5 g/l with a sensitivity of 0.99 and a positive predictive value of 0.60.	[122]
	A retrospective and observational study of 119 children <10 years old undergoing congenital cardiac surgery with CPB.	Blood was collected twice during surgery, after anesthesia induction and CPB.ROTEM EXTEM and FIBTEM were performed with citrated blood according to the manufacturer's recommendations. Intraoperative excessive blood loss was defined as estimated blood loss ≥50% of estimated blood volume. Logistic regression models were used to identify predictors for excessive blood loss.	Post-CPB FIBTEM A10<5 mm predicted massive blood loss with an odd ratio of 11.1 (95% CI 2.6-47.3, p=0.001) and AUC of 0.83.	[139]
Liver transplanta-tion (LT)	A retrospective observational study of 295 patients (254 living donors and 41 LT patients).	Citrated blood was collected from 1 h after induction of general anesthesia, 1 h after surgical incision, 30 min after hepatectomy, 30 min after graft reperfusion, and after hepatic artery anastomosis. ROTEM tests (EXTEM, INTEM and FIBTEM) were routinely performed according to the manufacturer's instructions (Tem International GmbH, Munich, Germany). Fibrinogen concentration was measured using the Dade thrombin reagent (Siemens Healthcare Diagnostics, Erlangen, Germany) and an automatic coagulation analyzer (Sysmex CA-7000, Siemens Healthcare Diagnostics, Erlangen, Germany).	FIBTEM MCF < 8mm predicted hypofibrinogenemia (fibrinogen < 1.28 g/L) with a sensitivity of 82%, a specificity of 90% and AUC of 0.94.	[126]
	A prospective study of 253 patients receiving orthotopic liver transplantation.	Citrated blood samples were collected after induction of general anesthesia, at the end of the hepatectomy, 20 min after graft revascularization, and 90 min after graft revascularization. The blood samples were tested just after collection by ROTEM gamma device operated according to manufacturer instructions and with the type and concentration of reagents as provided by Pentapharm (Munich, Germany). Fibrinogen concentration was measured by the PT-derived method, with values below 2 g/L being checked by the Clauss method.	Sensitivity, specificity and AUC of FIBTEM A10 for detection of plasma fibrinogen level (<1.3 g/L) 86%, 55% and 0.801	[141]
	A retrospective, single-centre, observational study of 243 adult liver transplant patients	Blood samples were collected immediately upon admission to ICU and once daily until the seventh postoperative day. ROTEM tests including EXTEM, INTEM, and FIBTEM were performed. Standard laboratory tests (PT, aPTT, fibrinogen) were performed using a BCS Analyzer (Siemens Healthcare Diagnostics Products GmbH, Erlangen, Germany).	FIBTEM A10/MCF predicted postoperative bleeding with a sensitivity of 90/90%, specificity of 33/32%, AUC of 0.636/0.632, better than fibrinogen concentration with 74%, 39% and 0.531	[184]
	A prospective observational study of 23 patients undergoing orthotopic liver transplantation.	Blood samples were collected after induction of general anaesthesia, during hepatectomy, at the anhepatic stage, 30–60 min after graft revascularization, at the end of surgery, and 24 h after surgery. ROTEM tests (EXTEM, INTEM, FIBTEM and APTEM) were performed in the operating theatre and by the anaesthesiologists treating the patients according to the manufacturer's instructions using equipment and test reagents provided by Pentapharm GmbH. Plasma fibrinogen concentration was determined by the Clauss method performed on ACL Top automates (Instrumentation Laboratory, Lexington, MA, USA).	ROTEM FIBTEM A10 ≤8 mm predicted hypofibrinogenemia (fibrinogen < 1 g/L) with a sensitivity of 0.83, specificity of 0.35, and AUC of 0.61, worse than EXTEM with corresponding values of 0.83, 0.75 and 0.84	[123]
	A retrospective of 401 patients who underwent liver transplantation.	Blood was sampled at 1 h after induction of general anaesthesia, 1 h after surgical incision, 30 min after hepatectomy, and 30 min after graft reperfusion and after hepatic artery anastomosis. A total of 1125 FIBTEM tests were performed according to the manufacturer's instructions. Fibrinogen level was measured using the Dade Thrombin Reagent (Siemens Healthcare Diagnostics) and an automatic coagulation analyser (Sysmex CA-7000, Siemens Healthcare Diagnostics).	ROC curve analysis showed that a cut-off value of FIBTEM A5 at 4 mm and A10 at 5 mm predicted fibrinogen < 1 g/L with a sensitivity of 81% and 76%, specificity of 77% and 82%, AUC of 0.86 and 0.87	[155]
Postpartum hemorrhage	A prospective observational study of 91 women at the third trimester of pregnancy: 37 with postpartum haemorrhage (study group) and 54 without abnormal bleeding (control group).	Standard FIBTEM was carried out by clinicians with citrated blood samples in the delivery room. Plasma fibrinogen was assayed within 5 min after sampling with a STAR automated coagulation analyser (Diagnostica Stago Inc., Franconville, France) according to standard procedures.	A cut-off value of A5 and A15 at 6 mm provided an sensitivity of 100% for both parameters, a specificity of 85 and 88%, and AUC of 0.96 and 0.97, respectively to detect a fibrinogen level <1.5 g/L in postpartum haemorrhage.	[124]

	A prospective observational pilot study including 217 healthy pregnant women	Blood samples were collected upon admission to the delivery room for labor and within 1 h after vaginal delivery. All ROTEM tests were performed with the recommended reagents and in accordance with the manufacturer's procedures (TEM International GmbH, Munich, Germany). Fibrinogen levels were measured with STA-fibrinogen reagent (Roche Diagnostics GmbH, Mannheim, Germany) using Clauss method.	The AUC of ROTEM FIBTEM MCF for prediction of postpartum hemorrhage defined as blood loss ≥ 500 mL was 0.52 (95% CI 0.41–0.64, p =0.699), similar to the predictive power of fibrinogen levels (AUC=0.53, 95% CI 0.40–0.65, p=0.644).	[191]
Neurosurgery	A prospective observational study of 92 patients undergoing emergent neurosurgery	Blood was sampled in the operating theater on citrated tubes and ROTEM analyses were performed within min of blood sampling by anesthesia nurses or physicians trained to perform the ROTEM tests according to the manufacturer's instructions (ROTEM; TEM Innovations GmbH, Germany) plasma fibrinogen concentration (Clauss method; Siemens-Dade Behring Healthcare Diagnostics, Marburg, Germany).	The need for transfusion (≥ 3 PRBCs) was best predicted by EXTEM and FIBTEM MCF (AUC of 0.72 and 0.71, respectively) and by fibrinogen concentration (AUC of 0.70), with a sensitivity of 38.2, 33.3, 25.6% and specificity of 85.1, 96.2 and 100%.	[135]

AUC: Area Under the receiver operating characteristic curve; CI: Confidence Interval; CPB: Cardiopulmonary Bypass; ICU: Intensive Care Unit; ISS= Injury Severity Score.

5. TEG and ROTEM for Guided Fibrinogen Administration

ROTEM has been widely used to guide FC administration in different perioperative settings (trauma [196], cardiovascular surgeries [24, 69, 197], liver transplantation [70], obstetric hemorrhage [198], orthopedic surgery [40] and craniosynostosis surgery [199]. A number of retrospective and prospective studies in cardiac surgery have shown that FIBTEM-guided fibrinogen replacement generally reduced blood transfusions [200].

TEG and ROTEM have been mostly implemented during active bleeding situations in emergency room and during surgery. As summarized in **Table 7**, case reports [201-204], retrospective [82, 84, 177, 178, 205, 206] and prospective clinical studies [179,207], RCTs [58, 180, 208, 209] demonstrated that ROTEM FIBTEM has been well used to guide fibrinogen administration in trauma, leading to reduced allogeneic blood transfusion [179, 203]. Similarly, case reports [210], retrospective [197, 211], prospective [212,213], RCTs [58, 132,208,214-216] in cardiac surgery, with most studies suggesting that the FIBTEM-guided FC reduced the transfusions of RBC and FFP except one study suggesting the opposite [58]. In liver transplantation, retrospective [184], prospective studies [86,217,218] have shown mixed results of the effect of ROTEM in particular FIBTEM-guided fibrinogen replacement on clinical benefits (e.g., blood transfusion and mortality). In obstetric hemorrhage, case report [219], retrospective [220], and prospective [198] studies have also been reported.

In contrast with ROTEM-guided fibrinogen replacement, there are fewer studies on TEG-guided fibrinogen replacement across various clinical settings, with most being focused on trauma. In addition, kaolin-activated TEG [11,221-226] and rapid TEG [19,23,27,87] rather than TEG FF have also been used to guide fibrinogen supplementation. In these studies, TEG α angle was the parameter used to guide fibrinogen supplementation, while MA was used to guide platelets transfusion. Some of these studies involved FFP [221] and cryoprecipitate transfusion guided by TEG [11,27,222,225,226] instead of FC for fibrinogen replacement. Disadvantages

of FFP and cryoprecipitate include the requirements for cold storage and time taken to thaw on average 17 min [182], risk of viral transmission and the large volume administered. FFP contains a low concentration of fibrinogen which can vary greatly between individual units, and when given in large volumes may dilute plasma fibrinogen levels [219].

Most clinically studied FC is Haemocomplettan P or RiaSTAP in the USA and Canada (CSL Behring GmbH, Marburg, Germany), other commercial available FC products include Clottagen (LFB Biomédicaments,Les Ulis, France) [217], Fibrinogen HT (Benesis, Osaka, Japan), and FibroRAAS (Shanghai RAAS, Shanghai, China) [227]. Fibryga (Octapharma, Lachen, Switzerland) is a new highly purified lyophilized FC [228]. *In vitro* and clinical studies showed a higher Factor XIII level (10.1 vs, 7.2 IU/mL) [229], a slower clearance (0.665 vs. 0.804 mL h^{-1} kg^{-1}), and a larger volume of distribution (70.158 vs. 76.631 mL kg^{-1}) [230] for Fibryga than for RiaSTAP. In contrast, another clinical study reported even smaller clearance (0.53 ml h^{-1} kg^{-1}) and volume of distribution for Clottafact (50.7 mL kg^{-1}) [231].

FC was generally administered by bolus intravenous injection, while one study showed potential advantage of using a continuous infusion rather than bolus injections during surgery being that continuous infusion allows rapid alterations in the delivery rate in response to changing plasma levels and thus avoids or reduces the peaks and troughs in plasma fibrinogen concentration and a plasma fibrinogen level associated with satisfactory hemostasis could be maintained during surgery [210].

Table 7: Summary of TEG/ROTEM-guided fibrinogen replacement.

Clinical settings	Study design	Guiding protocol for fibrinogen replacement	Main results	References
TEG				
Trauma	A randomized study of 111 adult trauma patients with a median ISS of 30 (24–43) treated by MTP directed either by TEG or SLT	Rapid TEG was performed upon MTP activation on native whole blood within 5 min from collection.If ACT≥140 ec, 2 units FFP, 10-pack cryoprecipitate, and 1 unit of PC were transfused; if ACT=111-139 ec, 2 units FFP; if α angle<63° 10 packs of cryoprecipitate; if MA< 55 mm 1 unit of PC	Mortality at 28 days was lower in the TEG group compared with the SLT group (19.6% vs. 36.4%, p=0.049). Less plasma and platelets were required in the TEG group than in the SLT group in the first 2 h of resuscitation.	Gonzalez et al. (2016) [23]
	A prospective study of 182 adult trauma patients with a median ISS of 17 (9-26) in a Level I trauma center	Blood was sampled immediately upon arrival to the trauma centre and kept at room temperature until analyzed by kaolin and rapid TEG, and TEG FF 1 h after sampling. When TEG FF MA<14 mm FFP 20-20 mL/kg or cryoprecipitate pool (3-5 mL/kg) or FC (adults 1-2 g) was transfused.	Non-survivors had lower clot strength by kaolin TEG and TEG FF, and lower rapid TEG α angle and LY30 compared to survivors. None of the TEG variables were independent predictors of massive transfusion or mortality.	Johansson et al. (2013) [79]
	A retrospective study of 390 and 442 adult patients (age≥ 15 years) who received more than 10 RBCs within 24 h before and after the implementation of HCR	Kaolin TEG was used in resuscitation and operation room and ICU. When Alpha<52°, 2 units FFP or 1-2 g FC; R=11-14 min, 2 × FFP or 10 mL/kg, R>14 min, 4 × FFP or 20 mL/kg; MA=46–50 mm, 1 unit PC; MA<46 mm 2 units PC were transfused.	PC transfusion within 24 h from admission was increased from 1.7 to 5 units and thirty- and nighty-day mortality was reduced from 31.5% to 20.4% and from 34.6% to 22.4%, respectively as a result of TEG-guided HCR.	Johansson et al. (2009) [221]

	A retrospective study of 165 and 124 trauma patients receiving ≥6 units of RBC in the first 24 h, respectively treated by TEG-guided or MTP resuscitation	TEG was performed in the operating room or ICU.If α angle<45°, 0.6 unit/kg cryoprecipitate; MA=41-48 mm 5 units of platelets, MA≤40 mm, 10 units of platelets were transfused. MTP involved transfusion with 1:1:1 ratio of RBC, FFP and platelets.	There was no difference in volume of blood products or mortality between the two groups. The mortality of the penetrating trauma patients who received ≥10 units RBC decreased from 54.1% for MTP to 33.3% for TEG-directed resuscitation (p = 0.04).	Tapia et al. (2013) [224]
	A case report of trauma patients treated by MTP transfusion with 1:1:1 ratio of RBC, FFP and platelets followed by TEG-guided transfusion	TEG was performed as soon as a blood sample could be obtained. If R>8 min FFP; K>4 min, or α angle<47°, cryoprecipitate; MA<54 mm, platelets were transfused.	TEG allowed for judicious and protocol assisted utilization of blood components more effectively manage blood products and resuscitation.	Walsh et al. (2011) [225]
	A retrospective study of 1974 adult patients with a median ISS of 17	Blood was collected on admission and analyzed by rapid TEG. When K>2.5 min or α angle<56° or MA<55 mm, cryoprecipitate or FC was transfused (dose not specified).	Rapid TEG was superior over SLT (PT, PTT, INR, platelet count and fibrinogen) and identified patients with an increased risk of early RBC, plasma and platelet transfusions, and fibrinolysis.	Holcombet al. (2012) [19]
	A case report of three trauma patients treated by TEG-guided transfusion within MTP	Rapid TEG was performed in the ER. If ACT>110 sec, 2 units of FFP; if α angle <63°, cryoprecipitate (dose not specified); MA< 55 mm, PC was required.	TEG-directed therapy showed potential to be both cost effective and lifesaving.	Sawyer et al. (2012) [87]
	A retrospective study of 80 trauma patients with an ISS of 29 ± 1	Native whole blood samples were analyzed by rapid TEG with 10 μL of rapid TEG solution (8% kaolin, human recombinant tissue factor, phospholipids, buffers, and stabilizers), used as an activator, were added to 0.36 mL of whole blood within 4 min of blood collection, placed in cuvettes, and warmed to 37.3°C. If α angle<60, cryoprecipitate was transfused.	Clot shear elasticity (G) was an independent predictor of massive transfusion. For prediction of mortality, G had the greatest adjusted AUC ROC (0.93) compared with the AUC ROC for base deficit (0.87), INR (0.88), and PTT (0.89).	Pezold et al. (2012) [27]
Cardiac surgery	A prospective study of 69 patients undergoing cardiac surgery randomized to either TEG- (study group) or SLT-directed (control group) blood transfusion	Kaolin TEG with or without heparin was performed before bypass, in the re-warming phase, and 15 min after protamine administration at the end of bypass. If kaolin/ heparin TEG MA>45 mm and Alpha<45°, 5 units of cryoprecipitate were transfused.	Blood transfusion was reduced with the greatest savings being for RBC and platelets. The grand total for all types of blood products administered was 90 units in the control group compared with 37 units in the study group. There were on average 2.4 units per patient in the control group vs. 1.15 units per patient in the study group—a reduction of 52%	Westbrook et al. (2009) [11]
	A retrospective study of patients undergoing cardiothoracic surgery before (n=367) and after (n=310) implementation of TEG-directed transfusion	Baseline kaolin heparinase TEG, post-protamine kaolin, and post-protamine kaolin heparinase TEG were performed. If α angle<45°, 0.06 units/kg cryoprecipitate was transfused.	TEG-directed transfusion reduced use of blood products (RBC, FFP, cryoprecipitate, PC), and led to lower incidence of reoperation, shorter length of stay and reduced 6-month mortality.	Redfern et al. (2019) [226]
Liver trans-planta-tion	A retrospective cohort observational study of 268 and 118 consecutive patients undergoing liver transplantation before and after the addition of TEG FF to a TEG-based transfusion algorithm	The tests were carried out on native blood within 4 min after collection and were performed according to the manufacturer's instructions at the temperature set at the patient's temperature at preset times: baseline (when the surgery patient first entered the operating room), laparotomy, pre-anhepatic, anhepatic, and 30, 60, 120, 180 min after reperfusion.Native TEG MA<30 mm and TEG FF MA≤7 mm, FC (Haemocomplettan P, CSL Behring GmbH, Marburg, Germany) was administered at 25-50 mg/kg.	The new algorithm increased the use of FC and reduced the need for transfusion of homologous blood, FFP and platelets with no impact on 30-d and 6-month survival, suggesting TEG FF helped in reducing the need for transfusion in patients undergoing liver transplantation.	De Pietri et al. (2016) [81]
	A randomized study of 28 patients undergoing orthotopic liver transplantation monitored during surgery using TEG analysis, or SLT of blood coagulation.	Blood samples were obtained 8 times: after induction, 1 h after induction, 5 min before the anhepatic interval, 10 min into the anhepatic interval, 5 min before recirculation, and 10, 30, and 60 min after reperfusion. Kaolin TEG was performed.Cryoprecipitate (5 pooled units) was transfused when α angle was less than 45°.	Less FFP was used in the TEG group than in the SLT group (12.8±7.0 units vs. 21.5±12.7 units). There was a trend toward less blood loss in the TEG group; however, the difference was not significant. There were no differences in total fluid administration and 3-year survival.	Wang et al. (2010) [222]

Scolio-sis surgery	A prospective study of 60 patients scheduled for scoliosis and randomized to TEG- and SLT-guided transfusion	Kaolin TEG was performed every 1 h during the surgery. If α angle < 72° fibrinogen 2 g; R> 8 min FFP 15 mg/kg; MA<70 mm 1 unit of PC was transfused.	There were less transfusions of RBC (4.5 vs. 7.1 units), FFP (234 vs. 514 mL), and platelets (2.5 vs. 4.2 units) and FC (2.4 vs. 4.6 g) in the TEG group than in the SLT group, but no difference in blood loss, re-bleeding incidence and hospital stay.	Cao et al. (2016) [223]
ROTEM				
Trauma	A case report of a 52-year-old male severely injured trauma patient who suffered a high velocity motorcycle accident	ROTEM (EXTEM, INTEM and FIBTEM) was performed immediately after admission, during surgery and in ICU. FIBTEM MCF=4 mm at admission. Accordingly, 12 g of FC (RiaSTAP/Haemocomplettan P, CSL Behring GmbH, Marburg, Germany) was infused as three doses of 4 g during surgery to increase FIBTEM MCF to 10 mm. According to FIBTEM MCF=8 mm at 6 h after admission to the ICU, another 2 g of FC were administered.	EXTEM results showed a slightly prolonged CT of 85 sec and reduced MCF of 49 mm at admission. EXTEM CT remained in the normal range during the entire surgical procedure, suggesting normal thrombin generation. On arrival at the ICU, EXTEM revealed a CT of 77 s, an MCF of 47 mm and a FIBTEM MCF of 13 mm. The patient was fully recovered upon release from hospital, 60 days after the accident.	Schochlet al. (2010) [201]
	A case report of a 68-year-old male patient with serious craniofacial trauma and massive haemorrhage	A blood sample was taken for ROTEM analysis (EXTEM, FIBTEM) upon arrival to ER. EXTEM CT and CFT were prolonged: 167 and 739 sec; MCF was below normal: 29 mm. In addition, FIBTEM A10 was only 2 mm, and a shorter clotting time was observed in the APTEM assay than in the EXTEM assay. Tranexamic acid (2 g) was administered to correct fibrinolysis. The patient was then treated with 1000 IU PCC (Uman Complex DI), 5 g FC (Haemocomplettan P; CSL Behring, Marburg, Germany) and 2 units of PC.	The patient's coagulation was normalized 2 h after the arrival, in terms of EXTEM CT (62 s) and MCF (50 mm) and FIBTEM MCF (10 mm), suggesting success of ROTEM-guided coagulation factor concentrate therapy for massive haemorrhage associated with craniofacial injury.	Grassettoet tal. (2012) [202]
	A case report on a 7-year-old boy with severe abdominal and pelvic injuries	Immediately upon ER admission, 1 and 2 h into surgery, blood samples were taken for EXTEM and FIBTEM. One unit of RBC concentrate (250 mL), 0.5 g of FC (Haemocomplettan P; CSL Behring, Marburg, Germany), and 250 mL of crystalloid were administered upon arrival at ER. FIBTEM MCF=9 mm at 1 h, another 0.5 g of FC was transfused, FIBTEM MCF=8 at 2 h, a further 1 g of FC was administered.	Transfusions of FFP and PC were avoided, showing the potential for pre-emptive fibrinogen supplementation followed by a goal-directed, theragnostic approach to hemostatic therapy to be applied to pediatric trauma.	Ziegleret al. (2013) [203]
	A case report of a 24-year-old man with a severe blunt abdominal trauma	ROTEM FIBTEM was performed 0.5 h after hospital arrival indicating afibrinogenemia, 4 g of FC (Haemocomplettan P) was intravenously administered; FIBTEM was performed 1 h after the arrival showing persistent afibrinogenemia, an additional 8 g of FC was administered followed by a further 4 g of FC 1 h later, resulting in normal FIBTEM.	ROTEM-guided FC treatment was successful and avoided FFP and platelets transfusions. ROTEM provided a better guide than INR and PTT for treatment decisions.	Brenniet al. (2010) [204]
	A retrospective analysis of 681 trauma patients with an ISS≥16, AIS for thorax and/or abdomen and/or extremity ≥3, and for head/ neck < 5	ROTEM analyses were performed on admission to the ER and at the end of the operation (arrival at the ICU). Haemostatic therapy consisted of administration of 2 to 4 g of FC (Haemocomplettan P, CSL Behring GmbH, Marburg, Germany) when FIBTEM MCF<10 mm, and administration of 1,000 to 1,500 IU of PCC, for patients showing prolonged EXTEM CT (> 1.5 times normal).	RBC transfusion was avoided in 29% of patients in the FC-PCC group compared with only 3% in the FFP group ($p<0.001$). Transfusion of PC was avoided in 91% of patients in the FC-PCC group, compared with 56% in the FFP group ($p<0.001$). Mortality was comparable between the two groups: 7.5% in the FC-PCC group and 10.0% in the FFP group ($p=0.69$).	Schochlet al. (2011) [206]

	A retrospective analysis of 131 trauma patients mean ISS was 38 ± 15 who received ≥ 5 units of RBC within 24 h	Blood was drawn immediately after admission to ER and ICU for ROTEM analysis performed according to the manufacturer's recommendations, and the analyses were started within five min of blood sampling. When FIBTEM MCF<10 mm, 2 to 4 g of FC (Haemocomplettan P, CSL Behring GmbH, Marburg, Germany) was administered. Patients showing prolonged EXTEM CT (>1.5 times normal) received an additional 1000 to 1500 IU PCC	The observed mortality was 24.4%, lower than the TRISS mortality of 33.7% (p=0.032) and the RISC mortality of 28.7% (p>0.05). After excluding 17 patients with traumatic brain injury, the difference in mortality was 14% observed versus 27.8% predicted by TRISS (p=0.0018) and 24.3% predicted by RISC (p=0.014). The results support ROTEM-guided haemostatic therapy, with FC as first-line haemostatic therapy.	Schöchlet al. (2010) [84]
	A prospective study of 144 patients with major blunt trauma (ISS>15), who received FC and/or PCC alone (CF group) were compared with those additionally receiving FFP transfusion	ROTEM was conducted with blood samples collected at ER admission and 4, 6, and 24 h thereafter. FC (Haemocomplettan P, CSL Behring GmbH, Marburg, Germany) was used to correct low fibrinogen concentration and/or poor fibrin polymerisation (fibrinogen concentration < 1.5–2.0 g/L which equals FIBTEM MCF<7 mm) at dosages of 25–50 mg/kg body weight.	Patients treated with CF alone showed sufficient haemostasis and received significantly fewer units of RBC and platelets than the FFP group. In addition, fewer patients in the CF group developed MOF or sepsis than in the FFP group. Propensity score-matching (n= 28 pairs) used to reduce the impact of treatment selection confirmed that additional FFP administration showed no benefit in restoring hemostasis but was associated with higher transfusion rates for RBC and platelets.	Innerhoferet al. (2013) [179]
	A retrospective study of 157 trauma patients with a median ISS of 29 treated with FC alone (FC group), FC and PCC (FC–PCC group) or FC with PCC and FFP (FC–PCC–FFP group).	Blood samples were drawn following ER admission for EXTEM and FIBTEM tests. FC (Haemocomplettan P; CSL Behring GmbH, Marburg, Germany) was administered, at a dose of 2–6 g (2–4 g if initial FIBTEM A10 4–6 mm; 6 g if initial FIBTEM A10 0–3 mm).	Plasma fibrinogen concentration was maintained within the normal range in all patient groups. Transfusion requirements were highest in the FC–PCC–FFP group and lowest in the FC group.	Schlimpet al. (2013) [178]
	A prospective observational, descriptive study of 77 trauma patients with a mean ISS score of 25.6 separated into three cohorts: patients who received no coagulation therapy (NCT group), patients treated with FC only (FC group), and patients treated with both FC and PCC (FC-PCC group)	ROTEM tests (EXTEM, FIBTEM and INTEM) were performed following ER admission, during initial operative treatment and ICU stay, and every morning thereafter up to day 7. For patients with obviously severe coagulopathy upon admission, immediate treatment with both FC (Haemocomplettan P, CSL Behring, Marburg, Germany) (6 to 8 g) and PCC (20 to 30 IU/kg body weight) was administered. Additional fibrinogen treatment was given when FIBTEM A10=0-3 mm, 6 g FC; FIBTEM A10=4-6 mm, 3-4 g FC to target 10 to 12 mm. If EXTEM CT remained prolonged (>80 sec) following FC treatment, PCC (Baxter, Vienna, Austria) was administered.	Endogenous thrombin potential (ETP) was higher in the FC-PCC group compared with the NCT group on days 1 to 4 and the FC group on days 1 to 3. Fibrinogen increased over time, with no significant between-group differences after ER admission.PT and PTT were prolonged in the FC-PCC group from admission until day 3 to 4.	Schöchlet al. (2014) [207]
	A retrospective observational study of 96 trauma patients with a median ISS of 34.0 (25.0–44.5) treated by FC only (FC-group); FC and PCC (FC + PCC-group); and PCC only (PCC-group).		Administration of FC resulted in a reduction of EXTEM and FIBTEM CT, and an increase of FIBTEM A10, but had no effect on INTEM CT, A10 and EXTEM A10. The combined administration of FC and PCC increased FIBTEM MCF and normalized EXTEM CT but did not change either INTEM or FIBTEM CT. PCC therapy normalized EXTEM and FIBTEM CT; decreased A10 in EXTEM, INTEM and FIBTEM.	Ponschabet al. (2015) [177]
	A retrospective observational study of 435 trauma patients treated with (treatment group) or without (control group) FC		In the treatment group (median FC dose 6 g), fibrinogen level was lower on admission and up to day 2 compared with the control group. In patients receiving high (≥10 g) doses of FC, fibrinogen level was lower up to day 5 as compared to the control. At other time points, there was no difference between the groups.	Schlimpet al. (2016) [205]

	A retrospective observational study of 36 adult patients with an ISS≥15	ROTEM analysis was conducted at various time points from ED admission to 48 h after the admission. A FIBTEM A5<10 mm in the setting of significant haemorrhage triggered fibrinogen replacement with FC.	It took a median of 22 min (IQR, 17–30 min) from time of a FIBTEM A5 analysis to FC administration. FIBTEM A5 and Clauss fibrinogen concentration were correlated (coefficients 0.7-0.8) and both increased significantly ($p<0.05$) by 24 h after admission.	Seeboldet al. (2019) [82]
	A randomized controlled trial of 100 trauma patients with an ISS>15 treated with FFP (15 mL/ kg of bodyweight, n=48) or CFC (primarily FC (50 mg/kg of body weight, n=52)	ROTEM analyses were conducted at ER until 24 h at the ICU. Patients received FC (CSL Behring, Marburg, Germany) at 50 mg/kg of body weight when FIBTEM A10<9 mm and four-factor PCC at 20 IU/kg of body weight when EXTEM CT>90 sec or prothrombin time index<35%.	High proportion of patients in the FFP group who required rescue therapy compared with those in the CFC group (52% vs. 4%, $p<0·0001$) and increased needed for massive transfusion (30% in the FFP group vs. 12% in the CFC group, $p=0·042$) in the FFP group. There was no difference in MOF between the two groups.	Innerhoferet al. (2017) [180]
	A case report of three patients undergoing type IV thoraco-abdominal aortic aneurysm repair	Blood samples were taken every 30 min during surgery for ROTEM tests. FC (Haemocomplettan P, CSL Behring GmbH, Marburg, Germany) was continuously infused with the infusion rate increased or decreased to maintain FIBTEM MCF within the range of 9 to 25 mm.	Treatment of coagulopathy in these patients was successful despite massive hemorrhage, without transfusions of FFP and cryoprecipitate.	Morrisonet al. (2012) [210]
Cardiac surgery	A retrospective study of 3865 patients undergoing CPB before and after implementation of ROTEM-supported coagulation management	After declamping of the aorta, if FIBTEM MCF=0, consider fibrinogen at 50 mg/kg; if EXTEM A10<30 mm, FIBTEM A10>6 mm, PC transfusion. For diffuse bleeding after protamine, if EXTEM A10≤40 mm, FIBTEM A10≤10 mm, administration of fibrinogen at 25-50-75 mg/kg body weight; if EXTEM A10≤40 mm, FIBTEM A10>10 mm, transfusion of PC; if EXTEM CT>90 ec, PCC at 20-30-40 IU/kg body weight	Transfusion of RBC and FFP was decreased with decreased incidence of thrombotic/ thromboembolic events. Transfusion of PC, FC and PCC was increased resulting from first-line administration of coagulation factor concentrates guided by ROTEM.	Görlingeret al. (2011) [197]
	A retrospective study of 18 patients undergoing elective thoracoabdominal aortic aneurysm surgery with and without FC therapy	Before the administration of PC or FFP, FC (Haemocomplettan P) was administered at the dose calculated as follow: $\frac{22\,(\text{mm}) - \text{FIBTEM MCF}\,(\text{mm})}{140} \times \text{body weight (kg)}$	Transfusion of FFP and PC after CPB and during the 24 h after surgical intervention was reduced, as was 24-hour drainage volume.	Rahe-Meyeret al. (2009) [211]
	A prospective study of 15 patients undergoing elective aortic valve operation and ascending aorta replacement treated with or without FC	FC (Haemocomplettan P/RiaSTAP, CSL Behring, Marburg, Germany) was given before any blood transfusions at a dose determined based on FIBTEM MCF at the removal of the aortic clamp and following formula: $\frac{22\,(\text{mm}) - \text{FIBTEM MCF}\,(\text{mm})}{140} \times \text{body weight (kg)}$	FIBTEM-guided FC administration reduced blood transfusions from 8.2 to 0.7 units and 24 h postoperative bleeding from 716 to 366 mL	Rahe-Meyeret al. (2009) [212]
	A randomized controlled study of 519 patients receiving FC or normal saline in complex cardiovascular surgery	The dose of FC (CSL Behring, Marburg, Germany) was based on FIBTEM MCF at the end of CPB, targeting a FIBTEM MCF of 22 mm.	More patients received blood products (RBC, FFP, PC) transfusion in the FC group (84.6%) compared with placebo (71.6%). The FC treatment immediately increased plasma fibrinogen concentration and fibrin-based clot strength. Adverse event rates were comparable in each group.	Rahe-Meyeret al. (2016) [58]
	A randomized controlled study of 116 patients undergoing cardiac surgery with CPB treated with placebo or FC	The treatment arm received FC at the end of CPB based on the value of FIBTEM MCF according to the following equation: $\frac{22\,(\text{mm}) - \text{FIBTEM MCF}\,(\text{mm})}{140} \times \text{body weight (kg)}$ to reach a target value of FIBTEM MCF of 22 mm.	FIBTEM MCF increased linearly with FC dose. A target value of FIBTEM MCF of 14 mm might be sufficient to prevent bleeding in cardiac surgery.	Ranucci and Baryshnikova (2016) [132[

	A placebo-controlled randomized trial of 61 patients undergoing aortic replacement surgery involving CPB treated with FC or 0.9% saline	FC (Haemocomplettan P/RiaSTAP; CSL Behring GmbH, Marburg, Germany) dose (g) = (target FIBTEM MCF − actual FIBTEM MCF) (mm) × (body weight [kg]/70) × 0.5 g/mm, targeting FIBTEM MCF of 22 mm and actual FIBTEM MCF at the end of CPB	The bleeding rate was reduced in the FC group compared to the placebo group. FC was more effective and rapid than FFP/platelets for hemostasis.	Rahe-Meyer et al. (2013) [208]
			Transfusion of allogeneic blood components was reduced in the FC group compared to the placebo group (median 2 vs. 13 units, p<0.001) and more patients avoided the blood transfusion (45% vs 100%, p<0.001). There was no observed safety concern with using FC.	Rahe-Meyeret al. (2013) [214]
	A prospective observational study of 50 pediatric cardiac surgery patients undergoing CPB (study group) compared with 50 procedure- and age-matched patients (control group).	During CPB, modified FIBTEM with a heparin-inhibiting agent included in the test was performed.When FIBTEM MCF<9 mm, FC (Haemocomplettan P; CSL Behring GmbH, Marburg, Germany) was given at a dose of 0.25 g to children weighing <5 kg, and 0.5 g to children weighing >5 kg.	Fewer patients in the study group received transfusions of packed RBC (58% vs. 78%, p=0.032) and FFP (14% vs. 78%, p<0.001), whereas more patients in the study group received transfusions of platelets (38% vs. 12%, p=0.002) and FC (16% vs. 2%, p=0.015). There was no difference in postoperative blood loss and hemoglobin levels between the two groups.	Romlin et al. (2011) [213]
	A pragmatic multi-center stepped-wedge cluster randomized controlled trial of a ROTEM–based transfusion algorithm in 7402 patients undergoing cardiac surgery with CPB at 12 hospitals	Blood samples were collected for ROTEM tests (EXTEM, FIBTEM) during the rewarmed. When FIBTEM A10≤8 mm, 4 g FC or 10 units cryoprecipitate were administered; when EXTEM CT>90 ec, 20 IU/kg body weight PCC or 2-4 units FFP were transfused.	The ROTEM algorithm reduced the transfusions of RBC, FFP, and major bleeding following cardiac surgery, and had no effect on platelet transfusion or major complications.	Karkoutiet al. (2016) [215]
	A randomized controlled pilot study of adult cardiac surgery patients at high risk for bleeding comparing transfusion algorithms either guided by ROTEM (n=12) or SLT (n=14)	Blood samples for coagulation monitoring were taken from the arterial line prior to induction, after the start of CPB, after aortic declamping and administration of protamine as well as at 1, 6, 24 and 48 h postoperatively. If FIBTEM MCF<6 mm or fibrinogen was ≤1.5 g/L, 2 g of FC were administered.	There were no differences in blood loss via chest tube drainage and transfusion amounts of RBC, FFP and FC when comparing ROTEM- and SLT-driven transfusion algorithms in subjects that underwent high-risk cardiac surgery.	Lehmannet al. (2019) [216]
	A randomized study of patients with significant postoperative bleeding (>200 mL/h) following elective isolated or combined cardiac surgery treated with ROTEM- (n=52) or SLT-guided (n=52) blood transfusion	Upon arrival at ICU, blood samples were collected. If FIBTEM MCF<8 mm or fibrinogen level<1.2 g/L, ≥2 g FC was administered.	There was no significant difference in transfusion requirements regarding RBC, platelets, plasma, fibrinogen or pooled factors and the re-thoracotomy rate between the two groups. In patients with long CPB-times, ROTEM-guided treatment may result in less bleeding, a marked reduction in costs and long-term mortality.	Haensiget al. (2019) [209]
Liver trans-planta-tion	A retrospective, single-centre, observational study of 243 adult liver transplant patients whose coagulation management was based on ROTEM-guided factor concentrate treatment.	EXTEM and FIBTEM were performed immediately upon admission to the ICU. If EXTEM MCF was reduced and FIBTEM MCF≤9 mm, 2 g FC (Haemocomplettan P; CSL Behring GmbH, Marburg, Germany) was infused; if FIBTEM MCF≤6 mm, 4 g FC was infused. If FIBTEM MCF≥9mm and EXTEM MCF<40mm, 1 apheresis or pooled unit PC was transfused.	EXTEM CT and FIBTEM MCF were predictive of postoperative bleeding with areas under the ROC curves AUC of 0.68 and 0.61, respectively. SLT predictive of bleeding were activated PTT and PT (AUC 0.688 and 0.623, respectively). Fibrinogen concentration, platelet count, and other ROTEM variables failed to demonstrate predictive value for postoperative bleeding (AUC<0.6).	Dötsch et al. (2017) [184]
	A prospective observational study of 20 patients undergoing orthotopic liver transplantation with blood component interventions according to ROTEM or SLT	INTEM and FIBTEM tests were performed with citrated blood within 4 h of collection according to the manufacturer's instructions. When FIBTEM MCF<8 mm fibrinogen replacement was required.	There was a moderate agreement between Clauss fibrinogen and FIBTEM assays to trigger fibrinogen transfusion (Kappa coefficient=0.42, p<0.05). FIBTEM monitoring may improve hemostasis management.	Coakleyet al. (2006) [86]

	A prospective study of 60 adult patients undergoing liver transplantation performed without and with ROTEM-based transfusion algorithm	EXTEM and FIBTEM were performed during the dissection of the native liver, 15 min after the anhepatic phase, 30 min after graft revascularization, and at the end of surgery. If EXTEM A10<26 mm or 26 mm<EXTEM A10≤29 mm and FIBTEM CA≤8 mm, FC (Clottagen; LFB Biomédicaments) was administered at 50 mg/kg body weight.	ROTEM-based transfusion led to a small increase in median fibrinogen transfusions (6.0 g vs. 4.5 g, p=0.50), but was not related to a decrease in blood transfusions or in the number of patients exposed to blood products (RBC, FFP, PC).	Roullet et al. (2015) [217]
	A prospective study of 200 liver transplantations, half treated according to the clinic's standards and half using ROTEM-based hemostasis management strategy	EXTEM and FIBTEM were performed immediately after blood collection at the following time points: after induction of general anaesthesia, at the end of the hepatectomy, 20 min after vascular clamping, and 20 min after graft revascularisation. If EXTEM MCF≤40 mm and FIBTEM MCF<4 mm or 4 mm≤FIBTEM MCF≤8 mm and active bleeding, FC (RiaSTAP™, CLS Behring GmbH, Marburg, Germany) transfusion was required	Significant reduction in RBC transfusion from 5 to 3 units, FFP from 2 to 0 and platelets from 1 to 0, massive transfusion from 13% to 2%, and reduced incidence of postoperative complications were achieved in the ROTEM group compared with the standard group.	Leon-Justel et al. (2015) [218]
Obste-tric hemo-rrhage	A case report of four patients with placental abruption	FC 3 g was administered if FIBTEM A5<7 mm, or <12 mm in the presence of ongoing bleeding.	ROTEM provided better detection of severe coagulopathy than PT and PTT. FC was preferred over FFP and cryoprecipitate for fibrinogen replacement.	McNamara et al. (2015) [219]
	A retrospective study of 255 women with major blood loss>1500 mL and ongoing bleeding or signs of clinical shock	When FIBTEM A5<7 mm or 7–12 mm with ongoing or high risk of hemorrhage FC (RiaSTAP; CSL Behring GmbH, Marburg, Germany) was given at an initial dose of 3 g.	ROTEM-guided algorithm for treatment of coagulopathy in major obstetric haemorrhage led to reduction in the number of units and total volume of blood products transfused, with a reduction in transfusion-associated circulatory overload.	McNamara et al. (2019) [220]
	A prospective study of 42 vs. 51 patients with major hemorrhage before and after ROTEM-guided FC replacement	When EXTEM A5<47 mm and FIBTEM A5<7 or EXTEM A5<47 mm and FIBTEM A5=7-12 mm and active high risk of bleeding 3 g FC (Haemocomplettan P/ RiaSTAP; CSL Behring GmbH, Marburg, Germany) was administered.	FC rapidly corrected coagulation deficits associated with major obstetric hemorrhage, reduced the requirement for blood component therapy from 8 to 3 units, and the attendant risks of complications (e.g., Transfusion-associated circulatory overload).	Mallaiah et al. (2015) [198]
Ortho-pedic surgery	A prospective study of 66 orthopedic patients randomly received modified gelatin solution, hydroxyethyl starch 130/0.4, or exclusively Ringer lactate solution	FIBTEM MCF<7 mm, 30 mg/kg FC (Haemocomplettan P, CSL Behring GmbH, Marburg, Germany) was administered to maintain a serum fibrinogen of about 1.5 g/L.	FIBTEM MCF decreased most significantly in the patients receiving hydroxyethyl starch, followed by gelatin solution and Ringer lactate solution. The dilutional coagulopathy could be reversed by administering FC, even during continuing blood loss and intravascular volume replacement.	Mittermayr et al. (2007) [40]

AIS: Abbreviated Injury Scale, AUC: Area under the curve, A5: Clot amplitude at 5 min after CT measurement; A10: Clot amplitude at 10 min after CT measurement; CFC: Coagulation Factor Concentrate; CPB: Cardiopulmonary Bypass; CT: Clotting Time; ICU: Intensive Care Unit; ER: Emergency Room; FC: Fibrinogen Concentrate; FFP: Fresh froze plasma; HCR: Hemostatic Control Resuscitation; INR: International Normalized Ratio; MCF: Maximum Clot Firmness; MOF: Multiorgan Failure, MTP: Massive Transfusion Protocol; PC: Platelet Concentrates; PCC: Prothrombin Complex Concentrate; PT: Prothrombin Time, PTT: Partial Thromboplastin Time; RBC: Red Blood Cell; RISC: Revised Injury Severity Classification; ROC: Receiver Operating Characteristics; SLT: Standard Laboratory Tests; TRISS: Trauma Injury Severity Score

As summarized in **Table 8**, different critical fibrinogen levels and cut-off values of TEG and ROTEM have been used to guide fibrinogen replacement in trauma [232-236], cardiac surgery [24, 197, 237-239], liver transplantation [70, 184, 217], and any acquired bleeding patients [76, 88]. Most of these thresholds are part of TEG- or ROTEM-guided transfusion algorithms for different blood products (RBC, FFP, platelets) [31, 78, 79, 107, 237-239]. Based on ROTEM measurements, FIBTEM MCF below 8–15 mm (corresponding to A10< 6–12 mm) can be used as a trigger value for fibrinogen substitution in bleeding patients in trauma, cardiovascular surgery, and liver transplantation [78]. Clinically, fibrinogen supplementation

has been recommended for plasma fibrinogen levels below 1 g/L [49] which approximately corresponds to TEG FF MA of 16 mm and ROTEM FIBTEM MCF of 8 mm based on the correlations obtained in our study [159]. Both values are higher than the lower thresholds of the normal ranges for TEG FF (11-24 mm) and ROTEM FIBTEM tests (7-24 mm) as recommended by each manufacturer. This is in agreement with the report that the frequently recommended threshold for fibrinogen substitution of 9 mm MCF in FITEM does not march the recommended threshold of ≤1.0 g/L fibrinogen plasma concentration measured by the Clauss method, although there was a high correlation between FIBTEM MCF and fibrinogen concentration (correlation factor r>0.8) [240]. In addition, divergent cut-off values of TEG and ROTEM have been used in algorithm-based coagulation management in bleeding patients [78, 79] as well as critical and target levels for fibrinogen replacement therapy [76]. These discrepancies should be considered carefully when developing goal-guided fibrinogen replacement using TEG and ROTEM.

A range of fibrinogen levels from 0.8 to 2.0 g/L have been recommended as transfusion triggers in trauma and massive hemorrhage [76,191], with 1 g/L in most guidelines [189]. As a result, a range of A10 and MCF in the FIBTEM assay from 7 mm (target FIBTEM A10: 10–12 mm) [32, 177] or MCF < 7 mm in trauma [179], A10<8 mm in cardiac surgery [241] and MCF<8 mm in liver transplantation [70] have been used to trigger fibrinogen replacement. These values were associated with fibrinogen levels. Moreover, FIBTEM A10 or MCF could determine FC dose. For example, 2–4 g FC was required in trauma patients if FIBTEM A10=4–6 mm; 6 g when FIBTEM A10=0–3 mm [178]. Alternatively, formula was used to calculate fibrinogen replacement dose in cardiac patients based on the targeted increase in MCF or A10 in FIBTEM and body weight as follow [78, 132, 242]:

$$\text{Fibrinogen dosage (g)}=\frac{\text{targeted FIBTEM MCF (mm)}-\text{current FIBTEM MCF (mm)}}{140}\times\text{body weight (kg)} \quad (1)$$

For example, a target of FIBTEM MCF of 22 mm has been used [132] and it requires 6.25 mg/kg body weight of FC to increase FIBTEM MCF by 1 mm [78]. Conversely, a target value of 14 mm may be used leading to a large reduction in FC dose [132].

FC administration was also based on plasma fibrinogen level with variation in the threshold [243, 244]. Specifically, fibrinogen dosage can be calculated based on the desired increment in fibrinogen concentration as follows [245, 246]:

$$\text{Fibrinogen dosage (g)}=0.07\times desired\ increment\ (\tfrac{g}{L})\times(1\text{-hematocrit})\times\text{body weight (kg)} \quad (2)$$

$$\text{Fibrinogen dosage (g)}=0.05\times desired\ increment\ (\tfrac{g}{L})\times\text{body weight (kg)} \quad (3)$$

In contrast, there are fewer studies of TEG-guided fibrinogen transfusion. Compared to ROTEM FIBTEM, TEG FF, the assay run with a platelet inhibitor, has been less employed

to measure fibrinogen levels and guide its administration. TEG FF MA<14 mm was used to trigger fibrinogen supplementation in patients with massive hemorrhage (107), MA≤7 mm in liver transplantation [81]. Alternatively, TEG K and Alpha have been used to guide fibrinogen supplementation with cryoprecipitate in trauma [28, 33, 224, 247-250] which may be not as good as TEG FF MA [101, 251].

Table 8: Summary of threshold values for the TEG- and ROTEM-guided fibrinogen replacement in difference clinical settings. Unless specified, TEG 5000 and ROTEM delta are the systems used to guide the fibrinogen replacement.

Clinical settings	Triggers	Fibrinogen dosage	References
Trauma	TEG FF MA<14 mm	1-2 g	Johanssonet al. (2013, 2014) [79, 107]
	Rapid TEG K>2.5 min Angle<56°	unspecified	
	FIBTEM MCF<7 mm which equals fibrinogen concentration<1.5-2.0 g/L	25-50 mg/kg body weight	Innerhofer et al. (2013) [179]
	FIBTEM MCF<10 mm	2-4 g	Schöchl et al. (2010, 2011) [84, 206]
	FIBTEM A5=4-6 mm FIBTEM A5=2-4 mm FIBTEM A5<2 mm	25 mg/kg body weight 50 mg/kg body weight 75 mg/kg body weight	David et al. (2016) [120]
	FIBTEM A10<7 mm	3-8 g	Schöchl et al. (2014) [207]
	Blood loss>50% with diffuse bleeding and FIBTEM MCF≤7 mm Blood loss>60% with on-going diffuse bleeding, EXTEM/INTEM CT normal, MCF<40 mm and FIBTEM MCF<7 mm	Fibrinogen 2–4 g (maximal 3x2 g), after a total of 6 g fibrinogen give Factor XIII Fibrinogen up to 6 g, followed by Factor XIII 15 IU/kg body weight	Theusinger et al. (2014) [232]
	FIBTEM A10≤7 mm	2-4 g	Nardi et al. (2015) [234]
	FIBTEM A10=0-3 mm FIBTEM A10=4-6 mm	6 g 2-4 g Until FIBTEM A10=10-12 mm	Schöchl et al. (2013) [33, 235] and Schlimp et al. (2013) [178]
	FIBTEM A10<7 mm	2-6 g until FIBTEM A10=10-12 mm	Schöchl et al. (2012) [32]
	EXTEM A10<45 mm and FIBTEM A10<15 mm	2-6 g	Lier et al. (2013) [246]
	FIBTEM A5<5 mm with bleeding or on-going surgery and FIBTEM A20<10 mm	50 mg/kg body weight	Fries et al. (2009) [236]
Cardiac surgery	FIBTEM MCF=0 mm EXTEM A10≤ 40 mm and FIBTEM A10≤ 10 mm	50 mg/kg body weight 25-50-75 mg/kg body weight for a target of EXTEM A10>50 mm and FIBTEM A10>15 mm	Weber et al. (2012) [24] and Görlinger et al. (2011) [197]
	FIBTEM MCF < 10 mm	2-6 g	Sartorius et al. (2014) [237]
	FIBTEM MCF=0 mm EXTEM MCF≤50 mm and FIBTEM MCF≤16 mm with diffuse bleeding after protamine	50 mg/kg body weight 25-50-75 mg/kg body weight	Hanke et al. (2012) (238)
	FIBTEM MCF<8 mm	2 g	Girdauskas et al. (2010) [239]
Liver transplantation	FIBTEM MCF≤9 mm FIBTEM MCF≤6 mm	2 g 4 g	Dötsch et al. (2017) [184]
	With diffuse bleeding FIBTEM MCF<8 mm FIBTEM MCF<4 mm Without diffuse bleeding EXTEM MCF<35 mm and FIBTEM MCF<8 mm	25 mg/kg body weight 50 mg/kg body weight	Goerlinger (2006) [70]
	TEG FF MA≤7 mm	25-50 mg/kg body weight	De Pietri (2016) [81]
	FIBTEM A10≤8 mm	50 mg/kg body weight	Roullet et al. (2015) [217]
Trauma, visceral, transplant and cardiovascular surgery	TEG FF MA 7-14 mm TEG FF MA 0-7 mm	20 mg/kg body weight 30 mg/kg body weight	Stensballe et al. (2014) [31]
	FIBTEM MCF 6-9 mm FIBTEM MCF 0-6 mm	20 mg/kg body weight 30 mg/kg body weight	
	EXTEM A10<40 mm and FIBTEM A10<10 mm	20-50-100 mg/kg body weight	Görlinger et al. (2012) [78]

Compared to ROTEM MCF, TEG α angle in particular kaolin-activated TEG has been mostly used as the parameter to guide fibrinogen replacement (mostly by cryoprecipitate), while TEG MA was used to guide platelets transfusion, but cannot distinguish fibrinogen from platelet deficiency when a single TEG assay was conducted without platelet inhibitors, and thus its use to guide fibrinogen transfusion may be inaccurate [251].

This underlines the necessity to implement different individual triggers for fibrinogen supplementation depending on the viscoelastic hemostatic tests used and clinical settings. For example, in bleeding trauma patients, a FIBTEM A10≤7 mm may serve as a trigger for FC administration with a target MCF of 10–12 mm. In contrast, when using TEG FF, MA<14 mm was recommended as the trigger [252].

The latest guideline from Society of Cardiovascular Anesthesiologists suggests fibrinogen supplementation in cardiac surgery patients at cut-off values of TEG FF MA<8 mm and ROTEM FIBTEM A10<10 mm [90]. Alternatively, cut-off values of kaolin TEG K>2.4 min, angle<60.6º and MA<51.2 mm have been recommended for diagnosis and treatment of severe hypofibrinogenemia (fibrinogen <1 g/L) in trauma patients, while K time could be used to guide early cryoprecipitate or FC transfusion [91].

Study suggested that clot amplitude 10 min after R or CT rather than MA/MCF reflects a more dynamic part of the hemostatic process and may lead to earlier goal-directed transfusion therapy [118]. In combination with EXTEM, FIBTEM and APTEM were used to guide transfusion of platelets and treatment of hyperfibrinolysis with tranexamic acid, respectively. Kaolin TEG, rapid TEG and TEG FF have been used in a RCT being conducted to investigate if early treatment with FC reduces blood transfusion in severe postpartum hemorrhage [253].

6. Comparison between TEG and ROTEM for Functional Fibrinogen Assays

A number of studies compared the reagents and devices between TEG FF and ROTEM FIBTEM. Solomon et al. showed that TEG FF MA was larger than FIBTEM MCF when performed with either their standard assay reagents (lyophilized tissue factor and abciximab on TEG and a combination of ex-tem and fib-tem on ROTEM) or the same assay reagent [100]. In addition, the TEG FF reagent produced higher values than the FIBTEM reagent on both TEG and ROTEM. Schlimp et al. compared different fibrinogen assays in eliminating platelet effects on TEG MA and ROTEM MCF. It was found that abciximab based on glycoprotein IIb/IIIa inhibition was less effective at inhibiting the platelet contribution to clot strength than cytochalasin D based on prevention of platelet cytoskeletal reorganization, resulting in larger TEG FF MA compared to ROTEM FIBTEM MCF and affecting their correlations and changes with fibrinogen concentration. In addition, the combination of both inhibition provided the most accurate assessment of the clot strength and fibrinogen function [254]. It has been speculated that the ROTEM FIBTEM reagent might contain stabilizing agents (e.g., dimethyl sulfoxide)

and more tissue factor than the TEG FF reagent [255]. These results are consistent with other studies comparing TEG and ROTEM FF assays for whole blood from surgical patients [102, 256], trauma patients and healthy volunteers [149, 254].

However, the differences between TEG FF MA and ROTEM FIBTEM MCF obtained using the same reagents [100,255] implies that TEG system itself may also be a contributing factor. The hardware differences between the two systems include the mechanisms for cup/pin rotation, detection of the rotation, cup materials and interior surface properties [257, 258].

Meyer et al. compared different TEG and ROTEM tests including TEG FF and FIBTEM, and Clauss method for detection of trauma-induced coagulopathy and goal-directed transfusion therapy [118]. Specifically, TEG FF and FIBTEM early amplitudes (A5,10) and MA/MCF had similar correlations with Clauss fibrinogen level, and could differentiate coagulopathic and transfused patients from non-coagulopathic and non-transfused patients.

Prüller et al. compared fibrinogen assays using TEG FF and ROTEM FIBTEM in surgical patients in terms of their MA and MCF values, and correlations with Clauss fibrinogen level [256]. It was found that TEG FF MA was higher than ROTEM FIBTEM MCF and their MA and MCF corresponded to different Clauss fibrinogen levels. The TEG FF MA showed a weaker correlation with Clauss fibrinogen than ROTEM FIBTEM MCF (R^2=0.542 vs. 0.671).

Different TEG (Rapid, Kaolin, FF) and ROTEM tests (EXTEM, INTEM, FIBTEM) were compared for their sensitivity to detect fibrinolysis induced by tissue plasminogen activator in whole blood [259]. Compared to other tests, TEG FF and ROTEM FIBREM provided more rapid detection of fibrinolysis, but TEG FF detected changes in clot strength as well. Comparison of tissue factor-triggered ROTEM FIBTEM and EXTEM with contact-activated kaolin TEG in patients undergoing liver transplantation showed the highest and lowest hyperfibrinolysis detection rates by FIBTEM and kaolin TEG, respectively, suggesting the effects of coagulation activators and platelet inhibitors on sensitivity to identifying hyperfibrinolysis [260].

In contrast with hyperfibrinolysis detection, we found only kaolin TEG and ROTEM EXTEM as the methods of measuring hypofibrinolysis (also called fibrinolysis shutdown) instead of TEG FF and ROTEM FIBTEM. In one study of 914 trauma patients (ISS≥15), the threshold for hypofibrinolysis was determined for EXTEM ML at 5.5% with a sensitivity of 61.6% and specificity of 58.4% [261]. The study reported 29.9% hypofibrinolysis. In another study of 550 severe trauma patients with a median ISS of 19, EXTEM ML<3.5% was selected to define hypofibrinolysis with a sensitivity 42.5% and specificity 76.5% [262]. The method identified 25.6% hypofibrinolysis. A number of studies have used TEG in particular kaolin TEG LY30<0.81% to detect hypofibrinolysis in trauma patients with a median ISS of 25 [263,264]. These studies reported fibrinolysis phenotypes with different prevalence: hypofibrinolysis at 29.9%, 25.6%, 46%; physiologic fibrinolysis at 63.0%, 70.7%, 36%. The ROTEM method

indicated physiologic fibrinolysis as the predominant phenotype with 63% [261] and 71% [262] followed by hypofibrinolysis, while the TEG method showed hypofibrinolysis as the most common phenotype with 46% followed by physiologic fibrinolysis with 36% [264]. The discrepancy could be the difference in patients characteristics (e.g., ISS) and method itself (tissue factor-activated ROTEM EXTEM vs. contact-activated kaolin TEG). A recent retrospective analysis of the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial found 61% of hypofibrinolytic patients as determined by kaolin TEG LY30<0.9%, followed by 22% of hyperfibrinolytic patients based on LY30≥3% [265]. The study also suggested that hypofibrinolysis did not reflect shutdown of enzymatic fibrinolysis with hypercoagulability, but rather a type of coagulopathy characterized by fibrinolytic activation with concurrent fibrinogen consumption and platelet dysfunction.

There is a lack of studies to compare the utilities of TEG and ROTEM for diagnosis of coagulopathy, prediction of mortality and the requirement for massive transfusion, although both have been reported useful [106,119]. We conducted a comparative study of FF assays using TEG and ROTEM in trauma patients [127,159] to determine 1) their interchangeability of the key parameter values obtained by the two systems in all trauma patients as well as severe trauma patients randomized to receive their fibrinogen concentrate or placebo (normal saline), and 2) utility of each system for predicting clinical outcomes and monitoring any changes in coagulation profiles in the trauma patients randomized for treatment with fibrinogen concentrate or placebo. In addition, a crossover analysis (ex-tem and fib-tem on TEG) was also conducted to confirm whether the assay reagents or the device could contribute to the observed differences. Overall, we found that TEG and ROTEM parameter values were correlated, being strongest between MA and MCF, but were significantly different, and their agreement fell outside acceptable limits and thus their values were not interchangeable, arguably due to differences in both devices and assay reagents used. Specifically, ROTEM FIBTEM MCF had a higher correlation with Clauss fibrinogen (ρ=0.87 vs. 0.75) and lower value than TEG FF MA (17.1±8.0 mm vs. 22.4 ± 7.5 mm). Clinically, TEG MA and ROTEM MCF showed reasonable predictive accuracy for coagulopathy and plasma transfusion, but poor accuracy for any red blood cells and cryoprecipitate transfusions. Both well predicted hypofibrinogenemia (fibrinogen concentration < 1 g/L) with AUC of 0.95 and 0.96. ROTEM FIBTEM MCF seems to be more consistent with the duration of the between-group difference as indicated by fibrinogen levels than TEG FF MA. In addition, ROTEM FIBTEM detected changes in clot lysis (LI30) over hospitalization time.

In a study similar to ours, TEG and ROTEM were compared for functional fibrinogen assays in trauma to determine specific cut-offs of TEG MA and ROTEM MCF for an increased risk of receiving a transfusion [140]. It was found that TEG FF MA and ROTEM FIBTEM MCF correlated well (ρ=0.71, $p<0.001$) and had the same correlation coefficient with Clauss

fibrinogen level (ρ=0.64, p<0.001). **Figure 3** shows a strong correlation between TEG FF MA and ROTEM FIBTEM MCF (r=0.77, p<0.001) based on the pooled data of our study [127] and Meyer et al. [140], but a larger TEG FF MA than ROTEM FIBTEM MCF on average (20.63±7.11 mm vs. 16.23±7.73 mm, n=363, p<0.001).

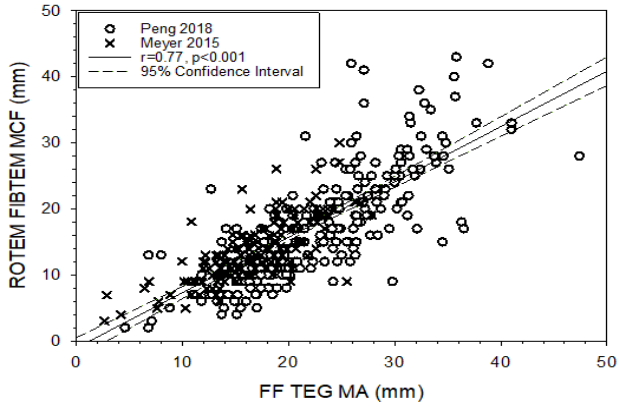


Figure 3: Comparison of TEG FF MA values and ROTEM FIBTEM MCF values. The correlation coefficient was obtained through linear regression of pooled data from Peng 2018 [127] and Meyer 2015 [140]. MCF=0.8384MA-1.065 (R^2=0.5938). The means of TEG FF MA and ROTEM FIBTEM MCF are 20.63 ± 7.11 mm and 16.23±7.73 mm (n=363).

7. Conclusions

TEG and ROTEM functional fibrinogen tests play important roles in diagnosis of fibrinogen-related coagulopathy, prediction of transfusion requirements, assessment and guidance for fibrinogen replacement including fibrinogen levels and its hemostatic effects.

Their potential clinical benefits are often inferred from trauma and cardiac surgery literature. The clot strength of TEG FF and ROTEM FIBTEM is mostly used parameter for discrimination of fibrinogen deficiencies, and increased in a fibrinogen concentration-dependent manner. Their correlations with Clauss fibrinogen levels are varied depending on patient population and range of fibrinogen concentrations. Since TEG FF and ROTEM FIBTEM have shown the strongest correlation with plasma fibrinogen level, they are recommended for guided fibrinogen replacement and monitoring its hemostatic effect.

In addition to TEG FF, both kaolin and rapid TEG have been used with parameters K time and α angle as measures of the hemostatic function of fibrinogen. However, ROTEM FIBTEM MCF has been mostly used for discrimination of fibrinogen deficiencies and assessment of its hemostatic effect.

When using TEG FF and ROTEM FIBTEM to diagnose hypofibrinogenemia, predict transfusion requirements and guide fibrinogen replacement, other variables such as hematocrits, Factor XIII levels, resuscitation fluids and fibrinogen concentration ranges should be taken into consideration. Both TEG and ROTEM have been used to detect systemic fibrinolysis (physiologic, hypo and hyperfibrinolysis) and monitor antifibrinolytic effects.

Studies comparing TEG FF and ROTEM FIBTEM suggest a stronger correlation of the latter with plasma fibrinogen concentration likely due to its more effective elimination of platelet contribution to clot strength. It should be aware that the studies supporting the use TEG and ROTEM are limited for trauma and surgical bleeding patients. Even without robust clinical data, TEG and ROTEM are likely to remain popular for the hemostatic management of bleeding patients.

Future studies comparing different intervention thresholds of TEG and ROTEM and the therapeutic effect of predefined thresholds for fibrinogen augmentation are required to optimize fibrinogen substitution (dosage and time of fibrinogen administration) to improve its efficacy and patient safety and reduce costs in various clinical settings. Studies comparing pre-emptive and guided fibrinogen replacement are also warranted.

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