Received: 30 June 2022 | Revised: 7 November 2022 | Accepted: 12 November 2022

https://doi.org/10.1016/j.rpth.2022.100031

ILLUSTRATED REVIEW

Viscoelastic testing: an illustrated review of technology and clinical applications

Jan Hartmann MD[1] | Daniela Hermelin MD[2,3] | Jerrold H. Levy MD[4]

[1]Haemonetics Corporation, Boston, Massachusetts, USA

[2]Department of Pathology Saint Louis University School of Medicine, Saint Louis, Missouri, USA

[3]Medical Affairs, ImpactLife, Davenport, Iowa, USA

[4]Duke University Medical Center, Durham, North Carolina, USA

Correspondence
Jan Hartmann, Haemonetics Corporation, Boston, MA 02110, USA.
Email: jan.hartmann@haemonetics.com

Handling Editor: M Sholzberg

Abstract

Viscoelastic testing (VET), including thromboelastography and thromboelastometry, provides a rapid and comprehensive picture of whole blood coagulation dynamics and hemostasis that can be reviewed and evaluated at the point-of-care. This technology is over 50 years old; however, over the past few years, there has been a significant increase in research examining the use of VET. Best practice guidelines for the use of VET exist in both the United States and Europe, particularly for elective cardiac surgery, although recommendations for implementation are somewhat limited in some clinical areas by the lack of studies constituting high-grade evidence. Other challenges to implementation surround validation of the technology in some care settings as well as lack of training. Nevertheless, there is a wide range of potential clinical applications, such as treating coagulopathies in liver disease and transplant surgery, critical care, as well as within obstetrical hemorrhage. In this illustrated review, we provide an overview of viscoelastic testing technology (also called viscoelastic hemostatic assays) and describe how the assays can be used to provide a broad overview of hemostasis from clot formation to clot lysis, while highlighting the contribution of coagulation factors and platelets. We then summarize the major clinical applications for viscoelastic testing, including more recent applications, such as in COVID-19. Each section describes the clinical context, and key publications, followed by a representative algorithm and key guidelines

KEYWORDS
blood coagulation, clinical applications, fibrinolysis, guidelines, hemostasis, ROTEM, TEG, thromboelastography, thromboelastometry, viscoelastic testing

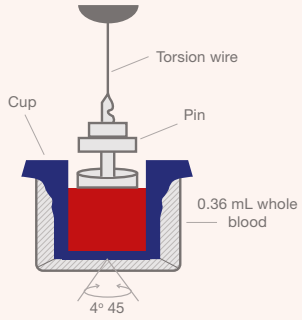
Essentials

- Viscoelastic testing (VET) provides a full hemostasis overview from a patient whole blood sample.
- VET can be rapidly reviewed and assessed at the point-of-care and acted upon in real-time.
- Clinical use cases area established in trauma, cardiovascular surgery, and liver transplant areas.
- More high-quality data is needed to identify and further establish clinical benefit areas with VET.

Viscoelastic testing: technology and principles

Viscoelastic testing technology [1,2]

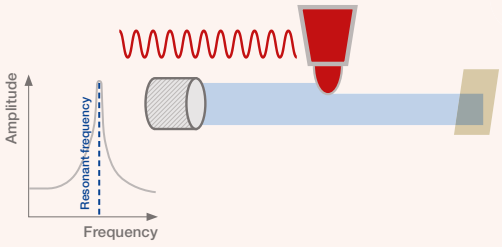
Mechanical viscoelastic testing



Example shows TEG®5000 system

TEG®5000: whole blood sample is placed in a heated rotating cup with a static pin **ROTEM®Delta/ROTEM®Sigma:** whole blood sample is placed in a stationary cup

Resonance viscoelastic testing



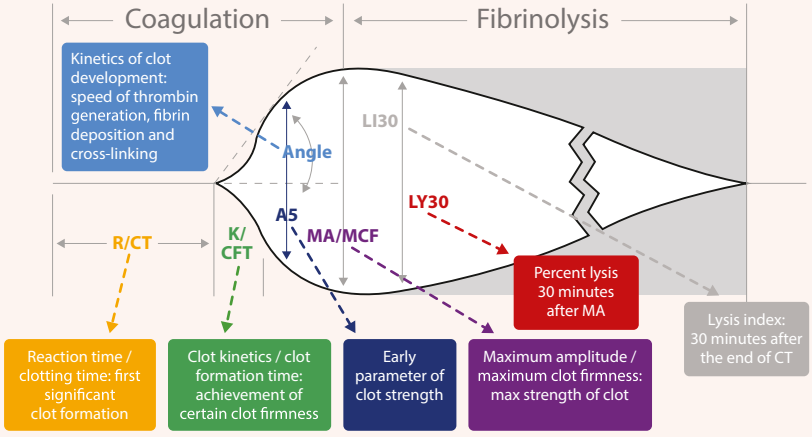
Example shows TEG®6s system

TEG®6s: Uses resonance frequency to measure whole blood viscoelasticity

TEG® Analyzer to conduct thromboelastography; ROTEM® Analyzer to conduct thromboelastometry

The viscoelastic tracing [3]

In healthy individuals, hemostasis is a tightly orchestrated process that culminates at the formation of a platelet-fibrin clot at the site of endothelial injury, followed by localized clot breakdown, known as fibrinolysis.



Taking a distinct shape, the viscoelastic tracing captures the cellular and plasmatic elements involved in the hemostasis process.

The overall tracing can offer insight to an individual's ex vivo whole blood clot formation status. The timepoints of the viscoelastic trace are simply divided into the coagulation and clot lysis stages, which can then be further broken down into additional parameters including clot initiation, clot kinetics and clot strength.

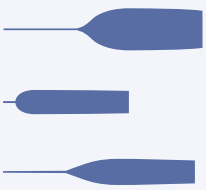
Viscoelastic testing for hemostasis management

Hemostatic imbalance [3,4]

There are a number of pathophysiologic mechanisms, either congenital or acquired, that can lead to hemostatic disturbances that sway the pendulum toward excessive bleeding or clotting. These imbalances can be captured and projected through the shape of the viscoelastic tracing. When applied clinically, viscoelastic testing is designed to support and guide, and not replace, clinical judgement.

Hypocoagulable (tendency to bleed)

- Clot initiation time increased: factor deficiencies or inhibitors
- Clot kinetics decreased: hypofibrinogenemia, thrombocytopenia
- Clot strength decreased: hypofibrinogenemia, thrombocytopenia, factor inhibitors
- Increased clot lysis: increased tissue plasminogen activator release or severe factor XIII deficiency, depletion of lysis inhibitors (e.g., PAI-1)



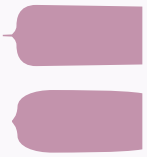
Low clotting factor function or anticoagulant effect

Low platelet function/low fibrinogen level

Low clotting factors, low platelet function

Hypercoagulable (tendency to clot)

- Clot initiation time decreased: increased thrombin formation, early disseminated intravascular coagulation
- Clot strength increased: thrombocytosis, hyperfibrinogenemia
- Decreased clot lysis: fibrinolysis shutdown

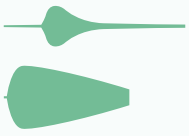


Platelet hypercoagulability

Platelet and enzymatic hypercoagulability

Fibrinolysis (excessive clot breakdown)

- Reaction time: can be short, normal or prolonged
- Maximum clot strength: continuous or sudden decrease
- Clot lysis after 30 minutes: increased



Primary fibrinolysis

Secondary fibrinolysis

Hypofibrinolysis (total fibrinolytic shutdown)

- Reaction time: can be short, normal or prolonged
- Maximum clot strength: continuous
- Clot lysis after 30 minutes: close to 0%

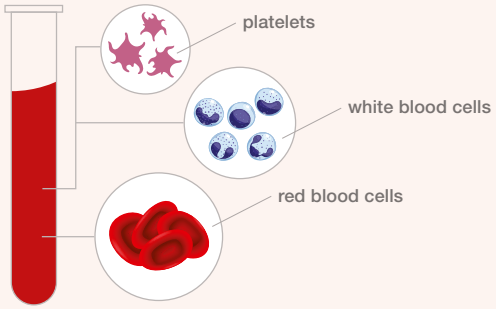
Total fibrinolytic shutdown

PAI-1; plasminogen activator inhibitor 1

Viscoelastic testing reflects insight from conventional laboratory tests and defines the hemostatic profile

Advantages of viscoelastic testing compared with conventional coagulation testing [5]

Viscoelastic testing



Conventional laboratory coagulation testing

Viscoelastic tests	Conventional laboratory coagulation assays
Whole blood sample	Platelet-poor plasma sample
Can be viewed and evaluated at the point-of-care	Tests take place in a central laboratory
Results within minutes	Longer turn-around time
Holistic overview of *ex vivo* clotting	Snapshot of individual steps in clotting process

Challenges associated with viscoelastic testing are detailed on page 16

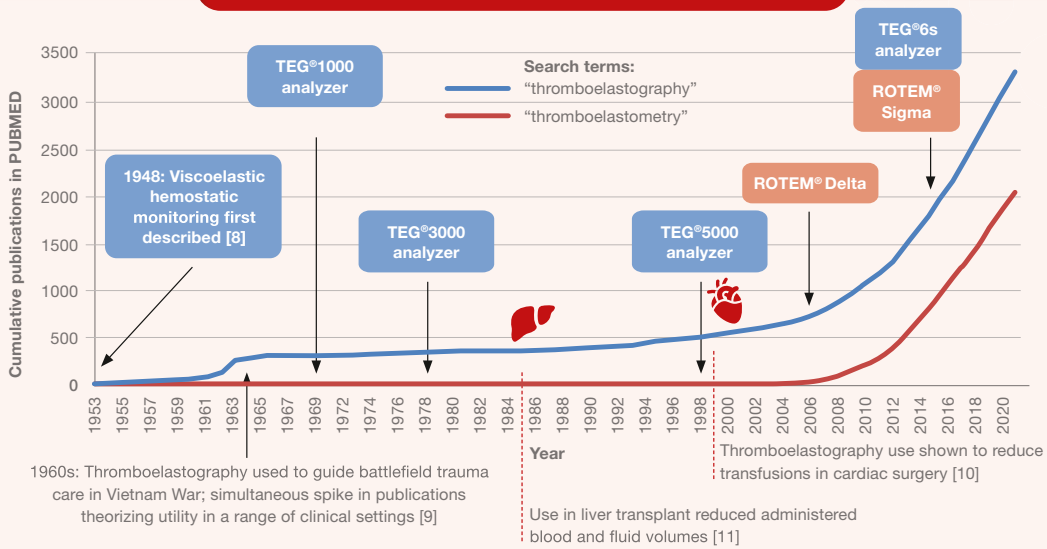
Specialized assays for assessing hemostasis [6,7]

Assay	TEG® assays (activator)	ROTEM® assays (activator)	Interpretation of assay
Contact activation pathway	Kaolin TEG® (Kaolin)	INTEM® (ellagic acid)	Assesses the contact activation pathway (intrinsic pathway) partially measured by aPTT
Tissue factor (TF) activation pathway	–	EXTEM® (tissue factor)	Assesses the tissue factor activated pathway (extrinsic pathway) partially measured by PT
Contact activation + TF pathway	RapidTEG® (Tissue factor + kaolin)	–	Assesses both activation pathways
Heparinase	Kaolin TEG® with lyophilized heparinase	HEPTEM® (ellagic acid + lyophilized heparinase)	Assesses the presence of systemic heparin via comparison with the Kaolin/INTEM assay
Fibrinogen	TEG® Functional Fibrinogen (tissue factor + abciximab)	FIBTEM® (tissue factor + cytochalasin D)	Uses a platelet inhibitor to assess the relative contribution of fibrinogen to clot strength independent of platelets
Native whole blood sample	Native TEG®	NATEM®	Used for custom hemostasis tests. Not for clinical use due to the long reaction rate
Platelet function via AA and ADP activation	TEG® PlateletMapping®	No platelet function test exists on the platform; however, it can be used in conjunction with VerifyNow™ & Multiplate® platelet function impedance aggregometry analysis	Platelet receptor-specific tracing to identify levels of platelet inhibition and aggregation

AA, arachidonic acid; ADP, adenosine diphosphate; aPTT, activated partial thromboplastin test; PT, prothrombin time; TF, tissue factor

Rapid growth of research within clinical specialties

Body of literature related to viscoelastic testing by year



Viscoelastic testing: clinical areas with active research [6]

Cardiothoracic and vascular surgery

- Presurgical platelet function tests
- Peri-operative hemostasis testing
- Intensive care unit management

Gynecologic and obstetric care

- Management of postpartum hemorrhage
- Identifying hypercoagulability as a potential cause for miscarriage

Interventional cardiology

- Assessing patients prior to surgery
- Personalized dual anti-platelet therapy
- Periprocedural monitoring in interventional cardiology

Liver disease and transplant

- Patients with cirrhosis undergoing invasive procedures
- Patients with cirrhosis experiencing active bleeding
- Liver transplant surgery

Trauma and emergency

- Trauma-induced coagulopathy
- Traumatic brain injury and associated coagulopathy

Critical care

- Management of clinical conditions associated with coagulopathy and thrombotic complications e.g., hemorrhage, mechanical support, sepsis and COVID-19

NOTE: indications for different viscoelastic assays vary by platform, see local label for full details of cleared indications

Clinical applications: cardiothoracic and vascular surgery

Clinical context

Bleeding after cardiopulmonary bypass occurs in approximately 20% of patients. There are multiple factors that lead to bleeding, which cannot always be distinguished by laboratory tests [12]:

- Hemodilution
- Platelet function defects
- Use of interoperative anticoagulants
- Activation of coagulation and inflammation
- Fibrinolysis

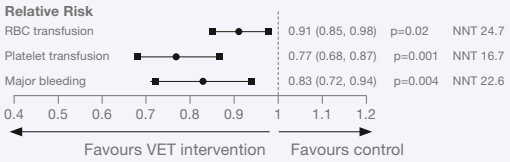
Implementation of viscoelastic testing into an integrated transfusion algorithm during cardiac surgery can lead to [13]:

- Reduced red blood cell transfusions
- Reduced platelet transfusions
- Reduction in major postsurgical bleeding

Viscoelastic testing (VET) is widely used to diagnose and differentiate between coagulopathic and surgical bleeding as well as guiding treatment in cardiac surgery patients.

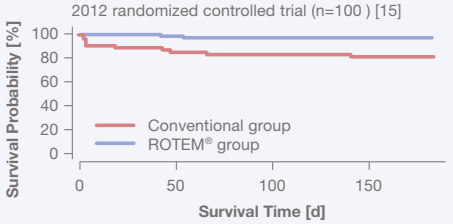
Key data: Improvements in transfusion and major bleeding [14] and Kaplan–Meier curve survival [15] with VET-algorithm management in cardiac surgery

Use of VET-guided transfusion versus current standard of care reduced transfusions and risk of major bleeding in a 2016 randomized controlled trial (n=7402) [14]



Reproduced with permissions from Karkouti 2016 [14]

Use of VET-guided transfusion improved survival in a 2012 randomized controlled trial (n=100) [15]



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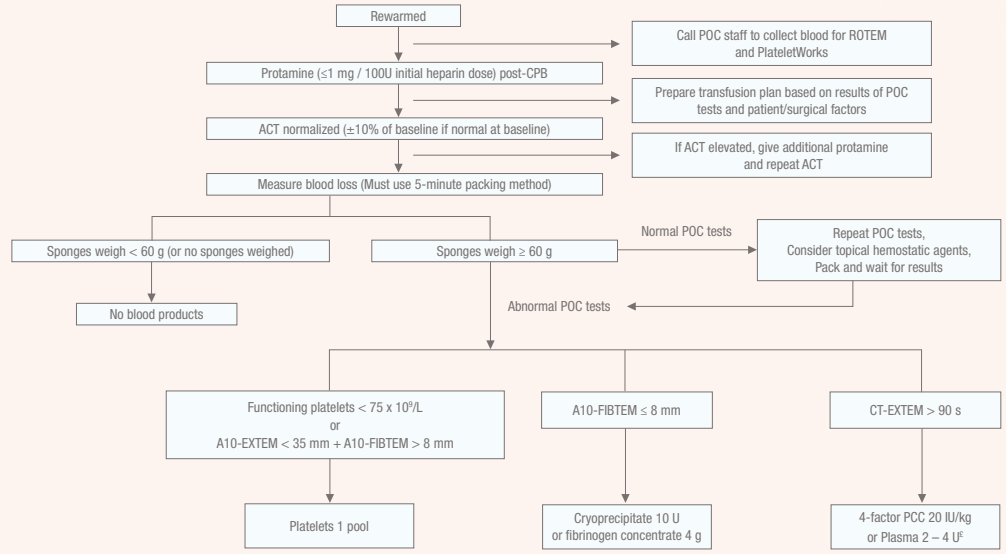
Key publications

Reference	Study design	Key results
Santos 2020 [16]	Meta-analysis of 21 randomized controlled trials (n=8,900)	Viscoelastic testing was associated with reductions in mortality, risk of acute kidney injury, as well as risk of blood product transfusion, when compared with standard of care
Meco 2020 [17]	Meta-analysis of 7 randomized controlled trials (n=1,035)	Viscoelastic testing algorithms reduce red blood cell and fresh frozen plasma use compared with clinician discretion. No difference found in platelet transfusions
Li 2019 [18]	Meta-analysis of 19 studies including 13 randomized controlled trials (n=15,320)	The use of viscoelastic testing-guided transfusion algorithms reduced blood loss volume, and relative risk of red blood cell, platelet and fresh frozen plasma transfusions compared with standard care
Serraino 2017 [12]	Meta-analysis of 15 randomized controlled trials (n=8,737)	The use of viscoelastic testing-guided algorithms reduced red blood cell and platelet transfusion compared with standard of care. The frequency of severe acute kidney injury was reduced in the viscoelastic testing group in the four trials where this was reported
Deppe 2016 [19]	Meta-analysis of 17 studies (n=8,332)	The use of viscoelastic testing-guided algorithms reduced the odds of receiving allogenic blood products and the incidence of thromboembolic events, compared with standard of care in RCTs and observational studies
Wikkelsø 2016 [20]	Meta-analysis of 15 randomized controlled trials (n=1,493)	Compared with transfusion guided by any other method, viscoelastic testing-guided transfusion reduced overall mortality (low quality evidence)
Karkouti 2016 [14]	Randomized controlled trial (n=7,402)	The use of viscoelastic testing reduced red blood cell transfusions, platelet transfusions and the incidence of major bleeding, compared with current standard of care
Weber 2012 [15]	Randomized controlled trial (n=100)	The use of viscoelastic testing reduced red blood cell transfusion, fresh frozen plasma and platelet transfusion and the 6-month mortality rate compared with current standard of care

VET, viscoelastic testing

Treatment algorithm for cardiac surgery

Suggested treatment algorithm for postsurgical bleeding in cardiac surgery patients [14]



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Key guidelines

"Both the consultants and ASA [American Society of Anesthesiologists] members agree that if coagulopathy is suspected, obtain viscoelastic assays (e.g., TEG and ROTEM), when available, as well as platelet count. They both strongly agree that if viscoelastic assays are not available, obtain standard coagulation tests
(e.g., INR, aPTT, fibrinogen concentration), as well as platelet count for monitoring."
Practice guidelines for perioperative blood management ASA 2015 [21]

Section 1.8.1 Cardiovascular surgery
"We recommend the use of standardised VHA-guided haemostatic algorithms with pre-defined intervention triggers [Evidence Grade 1B]"
Management of severe perioperative bleeding ESA 2016 [22]

"The evidence supports the use of perioperative point-of-care testing in patients having cardiac surgery to reduce transfusion requirements. Furthermore, it should be noted that most of the published studies included only viscoelastic coagulation tests… Cut-off levels for non-acceptable intraoperative and postoperative platelet function with the different devices and the subsequent interventions are yet to be determined."
EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery 2018 [23]

ACT, activated clotting time; aPTT, activated partial thromboplastin clotting time; POC, point-of-care; PT, prothrombin time; INR, international normalized ratio; VHA, viscoelastic hemostasis assays

Clinical applications: interventional cardiology

Clinical context

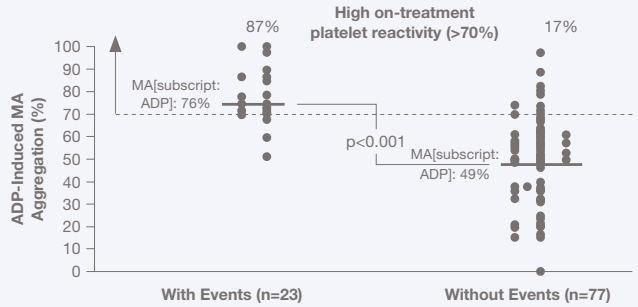
Non-surgical patients with acute coronary syndrome can be treated with dual antiplatelet therapy alongside with percutaneous coronary interventions.

Platelet function can be monitored in these patients using whole blood platelet function tests including: VerifyNow®, Multiplate® and TEG® analyzer with the PlateletMapping® assay.

Implementation of platelet function testing in non-surgical cardiac patients can [24]:

- Inform de-escalation/escalation of antiplatelet therapy
- Provide valuable prognostic information
- Predict risk of bleeding/thrombosis
- Determine timing for surgical interventions

Key data: ischemic events associated with high on-treatment platelet reactivity measured by ADP-induced thromboelastography



Higher platelet reactivity (measured by ADP-induced thromboelastography) is seen in patients who experience ischemic events compared with patients without events (p<0.001)

Dashed line indicates cut point for high platelet reactivity

Figure produced with permissions from Bliden 2007 [25]

Key guidelines and consensus statements

"PFT [platelet function tests] and genetic testing may be considered as optional tools for guidance of treatment when DAPT escalation or de-escalation is required. Each of these guided approaches has advantages and disadvantages"
Updated Expert Consensus Statement on Platelet Function and Genetic Testing for Guiding P2Y 12 Receptor Inhibitor Treatment in Percutaneous Coronary Intervention [24]

"Neither platelet function testing nor genetic testing can be recommended for tailoring DAPT. It may be considered in specific situations (e.g., patients suffering from recurrent adverse events) if the results may change the treatment strategy. This is the case for patients undergoing CABG who are exposed to DAPT"
ESC/EACTS focused update on dual antiplatelet therapy in coronary artery disease [26]

Key publications

Reference	Study design	Key publications
Xu 2022 [27]	Systematic review of 113 articles	Whole blood PlateletMapping (TEG®) was comparable to other platelet function tests in predicting ischemic risk and monitoring patient response to dual antiplatelet therapy
CREATIVE trial (Tang 2018) [28]	Randomized Controlled Trial (n=1,078)	The use of PlateletMapping (TEG®) and intensified antiplatelet therapies in percutaneous coronary intervention reduced the risk of major bleeding versus standard antiplatelet therapies
Wang 2011 [29]	Randomized Controlled Trial (n=306)	Modifying clopidogrel maintenance doses according to platelet reactivity in percutaneous coronary intervention reduced the rate of major adverse cardiovascular events compared to use of fixed doses

ADP, adenosine diphosphate; CAGB, coronary artery bypass graft; DAPT, dual antiplatelet therapy; PFT, platelet function tests

Clinical applications: trauma

Clinical context

Both penetrating and blunt trauma can lead to massive hemorrhage and hypovolemic shock warranting massive transfusions. Often these patients develop trauma-induced coagulopathy (TIC) and viscoelastic testing can help define the hemostatic defect from the formation of the clot to the degree of fibrinolysis.

Viscoelastic testing is recommended to monitor rapid alterations in hemodynamic function in patients who sustain traumatic injuries.

Viscoelastic testing, particularly PlateletMapping®, is utilized in neurotrauma to identify patients who arrive with platelet dysfunction.

The use of viscoelastic testing in trauma patients and goal-directed resuscitation transfusion algorithm may improve [30]:

- Survival rates
- Required blood products
- Hemorrhagic control

Key data: The ITACTIC trial – the only multi-center randomized controlled trial in trauma patients to date, conducted following diagnostic validation studies of TEG® and ROTEM® parameters [31]

Enrolment

- 203 allocated to conventional coagulation tests
- 208 allocated to viscoelastic testing – **see treatment algorithm on next page**

Measures/ follow-up

- Primary: proportion of patients alive and free of massive transfusion
- Secondary: 28-day mortality
- Pre-specified subgroups included severe traumatic brain injury patients

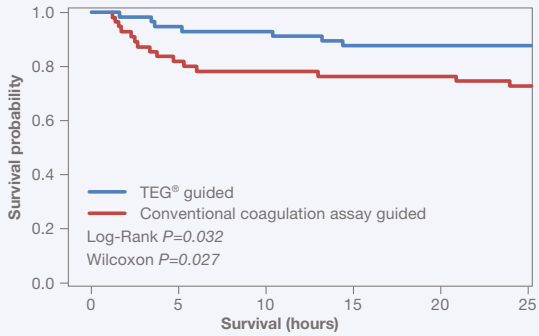
Results

- No differences in mortality or massive transfusion at 24 hours
  - Odds ratios favored use of a viscoelastic testing algorithm in patients with TBI (significant) and PT ratio >1.2 (non-significant) at baseline
- No difference in overall mortality at 28 days
- Incidence of thromboembolic events was lower for VET vs CCT: 9% vs 14% (non-significant)

Study limitations

- Low incidence of trauma-induced coagulopathy limited the power of the study
  - 75% showed no baseline coagulopathy
  - Only 36% in CCT group and 67% in VET group received any study intervention

Further data: use of a TEG®-guided algorithm improved survival compared with a conventional coagulation assay-guided algorithm in a randomized controlled trial of 111 trauma patients [32]



	TEG®-guided	Conventional coagulation assay guided	P-value
Deaths at 28 days	19.6%	36.4%	0.049
Deaths at 6 hours	7.1%	21.8%	0.032

Patients randomized to the TEG®-guided algorithm received similar or fewer frozen plasma and platelet units than the control group post-injury

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CCT, conventional coagulation tests; PT, prothrombin time; VET, viscoelastic tests

Treatment algorithm in trauma settings

Algorithm for viscoelastic testing-augmented protocols for major trauma hemorrhage: an example from the ITACTIC trial [31]

	ROTEM® device	TEG® device
Fibrinogen	If FIBTEM A5 <10 mm Give additional fibrinogen	If FF TEG MA <20 mm Give additional fibrinogen
Platelets	If (EXTEM A5 – FIBTEM A5) <30 mm Give additional platelets	If (rTEG MA- FF TEG MA) <45 mm Give additional platelets
Plasma	If EXTEM A5 ≥40 mm AND EXTEM CT >80 s Give additional units of plasma	If rTEG MA ≥65 mm AND rTEG ACT >120 s Give additional units of plasma
Tranexamic Acid	If EXTEM LI30 <85% Give additional tranexamic acid	If rTEG LY30 >10% Give additional tranexamic acid

Key guidelines

"We recommend that resuscitation measures be continued using a goal-directed strategy, guided by standard laboratory coagulation values and/or VEM (Grade 1B)… we suggest the use of POC platelet function devices as an adjunct to standard laboratory and/or POC coagulation monitoring in patients with suspected platelet dysfunction. (Grade 2C)."
European Multidisciplinary Task Force for Advanced Bleeding Care in Trauma [33]

"Once major bleeding has been controlled and the rate of transfusion has slowed it is appropriate to switch to a laboratory-or point-of-care (POC)-based transfusion."
ACS TQP Massive Transfusion in Trauma Guidelines [34]

"In patients with ongoing hemorrhage and concern for coagulopathy, we conditionally recommend using TEG/ROTEM-guided transfusions to guide blood component transfusions in each of the following three groups: adult trauma patients, adult surgical patients, and adult patients with critical illness. [Systematic Review/Meta-Analysis, Evidence level III]."
EAST Practice Management guidelines [35]

"In the setting of severe trauma, results are available more quickly with VETs than with laboratory tests. The GIHP proposes that VETs can be used for the early diagnosis of coagulopathy. The GIHP proposes that VETs, which have a poor performance in diagnosing the activation of fibrinolysis, should not guide the administration of tranexamic acid but that it should be administered as soon as possible."
French Working Group on Perioperative Haemostasis 2019 [36]

POC, point-of-care; CCA, conventional coagulation assays; VEM; viscoelastic method; VET, viscoelastic testing

Clinical applications: liver disease

Clinical context [37-39]

Cirrhosis often leads to abnormal hemostasis, which can present as both pro-hemorrhagic and pro-thrombotic profiles.

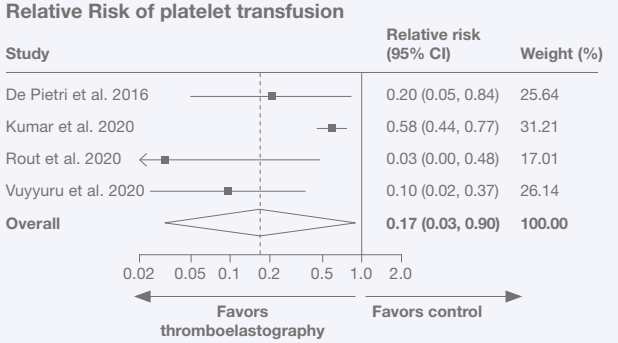
There are limited data guiding the use of coagulation tests in patients with liver disease either during bleeding or during/post therapeutic interventions.

Evidence from randomized, controlled trials suggest that the use of viscoelastic testing in adult patients with cirrhosis can lead to:

- Reduced blood product use (platelets, FFP)
- Reduced adverse events (including bleeding)
- Reduced mortality

when compared with conventional laboratory testing during treatment interventions, variceal bleeding, and liver transplant.

Key data: thromboelastography assays reduce blood product use in patients with cirrhosis and/or undergoing liver transplantation in a meta-analysis of 5 randomised controlled trials [39]



The study was a Meta-analysis of pooled data from 5 randomized controlled trials of patients with liver disease. Four studies reported data on platelet use that could be combined with meta-analysis methods.

Relative risk for platelet transfusion [95% CI] = 0.17 [0.03, 0.90] P = 0.04

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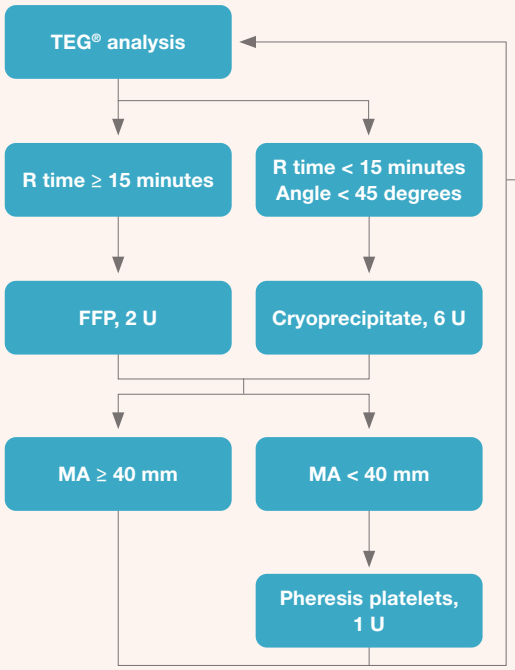
Key publications

Reference	Study design	Key results
Hartmann 2022 [39]	Meta-analysis of 5 randomized controlled trials (n=302)	The use of thromboelastography compared with standard of care reduced the use of blood products including fresh frozen plasma + platelets and cryoprecipitate
Tangchee-winsirikul 2021 [38]	Meta-analysis of 7 randomized controlled trials (n=421)	The use of viscoelastic testing compared with standard of care reduced the need for transfusion of fresh frozen plasma and platelets and reduced the risks of transfusion-related adverse events
Kovalic 2020 [37]	Meta-analysis of 8 randomized controlled trials (n=388) and 9 retrospective cohort studies (n=1,365)	The use of viscoelastic testing compared with standard of care reduced transfusion of fresh frozen plasma and platelets
De Pietri 2016 [40]	Randomized controlled trial (n=60)	The use of viscoelastic testing-guided transfusion strategy reduced the use of blood product (fresh frozen plasma and/or platelets) in bleeding patients with liver disease compared with standard of care
Wang 2010 [41]	Randomized controlled trial (n=28)	The use of viscoelastic testing-guided transfusion strategy reduced transfusion of fresh frozen plasma during liver transplant compared with standard of care

FFP, fresh frozen plasma

Treatment algorithm for liver transplant surgery

Algorithm for management with TEG® device in patients undergoing liver transplant



Initial randomized controlled trial algorithm parameter threshold (Wang 2010) [41]	Non-randomized restrictive algorithm threshold (Wang 2012) [42]
Titrated FFP to obtain R < 10 minutes	R > 15 minutes, give FFP
Alpha angle < 45 degrees, give cryoprecipitate	Alpha angle < 45, give cryoprecipitate
MA < 55 mm	After R and angle corrected, if MA < 40 mm, give apheresis platelets

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Key guidelines

"We recommend viscoelastic testing (TEG/ROTEM), over measuring INR, platelet, fibrinogen, in critically ill patients with ALF or ACLF undergoing procedures (strong recommendation, moderate-quality evidence)."
Society of Critical Care Medicine: Guidelines for the Management of Adult Acute and Acute-on-Chronic Liver Failure in the ICU [43]

"Further study of global measures of coagulation, such as TEG® and ROTEM®, to determine appropriate cutoffs for therapeutic intervention are urgently needed."
AGA Clinical Practice Update: Coagulation in Cirrhosis [44]

"Global assays such as rotational thromboelastometry (ROTEM)/thromboelastography (TEG) may be an attractive means to reassure the proceduralist that hemostasis is "normal" as these assays are frequently normal despite prolonged coagulation times."
Periprocedural management of patients with cirrhosis ISTH 2022 [45]

FFP, fresh frozen plasma; ICU, intensive care unit; INR, international normalized ratio

Clinical applications: postpartum hemorrhage

Clinical context

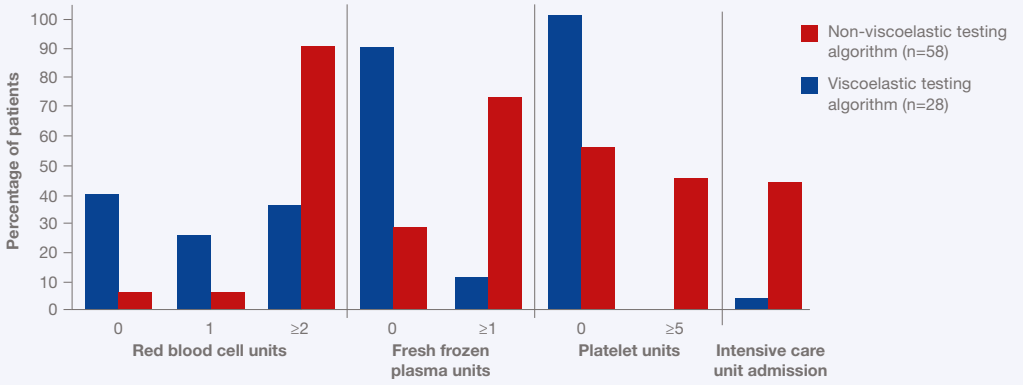
Altered hemostasis in pregnancy is associated with coagulation changes that may lead to bleeding or thrombosis events, including postpartum hemorrhage.

Viscoelastic testing can be used to assess patient coagulopathy and, in certain patient populations, the risk of postpartum hemorrhage prior to delivery [46].

Viscoelastic testing-guided algorithms may also be used to direct blood component transfusion requirements in postpartum hemorrhage patients.

Further trials, particularly randomized controlled trials, are required to assess the effect of viscoelastic testing-guided protocols on clinical outcomes in obstetric patients.

Key data: management of postpartum hemorrhage with ROTEM® Delta led to reduced blood product requirements in a retrospective cohort study of 86 patients (p<0.001 for all) [47]



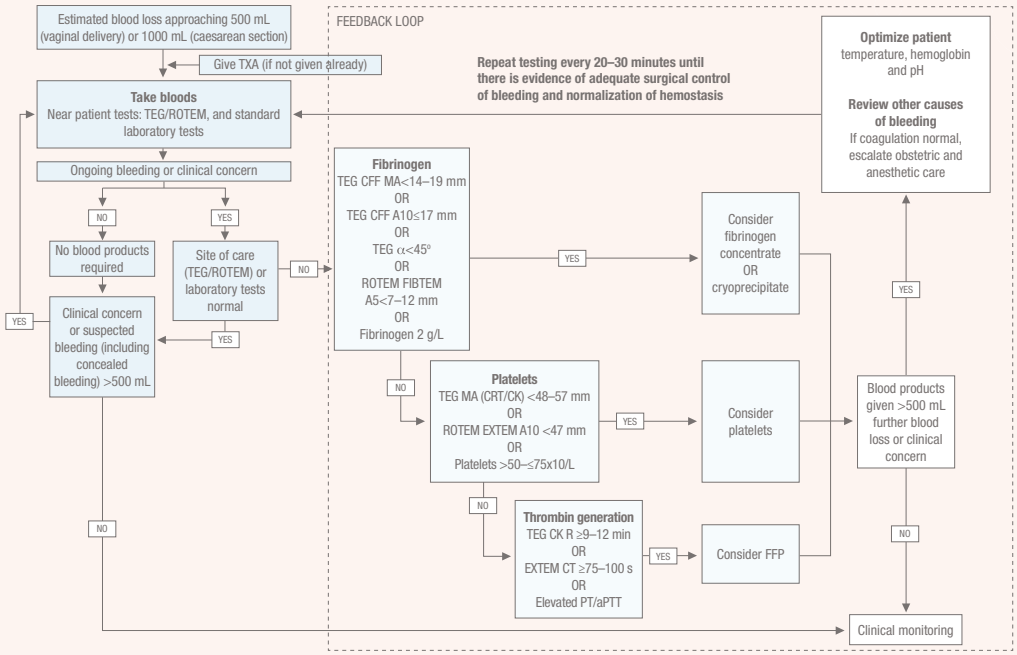
Reproduced with permissions from Snegovskikh 2018 [47]

Key publications

Reference	Study design	Key results
Rigouzzo 2020 [48]	Retrospective cohort analysis (n=98)	Viscoelastic testing assay parameters provided reliable detection of hypofibrinogenemia and thrombocytopenia in postpartum patients
Amgalan 2020 [49]	Systematic review (n=93 studies)	Only two randomized trials found and there was no standard of care control group. Further research is required to evaluate clinical effect of viscoelastic testing in postpartum hemorrhage
McNamara 2019 [50]	Prospective cohort study (n=255)	Transfusion-associated circulatory overload was significantly lower in patients treated with the use of viscoelastic testing than those who received treatment with a shock pack
Snegovskikh 2018 [47]	Retrospective cohort study (n=86)	Patients using ROTEM® Delta in management of severe postpartum hemorrhage received significantly fewer blood product transfusions compared with those who received standard care
Collins 2017 [51]	Double-blind randomized controlled trial (n=55)	FIBTEM A5 levels used to determine hemostasis levels and assess patient care. No improved outcomes seen in treatment with fibrinogen concentration versus placebo

Treatment algorithm
for postpartum hemorrhage

A postpartum hemorrhage TEG® and ROTEM® treatment algorithm (not clinically validated)



The presented algorithm is a collation of multiple sources covering both TEG® and ROTEM® methodology, including a clinically validated algorithm by OBS Cymru; Bell. 2020. [52] Algorithm reproduced with permissions from Dias 2022. [53]

Key guidelines

"We recommend monitoring hemostasis with either PT/aPTT and Clauss fibrinogen or POCTs using thromboelastometry during PPH. If bleeding persists serial measures should be performed. If thromboelastometry is used, blood component replacement should be based on a local algorithm and a quality control protocol agreed with hematology."
Management of coagulopathy associated with PPH; guidance from the SSC of the ISTH [54]

"We recommend assessing haemostatic competence and risk of coagulopathy in severe ongoing PPH through laboratory tests (platelet count, PT, international normalised ratio [INR], aPTT, fibrinogen level) or viscoelastic haemostatic tests to guide appropriate, goal-directed use of haemostatic blood components and pro-haemostatic agents [Evidence Grade 1B]."
NATA consensus statement on prevention and treatment of PPH [55]

"Risk awareness and early recognition of severe PPH are essential. [Evidence base C] VHA can identify obstetric coagulopathy. [Evidence base B] In severe PPH we suggest a VHA-guided intervention protocol. [Evidence base 2C]."
Management of severe perioperative bleeding ESA 2016 [22]

aPTT, activated partial thromboplastin clotting time; PPH, postpartum hemorrhage; PT, prothrombin time; POCT, point-of-care tests; INR, international normalized ratio; VHA, viscoelastic hemostatic assay

Clinical applications:
COVID-19 and critical care settings

Clinical context

Viscoelastic testing is able to determine hypercoagulability in a variety of states, including sepsis, COVID-19, malignancy, hemophilia, and complex coagulopathy management.

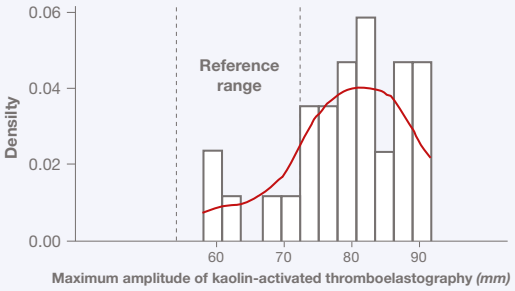
Septic shock commonly triggers coagulation abnormalities, particularly disseminated intravascular coagulopathy, leading to life threatening complications. Early implementation of viscoelastic testing can be utilized to capture and predict early coagulation defects. [56]

Viscoelastic testing in COVID-19 [57]:
- Early diagnosis of hypercoagulability
- Possible prediction of hemostatic outcomes
- Optimization and improvement of patient management based on individual hemostatic response

In COVID-19, there is a spectrum of coagulation abnormalities that unfold from normal to hypercoagulable, and hyperfibrinolytic to hypercoagulable state.

Key data: clotting strength distribution in TEG® assays identified for patients with COVID-19 [58]

- Thromboelastography can identify unique coagulopathic states in patients with COVID-19 that are not captured with traditional laboratory tests of plasma samples
- Graph shows distribution of maximum amplitude (maximum clot strength) in COVID-19 patients, with grey dashed vertical lines representing the reference range. Red curved line shows normal distribution of maximum amplitude (MA) in COVID-19 patients



Reproduced with permissions from Panigada 2020 [58]

Key publications

Reference	Study design	Key results
Maatman 2020 [59]	Observational cohort study (n=109)	Fibrinolytic shutdown assessed by viscoelastic testing associated with thromboembolism risk and mortality
Wright 2020 [60]	Observational cohort study (n=44)	LY30 value predicted venous thromboembolism and treatment for acute renal failure when combined with D-dimer levels
Kruse 2020 [61]	Observational cohort study (n=40)	Combining values for EXTEM maximum lysis (ML) with maximum D-dimer concentrations revealed high sensitivity and specificity of thromboembolic risk prediction in critically ill patients with COVID-19
Chaudhary 2020 [62]	Commentary of race-related differences in COVID-19 response	Clinical outcomes in COVID-19 may be determined by individual patient hemostasis response which could be determined by early viscoelastic testing clot analysis
Hartmann 2021 [57]	Systematic review and meta-analysis of 15 COVID-19 studies	COVID-19 virus associated with increased clot strength, reduced clot lysis, and shortened reaction-time on the TEG® device
Bareille 2021 [63]	Meta-analysis of 44 studies and 1,063 patients	COVID-19 associated with increased mechanical clot strength (with ROTEM®, TEG®, Quantra® and ClotPro® devices) and impaired or absent fibrinolysis
Kim 2021 [56]	Retrospective study (n=889)	MA value in the TEG® device may be a predictor of progressed disease status with end organ function and is associated with disseminated intravascular coagulation in septic shock patients
Kim 2022 [64]	Retrospective observational study (n=295)	MA in the TEG® device was predictive of early disseminated intravascular coagulation in sepsis

Clinical case studies

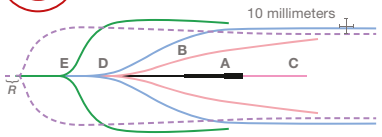
Clinical case studies: information from viscoelastic testing for diagnosis and treatment

Case 1: after-hours diagnosis and management of new onset severe coagulopathy [65]

54-year-old man with a history of Celiac disease admitted with acute onset abdominal pain and bruising

Conventional laboratory tests: prolonged aPTT; further "special" coagulation testing such as factor mixing and inhibitor studies could not be performed as "after business hours"

TEG®5000 testing, available 24-hours at the hospital, was performed shortly after admission



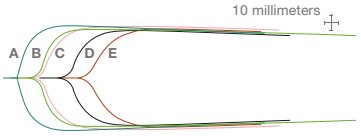
Patient's five TEG®5000 tracings during medical course. Purple dotted line: control; line A: trace at admission; traces B, C, D, and E: daily measurements until discharge at day 8 (the relapse seen in trace C is due to a delay in treatment dose on day 3). Reproduced with permissions from Lee 2022 [65]

Results showed complete lack of clot formation (prolonged R time and reduced maximal amplitude). Acquired hemophilia was suspected and followed up with confirmatory Factor VIII and Bethesda testing and patient started on activated prothrombin complex concentrates

The patient was treated with FVIII inhibitor bypassing agent and discharged after 8 days following improvement in coagulopathy

Case 2: patients with severe hemophilia A [66]

Viscoelastic tracings (TEG®5000) were taken from four patients with severe hemophilia A and similar coagulation factor levels assessed through laboratory methods (FVIII <1%)



TEG®5000 tracings for four patients with milder (B) to more severe disease, compared with normal control (A); longer reaction time and lower angle of clot formation can be seen in a range of phenotypes. Reproduced with permissions from Ramiz 2019 [66]

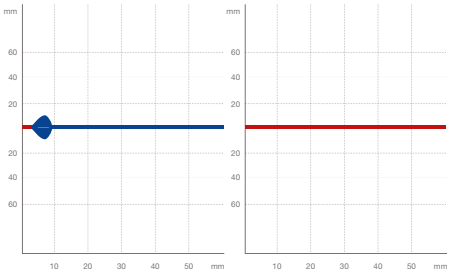
TEG®5000 was also used in these patients alongside conventional laboratory tests to monitor routine FVIII prophylaxis, assess response to treatment with prothrombin complex concentrate or bypassing agents to control bleeding, and encourage patient compliance with treatment

Case 3: rapid assessment of hyperfibrinolysis due to hemorrhagic shock [7]

A patient was brought into a major trauma center following a car accident

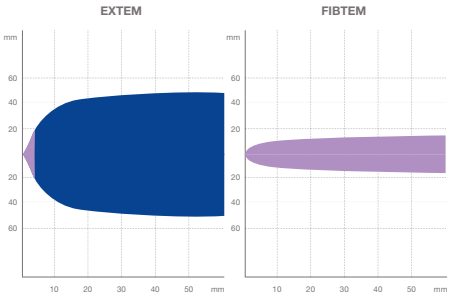
Viscoelastic testing (ROTEM®Delta) was carried out with EXTEM and FIBTEM assays indicating severe coagulation factor and fibrinogen deficiency along with severe hyperfibrinolysis

EXTEM and FIBTEM graphs on ROTEM® Delta on arrival to the trauma bay



Coagulation profile typically only seen in a minority of patients with major trauma and can be associated with very high mortality

EXTEM and FIBTEM graphs at 4 hours post resuscitation



Resuscitation was initiated, and EXTEM and FIBTEM assays 4h later showed normal coagulation and fibrinolytic profiles

Rapid, near-patient assessment of hyperfibrinolysis can allow quick treatment and improved clinical outcome

Tracing figures reproduced with permissions from Selby 2020 [7]

aPTT, activated partial thromboplastin clotting time; EXTEM, extrinsic hemostatic system; FIBTEM, EXTEM based assay for the fibrin part of the clot; MA, maximum amplitude

Implementing viscoelastic testing in clinical care settings

Challenges associated with viscoelastic testing in a clinical setting

- Cup and pin mechanism does not represent *in vivo* vascular mechanics
- Insensitivity for detecting von Willebrand factor and minor/moderate fibrinolytic activity. Low hematocrit (as seen in anemia) may reduce accuracy of viscoelastic testing [67]
- No detection of platelet factor receptor defects without additional testing
- Results are not interchangeable between technologies (e.g., TEG® and ROTEM®), and between device models
- Relative complexity of visual processes and need for training
- Potential for inter-user variability due to lack of training
- Lack of level 1 evidence from high quality randomized controlled trials
- Lack of regulatory clearance in pediatric settings
- Lack of acceptance, especially by traditional hematologists/pathologists (due to limited level of evidence), and overall lack of awareness/training

Solutions for implementation

Clinical validation studies

TEG®

- TEG®5000 and TEG®6s [68]
- TEG®6s between-device reliability [69]
- TEG®6s PlateletMapping [70]
- Fibrinolysis [71]
- In cardiac surgery [13]
- In trauma [72]

ROTEM®

- Reproducibility over time [73]
- ROTEM® Delta and ROTEM® Sigma [74]
- Fibrinolysis [75]
- In cardiac surgery [14]
- In trauma [76]

Institutional costs

Potential cost-benefit due to reduced blood product use, as per initial analyses in cardiac surgery* [13]

↓

Development of a financial model and reimbursement opportunities

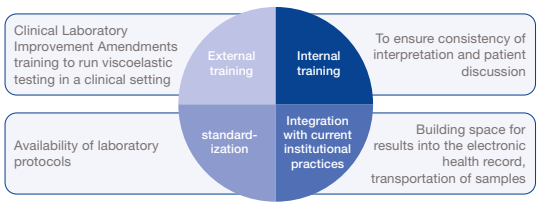
↓

Sub-specialty faculty (e.g., extracorporeal membrane oxygenation, trauma)

*Further studies are required to assess the true cost-benefit analysis of implementation

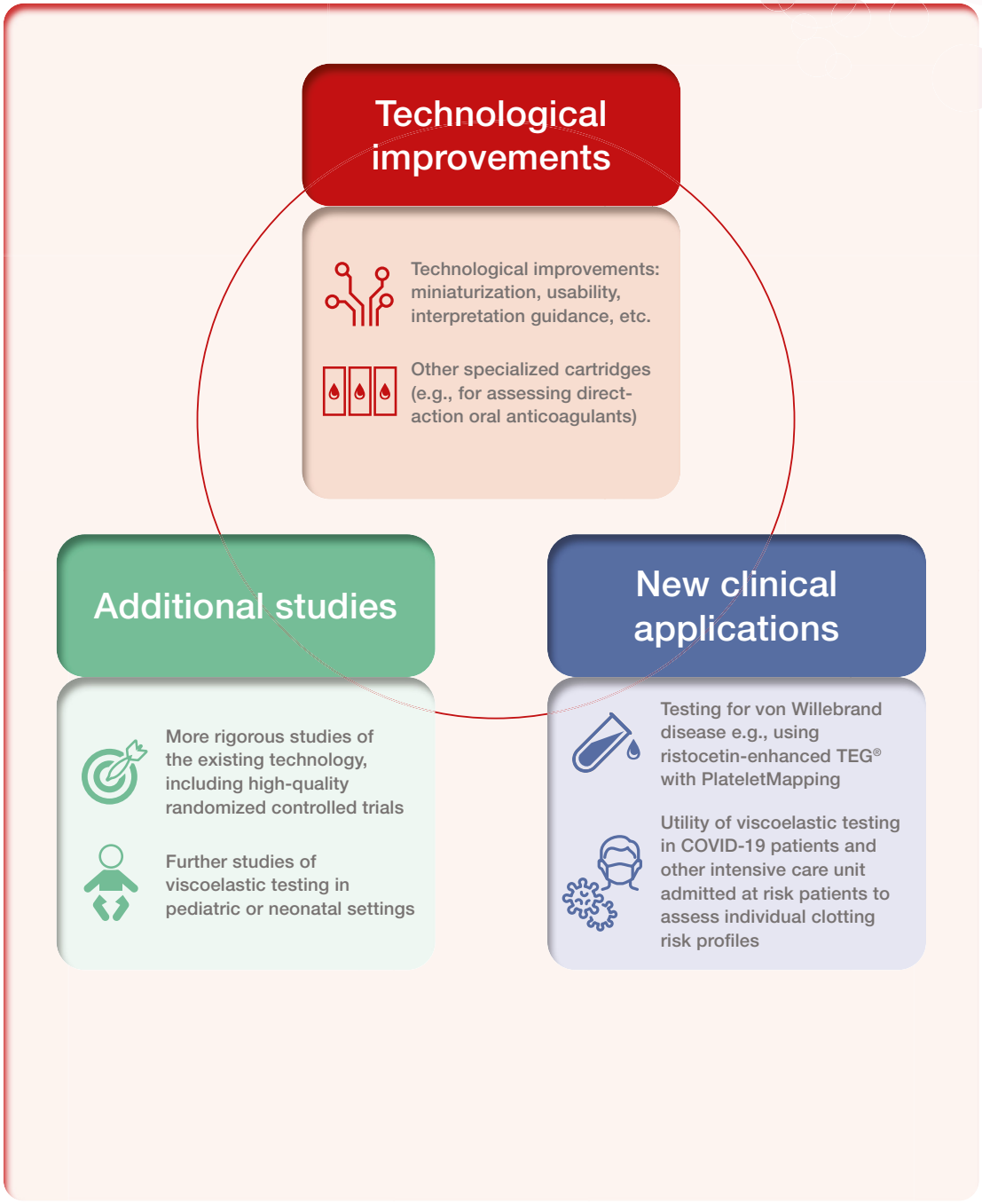
Training and competency

Identify where training is required: research coordinators, surgeons, clinical health care professionals



Quality control

Future outlook



ACKNOWLEDGMENTS

The authors thank Meridian HealthComms, Plumley, UK for providing medical writing support, in particular assistance with the illustrations, which was funded by Haemonetics S.A., Signy, Switzerland in accordance with Good Publication Practice (GPP4).

AUTHOR CONTRIBUTIONS

All authors contributed equally to the conception and writing of the review; all authors reviewed the manuscript and approved for it to be submitted.

RELATIONSHIP DISCLOSURE

J.H. is an employee of Haemonetics. D.H. is a member of TMSCC for AABB and has received meeting attendance/travel support from the St. Louis University Department of Pathology. J.H.L. has participated on a data safety monitoring boards for Merck and Octapharma and advisory boards for Leading Biosciences and Werfen.

TWITTER

Jan Hartmann @JanHartmannMD
Daniela Hermelin @HermelinMD
Jerrold H. Levy @JerroldLevy

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