REVIEW

Thromboelastometry for guiding bleeding management of the critically ill patient: a systematic review of the literature

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ABSTRACT

A systematic review of the published literature clearly demonstrates the usefulness of thromboelastometry (ROTEM®) in detecting coagulation disorders in severe trauma, cardiac and aortic surgery, liver transplantation, and postpartum haemorrhage reliably and within a clinically acceptable turn-around time. In all of the above-mentioned scenarios, the transfusion of any allogeneic blood products could be reduced significantly using ROTEM®-guided bleeding management, thereby minimising or avoiding transfusion-related side effects. Based on the current body of evidence as assessed by the GRADE system, the use of ROTEM® may be recommended in particular for management of severe bleeding after trauma and during cardiac and aortic surgery. However, as laboratory testing contributes only one part of severe bleeding management, the implementation of safe and effective treatment algorithms must be ensured at the same time. *(Minerva Anestesiol 2014;80:1320-35)*

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Clinical management of acute moderate to severe bleeding is one of the major challenges for an anaesthesia team. Though substitution of erythrocytes by transfusion of red blood cells (RBC) is a routine task, adequate maintenance of hemostasis may be considerably more demanding. In fact, the underlying cause of bleeding and subsequent treatment may be completely different depending on the clinical scenario. For example, a patient suffering a severe injury may not necessarily have pre-existing coagulation disorders but may present life-threatening bleeding through open wounds or inside the large cavities of the body. In contrast, patients undergoing cardiac surgery or liver transplantation may have additional intraoperative factors (*e.g.* contact with artificial surfaces, receive high doses of heparin, deliberate hypothermia, defect in synthetic function of the liver) contributing to coagulation abnormalities. In either situation, the patient should be treated in a timely manner to maintain hemostatic competency, thereby avoiding thromboembolic side effects due to overdosing or administration of unnecessary blood products.

Therapeutic options for effective haemostasis management range from the transfusion of whole blood or allogeneic component blood products to a targeted therapy using purified coagulation factors and/or specific procoagulant drugs. What makes this management even more complex is the fact that the underlying rationale for starting coagulation therapy might be either completely empiric, or based on standard lab tests (which are sometimes time-consuming such that empiric therapy has already started before results are available) or based on point-of-care testing (POCT). The common goal is simple: to stop bleeding and to reduce or minimize thrombotic risk. Although the sometimes suggested transfusion ratio of RBCs and FFP of 1:1 is used for treatment of life-threatening bleeding, its efficacy lacks high quality evidence, and in addition, it does not focus on the specific defects of haemostasis.[1-3] In addition, there is actually strong evidence that avoidance of exposure to allogeneic blood transfusion is of high importance, as it has been demonstrated to be associated with serious adverse events, such as transfusion-related acute lung injury, transfusion associated circulatory overload, nosocomial infections and sepsis, transfusion-related immunomodulation and organ dysfunction.[4-9] Conversely, all efforts to develop a single substance treatment to stop bleeding have failed, because of the heterogeneity of bleeding disorders and the necessity of maintaining minimal amounts of more than single crucial procoagulant proteins, such as fibrinogen and thrombin.

Thus, effective therapy to maintain hemostatic function appears to be linked to reliable laboratory tests that offer the results a short period of time and are reflective of the specific defects in hemostasis. Although traditionally used, standard plasmatic coagulation tests such as PT/INR, aPTT and plasma fibrinogen level have several major limitations for their use in guiding perioperative management of bleeding disorders.[10] This manuscript reviews recently published data and guidelines dealing with the use of thromboelastometry for bleeding management in severe trauma, cardiac and aortic surgery, liver transplantation and post partum hemorrhage to discuss the role of thromboelastometry in optimising coagulation management.

Characteristics of thromboelastometry

The technique of thrombelastography was introduced by Hartert in 1948 and was refined by two companies: TEM International GmbH (ROTEM®; Munich, Germany) and Haemoscope Inc (TEG®; Niles, IL, USA). Both devices have comparable working principles and use a mechanical-electrical transducer to graphically display clot formation and degradation in whole blood under low shear stress. However, the test results of both devices can not be used interchangeably because different activators at various concentrations are used resulting in different reference ranges.[11, 12] This review focuses on the ROTEM® device, as this device has a large market share in Europe. More detailed technical properties of the ROTEM® device are presented elsewhere.[13]

After starting a ROTEM® analysis, a typical trace is displayed providing information about clot formation (Figure 1). The clotting time (CT) reflects initial fibrin formation following thrombin generation and is defined by reaching an amplitude of 2 mm. Clot formation is further described by the time to increase amplitude from 2 mm to 20 mm (CFT; clot formation time) and alpha (α) angle (tangent of the slope). The amplitude of clot strength can be assessed 5, 10, 15, and 20 minutes after CT (A5, A10, A15, and A20, respectively) until the maximum amplitude is reached (MCF; maximum clot firmness). A5 and A10 can be used to predict MCF reliably for early decision making.[14-16] The MCF assesses the combined effect of platelet activation and aggregation, fibrin polymerization and cross-linking by FXIII. As all stages of clot formation are influenced by the activity of procoagulants and anticoagulants from clot formation to its dissolution, thromboelastometry (and thrombelastography) represents the gold standard in detecting hyperfibrinolysis. This is defined by detecting more than 15% breakdown in clot strength compared with MCF within one hour after the clotting time (ML; maximum lysis).

The ROTEM® analyses can be accelerated by adding specific activators to the blood specimens. This allows for obtaining more detailed information about hemostasis and suggests the

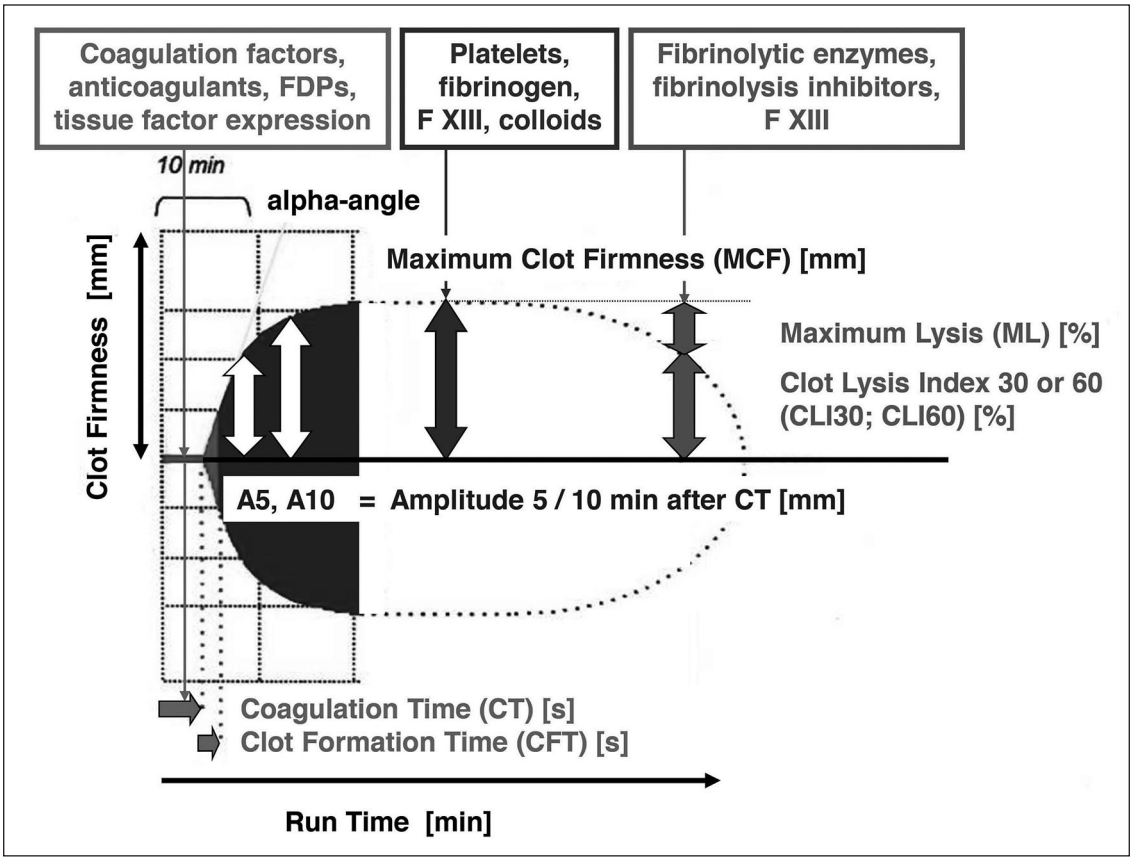

Figure 1.—ROTEM® parameters. FDPs, fibrin(ogen) degrading products; FXIII, coagulation factor XIII.

cause of the observed coagulopathy. The addition of a contact activator (ellagic acid) provides information on the so-called intrinsic pathway that is comparable to aPTT measurement (INTEM assay). Extrinsic activation can be initiated by adding recombinant tissue factor, an analogue to PT measurement (EXTEM assay). Fibrin polymerization can be assessed by running an EXTEM test with the addition of a platelet inhibitor Cytochalasin D (FIBTEM assay). Heparin effects can be identified by adding heparinase to an INTEM test (HEPTEM assay) and comparing the results to the INTEM test. To confirm hyperfibrinolysis, an EXTEM test with the addition of aprotinin can be performed (APTEM assay). To assess the effect of direct thrombin inhibitors such as hirudin, argatroban, bivalirudin, or dabigatran an ecarin-based test can be used (ECATEM assay).[17, 18] The ROTEM® device allows 4 tests to be run in parallel and can be performed at bedside by trained staff or in the central laboratory, which then transmits the display of the ROTEM® curve online to connected computers. With respect to reproducibility of the ROTEM® data, only minor, clinically negligible differences were shown, if ROTEM® was performed bedside or in the central lab.[19-21] Intra- and interindividual variability of ROTEM® test results have been demonstrated to be significantly lower compared with TEG®.[22] Thus, the location where the ROTEM® will be placed should be decided individually based on the local circumstances. It would make no sense to place a ROTEM® in the OR if a sufficient number of trained staff members or dedicated operators are not available at all times. Conversely, bedside placement may enable the medical crew to evaluate hemostatic defects in real time. This possibility is, in fact, one of the major advantages of the ROTEM®: the fast availabil-

ity of its test results. Here, early variables of clot firmness (A5 and A10), which have been demonstrated to predict MCF reliably, can be used for fast decision making in severe bleeding.[14-16] Therefore a clear procedure for transport of specimens should be established if the tests are not performed at the bed side. Regardless of the location of the ROTEM®, rigorous quality controls must be ensured for optimal and safe usage. The ROTEM® device has demonstrated good reproducibility of test results [22] and yields stable results over 120 minutes.[23] All other clinical benefits of a ROTEM®-guided bleeding management will be discussed in the following paragraphs.

There is a distinct influence of haematocrit on ROTEM® measurements. A low hematocrit (<25%) leads to an increase in the plasma fraction of the whole blood specimen, which in turn, may result in increased FIBTEM MCF.[24-26] However, the correlation between FIBTEM MCF and plasma fibrinogen levels is higher if haematocrit is decreased, and thus, the FIBTEM assay offers an adequate method to determine fibrinogen deficiency.

Bleeding patients are frequently treated with colloids, particularly with hydroxyethyl starch (HES), and this treatment has been demonstrated to have an impact on fibrinogen measurements. In the presence of HES, erroneously high levels of plasma fibrinogen have been measured using photometric assays. In this case, the ROTEM® FIBTEM test appears to be the most reliable method to detect fibrin polymerisation defects.[27] Photometric assays for plasma fibrinogen concentration produce erroneously low levels in the presence of direct thrombin inhibitors, whereas the FIBTEM MCF results are not changed.[28]

Thromboelastometry in severe trauma

Trauma-induced coagulopathy (TIC) and bleeding is responsible for 30% to 40% of trauma mortality and accounts for almost 50% of deaths within the initial 24 hours after admission to the emergency departments.[29] Therefore, fast and reliable assays for early detection of coagulopathy and guidance of treatment are urgently needed. Although there is a growing knowledge about the specific pathophysiology of TIC [30-33] and numerous clinical observations on trauma management as well as rigorous analyses of current trauma registries have been published, there is still a lack of evidence concerning the ideal approach to manage trauma-induced bleeding. Notably, current therapy for bleeding conditions in trauma patients is frequently based on plasmatic coagulation testing, which has demonstrated to be inappropriate for guiding the complex therapy in this setting, or on empirical coagulation therapy (*e.g.* RBC:FFP with a fixed 1:1 ratio) with the risk of unnecessary administration of allogeneic blood products.[29, 34] In addition, bleeding therapy itself displays high variability worldwide which in turn makes it even more difficult to compare study results.

The use of viscoelastic testing, such as the ROTEM®, in trauma settings allows for a more comprehensive overview of the haemostasis and provides clinically useful results within 10 minutes.[15, 35] Several studies have revealed that trauma patients regularly display an initial activation of coagulation and fibrinolysis followed by post-traumatic consumption, loss and dilution of coagulation factors. A comprehensive overview of 17 studies including more than 1500 patients dealing with changes of ROTEM® and TEG® in the trauma setting was published by Johansson in 2012.[36]

Although this is an important step towards a better TIC understanding the present manuscript intends to review those data dealing with ROTEM®-guided therapy in the trauma setting. The results of those studies evaluating the impact on ROTEM®-guided algorithms for bleeding management on transfusion requirements and outcomes in severe trauma are displayed in Table I. A total of 6 clinical studies (including one randomized controlled trial) were performed between 2010 and 2013 including almost 6970 patients.

Consequent and effective ROTEM®-guided treatment of trauma patients was demonstrated in a retrospective study published by Schöchl *et al.*[37] Of the 131 patients who entered the emergency room (ER), fibrinogen deficiency (FIBTEM MCF<5 mm) was diagnosed and consequently treated with fibrinogen concentrate in

Table I.—*ROTEM®-guided coagulation management in severe trauma.*

	Study type	Population	Methods	Main findings and major conclusions
Schöchl [37]	Retrospective analysis	131 trauma patients who received ≥5 units PRBC within 24 h after arrival at ED	Analysis of ROTEM®-guided substitution of fibrinogen, PCC and platelet concentrate, and comparison of mortality compared to predicted TRISS mortality	ROTEM®-guided therapy was effective and fast, showing favourable survival rates as compared to predicted TRISS mortality (24.4% *vs.* 33.7%; P=0.032)
Schöchl [38]	Retrospective matched-pair analysis	681 trauma patients; 601 patients from German Trauma Registry (TR-DGU) *vs.* 80 patients from Salzburg (Austria) Trauma Centre	Comparison of transfusion requirements and mortality of TR-DGU data (receiving ≥ 2 units of FFP, but no fibrinogen concentrate or PCC) *vs.* data from Salzburg (ROTEM®-guided administration of fibrinogen concentrate and PCC only)	Significantly reduced exposure to allogeneic blood transfusion if ROTEM®-guided coagulation management using coagulation factors was applied; (median of 6 units of FFP (range: 2-51) in TR-DGU *vs.* no FFP but 6 g fibrinogen concentrate (range: 0-15 g) and 1200 IU of PCC (range: 0-6600 IU); transfusion of RBCs in 97% of all patients in DR-DGU *vs.* 71% in ROTEM®-guided group (P<0.001); avoidance of platelet transfusion in 91% in the ROTEM®-guided group *vs.* 56% in TR-DGU (P<0.001). No changes in overall mortality
Nienaber [39]	Retrospective matched-pair analysis	18 patients from German Trauma Registry (TR-DGU) *vs.* 18 patients from Innsbruck Trauma Database (ITB)	Comparison or RBC transfusion and mortality of TR-DGU data (transfusion of FFP:PRBC at a ratio of 1:1) *vs.* data from ITB (ROTEM®-guided administration of fibrinogen concentrate and PCC)	Significant reduction of transfused RBC in the ROTEM®-guided patient group (1.0 unit of RBC (0-3 units) *vs.* 7.5 units (4-12 units) within 6 h after admission; P<0.005); no difference in mortality, but multiple organ failure was significantly reduced (16.7% *vs.* 61.1%; P=0.015)
Görlinger [40]	Retrospective cohort study	Mixed patient population in three centres; thereof 5590 trauma patients	Comparison of blood transfusion requirements in 2594 patients before and 2996 patients after implementation of a ROTEM®-based bleeding algorithm	ROTEM®-guided bleeding management was able to reduce FFP transfusion requirements by about 90%; amounts of RBCs and platelets could be reduced by 62% and 72%, respectively
Schaden [41]	Randomized controlled trial	30 consecutive patients undergoing surgical excision of burn wounds	Cumulative number of allogeneic blood units using a ROTEM®-guided algorithm *vs.* treatment according to clinicians' discretion	Significant reduction in allogeneic blood product transfusion following ROTEM®-based bleeding management (median (IQR) of cumulative transfused allogeneic blood products: 9.0 units (6.0-12.3 units) *vs.* 3.0 units (1.3-5.5 units); P=0.002; Transfusion of FFP 5.0 (1.5-7.5) units in the control group *vs.* no FFP in the ROTEM®-algorithm group (P<0.001)
Rourke [42]	Prospective cohort study	517 trauma patients (Queen Mary University of London)	Determination of admission fibrinogen level with the Clauss method and thromboelastometry (FIBTEM® A5)	Low admission fibrinogen level determined with thromboelastometry (FIBTEM A5<9.5 mm) was an independent predictor of mortality at 24 hours and 28 days (P<0.001) and administration of cryoprecipitate was associated with improved survival

FFP: fresh frozen plasma; PCC: prothrombin complex concentrate; RBC: red blood cells; ROTEM: rotational thromboelastometry; TRISS: Trauma and Injury Severity Score; IQR: interquartile range.

nearly all patients (128 patients; 97.7%) during 24 hours after admission to ER. Eighty-nine patients (74.8%) displayed signs of poor thrombin generation (EXTEM CT>1.5 times normal) and received additionally a four-factor prothrombin complex concentrate (PCC). The transfusion of platelet concentrate was necessary in 29 patients (22.1%; lack of improvement in EXTEM MCF after fibrinogen substitution), whereas only 12 patients (9.1%) received FFP transfusion due to ongoing bleeding. The observed mortality in this patient population was lower than the predicted TRISS mortality. Mortality was even more reduced, if patients with traumatic brain injury (N.=17) were excluded (14% *versus* 27.8% predicted by TRISS (P=0.0018). Another retrospective study from the same group indicated markedly reduced transfusion requirements by comparing patient data from the Salzburg Trauma Centre (N.=80) who were treated with coagulation factors only to a matched patient group from the German trauma register (N.=601), who were exclusively treated with FFP instead of coagulation factor concentrates.[38] A matched pair analysis published by a group in Innsbruck indicated significant reduction of RBC transfusion if ROTEM®-guided therapy was established.[39] Though all patients in the control group were transfused based on a 1:1 ratio between RBC and FFP, the patients in the ROTEM®-guided group were treated individually as indicated by the ROTEM® results. Overall mortality was comparable between both groups; however, the incidence of multiple organ failure was significantly lower in the group with ROTEM®-guided therapy. Similar results were produced in a retrospective analysis of three university hospitals in Germany and Austria analysing overall transfusion requirements in visceral and transplant surgery, trauma surgery and cardiovascular surgery.[40] In this study, ROTEM®-guided bleeding management was capable of reducing FFP transfusion requirements by approximately 90%; whereas the transfusion amounts of RBCs and platelets could be reduced by 62% and 72% respectively. In a single centre prospective randomised controlled study, Schaden *et al.* demonstrated that ROTEM®-guided bleeding management was also efficacious in significantly decreasing the requirements of allogeneic blood products in 30 consecutive patients undergoing surgical excision of burn wounds.[41]

A common finding of all reviewed manuscripts is that traumatic coagulopathy was typically combined with the need to restore fibrinogen levels. This need can be ideally detected and guided by ROTEM® analysis.[42] These results are in accordance with results from a retrospective study in more than 300 patients indicating that low FIBTEM MCF and FIBTEM A10 were highly predictive for massive transfusion in trauma patients.[43] In a prospective cohort study of 517 patients, a low admission fibrinogen level determined with thromboelastometry (FIBTEM A5<9.5 mm) was an independent predictor of mortality at 24 hours and 28 days (P<0.001) and administration of cryoprecipitate was associated with improved survival.[42]

In addition, viscoelastic tests such as ROTEM® are considered to be the gold standard in detecting hyperfibrinolysis,[44, 45] and fibrinolytic activation occurs in the majority of trauma patients.[46] However, overt hyperfibrinolysis detected by ROTEM® is a rare finding, with an admission incidence of 3-6%.[47-49] Here, the incidence of hyperfibrinolysis is dependent on the defined cut-off value for hyperfibrinolysis. Because in severe trauma there is already a reduction of clot firmness of 3% to 5% associated with increased mortality, the definition of hyperfibrinolysis or activated fibrinolysis should be adapted to the clinical setting.[50]

Thromboelastometry in cardiovascular surgery

Transfusion of allogeneic blood products during cardiovascular surgery is a major issue, and approximately 20% of all blood products are transfused in this setting worldwide.[51] Reducing allogeneic blood product transfusion is an important goal in cardiac surgery patients. A successful approach is based on the concept of "patient blood management" which includes preoperative optimisation of the hemoglobin levels, preservation of the patient's own blood, assessment of the tolerance to anaemia, use of restrictive transfusion protocols, and use of POCTs to

guide the diagnosis and therapy of perioperative bleeding. The existing treatment algorithms are based on viscoelastic coagulation tests, basically TEG® and ROTEM®.[52-54] Although most of the investigations were performed in adults, similar beneficial effects of ROTEM® testing were equally found in pediatric cardiac patients.[55-61] The results of 12 clinical studies investigating the impact of ROTEM®-guided bleeding management (including 3 randomized controlled trials) performed between 2006 and 2013 including overall 8549 patients were reviewed (Table II).

Two retrospective single centre cohort studies including 990 and 194 cardiac patients, respectively, reported significant reduction of all transfused allogeneic blood products after implementation of ROTEM®-guided coagulation management.[62, 63] Spalding *et al.* demonstrated that implementation of a ROTEM®-guided coagulation management decreased average monthly costs by 44%, although a markedly higher amount of administered fibrinogen concentrate was observed.[64] In addition, the need for resternotomy due to postoperative bleeding decreased from 6.6% to 5.5%. A reduction of transfused allogeneic blood products was likewise found in a retrospective analysis of 1676 cardiac surgery patients after ROTEM® placement.[65] However, in that study transfusion was also based on the discretion of the individual clinician without a strict algorithm. A study published by Rahe-Meyer *et al.* systematically investigated underlying changes of hemostasis by using a ROTEM® device during major aortic valve or aorta replacement surgeries, which were typically complicated by massive blood loss. In a first prospective pilot study, they treated fibrinogen deficiency after weaning from cardiopulmonary-bypass using fibrinogen concentrate compared with conventional FPP transfusion to a targeted FIBTEM MCF of approximately 22 mm, and compared the transfusion requirements with data from a historic control group.[66] The transfusion requirements and 24 h postoperative blood loss were decreased tremendously after ROTEM®-guided administration of fibrinogen. This group continued to perform the same FIBTEM-guided bleeding management in thoracoabdominal aortic aneurysm surgery.[67] Transfusion requirements in the prospective group were markedly reduced if ROTEM®-guided administration of fibrinogen concentrate was used as compared with a historic control group. Notably, in 4 out of 6 patients in the prospective FIBTEM-guided group, allogeneic blood transfusion could be completely avoided, and there were no signs of adverse events. Similar results were obtained in a pilot study in patients undergoing aortic replacement due to acute Type A aortic dissection.[68] Finally, a prospective randomized placebo-controlled trial using a ROTEM®-guided bleeding protocol during aortic surgery with circulatory arrest was performed.[69] The results of this study confirmed earlier findings that transfusion of allogeneic blood products was significantly reduced if ROTEM®-guided administration of fibrinogen concentrate was performed, and the total avoidance of transfusion was achieved in 45% of patients, whereas 100% in the placebo group received allogeneic blood transfusion. Girdauskas *et al.* found similar results in a randomised controlled study in 56 patients undergoing aortic surgery with hypothermic cardiac arrest.[70] In this study, protamine, tranexamic acid, FFP, platelets, PCC, and fibrinogen concentrate were used as haemostatic interventions in both groups, and, in one group treatment was based on ROTEM® results, and in the other group, treatment was based on conventional laboratory coagulation tests. Transfusion requirements of allogeneic blood were significantly reduced in the ROTEM® group. These results are in line with data from pediatric cardiac patients with ROTEM®-guided bleeding management which demonstrated a significant decrease of proportion of patients who needed any intraoperative or postoperative transfusion.[56] Görlinger *et al.* demonstrated in a large retrospective cohort of 3865 cardiac surgery patients who the implementation of ROTEM®-guided administration of coagulation factors concentrates was associated with significantly decreased overall transfusion rate (52.5% before *vs.* 42.2% after implementation; P<0.0001), decreased volumes of transfused RBCs (49.7% *vs.* 40.4%; P<0.0001) and fresh frozen plasma (19.4% *vs.* 1.1%; P<0.0001), whereas platelet transfusion was increased (10.1% *vs.* 13.0%; P=0.0041). In addition, a significant reduction in the inci-

Table II.—*ROTEM®-guided coagulation in cardiac and aortic surgical patients.*

	Study type	Population	Methods	Main findings and major conclusions
Anderson [62]	Retrospective cohort study	990 cardiac surgical patients 6 months before and after introduction of a ROTEM®-guided algorithm	Comparison of transfused allogeneic blood products (RBC, FFP and platelet concentrates) and patient outcome data	RBCs were transfused in 60% of all patients, and in 53% of all patients after implementing the new management; similar reductions were observed for transfused FFP (17% *vs.* 12%) and platelet concentrates (16% *vs.* 11%), but similar outcome data
Fassl [63]	Retrospective data analysis	194 patients undergoing elective and emergency cardiac surgery with hypothermic circulatory arrest	Comparison of transfused allogeneic blood products in 153 patients treated according to ROTEM®-guided algorithm and conventional treatment group (N.=41)	Number of transfused allogeneic blood products were reduced in the ROTEM®-guided treatment group (RBC, 78% *vs.* 41%; P<0.001; FFP, 71% *vs.* 22%;P<0.001; platelets, 32% *vs.* 16%; P=0.028)
Spalding [64]	Retrospective cohort study	1422 cardiac surgical patients (729 patients before and 693 after implementation of bedside ROTEM® analysis)	Comparison of cumulative costs for allogeneic blood transfusion and coagulation factors	Cumulative RBC expenditures were reduced by 25% and platelet concentrates by 50%. Costs for fibrinogen concentrate increased two-fold; costs for PCC and FXIII were markedly reduced (-80%), and rFVIIa was entirely omitted. Cumulative combine costs for bleeding management decreased by 44% after implementation of ROTEM®-guided management
Hvas [65]	Observational prospective study using historical control	1676 cardiac surgical patients (811 patients before and 865 patients after implementation of ROTEM®)	Comparison of transfused allogeneic blood products and coagulation factors before and after implementation of a ROTEM®	Decrease in blood products (36.3 *vs.* 38.6%; P=0.49) after implementation of ROTEM®; Average units of RBC per patient transfused decreased (4.1 *vs.* 5.1 units; P=0.04); use of rFVIIa decreased significantly (1.7 *vs.* 3.8%; P=0.04) and use of fibrinogen increased significantly (11.6 *vs.* 3.6%; P<0.001)
Rahe-Meyer [66]	Pilot study; two prospective groups *vs.* a historic control group	57 patients undergoing elective aortic valve operations and ascending aorta replacement.	Transfusion requirements and 24 h postoperative bleeding of a historic control group (N.=42), *vs.* data from prospective ROTEM®-guided FFP-group (N.=5) and ROTEM®-guided fibrinogen concentrate group (N.=10)	Transfusion requirements of all allogeneic products was decreased if ROTEM®-guided treatment with fibrinogen concentrate was used (mean 0.7 units *vs.* 8.2 units in the FFP group and 8.5 units in the historic control group); in addition, 24 h postoperative bleeding was reduced
Rahe-Meyer [67]	Pilot study; prospective group *vs.* a historic control group	18 patients undergoing throracoabdominal aortic aneurysm surgery	Transfusion requirements and 24 h postoperative bleeding of a historic control group (N.=12), *vs.* data from prospective ROTEM®-guided group (N.=6)	Allogeneic blood requirements were markedly lower in ROTEM®-guided treatment with fibrinogen concentrate *vs.* a historic control group (mean 2.5 units *vs.* 16.4 units); in 4 out of 6 patients of the prospective group, blood transfusion could be avoided completely. In addition, 24 h postoperative bleeding was reduced in the prospective group
Hanke [68]	Data analysis of prospective study group compared to matched control group	10 patients undergoing aortic arch replace-ment due to acute type A aortic dissection (5 before and 5 after ROTEM®-guided therapy	Comparison of blood component and coagulation factor requirements, thrombotic and bleeding incidents and costs	Postoperative FFP transfusion (1.6±2.2 units *vs.* 9.2±6.6 units; P=0.038), composite postoperative bleeding and thrombotic/ thromboembolic events (0% *vs.* 80%; P=0.048), and resulting cost on transfusion and coagulation treatment (average cost-saving per case of 2757 Euro; P=0.049) were significantly reduced in the ROTEM® group; reduced amounts of administered of blood products and coagulation factor concentrates, incidence of massive transfusion, ventilation time, ICU stay, hospitalization, and 6-month mortality in the ROTEM® group.

Table II.—*Continues from previous page.*

	Study type	Population	Methods	Main findings and major conclusions
Rahe-Meyer [69]	Randomized, placebo-controlled double-blind trial	61 patients undergoing aortic replacement surgery	Comparison of requirements of allogeneic blood transfusion and safety in a group treated with ROTEM®-guided administration of fibrinogen (target FIBTEM MCF=22 mm) *vs.* placebo and standardized transfusion protocol using FFP and platelet concentrates	24 h transfusion requirements were significantly lower in the fibrinogen group (median 2 *vs.* 13 units; P<0.001); total avoidance of allogeneic blood product transfusion in 13 patients (45%), whereas all patients in the standard treatment group were transfused. No observed safety concern
Girdauskas [70]	Randomized controlled trial	56 patients undergoing aortic surgery with hypothermic circulatory arrest	Comparison of cumulative amounts of transfused allogeneic blood products in a treatment group using a ROTEM®-guided algorithm (N.=27) *vs.* routine transfusion practice based on clinical judgement and standard plasmatic coagulation tests (N.=29)	Allogeneic blood product transfusion was significantly reduced in the ROTEM®-guided group (median 9 units [IQR, 2-30 units] *vs.* 16 units [9-23]). Postoperative blood loss and rate of re-exploration was similar between groups. Multivariate regression analysis revealed significant decreased need for massive transfusion in the ROTEM® group (odds ratio 0.45; 95% CI, 0.2-0.9; P=0.03)
Romlin [56]	Data analysis of prospective study group compared to procedure- and age-matched control group	100 paediatric cardiac surgical patients (50 patients before and 50 patients after implementation of ROTEM®)	Comparison of requirements of allogeneic blood transfusion and coagulation factors, and analysis of postoperative blood loss	Proportion of patients who received any intra- or postoperative transfusion were significantly decreased in the ROTEM®-guided treatment group (32 of 50 [64%] *vs.* 46 of 50 [92%]; P<0.001). No changes in postoperative blood loss
Görlinger [71]	Retrospective cohort study	3865 cardiac surgical patients (1718 patients before and 2147 patients after implementation of a ROTEM®- and Multiplate®-guided algorithm	Comparison of intraoperative transfusion of allogeneic blood products before and after implementation of a ROTEM® and Multiplate®-guided algorithm for bleeding management	Significant reduction of overall allogeneic blood transfusion: 42.2% before *vs.* 52.5% after implementation; P<0.0001; (RBC: 49.7% *vs.* 40.4%; P<0.0001; FFP: 19.4% *vs.* 1.1%; P<0.0001; platelets: 10.1% *vs.* 13%; P=0.0041), decreased incidence of massive transfusion (1.26% *vs.* 2.5%; P=0.0057), decreased unplanned re-exploration rate (2.24% *vs.* 4.19%; P=0.0007) and decreased composite thrombotic/thromboembolic adverse events (1.77% *vs.* 3.19%; P=0.01115). Overall costs for allogeneic blood products and coagulation factor concentrates per patient decreased by 6.5%
Weber [72]	Randomized controlled trial	100 patients undergoing complex cardiac surgery and suffering from diffuse bleeding after heparin reversal with protamine	Comparison of transfused units of RBC during 24 h after inclusion. One arm ROTEM® and Multiplate®-guided algorithm for bleeding management, second arm conventional coagulation testing	Significant decrease in erythrocyte transfusion rate (3 units [2-6] *vs.* 5 units [4-9]; median [IQR]; P<0.001). Secondary outcome parameters: FFP (0 units [0-3] *vs.* 5 units [3-8]; P<0.001) and platelet transfusion rates (2 units [0-2] *vs.* 2 units [0-5]; P=0.01), decrease in postoperative mechanical ventilation time (316 min [230-513] *vs.* 827 min [440-2835]; P<0.001), length of ICU stay (21 h [18-31] *vs.* 24 h [20-87]; P=0.019), composite adverse events rate (ARF, sepsis, thrombotic complications, and allergic reaction) (8% *vs.* 38%; P<0.001), costs of haemostatic therapy (average cost-saving per case of 1451 Euro), and 6-month mortality (4% *vs.* 20%; P=0.013)

FFP: fresh frozen plasma; RBC: packed red blood cells; ICU: intensive care unit; IQR: interquartile range; MCF: maximum clot firmness; Multiplate®: multiple electrode impedance aggregometry; PCC: prothrombin complex concentrate; rFVIIa: activated recombinant factor VII; ARF: acute renal failure; ROTEM: rotational thromboelastometry

dence of massive transfusion [(≥10 units packed red blood cells), (2.5% *vs.* 1.26%; P=0.0057)] and unplanned re-exploration due to bleeding (4.19% *vs.* 2.24%; P=0.0007) was observed.[71] In contrast to the previously discussed studies, Görlinger et al. used multiple electrode aggregometry (Multiplate®; Roche Diagnostics GmbH, Mannheim, Germany) in addition to thromboelastometry as a perioperative point-of-care device to guide transfusion of platelet concentrates. Furthermore, the authors demonstrated that not only transfusion requirements but also combined costs for bleeding management including allogeneic blood products and coagulation factor concentrates, as well as composite thrombotic/thromboembolic adverse events were decreased after implementation of the point-of-care-guided bleeding management. This concept of combined point-of-care-guided bleeding management using ROTEM® and Multiplate® was confirmed by a study published by Weber *et al.* which included 100 patients undergoing complex cardiac surgery with bleeding after heparin-reversal.[72] Using the same algorithm as previously described by Görlinger, this study demonstrated in a prospective, randomised, controlled design that transfusion of any allogeneic blood products could be reduced significantly, thereby also reducing postoperative ventilation time, length of stay in the ICU, total costs, and composite adverse events (acute renal failure, sepsis, and thrombotic events), as well as six-month mortality.

As a general observation, a ROTEM®-based approach to bleeding in cardiac surgery leads to a reduction in RBC and FFP use, variable changes in platelet concentrates transfusions (equal, lower, and even higher transfusion rates are reported), and a larger use of fibrinogen concentrate. In this last respect, it should be underlined that the optimal target value of fibrinogen after cardiac operations is still not defined. The target value of a FIBTEM MCF of 22 mm is not yet validated and leads to the use of huge amounts of fibrinogen concentrate. It is possible that lower target values of FIBTEM MCF may be effective and consequently, lower amounts of fibrinogen concentrates may be required to tackle fibrinogen consumption in bleeding patients after cardiac surgery.

Thromboelastometry in liver transplantation

Management of haemostatic changes during liver transplantation is usually challenging because of multiple factors: massive blood loss, decrease in the synthetic function of the liver and an unstable balance between pro- and anticoagulants.[73-75] Intraoperative coagulation testing using the ROTEM® device has been demonstrated to be a feasible and fast alternative compared with conventional coagulation tests and other point-of-care measurements.[76-81] Here, the results of 4 clinical studies, including 6600 patients overall, were reviewed to assess the clinical value of ROTEM®-guided bleeding management during liver transplantation (Table III). Unfortunately, data from prospective randomised controlled trials are lacking and urgently needed.

Retrospective data analyses over 10 years at a university hospital indicated that the implementation of a ROTEM®-based bleeding management including the use of purified coagulation factor concentrates resulted in significant reduction in allogeneic blood transfusion requirements and related costs for management of liver transplantation.[82] This study demonstrated that nearly 90% of FFP transfusion in patients undergoing liver transplantation can be avoided and patients may preferably be treated by a more targeted administration of purified fibrinogen concentrate and four-factor PCC. The early and reliable detection of fibrinogen deficiency using the FIBTEM assay, and the beneficial treatment effects using fibrinogen concentrate was likewise demonstrated in a further retrospective study including 79 patients undergoing liver transplantation.[83] In addition to consequent treatment of hypofibrinogenaemia, the ROTEM® device was demonstrated to be a reliable tool in detecting hyperfibrinolysis, which is a serious and common complication during liver transplantation. Trzebicki *et al.* demonstrated in a retrospective analysis of 78 patients undergoing orthotopic liver transplantation that severe hyperfibrinolysis occurred in 7.7% of all patients.[84] In all those cases, hyperfibrinolysis was detected early by ROTEM® measurements and was consequently treated with tranexamic acid. Notably, other authors have reported an incidence of hyperfi-

Table III.—*ROTEM®-guided bleeding management in patients undergoing liver transplantation*

	Study type	Population	Methods	Main findings and major conclusions
Görlinger [82]	Retrospective study	10 years experience (1999-2009) in 1105 patients undergoing liver transplantation performed during implementation of ROTEM®-guided management	Analysis of intraoperative used blood products and related costs	From 1999 to 2009 transfusion requirements for PRBCs, FFP, and platelets decreased by 60%, 89%, and 58%, respectively, while fibrinogen concentrate and PCC increased by 11-fold and 3.6-fold, respectively. No off-label-use of rFVIIa. Overall cost-saving for allogeneic blood products and coagulation factor concentrates of 1,765,280 Euro within 10 years
Noval-Padillo [83]	Retrospective analysis compared to prospective patient group	59 patients undergoing liver transplantation compared to prospective data of 20 patients with ROTEM® and laboratory-guided bleeding management	Analysis of allogeneic blood products	PRBCs, FFP, and platelets transfused per patient decreased from 8.4 to 3.9 by 53%, from 5.6 to 1.9 by 65%, and 1.5-0.7 by 50%, respectively after implementation of ROTEM®-guided management. 20% of transplant patients received no transfusion of blood products compared with 3.5% in the retrospective group
Trzebicki [84]	Retrospective study	78 patients undergoing liver transplantation (39 patients without antifibrinolytics *vs.* 39 patients after implementation of ROTEM®-guided management including administration of tranexamic acid)	Prove of concept and comparison of blood products requirements after implementation of ROTEM®-guided bleeding management	PRBC and FFP transfusion in the ROTEM® group was lower than in the control group (RBC: 4.1±4.76 *vs.* 5.53±4.89 units; P=0.2; FFP: 10.01±7.47 *vs.* 13.15±6.62; P=0.06). Severe fibrinolysis was found in 3 patients in the ROTEM® group (7.7%) and was successfully treated with tranexamic acid
Görlinger [40]	Retrospective study	5338 patients in three centres undergoing visceral surgery or liver transplantation from 1999 to 2010	Comparison of blood transfusion requirements in 2594 patients before and 2996 patients after implementation of a ROTEM®-based bleeding algorithm	ROTEM®-guided coagulation management in visceral surgery and liver transplantation decreased from RBC transfusions by 62%, for FFP by 95% and for platelets by 66%, while the incidence of massive transfusion (≥10 units of PRBC) was reduced by 66%

FFP: fresh frozen plasma; 4F-PCC: four-factor prothrombin complex concentrate; MCF: maximum clot firmness; PRBC: packed red blood cells; rFVIIa: activated recombinant factor VII; ROTEM: rotational thromboelastometry.

brinolysis during liver transplantation of up to 60%. However, in this study, one-third of the detected hyperfibrinolysis was self-limiting after reperfusion of the liver graft without the need for administration of an antifibrinolytic drug.[59]

Thromboelastometry in postpartum haemorrhage

Postpartum hemorrhage (PPH) is still the leading cause of maternal mortality worldwide and accounts for approximately 143,000 deaths per year.[85] Moreover, PPH contributes significantly to maternal morbidity and the need for hysterectomy. A recently published review on that topic summarized that coagulation testing would be useful in managing PPH but must be rapidly available.[86] Charbit *et al.* demonstrated that fibrinogen deficiency is a key step in developing severe PPH and consequently, fibrinogen levels should be used to guide PPH management.[87] A French study group published the effective usage of ROTEM® FIBTEM test in guiding fibrinogen transfusions in 37 patients suffering on PPH.[88] The results of this prospective study revealed that a cut-off value of FIBTEM A5 of 5 mm and A15 at 6 mm presented excellent sensitivity (100% for both parameters) and good specificity (85%

and 88%, respectively) to detect fibrinogen levels of <150 mg/dL in PPH. In addition, a currently published review on obstetric hemorrhage has suggested that the use of viscoelastic tests such as the ROTEM® device may offer great advantage in detecting haemostatic changes during delivery.[89] Huissoud *et al.* reported that A5 in FIBTEM rises to 16 (15-19) mm (median [interquartile range]) in the last trimester of pregnancy and decreases to 12 (8-15) mm in patients with PPH.[72] Therefore, targeting higher fibrinogen levels in patients suffering from PPH appears to be reasonable. Accordingly, Charbit has clearly demonstrated that fibrinogen levels <200 mg/dL at the beginning of PPH have a positive predictive value of 100% for the development of severe PPH.[87] However, studies proving safe thresholds to prevent and manage severe PPH are urgently needed. In addition to its advantages in guiding fibrinogen substitution, the ROTEM® device may be helpful in detecting hyperfibrinolysis, which may further deteriorate haemostatic competence during PPH.[90] Finally, the recently published European Guideline for the management of severe perioperative bleeding suggests the use of viscoelastic testing in managing patients suffering from PPH.[91] However, further studies are needed to define the ranges of reference values that should be considered normal in this setting.

Level of evidence for the use of ROTEM® in individual clinical settings

In order to generate recommendations based on the body of supporting evidence of all reported studies, we used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the level of evidence.[92] All recommendations and suggestions in this review are assigned as strong or weak (relating to the strength of the recommendation) and the quality of the supporting evidence (high, moderate, low, very low) according to the GRADE system (Table IV). Recommendations for the use of ROTEM® in individual clinical settings covered by this review were suggested and listed in Table V.

Limitations

The following limitations must be noted when interpreting ROTEM® results. First, the ROTEM® measurement takes place in a cuvette under no-flow conditions in the absence of endothelialised blood vessels, and thus, test results should always be interpreted in the context of the actual clinical condition of the patient (*e.g.*, overt or diffuse bleeding or not). Furthermore, the positive predictive value of ROTEM® analy-

Table IV.—*Grades of recommendation – GRADE system.*

Strength of recommendation	Definition of strength	Quality of evidence	Definition of grading the quality of the evidence
Strong recommendation	Benefits do, or do not, outweigh risks and burdens	High	Further research is very unlikely to change the confidence in the estimate of effect
		Moderate	Further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate
		Low	Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate
		Very low	Any estimate of effect is very uncertain
Weak recommendation	Benefits and risks/burdens are finely balanced, or appreciable uncertainty exists about the magnitude of benefits and risks	High	Further research is very unlikely to change the confidence in the estimate of effect
		Moderate	Further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate
		Low	Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate
		Very low	Any estimate of effect is very uncertain

Table V.—*Recommendations for the use of ROTEM® in individual clinical settings based on the GRADE system.*

Clinical setting	Strength of recommendation	Quality of evidence	Remarks
Thromboelastometry in severe trauma	Strong recommendation	Moderate	Only one randomized controlled trial demonstrated reduction in allogeneic blood transfusion using a ROTEM®-based algorithm. Further research to define safe and reliable thresholds for the ROTEM® to initiate coagulation therapy is urgently needed
Thromboelastometry in cardiovascular surgery	Strong recommendation	High	Three randomized controlled trials demonstrated efficacy in reducing blood loss and transfusion requirements, one study showed improvement in outcome including six-month mortality; however further research seems warranted
Thromboelastometry in liver transplantation	Strong recommendation	Low	Data from observational trials consistently demonstrate reduction of blood products transfused during liver transplantation following implementation of ROTEM® in bleeding management
Thromboelastometry in postpartum haemorrhage	Weak recommendation	Low	Data from observational trials demonstrate the importance of fast laboratory assessment of changes in haemostasis for adequate treatment

sis for bleeding in elective surgery is low, which is also true for all routine plasmatic coagulation tests. This means that abnormal ROTEM® results should only be treated in the presence of clinically relevant bleeding. On the other hand, the negative predictive value of ROTEM® analysis is high, which means that bleeding in the absence of abnormal ROTEM® results can be considered most often as surgical. Thirdly, ROTEM® analysis is not sensitive enough to detect platelet function disorders or anti-platelet drug effects. This diagnostic gap can be filled by whole blood impedance aggregometry (Multiplate®; Roche Diagnostics AG, Mannheim, Germany or ROTEM platelet®; TEM International GmbH, Munich, Germany) or other specific POCTs addressing platelet function.

Conclusions

In summary, the systematic review of the published literature clearly demonstrates the usefulness of the ROTEM® device in detecting perioperative coagulation disorders reliably and within a clinically acceptable short turn-around time. As laboratory testing contributes only one part to severe bleeding management, the implementation of safe and effective treatment algorithms must be ensured at the same time. As the current data demonstrate a multifactorial causality and, dependent on the clinical setting, different physiological changes in hemostasis, developing a universal bleeding management algorithm does not appear to be appropriate. A well-experienced physician is essential for the interpretation of all laboratory results within the clinical context. However, the ROTEM® device has been proven to be a helpful tool in bleeding management algorithms to guide haemostatic therapy in several clinical settings.

Key messages

— ROTEM®-guided bleeding management allows for fast and reliable detection of underlying coagulopathy in severe trauma, cardiovascular surgery, liver transplantation, and post-partum haemorrhage.

— Individualized, calculated and goal-directed therapy for perioperative coagulopathy can be safely guided by thromboelastometry in these settings.

— ROTEM® results should be ideally incorporated in a setting-specific clinical treatment algorithm for bleeding management.

— As ROTEM® analysis does not cover all aspects of haemostasis, the additional use of point-of-care platelet function testing should be considered, particularly in cardiovascular surgery.

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