Fixed ratio versus goal-directed therapy in trauma

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Purpose of review
This article compares the strategy of a fixed transfusion ratio of plasma and platelet concentrates to red blood cells to reconstitute 'whole blood' with the concept of individualized goal-directed coagulation therapy (GDCT).

Recent findings
Current data suggest that an early and high ratio of plasma and platelet concentrate transfusion, predominantly in a fixed 1 : 1 : 1 ratio with red blood cells, is associated with improved outcome. However, the optimal ratio is still under discussion. Moreover, storage time considerably affects the hemostatic competence of these products and no universal standard for the composition of these 'transfusion packages' has been established. Some European trauma centers instituted the concept of GDCT in trauma patients, which is based on early diagnosis of the coagulation deficit using point-of-care viscoelastic tests (VETs). These tests provide rapid information about the underlying hemostatic deficiencies, allowing targeted coagulation therapy according to the individual deficits of the patient. Treatment algorithms have been established for the administration of coagulation factor concentrates, and plasma and platelet concentrate based on VET results.

Summary
Individualized GDCT, guided by VET, offers several advantages over fixed ratio coagulation therapy. Studies comparing both hemostatic strategies are warranted.

Keywords
goal-directed coagulation therapy, ratio-driven coagulation therapy, trauma-induced coagulopathy, viscoelastic tests

INTRODUCTION

Despite substantial improvement in acute trauma care, uncontrolled bleeding remains the primary cause of preventable death [1,2]. Most of these patients die within 3–6 h of hospital admission [3]. Thus, many trauma centers implement massive transfusion protocols to rapidly identify patients at risk for massive transfusion and administer hemostatic agents without substantial time delay [4,5]. Recent data suggest that early transfusion of high ratios of plasma and platelet concentrate, predominantly in a fixed 1 : 1 : 1 ratio with red blood cells (RBCs), is associated with improved outcome in patients with severe bleeding [6▪▪].

Some European trauma units have established a more targeted approach to treat coagulopathic trauma victims. Viscoelastic tests (VETs), most commonly rotational thromboelastometry (ROTEM, TEM International GmbH, Munich, Germany) or thrombelastography (TEG, Haemonetics Corporation, Niles, Illinois, USA], are used to evaluate the hemostatic capacity of trauma patients. Tailored hemostatic therapy, largely consisting of purified coagulation factor concentrates (CFCs), can then be applied [7–13].

FIXED RATIO COAGULATION THERAPY

The concept of damage-control resuscitation has been adopted in many military and civilian trauma centers [14,15], and is essentially based on restricted fluid therapy, permissive hypotension, and consequent maintenance of normothermia [14]. Early and aggressive transfusion of plasma has been

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KEY POINTS

- FRCT, based on the concept of delivering a fixed ratio of blood components (i.e., platelet concentrate, plasma, and RBCs), has been implemented in many trauma hospitals across the world.
- FRCT can be rapidly applied without the need to wait for test results; however, the ideal ratio of blood components is still a matter of debate.
- Goal-directed coagulation therapy (GDCT) aims to offer individualized therapy based on the results of VETs, and the administration of CFCs.
- The GDCT approach allows for rapid and targeted therapy, while reducing allogeneic blood product exposure and the risk of volume overload.
- Further studies comparing the two approaches are warranted.

advocated to replace circulating volume and depleted clotting factors [4,6▪▪,16]. Consequently, in many trauma hospitals across the world, fixed ratio coagulation therapy (FRCT) proposing a 1 : 1 ratio of RBCs : plasma has been established [4,6▪▪,16–20]. Although platelet count is normal in many trauma patients upon emergency room admission, compromised platelet function has been observed [21–23]. Thus, current massive transfusion protocols also recommend early platelet concentrate transfusion [4,6▪▪,16].

ADVANTAGES OF FIXED RATIO COAGULATION THERAPY

In therapeutic plasma, the concentration of both procoagulant coagulation factors and inhibitors may be reduced because of the production process, although the ratio of procoagulant to inhibitor concentration remains balanced [24]. Timely plasma administration has the potential to avoid further dilution and prevent coagulopathy. Moreover, plasma serves as a volume replacement, which is essential to maintain tissue oxygenation in patients suffering from shock. It has also been suggested that plasma exerts a protective effect on the glycocalyx, a thin monolayer on the inner surface of the endothelium [25]. Glycocalyx shedding is associated with increased vascular permeability and release of heparin-like substances [26]. One further advantage of FRCT is that, initially, coagulation tests are not urgently required, as plasma and platelet concentrates are transfused in a predefined ratio rather than guided by specific laboratory thresholds.

DISADVANTAGES OF FIXED RATIO COAGULATION THERAPY

Plasma transfusion appears to be lifesaving only when administered in patients receiving more than 6–10 U RBCs [27]. Retrospective studies discovered that plasma administration in patients receiving less than 10 U RBCs was associated with considerable side-effects [28]. FRCT might increase the risk of both overtransfusion and wastage of valuable and expensive blood products.

Some types of plasma, such as fresh frozen plasma (FFP), have to be thawed prior to use, and only busy trauma units store prethawed universal donor AB plasma [29–31]. Thus, plasma transfusion is often associated with considerable time delays [32]. Lyophilized or freeze-dried plasma, a powder that can be reconstituted within minutes, might overcome this hindrance [33].

A predefined fixed ratio of plasma and platelet concentrate to RBCs aims to provide reconstituted whole blood. Ponschab *et al.* [34▪▪] challenged this concept recently and showed that reconstituted whole blood contains substantially lower amounts of coagulation factors than donated whole blood. Furthermore, the ideal ratio of plasma : RBCs is still a matter of debate, and there are considerable doubts that FRCT meets the individual needs for every trauma patient. In a study by Khan *et al.*, the incidence of patients with suggestive coagulopathy [defined as an extrinsically activated (EXTEM) clot amplitude of less than 35 mm after 5 min running time] increased from 43% on emergency room admission to 49, 62, and 68% after 4, 8, and more than 12 U RBCs, respectively. This is of particular interest as the ratio of plasma : RBCs was close to 1 : 1 [35]. In another recent study by the same group, only high-volume FFP transfusion combined with cryoprecipitate and platelet concentrate administration produced a consistent improvement in coagulation parameters; increasing amounts of plasma did not correct coagulopathy [36].

The value of pre-emptive platelet concentrate transfusion to overcome trauma-induced platelet dysfunction is not yet fully established. A recent meta-analysis, which investigated the effect of high ratio platelet concentrate transfusion in trauma, could not show a survival benefit [37▪▪]. This finding is potentially related to compromised platelet aggregability in reconstituted whole blood [38▪]; transfused platelets might interact with additive solutions and various anticoagulants, which have been added to preserve storage time of the individual blood components [39]. Furthermore, temperature and storage duration of platelets might influence their hemostatic competence [38▪]. For example,

Table 1. Advantages and disadvantages of fixed ratio coagulation therapy

Advantages	Disadvantages
Initially no coagulation tests are necessary as RBCs, plasma and PC are delivered in a predefined ratio	FRCT does not meet the needs of the individual patient resulting in over and undertransfusion
Plasma contains all coagulation factors and inhibitors	In most hospital settings, plasma has to be thawed prior to use resulting in time delay
Protective effects of plasma on the glycocalyx	Considerable side effects associated with most therapeutic plasmas
Plasma serves as volume replacement	Composition of PC and most forms of therapeutic plasma are not standardized
Early platelet transfusion overcomes trauma-related platelet dysfunction	

FRCT, fixed ratio coagulation therapy; PC, platelet concentrate; RBC, red blood cell.

Reddoch *et al.* [40] showed that cold-stored platelets (4°C) had better hemostatic competence and released fewer inflammatory mediators than platelets stored at room temperature. Importantly, no universal standard for the composition of the components of 'transfusion packages' has yet to be established. Advantages and disadvantages of an FRCT are outlined in Table 1.

STUDIES INVESTIGATING FIXED RATIO COAGULATION THERAPY

Numerous retrospective studies from military and civilian trauma centers have been published over the last decade showing improved outcomes of patients receiving high-volume plasma and platelet concentrate transfusion [4,16–19]. However, many of these reports suffer from methodological flaws such as survivorship bias [5,41].

In a small, prospective, feasibility study, Nascimento *et al.* [32] compared FRCT with lab-guided coagulation therapy. No substantial differences in 28-day mortality and acute respiratory distress syndrome could be observed between groups. A transfusion ratio of 1 : 1 : 1 was achieved in 57% of patients in the FRCT group compared with 6% in the lab-guided group. Plasma wastage was higher in the FRCT group than the control group (22 versus 10%). Importantly, the time between the first RBC and plasma transfusion was 60 (40–77) min in the FRCT group versus 78 (49–112) min in the lab-guided group [32].

These findings are in contrast to data from the Pragmatic, Randomized Optimal Platelet and Plasma Ratios study performed in 12 Level 1 US trauma centers [6▪▪]. This trial randomized 680 major trauma patients to receive RBCs, plasma, and platelet concentrate in either a 1 : 1 : 1 or a 2 : 1 : 1 ratio. No significant differences in mortality at 24 h or 30 days were observed between groups. However, more patients in the 1 : 1 : 1 group achieved hemostasis and fewer experienced death because of exsanguination by 24 h. In contrast to other studies, higher transfusion rates of plasma and platelet concentrate did not result in significant safety differences. Importantly, less than half of the study patients received massive transfusion (<10 U RBCs/24 h) [6▪▪].

GOAL-DIRECTED COAGULATION THERAPY

A major criticism of FRCT is that trauma-induced coagulopathy is not a uniform coagulation disorder [42▪]. Thus, resuscitation protocols proposing a predefined ratio of blood products do not fully address the specific needs of any patient. In contrast, the concept of GDCT tailors therapy to the individual hemostatic deficit, as well as to the dynamic changes within the course of initial resuscitation.

MONITORING FOR GOAL-DIRECTED COAGULATION THERAPY

A recent systematic review revealed no evidence that standard coagulation tests (SCTs), such as prothrombin time, international normalized ratio or activated partial thromboplastin time have the potential to guide coagulation therapy [43]. Furthermore, VETs identify hemostatic deficiencies substantially faster and more accurately than SCTs [44–47]. VET analyses are performed in whole blood, which avoids preanalytic preparation of the samples and, in contrast to plasma-based SCTs, corpuscular blood elements remain in place. VETs provide a comprehensive overview of the whole coagulation process, including speed of clot formation, overall clot strength, and clot lysis [45]. Various reagents also allow for differentiation of the underlying causes of coagulopathy [45,47]. Additionally, VET results have the potential to

rapidly identify patients at risk for massive transfusion [44,48].

TARGETS OF GOAL-DIRECTED COAGULATION THERAPY ACCORDING TO VISCOELASTIC TEST RESULTS

The results from VETs can be used in GDCT to diagnose the specific requirements of the patient and to guide therapy accordingly.

Hyperfibrinolysis and antifibrinolytic therapy

Shock-related hypoperfusion has been identified as the main driver of endogenous trauma-induced coagulopathy [49]. Substantial amounts of tissue plasminogen activator convert considerable quantities of plasminogen into plasmin, resulting in a profibrinolytic state [42▪,50], and glycoprotein IIIa receptors on the surface of activated platelets are cleaved by plasmin, accompanied by significant reductions in fibrinogen binding, and aggregation response [51].

VETs are highly specific for hyperfibrinolysis, with time of onset and magnitude of clot lysis strongly related to poor outcomes [52–54]; however, these tests have a poor sensitivity [44] and identification of hyperfibrinolysis by VET results may take considerable time. For example, TEG findings suggest that clot lysis of more than 3% 30 min after maximum clot strength has been reached is associated with higher bleeding rates, increased transfusion requirements and unfavorable outcomes [55,56]. More rapidly obtainable VET parameters have been suggested as a surrogate for profibrinolytic activation; these include clot amplitude after 5 min running time (CA5) of less than 35 mm and, importantly, a flat line in extrinsically activated test plus cytochalasin D that inhibits platelet contribution to clot firmness (FIBTEM) [44] (Figs 1 and 2).

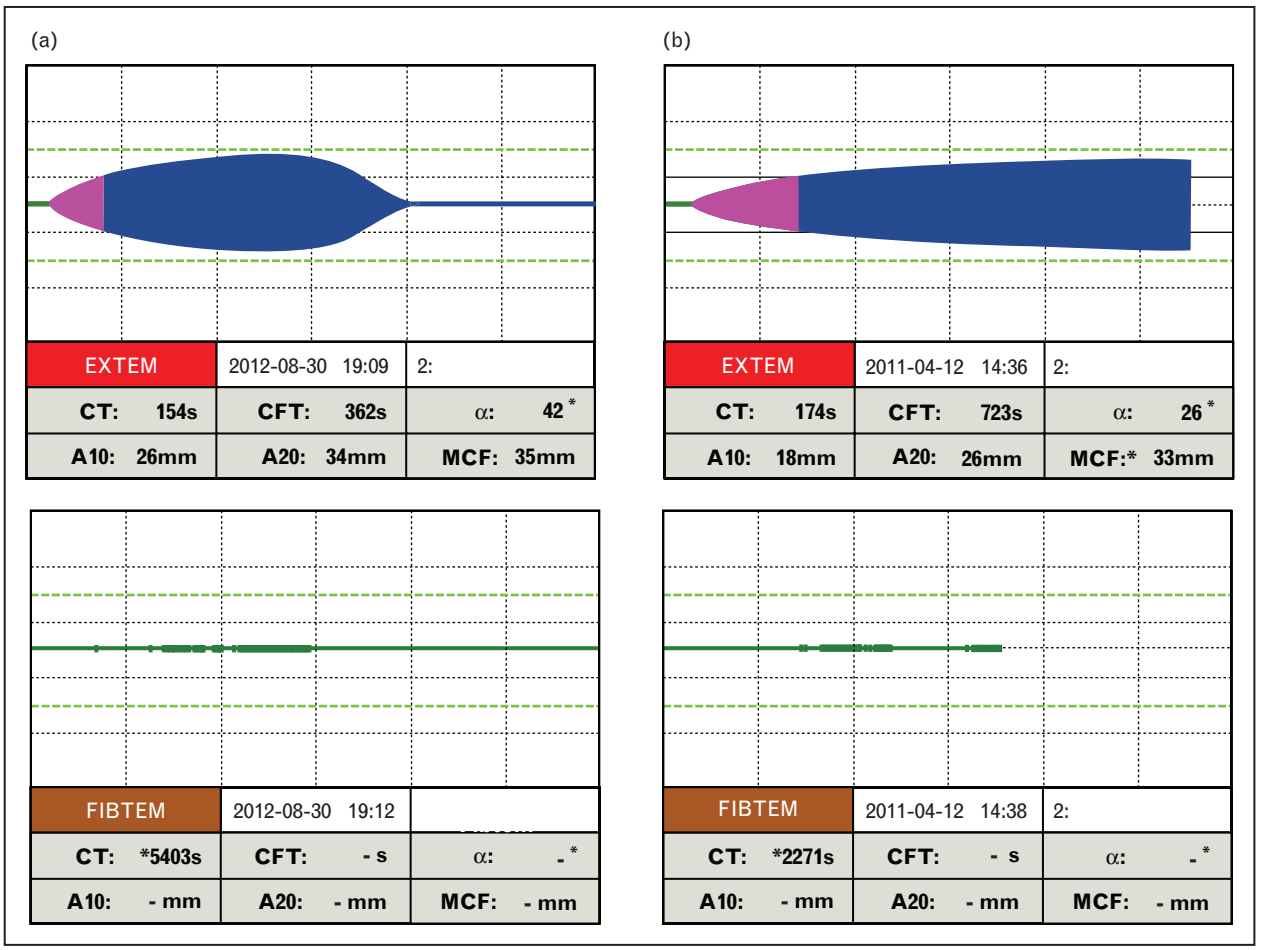

FIGURE 1. An example of EXTEM and FIBTEM traces observed during hyperfibrinolysis. (a) Typical pattern of hyperfibrinolysis with an early dissolution of the clot in the EXTEM assay and no clot formation in the FIBTEM assay. (b) Low EXTEM MCF but with no clot lysis. No clot formation in the FIBTEM assay is suggestive of profibrinolytic activation. A10, clot amplitude after 10 min; A20, clot amplitude after 20 min; CFT, clot formation time; CT, clotting time; MCF, maximum clot firmness.

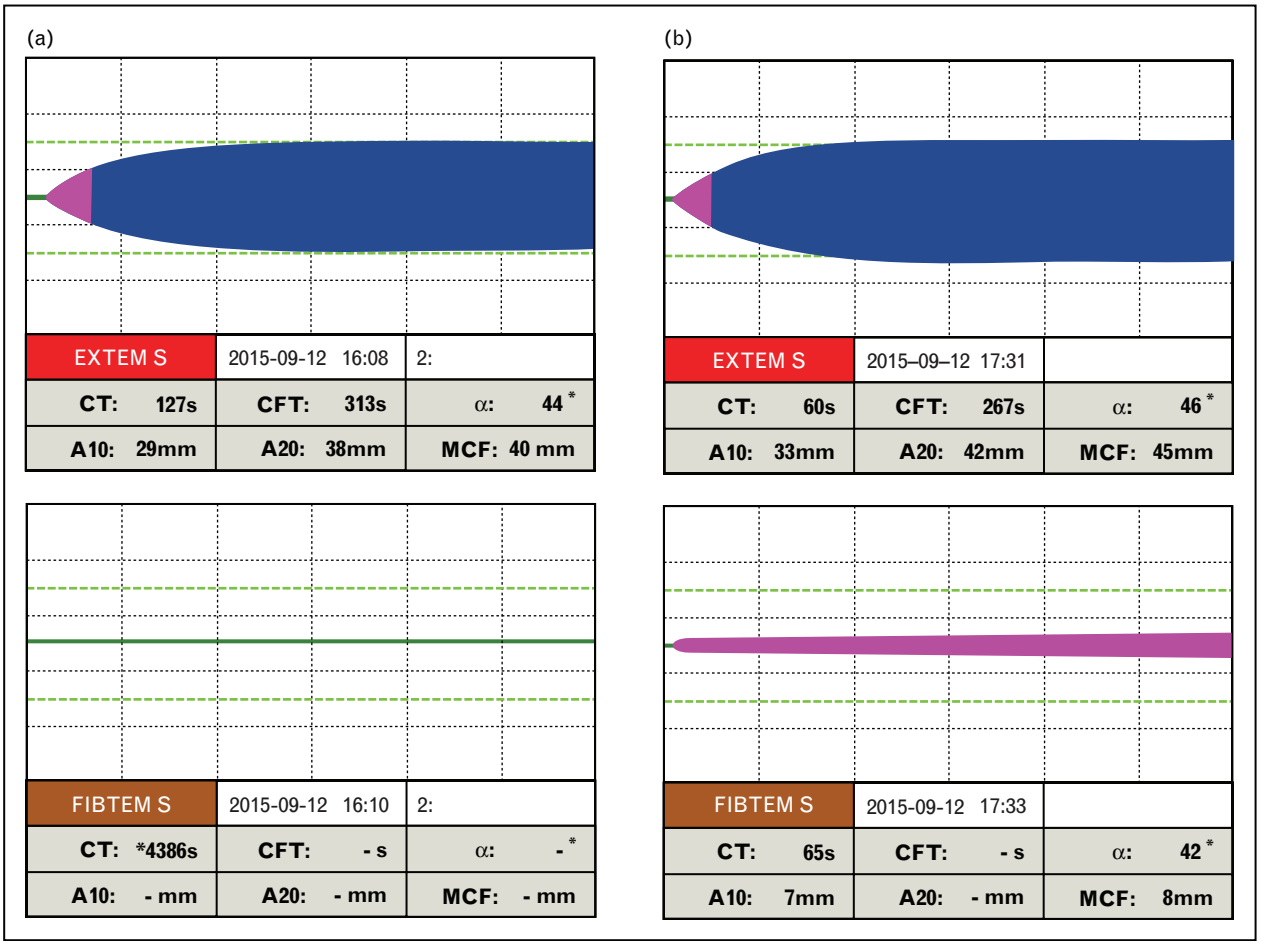

FIGURE 2. Therapeutic effect of fibrinogen concentrate on EXTEM and FIBTEM clot firmness. (a) EXTEM and FIBTEM traces at ER admission. FIBTEM CA10 is 0 mm; plasma fibrinogen concentration 0.66 g/l. (b) FIBTEM CA5 increased to 7 mm after treatment with tranexamic acid and 7 g FC. Importantly, this also results in normal EXTEM CT values. A10/CA10, clot amplitude after 10 min; A20, clot amplitude after 20 min; CA5, clot amplitude after 5 min; CFT, clot formation time; CT, clotting time; ER, emergency room; FC, fibrinogen concentrate; MCF, maximum clot firmness.

Following the results of the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage-2 trial, tranexamic acid (TXA) has become a standard of care for major trauma patients across the world [57], although the optimal cutoff values of VETs for treatment with TXA are yet to be determined. So far, there is only one published study, which used VET results to guide TXA therapy, in which Harvin *et al*. [58] treated patients with TXA when estimated clot lysis after 30 min was at least 3%. Logistic regression failed to find a difference in mortality among those receiving TXA compared with those who did not ($P = 0.80$). Interestingly, administration of TXA was not related to an increased likelihood of correction of lysis to less than 3% in follow-up TEG analyses [58].

An expert panel recently recommended that VETs should be used early in trauma resuscitation to identify injured patients with systemic hyperfibrinolysis, and it was clearly stated that normal lysis in VETs does not rule out profibrinolytic activation [44]. Thus, withholding antifibrinolytic therapy based on VETs is not justified. TXA might be a useful adjunct in some major trauma patients, in particular those arriving in substantial shock. Therefore, TXA should be given based on a clinical decision rather than on the basis of VET findings [59].

Clot firmness

Maximum clot firmness (MCF) demonstrates the interaction between the fibrin network, activated platelets, and activated factor XIII [44,45]. Thus, diminished clot strength implies alterations in the number and/or function of platelets or impairment of fibrin polymerization [45], and is associated with increased bleeding rates, higher transfusion

requirements, and increased mortality [60–64]. Good correlation between MCF and clot amplitude after 10 min running time (CA10) has been observed [65]. Therefore, CA5 or CA10 may serve as surrogates for MCF, thus aiding timely decision-making [44,45,64].

Role of fibrinogen in clot firmness

Fibrinogen is often the first coagulation factor to reach a critical level in major trauma patients [37▪▪], and hypofibrinogenemia upon emergency room admission is an independent predictor of poor outcome and is strongly related to the severity of shock [66–72].

Fibrin polymerization assays such as FIBTEM (ROTEM) or the functional fibrinogen assay (TEG) inhibit platelet contribution to clot firmness [66]. Simultaneous measurements of EXTEM and FIBTEM or TEG and functional fibrinogen allow prompt differential diagnoses between platelet deficiencies and impaired fibrin polymerization, the latter of which may be a result of low or dysfunctional fibrinogen. FIBTEM CA10 less than 7 mm or a FIBTEM MCF less than 10–12 mm might serve as triggers for fibrinogen replacement (Fig. 2) [44]; consequently, replenishment of consumed or inactivated fibrinogen should be an initial step to normalize clot amplitude [8,73,74]. Owing to the use of different platelet inhibitors with differing mechanisms of action, FIBTEM and functional fibrinogen do not provide interchangeable test results [66]. Thus, higher trigger values are recommended for functional fibrinogen [47].

Many studies have revealed that plasma transfusion is insufficient to maintain or increase fibrinogen concentration in massively bleeding patients [69,75]. In particular, reconstituted whole blood comprised RBCs, plasma, and platelet concentrate in a 1 : 1 : 1 ratio contains only low amounts of fibrinogen [34▪▪]. Thus, it remains challenging to increase fibrinogen levels using plasma-based resuscitation protocols [76]. Cryoprecipitate and purified fibrinogen concentrate contain higher concentrations of fibrinogen and are, therefore, more effective for rapidly restoring plasma fibrinogen concentration in bleeding trauma patients.

Platelet function

Normal FIBTEM CA10 (10–12 mm) and low EXTEM CA10 (<40 mm) might be considered as an indirect measure of low platelet count or impaired platelet function [77]. Thus, platelet concentrate transfusion might be indicated [8,47,59,78] (Fig. 3). However, both platelets and fibrinogen contribute to clot firmness and one component may compensate for a lack of the other. For example, in situations where platelet concentrates are not available and platelet count and clot amplitude are low, fibrinogen supplementation might be considered as an alternative treatment to increase clot strength. There is evidence that fibrinogen administration increases EXTEM clot amplitude in thrombocytopenic patients [79]. On the other hand, high fibrinogen levels can mask the effect of abnormal platelet count or function on clot firmness [44].

Thrombin generation

Persistent bleeding after improvement of clot firmness is often a sign of endogenous thrombin generation deficiency. Thrombin is the most potent enzyme in the coagulation process that activates other coagulation proteins, platelets, and cleaves fibrinogen to fibrin [80,81▪]. However, it remains challenging to quantify thrombin generation by both SCTs and VETs [82,83].

Although it may be possible to detect abnormalities in clot initiation by measuring the time from initiation of coagulation until a clot amplitude of 2 mm is reached [clotting time (ROTEM), r-time (TEG)], sound methodologies to guide augmentation of thrombin generation [e.g., via administration of plasma, prothrombin complex concentrate (prothrombin complex concentrate) or activated recombinant factor VII] to normalize clot initiation are still lacking [44]. It has to be kept in mind that low platelet count and low fibrinogen levels may also prolong clotting time or r-time and should, therefore, be considered if these values are to be used as a transfusion trigger [44]. In many cases, treatment with thrombin-generating agents can be avoided by providing a higher quantity of substrate (e.g., fibrinogen) for initial clot formation, thereby shortening clotting time (Fig. 2).

According to the treatment algorithm developed by our group, thrombin generation should be augmented only if the EXTEM clotting time exceeds 80 s after normalization of FIBTEM clot amplitude [78]. We chose this threshold as EXTEM clotting time exceeds the upper limit of 80 s when the activity of the coagulation factors falls to less than 35% [84]. Therefore, we do not recommend administration of thrombin-generating agents prior to normalization of FIBTEM clot amplitude. Figure 4 illustrates a treatment algorithm as suggested by the 2014 consensus conference on VET-based transfusion guidelines for early trauma resuscitation [44].

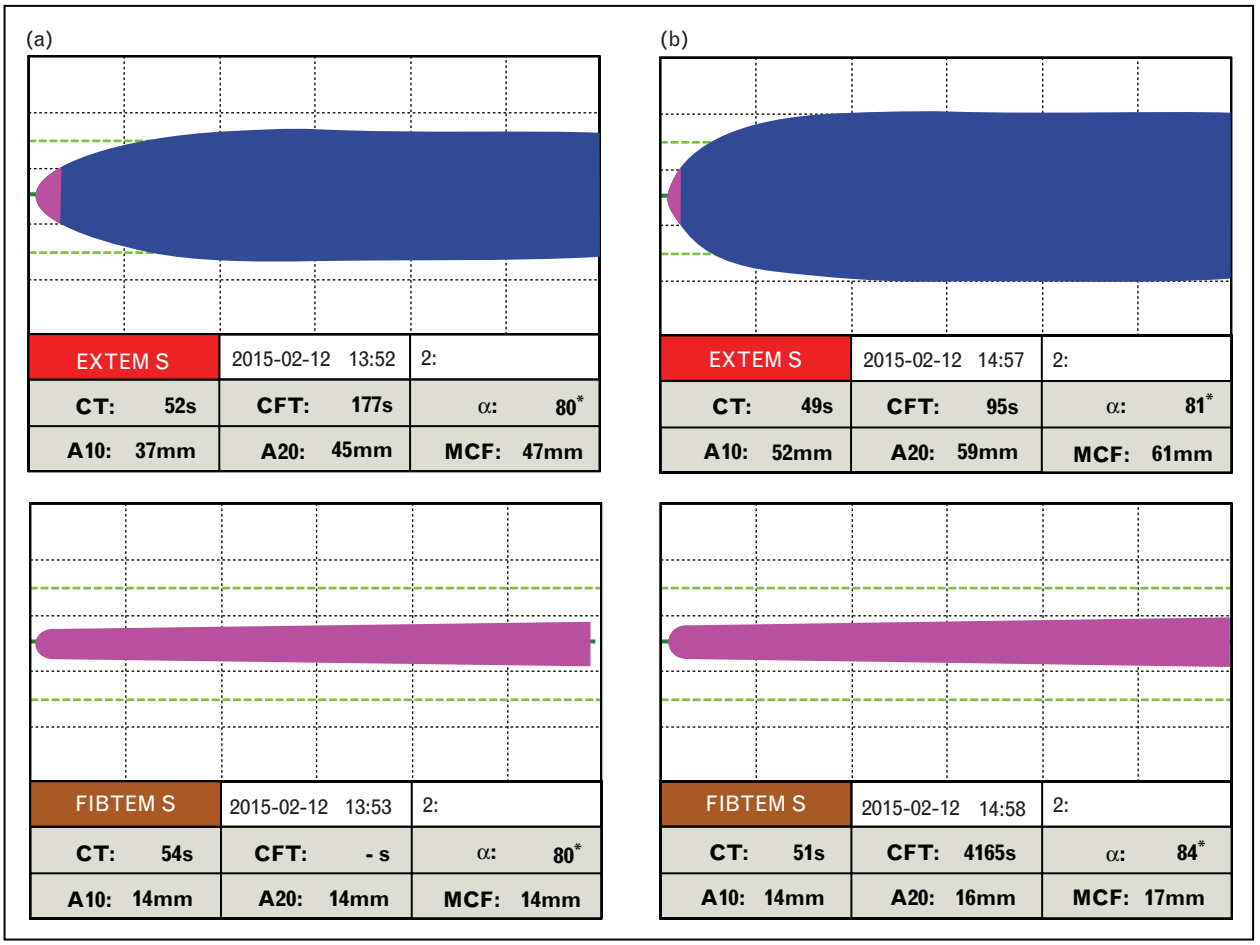

FIGURE 3. Differential diagnosis of low clot amplitude by simultaneous measurements of EXTEM and FIBTEM. (a) Low EXTEM CA10 (37 mm) and normal FIBTEM CA10 (14 mm). Platelet count is 86 000/μl, fibrinogen. (b) After 2 U apheresis PC, EXTEM CA10 increased to 52 mm and FIBTEM CA10 remained unchanged. A10/CA10, clot amplitude after 10 min; A20, clot amplitude after 20 min; CFT, clot formation time; CT, clotting time; MCF, maximum clot firmness; PC, platelet concentrate.

ADVANTAGES OF GOAL-DIRECTED COAGULATION THERAPY

Hemostatic therapy based on CFC allows for rapid and targeted coagulation intervention. Thus, earlier establishment of sufficient hemostasis might reduce exposure to allogeneic blood products [9,85] and reduce the risk of volume overload (Table 2).

DISADVANTAGES OF GOAL-DIRECTED COAGULATION THERAPY

In contrast to FRCT, GDCT requires additional training and adherence to predefined treatment algorithms. In a hectic emergency room environment it is often challenging to follow these protocols. A thorough understanding of trauma-induced coagulopathy, the coagulation process and appreciation for VETs are imperative for appropriate use of blood components and CFCs.

Until now, none of the published algorithms have been validated in prospective studies, and there are no published data on trauma patients available to demonstrate a survival or cost benefit of GDCT over FRCT. Moreover, a recent Cochrane review revealed no clear survival benefit for the use of VETs in trauma [86] (Table 2).

STUDIES INVESTIGATING GOAL-DIRECTED COAGULATION THERAPY

Until now, only a few small retrospective studies and some case reports have been published using GDCT [7,9–11,85,87–89].

In a study of 131 major trauma patients, a median of 6 g fibrinogen concentrate was administered as first-line therapy to increase FIBTEM MCF to more than 10 mm [87]. In patients with prolonged EXTEM clotting time (>80 s) additional prothrombin

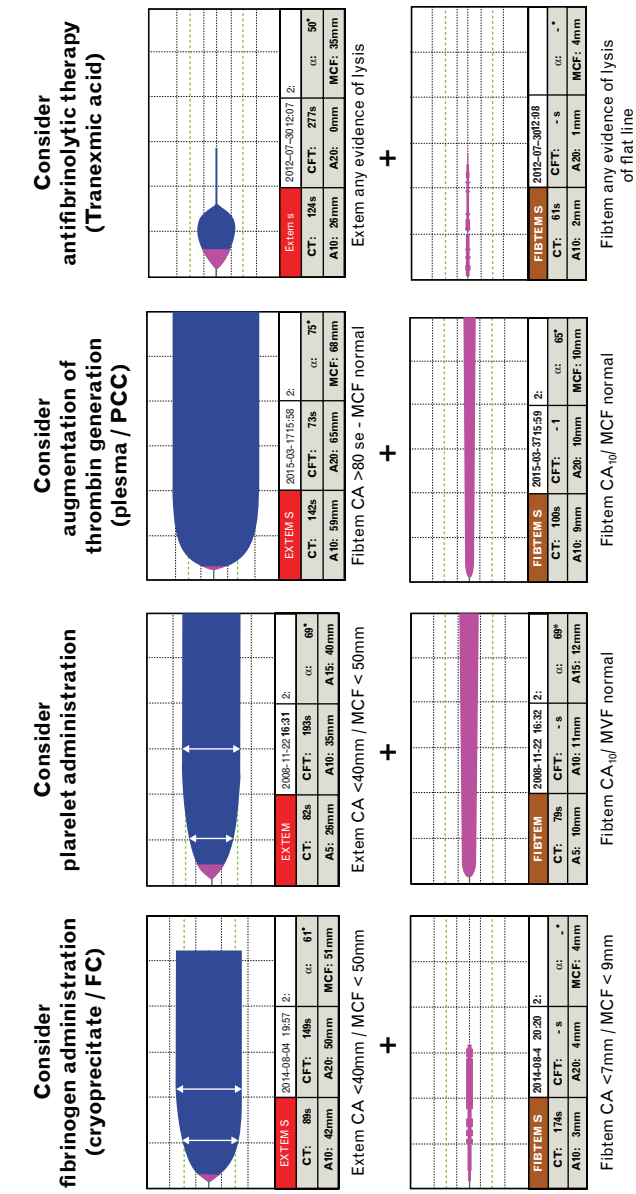

FIGURE 4. Therapeutic algorithm according to EXTEM and FIBTEM test results (modified according to Inaba *et al.* [50]). A10, clot amplitude after 10 min; CT, clotting time; FC, fibrinogen concentrate; MCF, maximum clot firmness; PCC, prothrombin complex concentrate.

Table 2. Advantages and disadvantages to goal-directed coagulation therapy

Advantages	Disadvantages
Allows for targeted therapy according to the individual's needs	Education of the team is necessary
VETs provide a comprehensive overview of the coagulation process	Viscoelastic monitors required
CFCs are quickly available, are well standardized and contain high amounts of coagulation factors in a low volume	No prospective validation of treatment algorithms

CFC, coagulation factor concentrates; VET, viscoelastic tests.

complex concentrate was given (median dose 1800 U). Observed mortality was significantly lower than predicted according to the Trauma Injury Severity Score and the revised injury severity classification methodology [87]. Another study by the same group showed that CFC-based therapy reduced exposure to allogeneic blood products when compared with FFP-based therapy [85]. Transfusion of RBCs and platelet concentrate were avoided by 29 and 91% of patients receiving CFC-based hemostatic therapy compared with 3 and 56% of those treated with FFP, respectively. No difference in mortality was reported between groups [85].

Tapia *et al.* [88] compared a TEG-guided algorithm to FRCT. For blunt trauma patients transfused with at least 10 U RBCs, those in the FRCT group received more FFP ($P = 0.02$) than those in the TEG-guided group, with no observed difference in mortality. Among patients with penetrating trauma, lower mortality was observed in the TEG-guided cohort.

Yin *et al.* [89] investigated the effect of GDCT in adult patients with abdominal trauma who received at least 2 U RBCs within 24 h. In a subgroup of patients with injury severity score at least 16, GDCT significantly reduced transfusion of blood products compared with the control group (7 U versus 37.6 U, $P = 0.015$). No differences between groups in ICU and hospital length of stay or 28-day mortality were observed [89].

COMBINED FIXED RATIO COAGULATION THERAPY/GOAL-DIRECTED COAGULATION THERAPY APPROACH

The Copenhagen concept proposes an approach which sits between FRCT and GDCT [90]. Initially, blood products are transfused in a predefined 1 : 1 : 1 ratio. VETs are performed on arrival and, once the results are available, coagulation therapy is adjusted to GDCT.

Nardi *et al.* [91] recently published data from an Italian multicenter study on the impact of a newly established early coagulation support protocol, whereby coagulation is monitored via VETs. Initial treatment, comparable with the Copenhagen concept, was based on clinical signs of shock and on results of early blood gas analyses. According to the new protocol, patients in shock received a standard dose of 2 g fibrinogen concentrate. Blood product consumption, mortality, and costs were compared before and after the initiation of the protocol, and a significant reduction in plasma and platelet concentrate transfusion ($P < 0.05$) and a trend toward decreased use of RBCs and decreased mortality were observed [91].

CONCLUSION

Trauma-induced coagulopathy is not a universal phenotype of hemostatic disorder. Therefore, individualized coagulation management holds many theoretical advantages over the ratio-driven approach. The availability of both rapidly obtainable VET results in association with hemostatic agents is key to the targeted supplementation of procoagulants. Although there are significant potential benefits with this concept, a consensus among physicians regarding this treatment strategy does not currently exist. Thus, prospective studies comparing GDCT with FRCT are warranted.

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Conflicts of interest

H.S. and M.M. received study grants and speaker's fees from TEM International and CSL Behring. W.V. declares no conflicts of interest.

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- ■■ of outstanding interest

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