



## Review article

## Updated concepts on the pathophysiology and the clinical management of trauma hemorrhage and coagulopathy

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## ABSTRACT

Uncontrolled hemorrhage and subsequent trauma-induced coagulopathy (TIC) are still the principle causes for preventable death after trauma and early detection and aggressive management have been associated with reduced mortality. Despite increasing knowledge about trauma resuscitation, best practice to treat this newly defined entity is still under debate. A synopsis of best current knowledge with reference to the updated European trauma guideline on the management of severe trauma hemorrhage and TIC is presented. The implementation of evidence-based local protocols and algorithms including clinical quality and safety management systems together with parameters to assess key measures of bleeding control and outcome is advocated.

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## Introduction

Uncontrolled hemorrhage and trauma-induced coagulopathy (TIC) are still the principle causes for preventable death after trauma and one out of four severely injured trauma patients admitted to the hospital is bleeding with variable signs of laboratory coagulopathy.<sup>1–3</sup> Meanwhile, TIC is recognized as an own clinical entity with substantial impact on both morbidity and mortality after trauma.<sup>3,4</sup> There has been speculation about the potential mechanisms underlying TIC but much of the data continues to be rather correlative than causative with robust links still lacking.<sup>5</sup> The current understanding of TIC is summarized in Fig. 1.

## The current understanding of TIC

*Traumatic coagulopathy (TC) is initiated by injury and hypoperfusion*

The current concept of trauma-induced coagulopathy separates traumatic coagulopathy (TC), which is essentially triggered by the traumatic event itself, from iatrogenic coagulopathy (IC), which aggravates TC in the further sequelae. The key drivers of TC are tissue injury<sup>3,6</sup> and hypoperfusion.<sup>7,8</sup> The latter modulates the protein C pathway thereby inducing (hyper)fibrinolysis and the inhibition of coagulation factors V and VIII (Fig. 2).<sup>7,8</sup> Fibrinolytic activation has been identified as integral to the pathogenesis of TC being associated with massive transfusion requirement and poor clinical outcome.<sup>9,10</sup> Fig. 3 displays a clinical example of a fulminant lysis occurring within minutes after an injured patient was admitted to the emergency department (ED). Most recent data suggests that elevated and overwhelming tissue plasminogen activator (tPA) and not plasminogen activator inhibitor (PAI-1) degradation promote hyperfibrinolysis in the context of severe trauma.<sup>11,12</sup> Inflammatory processes lead to impaired platelet function and coagulation factor synthesis. In a prospective

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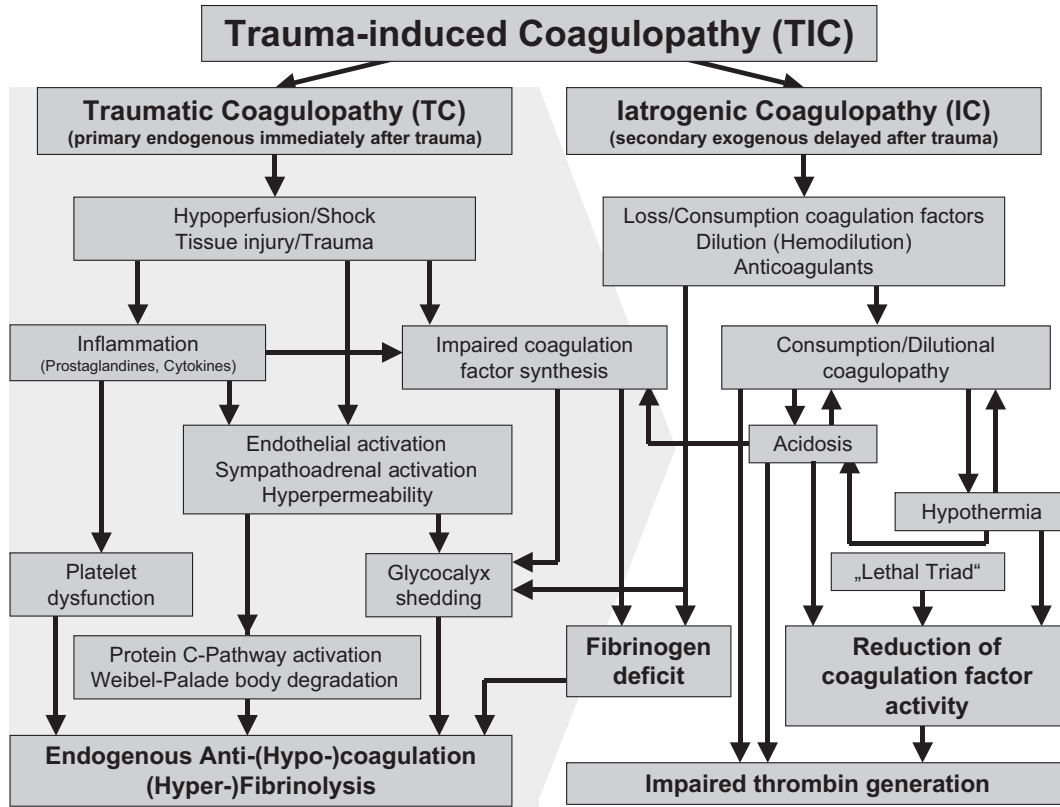


Fig. 1. Current concept and understanding of the mechanisms underlying TIC.

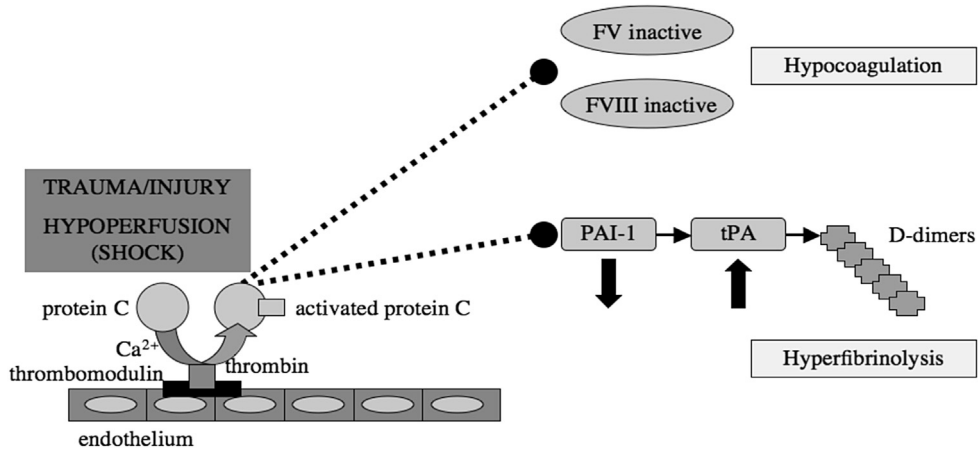


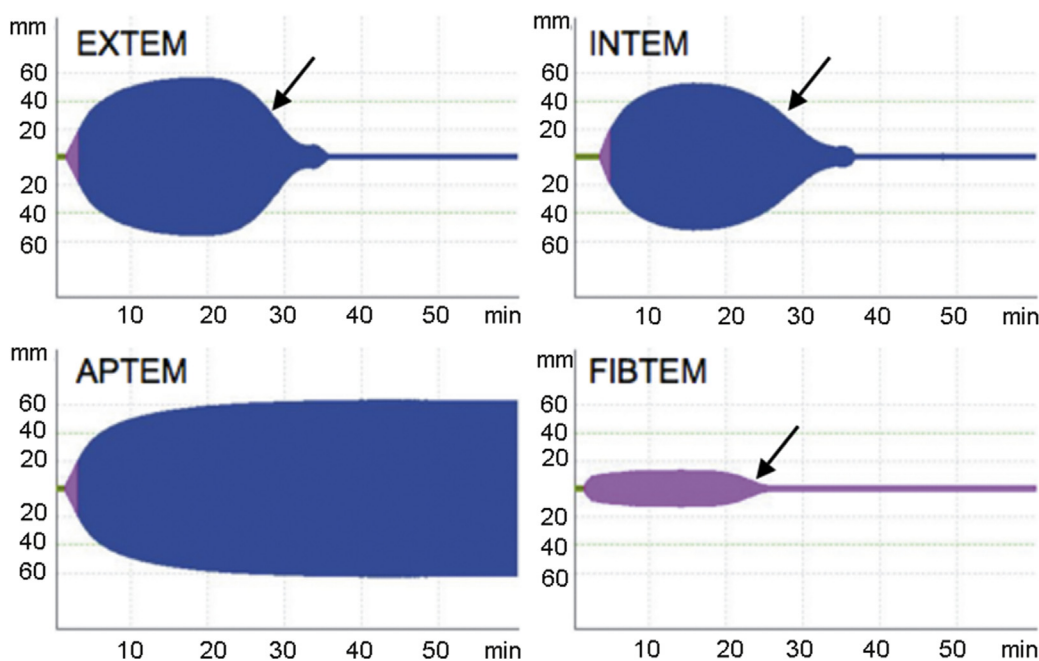
Fig. 2. Activation of the protein C pathway when (tissue) injury is associated with (tissue) hypoperfusion/shock. Combined trauma and hypoperfusion/shock may lead to a hypocoagulable state via formation of an anticoagulant complex (thrombin–thrombomodulin complex/TTC), which converts protein C into activated protein C, leading to an inactivation of the coagulation factors V and VIII. Activated protein C in surplus also consumes PAI-1 (plasminogen activator inhibitor-1), which may lead to an increase in tPA (tissue plasminogen) in the context of severe trauma.

observational cohort involving more than 400 trauma patients, one third displayed laboratory signs of coagulopathy, which was associated with sympathoadrenal activation, endotheliopathy and excess mortality.<sup>13</sup> High adrenalin and biomarkers reflecting endothelial cell junction and glycocalyx activation were independently associated with hypocoagulability and hyperfibrinolysis. A follow-up study showed that endothelial glycocalyx degradation may induce endogenous heparinization in patients with severe injury and early traumatic coagulopathy.<sup>14</sup> Vice-versa, chemical sympathectomy attenuated inflammation, glycocalyx shedding and

coagulation disorders in acute experimental traumatic coagulopathy.<sup>15</sup>

*Iatrogenic coagulopathy aggravates TC*

The iatrogenic arm of TIC includes loss, consumption and dilution of coagulation factors, the latter often being related to uncritical volume administration during the initial phase of care to stabilize circulatory function.<sup>3</sup> Fibrinogen, considered as coagulation factor 1 and thereby as the substrate of clot formation, is usually the first



**Fig. 3.** Clinical example of a patient with fulminant fibrinolysis (clot breakdown; arrows) within minutes after ED admission as detected via viscoelastic testing assay (ROTEM®). The ROTEM® assay is performed in whole blood at the point of care or in emergency laboratories and investigates the interaction of coagulation factors including their inhibitors, anticoagulant drugs, blood cells including platelets, during clotting and subsequent fibrinolysis. It detects both hypo- and hyper-functional states of the clotting process and is likely to represent the only reliable rapid test for the diagnosis of hyperfibrinolysis to date. The **EXTEM** assay activates hemostasis via the physiological activator tissue factor (TF), is a screening test for the (extrinsic) hemostasis system and the result is influenced by extrinsic coagulation factors, platelets and fibrinogen. The **INTEM** assay activates the contact phase of hemostasis and the result is influenced by coagulation factors, platelets, fibrinogen and heparin. The **APTEM** assay is EXTEM based in which fibrinolysis is inhibited by aprotinin. A significant improvement of the clot in the APTEM assay as compared to EXTEM, as demonstrated, allows to detect fulminant hyperfibrinolysis and supports in identifying the need for the administration of an antifibrinolytic drug, e.g. tranexamic acid (TXA). The **APTEM** assay further enables the estimation if such a therapy alone normalizes coagulation or if additional measures are needed (e.g. administration of fibrinogen or platelets). The **FIBTEM** assay is EXTEM based as well but for the fibrin part of the clot. The assay eliminates the platelet contribution to the clot via inhibition of platelets with cytochalasin D which is a potent inhibitor of actin polymerization. The **FIBTEM** assay allows for the detection of fibrinogen deficiency or fibrin polymerization disorders.

coagulation factor to reach critical levels in the acute phase and this as a function of injury severity.<sup>16</sup> Low fibrinogen levels in injured patients on ED admission have been independently associated with poor outcomes.<sup>17</sup> Existing TC together with acidosis and hypothermia create the “lethal triad” of death and reductions and/or deficits in coagulation factor activity lead to impaired thrombin generation thereby substantially aggravating TC.

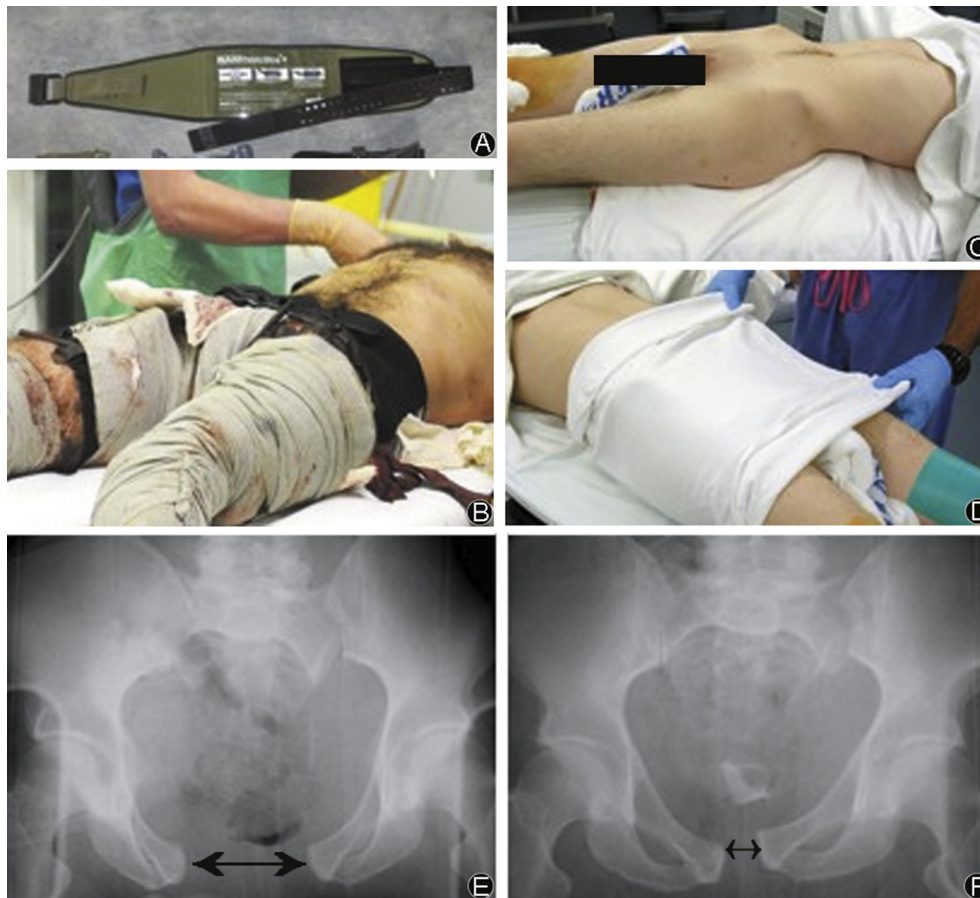
### Updated concepts on the clinical management of trauma hemorrhage and TIC

Early detection and aggressive management of TIC have been associated with improved outcomes and there is need for the implementation of evidence-based local protocols and algorithms including clinical quality and safety management systems together with parameters to assess key measures of bleeding control and outcome.<sup>18</sup> Recent surveys confirm a substantial diversity and heterogeneity in the clinical diagnosis and management of acute trauma hemorrhage and TIC across even specialized trauma centers.<sup>19</sup> The “European guideline on management of major bleeding and coagulopathy following trauma: fourth edition” has recently been updated and presents a total of 39 evidence-based recommendations for improved care for bleeding trauma patients and TIC.<sup>18</sup> Major aspects of the European trauma guideline have also been adopted by national and local guidelines.<sup>4</sup> The overall therapeutic aim, if possible, is to rapidly detect and to stop the bleeding. The recommendations given by the European trauma guideline are graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.<sup>20</sup> The number associated with the recommendation reflects the strength of the

recommendation being GRADE 1 considered as the authors group's strong recommendation and being GRADE 2 considered as the authors group's weak recommendation/suggestion; the following letter reflects the quality of the scientific evidence ranging from A (high quality evidence) to C (low quality evidence).

### Prehospital management of the bleeding trauma patient

Only a few hospitals offer the entire spectrum of care for the severely injured and bleeding trauma patient and a number of health care systems have thus developed and implemented trauma networks and systems. The goal is to optimize patient flow and to deliver appropriate and adequate care to the bleeding trauma patient as quickly as possible. This is mirrored by the European trauma guideline as the time elapsed between injury and (surgical) bleeding control be minimized (GRADE 1A). Despite low evidence, there is strong consensus that organizing a trauma system is associated with a 15% reduction in trauma mortality with cases of preventable deaths reduced by half.<sup>21</sup> In the context of time-sensitive pathologies such as traumatic brain injury (TBI), spinal cord injury, severe burns and hemorrhage, direct admission to a designated trauma center offering the maximum spectrum of care to these particular entities has been linked to improved survival.<sup>22</sup> Therefore, the European trauma guideline suggests that the severely injured patient be transported directly to an appropriate trauma center (GRADE 1B). Experiences from the battlefields of Iraq and Afghanistan over the past has led to the introduction of tourniquets and pelvic binders into the civilian arena to stop life-threatening bleeding from open extremity injuries and internally from pelvic fractures (Fig. 4). The recommendation for their early use has been lifted from GRADE 1C



**Fig. 4.** Prehospital closure and stabilization of the pelvic ring by using commercial pelvic binders/slings (A and B, please also note the tourniquet applied to the right lower limb for acute hemorrhage control!) and circumferential sheeting (C and D). Radiological control in a.-p. projection before and after circumferential sheeting (E and F).

to GRADE 1B recommendation in the updated European trauma guideline and, in Germany, all emergency vehicles are currently being equipped with these life-saving devices.

#### *Initial resuscitation of the bleeding trauma patient*

In severely injured and hypotensive trauma patients, volume replacement should be initiated at a reduced level if there is uncontrollable bleeding in order to keep the circulation stable at target blood pressure and not exacerbate the bleeding until the bleeding can be controlled (GRADE 1B). The European trauma guideline suggests for adult trauma patients with active bleeding to conduct permissive hypotension with a target mean arterial pressure (MAP) of 65 mmHg and/or with a target systolic blood pressure (SBP) of 80–90 mmHg until major bleeding control has been achieved (GRADE 1C). The fluid of choice in the hypotensive bleeding trauma patient is isotonic crystalloid solution (GRADE 1A); the use of colloids be restricted due to their adverse effects on hemostasis (GRADE 2C). Specific recommendations apply for patients with injuries to the brain (TBI) and to other structures of the central nervous system.

#### **In-hospital management**

##### *Clinical assessment of the bleeding trauma patient*

The extent of trauma hemorrhage is clinically assessed by using a combination of patient physiology, anatomical injury, mechanism of

injury and the individual's response to initial resuscitation as outlined in the Advanced Trauma Life Support-protocol (GRADE 1C, Table 1).<sup>23</sup> This concept suggests four classes of hypovolemic shock based upon initial presentation which trigger specific strategies for fluid resuscitation. Early and repeated imaging such as computed tomography (CT) and ultrasound, e.g. in the context of focused assessment sonography in trauma (FAST), is recommended to detect or exclude extravasal fluid (GRADE 1B). The number of CT scans including whole-body CT scans has seen an explosion since the landmark study by Huber-Wagner and colleagues from the TR-DGU<sup>®</sup> indicating a survival benefit in severely injured patients along with the integration of whole-body CT into early trauma care.<sup>24</sup> Currently, three out of four trauma patients receive CT diagnostics (either cranial CT or whole-body CT) within mean  $23 \pm 17$  min after hospital admission and over four out of five patients receive FAST ultrasound diagnostics within mean  $6 \pm 10$  min after hospital admission in trauma centers affiliated with the German Trauma registry (TR-DGU<sup>®</sup>).

##### *Laboratory parameters*

Monitoring and measures to support coagulation function should be initiated immediately after ED admission of the bleeding trauma patient. This recommendation has been lifted from initially GRADE 1C to GRADE 1B in the updated guideline. Low initial hemoglobin (Hb) is considered indicative for severe bleeding associated with coagulopathy and repeated Hb measurements are recommended as an initial value within the reference ranges may mask the bleeding (GRADE 1B). Laboratory parameters to assess and monitor volume deficits and

**Table 1**

Estimated blood loss based upon the patient's initial presentation according to ATLS. Recommendations are given for a 70 kg male and based on the empiric 3:1 rule that most patients suffering from hemorrhagic shock require as much as 300 ml crystalloid solution for each 100 ml blood loss. Note that if these recommendations are applied blindly this may result in excessive and/or inadequate volume resuscitation.

	Class I	Class II	Class III	Class IV
Blood loss (ml)	<750 (<15%)	750–1500 (15%–30%)	1500–2000 (30%–40%)	>2000 (>40%)
Heart rate (bpm)	<100	100–120	120–140	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Respiratory rate	14–20	20–30	30–40	>35
Mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic
Fluids	Crystalloids	Crystalloids	Crystalloids and blood	Crystalloids and blood

shock include lactate, ScvO<sub>2</sub>, hematocrit and base excess (BE). The European trauma guideline advocates repeated and independent measurements of BE and/or lactate as sensitive tests to assess adequate perfusion, to estimate and monitor the extent of bleeding and shock and to guide volume replacement therapy (GRADE 1B). A BE of less than –6 mEq/l is considered as an alert criteria for TIC being strongly associated with hypofibrinogenemia. The reliability of lactate may be lower when trauma is coincident with alcohol consumption; in these cases BE may be a superior predictor.

#### Conventional coagulation (CCAs) and viscoelastic testing assays

The routine practice should include the early and repeated monitoring of coagulation, using either conventional coagulation assays (CCAs) such as prothrombin time (PT), activated partial thromboplastin time (aPTT), platelet counts and fibrinogen (GRADE 1A) and/or viscoelastic testing assays (GRADE 1C). Viscoelastic testing assays can be used as point of care (POC) directly in the ED and provide a faster and much more detailed picture about the quality of the coagulation disorder present.<sup>25</sup> As early variables of clot firmness detected via viscoelastic testing assays have been associated with outcome in bleeding trauma patients, a rapid and more complete monitoring of the individual's coagulation profile including fibrinolysis may facilitate a more accurate targeting of therapy as compared to isolated CCAs. In addition, CCAs only monitor the initiation phase of the clotting process and only 4% of the overall thrombin generation.<sup>26</sup> Turn-around times for CCAs, even in advanced trauma centers, may be substantial as compared to results from viscoelastic testing assays and are likely to delay effective hemostatic treatment.<sup>25</sup> Fibrinogen levels deteriorate prior to any other routine coagulation parameters and massive transfusion in the early phase of severe trauma and low levels on admission have frequently been associated with poor outcome.<sup>17</sup>

#### Surgical bleeding control

Patients with significant intrathoracic, intraabdominal or retroperitoneal bleeding and hemodynamic shock and instability with ongoing bleeding and coagulopathy need to undergo urgent and immediate surgical intervention (GRADE 1A) according to "damage control"-surgery principles (GRADE 1B).<sup>27</sup> Meanwhile, the procedure of emergency thoracotomy has clear and accepted indications,<sup>28</sup> while procedures such as REBOA (Resuscitative Endovascular Balloon Occlusion of the Aorta) need further evaluation.<sup>29</sup> Interventional radiology may be useful in pelvic bleeding but requires corresponding infrastructure.

#### Initial coagulation management including massive transfusion

In the acute phase, the clinical management of severe and bleeding trauma patients usually follows the damage control

resuscitation (DCR)-concept which advocates the empiric administration of blood products in predefined and fixed ratios.<sup>30</sup> However, the optimum ratio is still under debate and no universal standard for the composition of these transfusion packages has yet been established and storage time may considerably affect the hemostatic competence of these products. Recent evidence suggests that this approach may also not be adequate to correct hypoperfusion or coagulopathy during the acute phase of trauma hemorrhage.<sup>31,32</sup> As an alternative, several European but also a few US trauma centers have instituted the concept of goal-directed coagulation therapy (GDCT) based upon results obtained from early POC viscoelastic testing assays.<sup>33</sup> Viscoelastic testing assays provide rapid information about the underlying deficiencies with particular focus on the different aspects of hemostasis such as initiation, dynamics and sustainability of clotting thus allowing targeted coagulation monitoring and therapy according to the individual's needs thereby supporting the innovative concept of precision medicine (Fig. 5). A recently updated Cochrane-review provided, apart from the known reductions in transfusion requirement, for the first time, a survival benefit with the use of viscoelastic testing assays in adults or children with bleeding.<sup>34</sup>

#### Massive transfusion

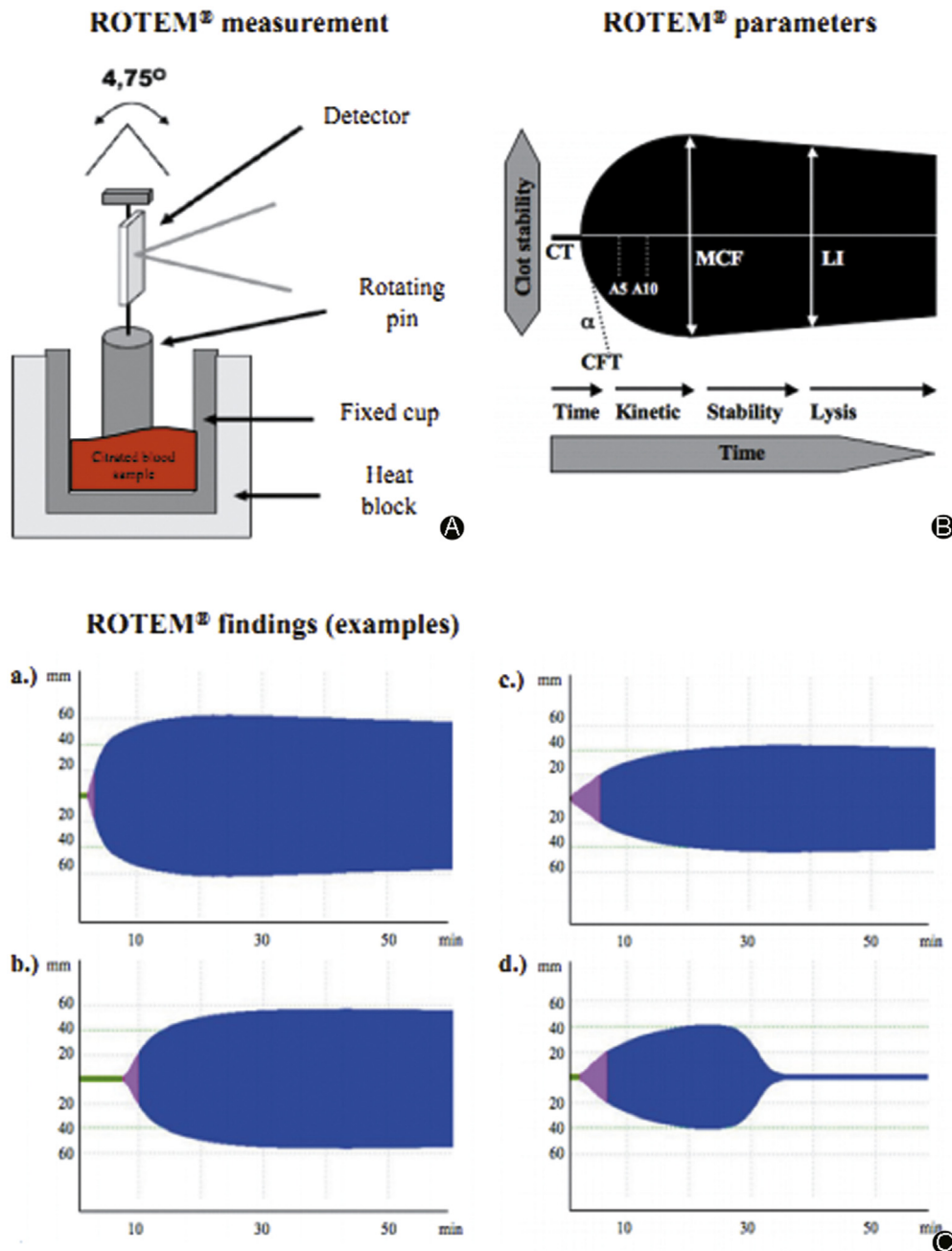
The European trauma guideline currently advocates one of the two following strategies for the initial management of patients with bleeding and (expected risk of) massive transfusion:

- 1) Plasma (fresh frozen plasma or pathogen-inactivated plasma) in a plasma: packed red blood cell (pRBC) ratio of at least 1:2 (GRADE 1B), or
- 2) Fibrinogen concentrate and pRBC according to the individual hemoglobin level (GRADE 1C).

Further resuscitation measures should be continued using a goal-directed strategy guided by CCAs and/or viscoelastic testing assays (GRADE 1C).

#### Plasma-based versus factor-concentrate based strategies

In the absence of massive transfusion and if a plasma-based coagulation resuscitation strategy is used, the European trauma guideline recommends plasma (FFP or pathogen-inactivated plasma) be administered to maintain PT and aPTT <1.5 times the normal control (GRADE 1C). It is generally accepted and emphasized that plasma transfusion be avoided in patients without substantial bleeding (GRADE 1B). If a factor concentrate-based strategy is executed, the treatment with fibrinogen concentrate (or cryoprecipitate) is advocated if significant bleeding is accompanied by viscoelastic signs of a functional fibrinogen deficit or a fibrinogen level <1.5–2.0 g/l (GRADE 1C). Once fibrinogen levels have been corrected and provided that fibrinogen levels are



**Fig. 5.** Example of a viscoelastic testing assay via thromboelastometry (ROTEM<sup>®</sup>). **Panel a** displays the measurement. A rotating pin is entered into a cup containing the citrated blood sample including a coagulation activator. Once the coagulation process is initiated, the clot builds up and increases the resistance against the rotating pin. The degree of resistance is translated into a curve signal. **Panel b** depicts the different parameters of the ROTEM<sup>®</sup> test.  $\alpha$  = alpha angle (indicates the dynamics of the clotting process); CT = clotting time (indicates the speed of the clotting process until clot initiation begins); CFT = clot formation time (indicates the time until a sufficient clot has been generated); MCF = maximum clot firmness (indicates the stability of the clot); LI = lysis index (indicates fibrinolysis). Results are provided at 5 (A5) and 10 (A10) minutes after test initiation. **Panel c** shows typical test results: a) normal clotting; b) delayed clotting (coagulation factor deficit); c) reduced clot strength (fibrinogen deficit); and d) fibrinolysis.

within the reference ranges but coagulation initiation is still delayed based on evidence from viscoelastic monitoring, the European trauma guideline suggests the administration of prothrombin complex concentrate (PCC) or plasma in the bleeding trauma patient (GRADE 2C). Repeated factor doses should be guided by viscoelastic monitoring and laboratory assessment of fibrinogen levels (GRADE 2C). A target level for hemoglobin (Hb) of 70–90 g/L (GRADE 1C) is suggested while platelet concentrations should be kept  $>50 \times 10^9/L$  (GRADE 1C); in patients with TBI and/or ongoing bleeding  $>100 \times 10^9/L$  (GRADE 2C).

#### Viscoelastic testing assays (ROTEM<sup>®</sup>) to guide hemostatic therapies

Thromboelastometry (ROTEM<sup>®</sup>) is increasingly being used to diagnose, monitor and guide treatment strategies in trauma hemorrhage but currently, no uniformly accepted guideline exist for how this technology should be integrated into clinical care. In September 2014, an international multidisciplinary group of leaders mostly from Europe but also from the Americas in the field of trauma coagulopathy and resuscitation was assembled to agree upon viscoelastic thresholds which could trigger the initiation of

specific treatments including fibrinogen, platelets, plasma, and prothrombin complex concentrates (PCCs) in the acutely bleeding trauma patient.<sup>25</sup>

#### Tranexamic acid (TXA)

Fibrinolysis has been identified as an integral component to the pathogenesis of TIC<sup>9</sup> and based upon CRASH-2, the use of the synthetic lysine analogue tranexamic acid (TXA) as early as possible in the trauma patient who is bleeding or is at risk of significant hemorrhage is recommended.<sup>35</sup> Despite substantial methodological problems associated with this study, the recommendation in favor of the early administration of TXA is one of the very few GRADE 1A recommendations of the European trauma guideline. TXA should not be given after 3 h of injury due to potentially adverse effects (GRADE 1B); the prehospital administration of TXA in bleeding trauma patients en route to the hospital may be considered (GRADE 2C). A number of Emergency Medical Services (EMS) around the globe have yet implemented TXA into their local prehospital treatment algorithms.

#### Recombinant activated coagulation factor VII (rFVIIa) and desmopressin (DDAVP)

Due to insufficient high-level evidence and failure in large clinical trials, recombinant activated coagulation factor VII (rFVIIa) is currently recommended only for off-label use if major bleeding and TIC persist despite all other attempts to control the bleeding and best practice use of conventional hemostatic measures (GRADE 2C). It needs to be emphasized that rFVIIa acts on the individual's own coagulation system with sufficient amounts of platelets and fibrinogen provided. The European trauma guideline argues against the routine use of desmopressin (DDAVP) in the bleeding trauma patient (GRADE 2C).

#### Environmental conditions

Even small reductions in pH and temperature result in reduced coagulation enzyme kinetics. The European trauma guideline recommends to avoid hypoxemia and acidosis rather than to correct (GRADE 1A) as experimental correction of the arterial pH with bicarbonate was not sufficient for the reversal of coagulopathy due to acidosis.<sup>36</sup> Likewise, the early application of measures to reduce heat loss and warm the hypothermic patient in order to achieve and maintain normothermia is recommended (GRADE 1C). Ionized calcium levels should be monitored and maintained within the normal reference ranges during (massive) transfusion (GRADE 1C).

#### Implementation of quality and safety management systems

The European trauma guideline strongly advocates that institutions that admit and treat severely injured and bleeding trauma patients should develop and provide local and evidence-based treatment algorithms (GRADE 1B) while simultaneously take measures to control the adherence to these algorithms in the context of quality control and safety (GRADE 1C).

#### Conflicts of interest

Marc Maegele has received honoraria from Astra Zeneca, CSL Behring, LFB Biomedicaments France, and TEM International.

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