

Coagulation factor concentrate-based therapy for remote damage control resuscitation (RDCR): a reasonable alternative?

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This article is a counterpoint to: Yonge JD, Schreiber MA. The pragmatic randomized optimal platelet and plasma ratios trial: what does it mean for remote damage control resuscitation?

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The concept of remote damage control resuscitation (RDCR) is still in its infancy and there is significant work to be done to improve outcomes for patients with life-threatening bleeding secondary to injury. The prehospital phase of resuscitation is critical and if shock and coagulopathy can be rapidly minimized before hospital admission this will very likely reduce morbidity and mortality. The optimum transfusion strategy for these patients is still highly debated and the potential implications of the recently published pragmatic, randomize, optimal platelet, and plasma ratios trial (PROPPR) for RDCR have been reviewed. Identifying the appropriate transfusion strategy is mandatory before adopting prehospital hemostatic resuscitation strategies. An alternative approach is based on the early administration of coagulation factor concentrates combined with the antifibrinolytic tranexamic acid (TXA). The three major components to this approach in the context of RDCR target the following steps to achieve hemostasis: 1) stop (hyper)fibrinolysis; 2) support clot formation; and 3) increase thrombin generation. Strong evidence exists for the use of TXA. The data from the prospective fibrinogen in trauma induced coagulopathy (FlinTIC) study will inform on the prehospital use of fibrinogen in bleeding trauma patients. Deficits in thrombin generation may be addressed by the administration of prothrombin complex concentrates. Handheld point-of-care devices may be able to support and guide the prehospital and remote use of intravenous hemostatic agents including coagulation factor concentrates along with clinical presentation, assessment, and the extent of bleeding. Combinations may even be more effective for bleeding control. More studies are urgently needed.

INTRODUCTION

Uncontrolled bleeding remains the primary cause of preventable death in trauma and most patients die within 3-6 hours of hospital admission.^{1,2} The concept of damage control resuscitation (DCR) has been adopted in many military and civilian centers to rapidly identify and treat bleeding trauma patients at risk for life-threatening bleeding.^{3,4} It represents the natural evolution of the initial concept of damage control surgery (DCS) and currently includes early blood product transfusion, immediate arrest, and/or temporization of ongoing hemorrhage (i.e., temporary intravascular shunts and/or balloon tamponade) as well as restoration of blood volume and physiologic/hematologic stability. The early and aggressive transfusion of plasma has been advocated to replace circulating volume and depleted coagulation factors.⁵⁻⁷ Subsequently, many trauma centers around the world have adopted fixed ratio coagulation therapy (FRCT) proposing a 1:1 ratio of red blood cell (RBC): plasma concentrates for bleeding trauma patients.⁸⁻¹⁰ Current massive transfusion protocols also recommend early platelet concentrate transfusion as early drops in platelet counts as well as early

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compromised platelet functions have been observed in bleeding trauma patients.^{5-7,11-14}

Remote damage control resuscitation (RDCR) and the pragmatic, randomize, optimal platelet and plasma ratios trial (PROPPR)

The Trauma Hemostasis and Oxygenation Research (THOR) network has been founded as a multidisciplinary group of investigators with a common interest in improving outcomes and safety in patients with severe traumatic injury.¹⁵ The network's mission is to reduce the risk of morbidity and mortality from traumatic hemorrhagic shock in the prehospital phase of resuscitation by research, education, and training. Remote damage control resuscitation (RDCR) has been defined as the prehospital application of DCR concepts.^{16,17} The term RDCR was first published by Gerhardt and colleagues from the United States Institute of Surgical Research and since been promoted by the THOR Network.¹⁶⁻¹⁸ In the present issue of **TRANSFUSION**, Yonge and Schreiber speculate on the implications of the recently published pragmatic, randomize, optimal platelet, and plasma ratios (PROPPR) trial for RDCR and on the question to export DCR principles to remote locations.¹⁹ PROPPR was performed in 12 level 1 US trauma centers including 680 patients to determine if resuscitation with higher ratios of RBCs, plasma, and platelet units (1:1:1) improved outcomes in severely injured patients compared with the use of lower ratios of blood components (2:1:1⁶). The early administration of RBCs, plasma, and platelets in a 1:1:1 ratio compared with a 2:1:1 ratio did not result in significant differences in mortality at 24 hours or at 30 days. However, more patients in the 1:1:1 group achieved hemostasis and fewer experienced death due to exsanguination by 24 hours. Less than half of the study patients received massive transfusion defined as >10 units of RBCs in a 24 hours period.

Blood products far forward

Since earlier identification and treatment of hemorrhagic shock may improve outcomes, the distinction between RDCR and DCR is important since there are differences in capabilities, and in some cases optimal management strategies between prehospital and in-hospital care. For example, differences include the availability of all blood products and monitoring capabilities, as well as less evidence to support the use of hypotensive resuscitation strategies for transport times that are delayed and increased risks with airway management for casualties in hemorrhagic shock.¹⁵ The logistical obstacles and challenges associated with blood component-based resuscitation regimes for patients with severe shock and coagulopathy under most forward military conditions and in civilian austere settings have been identified and described.¹⁵ The supply of temperature sensitive blood products with a limited shelf life to the prehospital arena poses a significant logistical challenge, a

challenge that increases in direct relation, and to the degree of austerity. In addition, the context challenges the requirements to meet national and international regulatory standards such as hemovigilance and traceability.

Over the past, several approaches have been undertaken to overcome blood bank limitations in providing blood products to the prehospital setting.¹⁵ The Mayo Clinic, for example, has placed three units of 0 RBCs and two units of group A fresh frozen plasma (FFP) onboard their rotary wing ambulances and reported on the use of over 300 units of RBCs and 350 thawed plasma transfusions.²⁰ Investigators from Bergen (Norway) have published their experience with placing two RBCs units and AB freeze dried plasma (FDP) on their rotor wing ambulances.²¹ Both used clinical signs of bleeding and point-of-care (POC) devices on scene for decision making. To overcome the logistic barriers of plasma availability in the prehospital arena, FDP is now available in some countries and military environments and is being used in the prehospital setting.²¹⁻²⁴ FDP can be stored at room temperature for extended periods of time, and offers the potential of resolving the problem with thawing, cold storage, and limited shelf life after being thawed. Frozen platelets are available in the Netherlands, but the same field-availability constraints exist as for frozen plasma. Since there are no licensed dried platelet products available, the prehospital availability of platelet units is rare. To address the perceived need for platelets for patients with severe life-threatening bleeding, and in particular in settings where the transport time is prolonged, trauma programs in both Norway and the United States have begun to transfuse low titer group 0 whole blood.^{25,26} Platelets are a major component of FRCT concepts as current massive transfusion protocols strongly recommend early platelet concentrate transfusion.⁵⁻⁷ Early platelet transfusion in this context is supposed to overcome the trauma-related platelet dysfunction but its value is not yet fully established.²⁷ However, a systematic review including seven observational studies (4230 patients) failed to show a survival benefit and concluded insufficient evidence to strongly support the use of a precise platelet:RBC ratio for trauma resuscitation, especially in nonmassively bleeding patients.²⁸ This finding may be related to compromised platelet aggregability in ratio-based "reconstituted whole blood."²⁹ In experimental models of coagulopathy, platelet counts had only a moderate correlation to clot strength.

The overall median time of death from exsanguination of 2.3 hours in the PROPPR trial makes it clinically appealing to push transfusion medicine and concepts for early resuscitation and bleeding control into the prehospital arena.⁶ This would increase the likelihood of delivering patients alive to appropriate centers to receive definitive care. However, the optimum approach is still highly debated and identifying the appropriate transfusion strategy is mandatory before adopting prehospital hemostatic resuscitation strategies.³⁰

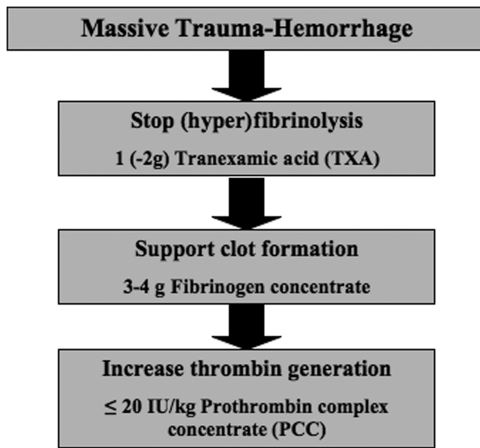


Fig. 1. The three major components to a step-wise approach to achieve hemostasis in the context of RDCR using coagulation factor concentrates combined with an antifibrinolytic agent.

Fixed-ratio coagulation therapy

The obvious advantages of FRCT include plasma to contain both coagulation factors and inhibitors, the protective effect of plasma on the glycocalyx, and the volume effect of plasma.²⁷ Coagulation tests are not required as transfusion occurs in predefined and fixed ratios but this may impart both the risk of overtransfusion and increase wastage of valuable products.³¹ However, plasma transfusion has been shown to be only lifesaving when given to patients in quantities above 6-10 RBCs or to patients with high risk for massive transfusion; in patients receiving less than 10 RBCs or not predicted for massive transfusion plasma administration was associated with significant morbidity.³²⁻³⁴ It was demonstrated that „reconstituted whole blood “via RBCs, plasma, and platelets 1:1:1 contains substantially lower concentrations of coagulation factors as compared to donated whole blood thus contributing to dilution.^{35,36} Results from a prospective cohort study on bleeding trauma patients who received at least four RBCs including 34 with massive transfusion and coagulopathy on admission as reflected by a ROTEM CA5 ≤ 35 mm demonstrated that DCR with standard doses of blood components close to 1:1 did not consistently correct trauma-induced coagulopathy.³⁷ However, the 1:1 approach was not compared with another strategy in this context. On average, all functional coagulation parameters and procoagulant factor concentrations deteriorated during hemorrhage and the initial percentage of coagulopathic patients increased from initially 40% to 58% after four RBCs to 81% after eight RBCs. There was no clear benefit to high-dose FFP therapy in any parameter; and only combined high-dose FFP, cryoprecipitate and platelet therapy with a high total fibrinogen load appeared to produce a consistent improvement in coagu-

lation.³⁷ While hemostatic resuscitation offers several advantages over historical strategies including a potential survival benefit in some studies, it still does not achieve correction of hypoperfusion or coagulopathy during the acute phase of trauma hemorrhage.³⁸ This corresponds to the guideline issued by the German Medical Association (Bundesärztekammer) concluding that even high dose plasma administration only leads to a moderate increase in the activity of coagulation factors and inhibitors in the recipient.³⁹

Coagulation factor concentrate based treatment

A coagulation factor concentrate based treatment, even prehospital and in remote settings, guided by POC testing or even without may represent a more rational and timely alternative to empiric blood component transfusion. In-hospital, coagulation factor concentrate-based treatment may be guided by viscoelastic test results that provide rapid information on individual clot dynamics and quality thus allowing an individualized and goal-directed approach to manage bleeding trauma patients.^{40,41} Coagulation factor concentrates are quickly available, if carried along also in remote settings, are well standardized and contain high amounts of coagulation factors in a low volume. Results from retrospective observational studies have associated this approach with reductions in the use of allogenic blood products and favorable outcome if compared with predicted mortality scores.^{40,42} Noteworthy, that no prospective validation of these treatment algorithms has ever been conducted yet. However, a targeted coagulation factor concentrate treatment approach may also be administered in the absence of viscoelastic testing and may therefore also be feasible during the pre-hospital phase of care and in remote settings. Instead of viscoelastic testing, portable POC devices such as blood gas analyzers for base excess (BE) measurement, and portable coagulation monitors for international normalized ratio (INR) may be used to support prehospital guidance of coagulation factor concentrate-based treatment. The three major components to this approach in the context of RDCR are summarized in Fig. 1 and target the following steps to achieve hemostasis:

1. stop (hyper)fibrinolysis (e.g., tranexamic acid [TXA])
2. support clot formation (e.g., fibrinogen concentrate)
3. increase thrombin generation (e.g., prothrombin complex concentrate [PCC])

Stop (hyper)fibrinolysis (e.g., TXA)

Fibrinolytic activation occurs in the majority of trauma patients and the magnitude correlates with poor clinical outcome.^{43,44} The mortality in cases of fulminant or intermediate hyperfibrinolysis is above 90%.⁴³ In a prospective cohort study of 303 consecutive trauma patients, only 5% of patients had severe fibrinolysis, but 57% of patients had

evidence of moderate fibrinolysis.⁴⁴ Recent data suggest that hyperfibrinolysis represents an additional important confounder to the disturbed coagulation process with severe shock and major tissue injury being the principle drivers.⁴³ In 2011, results from a multicenter, randomized, and placebo-controlled trial (Clinical randomisation of an antifibrinolytic in significant hemorrhage [CRASH]-2 trial) showed that TXA (1 g loading dose over 10 min followed by an infusion of 1 g over 8 hr) safely reduces mortality in bleeding trauma patients.^{45,46} The optimum dose for TXA is still under debate but most clinicians follow the dosing used in CRASH-2. Meanwhile, hyperfibrinolysis is considered as a strong independent predictor of mortality in trauma.⁴⁷ and its early use within 3 hours of trauma is strongly supported by the updated European guideline as a grade 1A recommendation.⁴⁸ When given after 3 hours from injury, TXA was associated with death as secondary outcome in CRASH-2 but this finding is not fully understood yet.^{45,46} The risk-benefit profile of TXA supports its use even in the absence of clinically or laboratory diagnosed fibrinolysis⁴⁶ and in the context of RDCR.⁴⁹ In the prehospital setting, the United States, French, British, and Israeli militaries as well as the British, Norwegian, and Israeli civilian ambulance services have implemented TXA use as part of their RDCR policies. High-level evidence strongly suggests that its implementation in the prehospital setting offers a survival advantage to many patients, particularly when evacuation to surgical care may be delayed. Thus, TXA plays a central role in the development of RDCR strategies.⁵⁰ The updated European guideline suggest that protocols for the management of bleeding trauma patients consider the administration of the first dose of TXA en route to the hospital as a grade 2C recommendation.⁴⁸

Support clot formation (e.g., fibrinogen concentrate)

Fibrinogen can be considered as the substrate of the coagulation process.⁵¹⁻⁵⁵ If sufficient thrombin is formed, it converts fibrinogen into stable fibrin, which determines the firmness of the developing clot in the presence of activated coagulation factor XIII.^{55,56} As a consequence of blood loss, consumption of coagulation factors, dilutional coagulopathy, hypothermia and acidosis, and profibrinolytic activation, fibrinogen may reach critical levels earlier than any other procoagulant factor and also platelets even before RBC concentrate administration becomes necessary.^{57,58} Floccard and coworkers have described significant drops in fibrinogen levels as a function of injury severity to occur already during the ultra early prehospital phase of care.⁵⁹ Hypofibrinogenaemia and impaired formation/polymerization on admission and during initial management are frequently observed in trauma patients and have strongly been associated with the severity of injury and shock, prehospital volume administration, degree coagulopathy, and poor clinical outcome.⁵⁹⁻⁶⁴ Sev-

eral studies have identified low admission fibrinogen levels (<1 g/L) as an independent predictor for mortality.^{63,64} Among injuries to different body regions, a strong contributor to low fibrinogen concentrations may be the occurrence of severe injuries to the extremities and the pelvic ring. In the presence of decreasing platelet counts, as frequently observed in massively bleeding trauma patients, it may appear that strong fibrin polymerization can compensate for decreased platelet contribution to clot firmness.⁶⁵⁻⁶⁷ Therefore, fibrinogen supplementation is considered as a key step for managing coagulopathic bleeding but data from prospective trials are still lacking.

Fibrinogen concentrate allows rapid and small volume resuscitation with a standardized dose of fibrinogen with a good safety profile as it is virally inactivated as standard.⁵⁸ For practical use in remote settings, it may be stored at room temperature up to three years. Early fibrinogen supplementation to bleeding trauma patients is feasible⁶⁸ and maintains fibrinogen levels above critical levels during early resuscitation and active haemorrhage until intensive care unit (ICU) admission.^{69,70} For patients undergoing massive transfusion after injury, a stepwise improvement in survival was reported with the prevention of fibrinogen depletion.⁶² Fenger-Eriksen and coworkers have observed that the use of fibrinogen concentrate may improve standard coagulation parameters (e.g., prothrombin time [PT] and activated partial thromboplastin time), increase fibrinogen levels, and decrease bleeding in patients with massive haemorrhage and lower fibrinogen levels.⁷⁰ Results from retrospective observational studies have shown that administration of fibrinogen alone or in combination with PCC may result in a significant improvement of fibrin polymerisation.^{69,71} The dynamics of clotting are dependent not only on thrombin generation but also on the availability of substrate, for example, fibrinogen. Accelerated fibrin polymerisation rate results in earlier clot formation and consequently decreased clotting times.⁶⁹ Two registry studies have retrospectively compared the impact of FFP only versus coagulation factor concentrates (fibrinogen and/or PCC) without plasma for outcome in bleeding trauma patients although there was no difference in overall mortality between both groups, significant differences with regard to morbidity and need for allogenic transfusion provided a signal supporting the management of acute posttraumatic coagulopathy with coagulation factor concentrates rather than with traditional FFP transfusions.^{42,72} However, it has to be acknowledged that platelet transfusion administered to patients may also contain substantial amounts of plasma.

The updated European guideline currently recommends maintaining plasma fibrinogen levels at 1.5-2 g/L in coagulopathic patients.⁴⁸ An initial fibrinogen concentrate dose of 3-4 g may be suggested for administration already during the prehospital phase of care but repeated doses should then be guided by viscoelastic monitoring

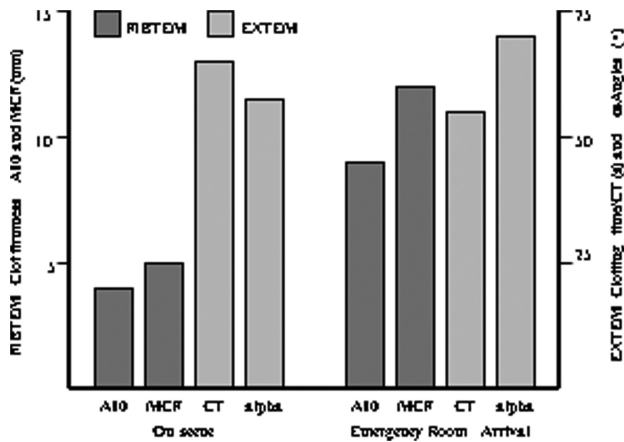


Fig. 2. Rotational thromboelastometric (ROTEM®) FIBTEM amplitudes (mm) and EXTEM clotting time (sec) and α -angle (°) data from blood samples obtained from a severely injured and bleeding trauma patient on scene and on emergency room (ER) arrival who had been treated prehospital en route to the hospital with fibrinogen concentrate. Note that FIBTEM amplitudes as well as EXTEM α -angles had increased on ER arrival while EXTEM clotting times had decreased on ER arrival indicating improved clot firmness and accelerated initiation of clotting. A10 = measurement at 10 minutes after test begin; CF = clot formation time; MCF = maximum clot firmness.

and laboratory assessment of fibrinogen levels once the patient has been admitted to the receiving hospital. For guidance in the absence of viscoelastic testing, fibrinogen concentrations have been shown to strongly correlate with rapidly obtainable parameters such as hemoglobin (Hb) and BE, which may be assessed via portable devices prehospital and could be used to rapidly identify major trauma patients at risk of acquired hypofibrinogenemia, as well as to dose and guide the prehospital use of fibrinogen concentrates.⁷³ However, the evidence supporting this practice is limited and largely derived from controlled trials in cardiac surgery and postpartum haemorrhage and prospective studies are lacking.

The fibrinogen in trauma induced coagulopathy (FlinTIC) study is the first of its kind to prospectively assess the effect of early treatment with fibrinogen concentrate in the trauma population presumed to bleed.^{74,75} Severe traumatised patients with visible significant bleeding and/or with clinical signs of internal significant bleeding in shock treated by an emergency physician of the helicopter service or the ground team were enrolled in the study at the scene. Thirty patients had been randomized to receive 50 mg/kg fibrinogen concentrate (FGTW fibrinogen concentrate 1.5 g in 100 mL; LFB France), while the other 30 patients received placebo. The primary outcome of this study will include changes in plasma coagulation as reflected by fibrinpolymerization via FIBTEM MCF

(maximum clot firmness), secondary outcomes will include transfusion requirement/blood loss, thromboembolic complications, and clinical endpoints such as morbidity and length of stays on ICUs and overall in-hospital. The FlinTIC study is a multicenter double-blind, placebo controlled, randomized pilot trial conducted in the difficult environment of the prehospital setting currently involving different helicopter and ground emergency medical service stations across Austria, Germany, and the Czech Republic. The recruitment has been finished and the data are currently being analyzed.

The risks associated with early fibrinogen supplementation appear rather low but the issue to whether its administration may be associated with an increased risk for posttraumatic venous thromboembolism has not been addressed yet and a causative relationship between high fibrinogen levels and thromboembolic events in the further sequelae after trauma is not established.⁷⁶⁻⁷⁸ Human fibrinogen concentrate does not suppress endogenous fibrinogen synthesis.⁷⁹ In cardiac surgery, the prophylactic infusion of 2 g fibrinogen concentrate has not been shown to trigger any postoperative thromboembolic events.⁷⁷ In experimental models of trauma hemorrhage even doses up to 600 mg/kg fibrinogen to correct coagulation profiles and blood loss were not associated with signs of thromboembolism as detected via organ histology.^{80,81} Figure 2 shows exemplar rotational thromboelastometric (ROTEM®) FIBTEM and EXTEM data from blood samples obtained from a severely injured and bleeding trauma patient on scene and on emergency room arrival who had been treated en route to the hospital with fibrinogen concentrate.

Combined effects of fibrinogen-containing agents and TXA

The MATTERS II study retrospectively assessed the impact of fibrinogen-containing cryoprecipitate in addition to the antifibrinolytic TXA on survival in 1332 combat injured.⁸² Despite greater magnitude of injuries as reflected by Injury Severity Scores (ISS) and transfusion requirements, mortality was lowest in the cryoprecipitate/TXA (11.6%) and TXA groups (18.2%) compared with the cryoprecipitate (21.4%) and no cryoprecipitate/TXA (23.9%) groups. Cryoprecipitate and TXA were independently associated with a similarly reduced mortality (OR 0.61, 95% CI 0.40-0.94; $p = 0.02$ and OR 0.61, 95% CI 0.42-0.89; $p = 0.01$). Thus, fibrinogen-containing cryoprecipitate may independently add to the survival benefit of TXA in the seriously injured requiring transfusion.

Increase thrombin generation (e.g., PCC)

Deficits in thrombin generation have been associated with mortality in trauma patients with life-threatening postinjury coagulopathy.⁸³ One option to increase thrombin generation is the administration of PCC, which contains a combination of blood coagulation factors II, VII,

IX, and X, as well as protein C and S. The classical indication for PCC is the emergency reversal of vitamin K-dependent oral anticoagulants.⁴⁸ However, the updated European trauma guideline has included PCC as a component and suggests its use in the bleeding trauma patient in the context of a coagulation factor concentrate-based treatment strategy if delayed coagulation initiation is detected.⁴⁸ The best available evidence for PCC in nonanticoagulated surgical patients stems from retrospective observational studies.⁸⁴ In bleeding surgical patients, the infusion of PCC significantly reduced INRs which was unrelated to FFP or vitamin K administration. Bleeding stopped after PCC administration in 36% patients with surgical bleeding and 96% patients with diffuse bleeding, the hemoglobin (Hb) levels increased significantly from baseline in bleeding patients and the mean arterial pressure stabilized with no thrombotic events or changes in organ function reported.⁸⁴ As mentioned above, two registry studies have retrospectively compared PCC either alone or combined with fibrinogen versus FFP only for outcome in bleeding trauma patients and observed significant reductions in both morbidity and the need for allogenic transfusion in favor of the coagulation factor based approach.^{42,72} However, health care professionals must remain aware of the differences in products and interpret how three- versus four-factor products may affect patients.⁸⁵ Safety data on PCC are lacking and the potentially increased thromboembolic risk has to be taken into account. The prehospital POC INR may be considered to circumnavigate potentially unguided PCC administration. To avoid potential side effects associated with PCC administration prehospital, PCC may be administered at the lowest possible dose at ≤ 20 IU/kg bodyweight. PCCs should be considered as first-line for thrombin deficit correction. An alternative to PCC in cases the bleeding and the traumatic coagulopathy remains unresponsive despite standard attempts to control bleeding and best-practice of conventional hemostatic therapies is the use of recombinant activated coagulation factor VIIa (rFVIIa) but side effects such as the increased risk of thromboembolic events need to be considered.⁴⁸ For appropriate use of rFVIIa adequate concentrations of platelets and fibrinogen are a prerequisite.

CONCLUSION

The concept of RDCR is still in its infancy and there is a significant amount of work that needs to be done to improve outcomes for patients with life-threatening bleeding secondary to injury. The prehospital phase of resuscitation is critical in these patients and if shock and coagulopathy can be rapidly identified and minimized before hospital admission this will very likely reduce morbidity and mortality. The optimum transfusion, as reflected by the presentation of different approaches in

this volume of **TRANSFUSION**, is still highly debated. Identifying the appropriate transfusion strategy is mandatory before adopting prehospital hemostatic resuscitation strategies. As presented, the coagulation factor concentrate-based approach, which aims to substitute what is depleted and to prevent lysis, is largely based on observational and mechanistic data as well as on own experience. So far, the strongest evidence exists for the prehospital use of TXA.^{45,46,48} The data expected from the prospective FlinTIC study will inform on the prehospital use of fibrinogen in bleeding trauma patients.^{74,75} More studies of this kind are urgently needed. Deficits in thrombin generation may be addressed by the administration of PCC. Handheld POC devices may be able to support and better guide the prehospital and remote use of hemostatic agents including coagulation factor concentrates along with clinical presentation, assessment, and extent of bleeding.⁸⁶ Combinations of the three steps presented here may even be more effective for bleeding control.^{42,72,82} However, this approach does not address the need to increase oxygen delivery to reverse or prevent shock and shock related coagulopathy. Financial issues may also be considered. The prevention of hypothermia and acidosis as well as controlled volume administration are cornerstones for RDCR to provide an optimum framework for coagulation.⁴⁸

CONFLICT OF INTEREST

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