CHAPTER 8

Summary, conclusions and future directions
Management of trauma patients with life-threatening hemorrhage

Hemorrhage from injuries that lead to exsanguination is not only a leading cause of trauma mortality, but appears to be the most common preventable cause of death in trauma, especially during the first 24 hours after hospital admission. Management and treatment of trauma patients with life-threatening hemorrhage includes many challenges concerning logistics, diagnostics and treatment throughout the (pre-)hospital course. The three mainstays of treatment are hemorrhage control (stop the bleeding), volume support (treatment of hemorrhagic shock) and correction of traumatic coagulopathy. The aim of this thesis was to evaluate important aspects of the management and treatment in order to delineate points of application for improvement of care and further research. This thesis focuses on the evaluation of effects of current practice (2005-2013) regarding volume support, massive transfusion and coagulation on hemorrhage control and patient outcome. For each chapter of this thesis, a summary and conclusion is given, and future directions are indicated regarding research and further developments.

In Chapter 1, a brief overview is given of the history of understanding hemorrhagic shock as an important feature of major trauma. Roughly, throughout the last hundred years, treatment changed from solely administering human plasma to transfusion of whole blood, and from there to predominantly resuscitating using packed red blood cells and large volumes of crystalloid fluids. Subsequently, the traumatic coagulopathy that resulted from the last therapeutic modality and which had been applied for decades was acknowledged. The procoagulant rFVIIa appeared not to be the ‘magic bullet’ for treatment of traumatic coagulopathy. But, in the last decade, the whole resuscitation process has been revisited, aiming at prevention of coagulaopathy and normalization of hemostatis. Currently, massive transfusion in traumatic hemorrhage is based on the reconstitution of whole blood with blood components. With transfusion of packed red blood cells (PBRC), fresh frozen plasma (FFP) and platelets (PLTs) in ratios varying from 1:1:1 to 5:3:1, whole blood is in fact reconstituted. The current treatment concept has developed into damage control resuscitation (DCR). DCR consists of 1) empirical transfusion of reconstituted whole blood, 2) damage control surgery, 3) permissive hypotension and 4) prevention of resuscitation injury by limiting the intravenous administration of crystalloid fluids. Clinical trials are currently being conducted to elucidate the ideal reconstituted whole blood transfusion strategy, as well as to evaluate the efficacy of transfusion of preserved whole blood versus reconstituted whole blood transfusion in trauma. Recently, the classical concept of traumatic coagulopathy has been extended by
the Acute Coagulopathy of Trauma-Shock (ACoTS) theory. The idea is based on the development of early coagulopathy in trauma due to the presence of tissue hypoperfusion, which is characterized by anticoagulation through activation of the protein C pathway. This discovery led to the redefinition of traumatic coagulopathy into Trauma-Induced Coagulopathy (TIC). ACoTS is defined as an endogenous precursor of TIC, and should be considered alongside classical mediators of coagulopathy in trauma such as hemodilution, inflammation, tissue trauma, hypothermia and acidosis. A better understanding of TIC, the recognition of the new cell-based model of coagulation and the re-emergence of the use of point-of-care viscoelastic coagulation tests like thromboelastography or thromboelastometry will allow for early, individualized goal-directed therapy with coagulation factor concentrates and procoagulants in exsanguinating trauma patients. Research is warranted to investigate the efficacy, safety and cost-effectiveness of this tailored, goal-directed therapy versus the empirical transfusion of reconstituted whole blood in patients with massive hemorrhage.

Chapter 2 illustrates the treatment strategies applied in patients with excessive traumatic hemorrhage in 2004. A patient with exsanguinating trauma due to an unstable pelvic injury is presented. Time is a critical factor in the trauma chain of care, and the multidisciplinary aspects of treatment are illustrated. The challenges faced by the trauma team are shown and the three mainstays of treating massive bleeding are discussed. During massive transfusion under these hectic conditions, blood components were administered blindly, and several hemostatic surgical and interventional radiological procedures were required to control bleeding. The procoagulant rFVIIa was administered off-label to counter the non-surgical bleeding due to traumatic coagulopathy. Overall treatment appeared to be successful and the patient survived. At the time the case was presented, many advances had been made with regard to the three mainstays of treatment as extensively described in Chapter 1. Hence, it cannot be overstated that treating exsanguinating trauma patients is teamwork, with critical decision-making under the final responsibility of the trauma surgeon. To further improve trauma care, team training of care providers at regional as well as at institutional level is warranted in addition to proper training at individual level.

In Chapter 3, a state-of-the-art review is given of the diagnostic and treatment options throughout the chain of survival of exsanguinating trauma patients. Current concepts and therapies are discussed regarding hemorrhage control, volume support and coagulation management within the pre-hospital and hospital setting. The aim of pre-hospital care of bleeding trauma patients is to deliver the patient to a facility for definitive care within the shortest amount of time by rapid transport, and to limit therapy to
what is necessary to maintain adequate vital signs. Rapid decisions have to be made using regional trauma triage protocols that have incorporated patient condition, transport times and the level of care that can be performed by the pre-hospital care providers and receiving hospitals. Fluid resuscitation should allow for preservation of vital functions without increasing the risk for further (re)bleeding, and permissive hypotension is preferable. Within the hospital, a sound trauma team activation system is essential for a fast and adequate response. After diagnosing of hemorrhagic shock, all efforts have to be directed to stop bleeding in order to prevent exsanguination. A simultaneous effort is made to restore blood volume and correct coagulation. The Focused Assessment with Sonography for Trauma (FAST) protocol replaced the diagnostic peritoneal lavage for detection of intra-abdominal hemorrhage. With the development of sliding-gantry-based computed tomography (CT) diagnostic systems and the placement of these systems within the emergency department, rapid evaluation by computed tomography scanning of the trauma patient is possible during resuscitation. The concept of damage control surgery, the staged approach in treatment of severe trauma, has proven to be of vital importance in the treatment of life-threatening hemorrhage in trauma and is adopted worldwide. Selection of suitable patients for this approach is a continuing challenge. During these procedures, a predetermined fixed ratio of blood components may result in a higher rate of fresh frozen plasma and platelets administration, and increasing evidence suggests that this may also improve outcome. The role of thromboelastography and thromboelastometry as point-of-care tests for bedside monitoring of the coagulation status in massive blood loss is emerging. These techniques provide information about actual clot formation and stability shortly after the blood sample is taken. Thus, therapy can be directed by the test results. This allows for administration of specific coagulation factors that may be depleted despite administration with fresh frozen plasma during massive transfusion of blood components. As a differentiated approach is warranted, future treatment of patients with exsanguinating injuries may point in the direction of efforts to improve pre-hospital care by having experts at the scene for critical decision-making. With regard to resuscitation, pre-hospital blood transfusion in cases of ‘stay and play’ and/or long transport times may be feasible, while awaiting results from oxygen carriers trials. Further research has to clarify optimal pre-hospital fluid resuscitation and possibilities for early coagulation management.

The concept of operating room resuscitation should be further developed. Advanced trauma resuscitation protocols incorporating sliding-gantry-based CT may reduce time to definitive hemorrhagic control. Surgeons taking care of these patients should be familiar with the concept of damage control and operative techniques for rapid hemorrhage control. This necessitates frequent hands-on training on
live tissue for surgeons in low-volume trauma centers. Future research towards evidence-based massive transfusion protocols and coagulation management using point-of-care tests is mandatory.

Chapter 4 shows the results of a study into the effects of pre-hospital intravenous fluid volumes upon arrival in the emergency department in trauma patients who were hypotensive at the accident scene. Traditionally, intravenous fluid resuscitation consists of early, rapid volume replacement (one volume of blood loss is replaced by three volumes of crystalloid fluids), which is based on the idea that restoration of circulating volume and blood pressure will help to maintain vital organ perfusion. However, overzealous resuscitation with fluids may cause coagulopathy and tissue edema, leading to significant morbidity and mortality. A Cochrane review including three clinical trials was not conclusive about the best intravenous fluid resuscitation strategy in trauma patients, and the controversy about pre-hospital fluid resuscitation in trauma has further been acknowledged in the latest guidelines of the European Resuscitation Council. We investigated the effects of prehospital volume therapy on clinical signs of shock in trauma patients, and focused on the need for blood transfusion and survival outcome. The patient cohort included 941 trauma victims with field hypotension who were presented to a level 1 trauma center. Regression models were used to investigate the association between pre-hospital fluid volumes and 1) shock upon arrival in the emergency department, 2) the need for blood transfusion in the emergency department and 3) mortality within 24 hours. We found that pre-hospital fluid administration was associated with a dose-dependent, mitigating effect on shock in the emergency department. However, volumes exceeding one liter were beneficial for the treatment of shock, but were also associated with an increased risk for blood transfusion. Moreover, volumes exceeding two liters were not associated with amelioration of shock but, instead, with a strongly increased risk for blood transfusion. Pre-hospital fluid resuscitation volumes were not associated with 24-hour mortality. Because of the contrasting effects, decision-making regarding pre-hospital fluid resuscitation is of critical importance. Treatment must be tailored to the individual situation while weighing risks and depends on the patient's injuries, clinical condition and expected time to definitive care. Options include titration of fluid volumes against acceptable vital signs such a palpable radial pulse or effective mentation.

In Chapter 5, we present a study that was designed to evaluate massive transfusion practice in trauma patients who ultimately died from blood loss. As a transfusion strategy in exsanguinating patients cannot be based on standard coagulation tests, transfusion of blood components is frequently performed in an empirical or 'blind' fashion. Seventeen trauma patients were examined who had died due to uncontrolled
bleeding despite aggressive hemostatic interventions within 24 hours after level 1 trauma center admission whilst receiving more than 12 units of packed red blood cells (PRBC). Transfusion data was compared to a theoretically optimal transfusion model with a fixed ratio between units of PRBC, fresh frozen plasma (FFP), and platelets (PLTs). This model was based on the composition of whole blood. We found that 82% of the patients received an insufficient amount of FFP and PLTs when compared to the theoretical model. In particular, the total number of transfused FFP units and PLTs was on average 50% lower than the calculated amount. Although regression analysis showed an increase in FFP and PLTs administration with increasing administration of PRBC, this never reached sufficient quantities. It was demonstrated that ‘blind’ transfusion during treatment of exsanguinating trauma patients results in insufficient transfusion of FFP and PLTs, and the great variability in treatment that we observed exemplifies the need for a structured approach. We advised that a blind transfusion strategy consisting of a guideline with a predefined ratio of different blood products, timing of laboratory tests as well as sound logistics to facilitate this procedure, involving the blood bank and treating physicians, is urgently required. Nowadays, the use of massive transfusion protocols for trauma are standard practice in level 1 trauma centers, and have evolved into so-called trauma exsanguination protocols that facilitate damage control resuscitation. However, there is no unified massive transfusion protocol for the Netherlands, and the fixed ratios of PBRC:FFP:PLTs still vary from 1:1:1 to 5:3:1. As previously indicated in Chapter 1, a clinical trial is currently being conducted to define the best, empirical blood component transfusion strategy in trauma.

In the study presented in Chapter 6, we evaluated the effects of the introduction of a massive transfusion protocol (MTP) in a civilian level 1 trauma center in 2006. The protocol complied with the scientific knowledge and insight available at that time, but did not provide for rapid administration of blood components in a 1:1:1 ratio as this advice only emerged around 2007. A retrospective before-and-after study was performed in trauma patients who were admitted over an 8-year period. Patients who had received either 10 or more units of PRBC in the first 24 hours after admission after the introduction of an MTP were compared to a historical control group. Between the groups we found no differences regarding mortality, intensive care unit stay, ventilator days and total hospital stay. Moreover, the transfused amounts of units PRBC, FFP and PLTs over 24 hours and in total were similar between groups. As a result, introduction of an MTP in a trauma center in 2006 was not associated with improvement of outcome or reduction of blood product usage. Although our study was limited to one
single center, it may reflect common practice at similar civilian trauma centers since the incidence of massive transfusion in trauma is low. Insufficient compliance to the protocol may have been an issue. Compliance is challenged by the rarity, complexity and hectic conditions of the clinical situation. Because of the retrospective nature of our study we were not able to evaluate compliance. An MTP should be updated regularly and implementation should be accompanied by compliance monitoring. Meanwhile, results of clinical trials on blood component transfusion strategies are still awaited. And since life-threatening hemorrhage in trauma is a relatively rare event, even in busy trauma centers, alternative or adjuvant treatment options are also being investigated and which may be easier to apply in the acute setting of massive hemorrhage. Although goal-directed therapy guided by point-of-care viscoelastic coagulation tests are promising, they have not yet proven to be of benefit in clinical trials when compared to blood component therapy. Ideally, goal-directed therapy provides for the judicious administration of fibrinogen concentrate and prothrombin complex concentrate instead of, or in addition to, empirical FFP administration. In this way, treatment may become less dependent on instant blood component availability, blood bank resources & personnel or on demanding logistics and operating procedures that need to be followed during these rare but hectic occurrences.

At the end of the second millennium, the anecdotal administration of the recombinant coagulation factor VIIa (rFVIIa) was reportedly to successfully rescuing trauma patients from exsanguinating, non-surgical bleeding ('oozing') when there were no other treatment options left. These findings stimulated the off-label use of rFVIIa, which was primarily produced to treat bleeding in hemophiliacs. In Chapter 7 the results are shown of a study aimed at evaluating off-label treatment with rFVIIa in blunt trauma patients with uncontrolled bleeding. Eight consecutive patients with exsanguinating hemorrhage due to blunt trauma who were treated with rFVIIa were selected. After rFVIIa treatment, the need for transfusion of packed red blood cells (PBRC) was significantly decreased. Moreover, the administration of FFP and platelets decreased significantly after the administration of rFVIIa. Finally, treatment with rFVIIa reduced or stopped clinical bleeding in all patients, although three patients died of non-bleeding complications. The other five patients fully recovered. No adverse events were registered. Many other observational studies of rFVIIa showed promising results in trauma patients. At that time it was advised that the optimal timing and dose of administration remained to be established, and that prospective randomized trials were needed with emphasis on safety, survival rates and need for blood component transfusion to elucidate the role of rFVIIa as an adjunct to hemorrhagic control in trauma. However, in a double-
blinded, placebo-controlled randomized clinical trial, the early and routine administration on rFVIIa during massive transfusion in severely bleeding trauma patients caused some reduction in the need for transfusion of PRBC units, but did not affect mortality. Subsequently, a phase 3 randomized clinical trial focusing on the effect of rFVIIa on 30-day mortality in major trauma was terminated early after futility analysis; since both groups showed an unexpected low mortality. It is only speculative that this low mortality could be related to a Hawthorne-effect caused by the renewed awareness, insights and treatment options of exsanguinating hemorrhage in trauma during the last decade. Nevertheless, rFVIIa may still have a role in treatment. Viscoelastic coagulation tests may allow for exact indication and potential use of rFVIIa in trauma.

In this thesis, results are shown from observational studies that were performed to evaluate current practice of treatment of trauma patients with life-threatening hemorrhage. In the meantime, awareness and care has been improved but there are still many questions to be answered in order to further improve outcome. The design of prospective, clinical studies on this subject is challenging but not impossible. At the same time, experimental research on pathophysiology and treatment of hemorrhagic shock and coagulopathy in trauma is needed to expand our knowledge about this ‘disease’ and provide for possible treatment options and interventions in the future. An experimental model should reflect the (pre)clinical course of the ‘disease’ regarding resuscitation and must contain the aspects of 1) tissue trauma, 2) hypoperfusion (shock) and 3) ongoing blood loss. In such a model, the possibility to perform transfusion of blood or blood components is mandatory. Models that will also allow for monitoring or evaluation of processes at microcirculatory level are preferable.