CHAPTER 1

Introduction and outline of this thesis
Introduction

In 2000, the World Health Organization (WHO) estimated that death from injuries accounted for 9% of the global annual mortality, and that 12% of the global disease burden resulted from injuries. Moreover, traumatic injury-related mortality is the leading cause of lost life years because half of those who die are between 15 and 44 years old. There is a lasting impact of trauma-related morbidity and its effect on the quality of life. In particular, the economic burden of trauma is considerable due to costs of care and loss of productivity and working hours. The suffering of injuries is a recurrent theme through the history of man. Because most survivable injuries are superficial or observable, it has been stated that trauma care must have been the origin of medical practice. Through the ages trauma care has been much improved through increasing knowledge and experience in three key areas; management of wounds and injuries, treatment of shock and systems of trauma care organization.

Shock in trauma is most often caused by hypovolemia due to hemorrhage from injuries. Massive hemorrhage may lead to exsanguination. Exsanguination is a leading cause of death in trauma and accounts for 30-40% of trauma mortality. Central nervous system (CNS) injury is the other major cause of trauma deaths but in contrast to hemorrhage, CNS injury is less amenable to interventions that reduce mortality and morbidity. In the acute period immediate after injury, hemorrhage is the main cause of trauma mortality and is recognized as the leading cause of preventable death, especially in the initial 24 hours after admission to hospital. Recently, it has been estimated that in the United States, between 10,000 and 24,000 hemorrhagic trauma deaths are potentially preventable. The exact proportion of surviving trauma patients with potential exsanguinating hemorrhage that are admitted to hospital is unknown. However, 8-10% of trauma patients will receive an allogeneic blood transfusion for the correction of blood loss due to hemorrhage. Moreover, 5-10% of those patients will receive massive transfusion for treatment of exsanguinating hemorrhage. In military trauma, massive transfusion occurs in 8-16% of all trauma admissions. In contrast, massive transfusion in civilian trauma is required in 1-3% of trauma admissions. Thus, even in the busiest civilian trauma centers, the number of trauma patients requiring massive transfusion, which is indicative of potential exsanguinating hemorrhage, typically will not exceed 100 per year. Nevertheless, despite the relatively low incidence of exsanguinating hemorrhage in the civilian trauma hospital setting, it is worthwhile to study this clinical condition and its current treatment because of the close association of massive hemorrhage and mortality. The work in this thesis was performed in an effort to contribute to further understanding and improvement of the
treatment of major traumatic hemorrhage, as this has a major impact on patients, their families and society. The three mainstays of treatment of trauma patients with massive blood loss are; hemorrhage control, volume support (treatment of shock) and correction of traumatic coagulopathy. This thesis concentrates mainly on aspects of treatment of shock during resuscitation of exsanguinating trauma patients. It was only at the beginning of last century that hemorrhage was recognized as the actual cause of ‘the shocked state’ in trauma. Therefore, to put insights and advances in the clinical management and research of the last decade into perspective, a brief history of trauma hemorrhage, shock and resuscitation is given. The rationale for the specific studies as described in this thesis is then outlined.
Understanding hemorrhagic shock

During the last centuries, several landmarks in the history of surgery can be recognized that greatly influenced the understanding and treatment of exsanguinating trauma patients. In the seventeenth century, the English physician William Harvey published his treatise *De Motu Cordis* in which he explained his observations on the actual circulation of blood. In 1656, Christopher Wren was the first to administer medicines by an intravenous route and in 1666, Richard Lower performed the first homologous transfusion of blood in animals. Unfortunately, allogeneic blood transfusion in humans was legally forbidden after the occurrence of fatal transfusion reactions and was not continued until the beginning of the 20th century. As previously stated, the recognition of shock due to trauma as the result of circulatory failure and hypovolemia did not take place until the beginning of the 20th century. As a consequence, fluid resuscitation was not routinely performed and surgeons mainly focused on control of hemorrhage from injuries and the treatment of septic complications of wounds. In the meanwhile, surgical advances considerably increased survival rates of exsanguinating trauma patients. These advances included the arrest of hemorrhage by ligating individual blood vessels (Ambroise Pare, 16th century) and the rapid retrieval and transport of the injured from battlefields to facilitate early treatment (Dominique Jean Larrey, late 18th and early 19th century). The introduction of sulphuric ether to induce general anesthesia allowed for more extensive and prolonged surgical procedures of the chest and abdomen (William Morton, 19th century). Furthermore, the understanding of the nature of infection and antisepsis through the use of carbolic acid and sterile catgut suture material (Joseph Lister, 19th century) prevented postoperative septic complications. The elucidation of X-rays (Wilhelm Röntgen, 19th century) allowed for diagnosis and location of fractures and dislocations as well as the removal of foreign bodies. The aforementioned developments enabled surgeons to turn their attention from surgical challenges such as septic complications and hemorrhage control to the clinical phenomenon of 'the shocked state'. Studies on the nature and treatment of shock were stimulated by the onset of mass casualties in World War I (WWI). The work of the physiologist W.B. Cannon, amongst others, has laid the foundation for the modern understanding of shock. However, it was not until the 1940s that it was generally accepted that the clinical manifestations of shock mainly depended on an insufficient circulating volume, either by loss of plasma or blood, or both, to a point at which actual circulatory failure and tissue anoxia occurred. Although many agreed that loss of plasma and blood would produce shock, there were many disagreements about the actual site and cause of fluid loss at that time. There
was a neurogenic hypothesis that pointed at an excessive stimulation of the vasomotor center. In the hematogenic hypothesis, shock ensued from decreased total blood volume caused by loss of large quantities of plasma or blood into or from traumatized tissues. In contrast, in the vasogenic or toxigenic hypothesis, the formation of a histamine-like toxin at the site of injury was believed to cause a generalized increase in capillary permeability and transudation of plasma. This mechanism explained why shock caused by fluid loss was not always related to blood loss. The last hypothesis could not, however, be confirmed by experimental work of different researchers. Although currently not widely accepted, the idea of the existence of a ‘toxic factor’ or ‘shock toxin’ in trauma persisted throughout the 1950s, and this phenomenon was reintroduced in studies focusing on adult respiratory distress syndrome (ARDS) or the multiple organ dysfunction syndrome (MODS). Nowadays, shock is defined as a pathophysiological state that is characterized by a systemic reduction of tissue perfusion below what is necessary to meet the metabolic needs of tissues and organs. In trauma, hypovolemia caused by hemorrhage is the most common cause of shock.
Plasma transfusion and other blood substitutes

In 1668, homologous blood transfusion between animals was demonstrated between animals by Lower. However, clinical application of Lower’s work did result in fatal transfusion reactions. Blood transfusion was legally forbidden until the problem of transfusion reactions was solved in the early 1900s through discovery and research of the human blood groups and Rhesus blood group factor by Landsteiner, Moss and Wiener. Despite the fact that Thomas Latta had used saline infusions for the treatment of patients with cholera as early as in 1831, it was only during the first decades of the 20th century that intravenous fluid replacement therapy became one of the chief elements of the treatment of shock. Plasma was considered to be the best possible substitute for lost blood. However, in case of the unavailability of plasma, other substitutes such as crystalloid fluids, glucose solutions and colloid solutions were required for resuscitation and to bridge the period of preparation of donor whole blood for transfusion. Unfortunately, the sole administration of blood substitutes was insufficient to restore the circulating blood volume and tissue oxygenation. Normal saline infusion, as supportive care but not as therapy for shock, was clearly recognized and it was advised that the total volume should be safely limited to 1000-1500 mL. Earlier experiments indeed indicated that excessive use of crystalloid solutions might be harmful in shock. After World War II (WWII), the use of normal saline for bridging the time period to transfusion of whole blood was replaced by the use of plasma. Plasma could be easily derived either from fresh whole blood or from banked whole blood and stored for several days at 4°C. It could also be preserved by the process of desiccation and intravenously administered without cross matching. As a sterile powder, plasma was preserved in bottles, negating the need for refrigeration and allowing for almost indefinite storage and easy availability. Thousands of trauma packages made of dried plasma, sterile distilled water for plasma reconstitution and medical equipment were used during WWII. In patients who required transfusion either preserved (stored/banked) whole blood or fresh whole blood was used. Since dried plasma was derived from pooled donor plasma at that time, and any viral contamination was rapidly spread through large batches of product, the use of dried plasma was eventually abandoned around the world. Interestingly, nowadays, freeze-dried plasma has gained renewed attention. New insights have confirmed the necessity of early administration of fresh frozen plasma (FFP) in sufficient quantities during massive transfusion of blood components to replenish coagulation factors that are consumed, diluted or lost, in cases of major hemorrhage. Because of its convenient properties in terms of storage and availability, especially under adverse conditions, it has
been proposed that freeze-dried plasma should be a research and development priority as a replacement for fresh frozen plasma.\textsuperscript{20,21}
From plasma transfusion to transfusion of whole blood

Until the onset of WWII, shock in trauma was treated by transfusion of plasma according to the beliefs and insights at that time. In particular, it was assumed that trauma was associated with plasma leakage into the extravascular space, and the volume deficit had to be replenished by plasma. However, during WWII, it was noted by surgeons in forward hospitals that patients in shock often responded unsatisfactorily to plasma transfusions and that transfusion of whole blood was needed to optimize further treatment.\(^{13}\) This experience added to the belief that blood rather than plasma is lost at the injury site(s) in 'shocked' trauma patients. Patient studies done by Emerson\(^{22}\) and Evans\(^{23}\) confirmed that the clinical state of shock was indeed a reflection of a diminished circulating volume due to the loss of whole blood. They found that a minimum loss of 15% of the total blood volume was especially observed in patients with shock, while severely shocked patients had lost 35-40% of their blood volume. The paradigm-shift from plasma transfusion to whole blood transfusion and the subsequent banking and distribution of whole blood can be regarded as one of the major advances in the treatment of hemorrhagic shock.\(^4\)
From transfusion of whole blood to resuscitation with blood components and crystalloid fluids

The increased need for readily available whole blood during WWII stimulated blood banking. The blood banking field service of the United States Army supplied large quantities of whole blood to field and evacuation hospitals. Despite its slight inferiority when compared to fresh whole blood, preserved whole blood had gained wide acceptance as a substitute in treatment of traumatic hemorrhage at the end of the 1950s. Before WWII, during the preparation and preservation of plasma, red blood cells were discarded as a by-product. Later, these fresh discarded red blood cells were resuspended in an amount of sterile saline and were used at various hospitals as an alternative for whole blood transfusion. However, it was already noted that the use of red cell suspensions, as a blood component, appeared to be satisfactory in the treatment of anemia but less satisfactory in other conditions, such as trauma, that required transfusion of whole blood. In the 1950s (Korean War) and 1960s (Vietnam War), improved efficiency in battlefield transport systems due to the use of helicopters for rapid medical evacuation led to more casualties with traumatic hemorrhage surviving. In these victims, the estimated amount of blood lost was replaced by transfusing an equivalent of whole blood. However, due to under-resuscitation there were reports of high renal failure rates. Subsequent experimental work showed that in severe hemorrhagic shock a large extracellular fluid deficit occurred, and this phenomenon was also confirmed in patients. Resuscitation of dogs with blood and lactated Ringers’s solution substantially lowered mortality when compared to resuscitation with blood alone or with blood and plasma. Moreover, other experimental studies confirmed that the uptake of fluid by the intracellular compartment, resulting from dysfunction of the cellular membrane, was a major site of fluid sequestration following prolonged hemorrhagic shock. The concept of aggressive fluid resuscitation with normal saline or lactated Ringers’s solution in addition to red blood cell transfusion in patients with hemorrhagic shock was especially applied during the Vietnam-conflict. Shires et al. recommended three liters of crystalloid fluid resuscitation for each liter of blood lost. However, this practice resulted in over-resuscitation causing massive fluid overload with consequent edema and a new condition: Da Nang-Lung (or Adult Respiratory Distress Syndrome: ARDS). Despite the fact that Shires and Moore editorialized against this practice in 1968, aggressive resuscitation with crystalloids became established in civilian practice and remained the norm for almost 40 years. In the 1990’s it appeared that overzealous resuscitation with crystalloid fluids may however contribute to the pathophysiology of the abdominal compartment syndrome. Also, in the 1970’s, another element of resuscitation changed: whole blood
was separated into components which were supplied as blood products in the form of packed red blood
cells (PRBC), platelets (PLTs) and fresh frozen plasma (FFP), to maximize blood product availability
under conditions of scarcity. Although there were no data to support that transfusion of blood
components was equally efficacious as the use of whole blood in trauma-related hemorrhagic shock,
blood component therapy, combined with aggressive crystalloid infusion, became standard in civilian
practice.21 In the 1980’s and 1990’s the initial resuscitation of trauma patients became more
standardized through the introduction of the Advanced Trauma Life Support (ATLS) guidelines.
Nowadays, the guideline for initial intravenous fluid therapy still recommends the “3 for 1 rule”, which
comprises of 3 mL of lactated Ringers’s solution for each mL of blood loss.17,31,32 By doing so, an initial
intravenous fluid bolus of 1 to 2 liters is infused, followed by monitoring of the response of the patient.
Depending on the depth of shock and the response to this initial fluid bolus, the guidelines further
recommended the transfusion of blood components in addition to ongoing crystalloid infusion.
Interestingly, only packed red blood cells were advised to be routinely transfused in a blind fashion in
order to restore the oxygen-carrying capacity of the intravascular volume. Routine transfusion of other
blood components (FFP, PLTs) should, however, be guided by coagulation tests. In the 2008 edition of
the ATLS Student Course Manual, it is recommended to consider early and immediate blood component
therapy, consisting of PRBC, PLTs and FFP, in patients with severe hemorrhagic shock.17 In the
October 2012 edition, the establishment of a massive transfusion protocol is advised to provide for
immediate availability of all blood components.32
From resuscitation with blood components and crystalloid fluids to traumatic coagulopathy

Despite some early reports\textsuperscript{33,34} about the association of coagulopathy with massive blood transfusion in trauma, coagulopathy was supposed to be a rare problem in the first hour of treatment. It was advised that routine transfusion of blood components other than PRBC, such as PLTs, cryoprecipitate and FFP, was not warranted in trauma. Moreover, blood component transfusion was only advised when coagulation abnormalities were indicated by laboratory tests. However, over the last 10-15 years it has become widely accepted that hemorrhage in trauma and subsequent massive blood transfusion are associated with coagulopathy. The mechanisms underlying tissue injury, dilution, and consumption and loss of clotting factors and platelets caused by blood loss and resuscitation are held responsible for traumatic coagulopathy. Coagulopathy in trauma also appeared to be enhanced by acidosis due to shock and inadequate ventilation as well as by hypothermia. Coagulopathy, acidosis and hypothermia therefore constitute the ‘bloody vicious cycle’\textsuperscript{35} or the ‘lethal triad’\textsuperscript{36} of trauma. As the trauma patient cannot be properly resuscitated until hemorrhage has been stopped, rapid control of hemorrhage is of vital importance to improve patient outcome. To minimize the time to hemorrhage control and to prevent the patient from entering the ‘bloody vicious cycle’, the concept of damage control surgery in trauma emerged.\textsuperscript{37,38} As opposed to lengthy, definitive surgical operations, rapid and abbreviated surgical techniques (to control hemorrhage and prevent contamination) are increasingly performed in trauma patients with severe hemorrhagic shock. Definitive surgical repair is only performed after further resuscitation and stabilization in ICU and normalization of physiological functions like body temperature, tissue perfusion and coagulation. Interestingly, some of these abbreviated surgical techniques were not ‘new’. In 1908, Hogarth Pringle already described the arrest of hemorrhage in hepatic trauma by compression and packing.\textsuperscript{39} Moreover, transfusion of large amounts of blood components appeared not to be futile but, in contrast, improved survival in trauma patients.\textsuperscript{40,41} Despite surgical control of bleeding and massive transfusion, persistent microvascular bleeding or so-called ‘oozing’, which is indicative of traumatic coagulopathy, frequently led to exsanguination.

At the end of the 20th century, the anecdotal administration of the recombinant coagulation factor VIIa (rFVIIa) was reportedly successful in rescuing trauma patients from exsanguinating due to non-surgical bleeding when no other treatment options were available anymore.\textsuperscript{42,43} These findings stimulated the off-label use of recombinant FVIIa, which was primarily produced to treat bleedings in hemophiliacs, in bleeding patients without preexisting coagulation disorders. Many observational studies of rFVIIa
showed promising results in trauma patients. However, in a double-blinded, placebo-controlled randomized clinical trial, the early and routinely administration of rFVIIa during massive transfusion in severely bleeding trauma patients caused some reduction in the need for transfusion of PRBC but did not affect mortality.\textsuperscript{44} Subsequently, a phase 3 randomized clinical trial that focused on the effect of rFVIIa on 30-day mortality in major trauma was terminated early after futility analysis; both groups showed an unexpected low mortality.\textsuperscript{45} Apparently, rFVIIa was no magic bullet in the treatment of coagulopathy in exsanguinating trauma patients. Nevertheless, exsanguination - as one of the major and preventable causes of death in trauma - had gained much attention. Interestingly, at the time the U.S. Army became active in Iraq and Afghanistan, the treatment of bleeding trauma patients including the initial resuscitation with crystalloids and blood components was revisited. This resulted in an increasing number of international publications that focus on treatment of traumatic hemorrhage.
From traumatic coagulopathy to ‘reconstituted whole blood’, damage control resuscitation and fresh whole blood.

Due to the publication of Hirsberg et al. it became apparent that during massive transfusion of PRBC, insufficient amounts of FFP and PLTs were administered. In addition, the administration of fresh frozen plasma was often started after the administration of significant amounts of packed red blood cells. In combination with overzealous resuscitation with crystalloid fluids, this practice induced and/or enhanced traumatic coagulopathy. A retrospective study showed that during massive transfusion in trauma, survival increased when blood components were administered in a ratio of 1.4:1 units (PRBC:FFP). Although ‘survivorship bias’ was reported as potential confounder of results, these findings resulted in a revision of the transfusion ratio of blood components during massive transfusion in trauma. From then on, it was advised to administer blood components in a ratio of 1:1:1 units (PRBC:FFP:PLTs). Interestingly, by doing so, a volume of whole blood was reconstituted by separate units of blood components. Massive transfusion protocols (MTP) were revisited and adjusted to provide for early delivery and administration of packages of reconstituted whole blood to the patient. The aim of this was to facilitate empirical transfusion to restore blood volume, perfusion and oxygenation while reversing coagulopathy, acidosis and hypothermia. Major trauma institutions had thawed fresh frozen plasma at hand to comply with their protocols. Inevitably, the role of the hospital blood bank needed to become more and more proactive in order to satisfy the increasing demand for plasma and platelets. Massive transfusion protocols evolved into Trauma Exsanguination Protocols (TEP) that facilitate the so-called ‘damage control resuscitation’ (DCR) consisting of:

1) empirical, massive transfusion of reconstituted whole blood (1:1:1 ratio),
2) damage control surgery,
3) ‘permissive hypotension’ and
4) prevention of resuscitation injury by limiting the administration of intravenous (i.v.) crystalloid fluids

The aims of damage control resuscitation were rapid control of hemorrhage, reversal of shock and prevention of traumatic coagulopathy. The concept of permissive hypotension as opposed to achieve normotension during resuscitation of bleeding trauma patients regained attention in the 1990s. During hypotensive resuscitation, a lower blood pressure than normal was accepted or achieved until surgical control of the bleeding was established. In this way, clot formation at the sites of tissue injury is not
disturbed and increased bleeding is prevented. Interestingly, a statement about the role of permissive hypotension in the treatment of bleeding trauma patients was already made by W.B. Cannon in 1918\textsuperscript{56} after careful observation of casualties in France during WWII: ‘Injection of a fluid that will increase blood pressure has dangers in itself. Hemorrhage in case of shock may not have occurred to a marked degree because blood pressure has been too low and the flow too scant to overcome the obstacle offered by a clot. If the pressure is raised before the surgeon is ready to check any bleeding that may take place, blood that is sorely needed may be lost’.

Nowadays it is advised that in hemorrhagic shock due to trauma, fluids should only be administered in case of a weak or absent radial pulse or a decreasing level of consciousness in the absence of head injury until the bleeding is controlled.\textsuperscript{21} If fluid resuscitation is commenced, small boluses should be used while titrating against a palpable radial pulse and/or effective mentation.\textsuperscript{21,57,58,59} The application of restricted use of crystalloid fluids during resuscitation did not only prevent fluid overload and related complications, but also mitigated the contribution of hemodilution to traumatic coagulopathy. In the meanwhile, more attention was directed to fresh whole blood (FWB) again due to the limited availability of large amounts of blood components in tactical military situations. It also became apparent that a volume of FWB was superior in the treatment of coagulopathy and shock than a volume of ‘whole blood’ reconstituted from stored blood components. Fresh whole blood consists of better-functioning red blood cells due to the absence of storage lesions, and contains a higher hematocrit, higher clotting factor activity, and more functioning platelets.\textsuperscript{60,61} Moreover, because of the addition of solution additives to the blood components, the total volume of reconstituted whole blood is larger than the volume of fresh whole blood. In this way, massive transfusion of reconstituted whole blood augments hemodilution and may therefore contribute to the development of coagulopathy. The use of a ‘walking blood bank’ under military conditions was shown to be feasible and allowed the availability of warm fresh whole blood one hour after activation.\textsuperscript{60} Although the exact mechanism is still undetermined, a large retrospective study showed that transfusion of warm fresh whole blood was associated with improved survival in patients with combat-related traumatic injuries when compared to blood component therapy.\textsuperscript{61} Prospective studies to compare the use of fresh whole blood with reconstituted whole blood are warranted. Furthermore, it is uncertain if transfusion of fresh whole blood can be applied in the civilian setting because of safety and logistical issues. A prospective, randomized trial that evaluates early transfusion of stored whole blood versus blood component therapy in trauma patients is currently active, and may provide information on the feasibility of fresh whole blood transfusion in the civilian setting.\textsuperscript{62}
In the meantime, component therapy in the form of ‘reconstituted whole blood’ will be the mainstay for massive transfusion in exsanguinating trauma. Recently, a prospective, observational and multi-center study focusing on transfusion practices in civilian trauma centers was completed.\textsuperscript{63} In this study, about five trauma patients with massive transfusion could be included per week, showing that collaborative, multi-center initiatives provide an unique opportunity to gain insight in the development and management of traumatic coagulopathy and that prospective trauma transfusion studies are feasible. Moreover, a phase III clinical trial has been designed to evaluate the optimal PLTs and FFP to PRBC ratios for massive transfusion in trauma. The use of blood product ratio 1:1:1 (PRBC:FFP:PLTs) will be compared to 2:1:1 (PRBC:FFP:PLTs) in the context of 24-hour and 30-day mortality. Completion of this trial is to be expected in 2015.\textsuperscript{64}

\textbf{Goal-directed therapy of trauma-induced coagulopathy: the theragnostic concept?}

Until the early 2000s, traumatic coagulopathy was supposed to be primarily caused by loss and consumption of coagulation factors, hemodilution due to the administration of large fluid volumes and massive transfusion with blood components, hypothermia and acidosis. Although this concept remains relevant for the majority of trauma cases, Brohi \textit{et al.} introduced a novel concept that may contribute to the development of traumatic shock. In their large observational study they showed that acute coagulopathy was related to injury severity. However, in contrast to others, they were unable to attribute the coagulopathy to the volume of fluid resuscitation. In nearly one-quarter of the trauma patients studied, coagulopathy was already established upon arrival in the emergency department,\textsuperscript{65} and those patients had a significant higher mortality. Further research showed that this early traumatic coagulopathy occurred only in the presence of tissue hypoperfusion and was characterized by anticoagulation through the activation of the protein C pathway\textsuperscript{66} and hyperfibrinolysis.\textsuperscript{67} Subsequently, the definitions and mechanisms of traumatic coagulopathy were revisited. The newly discovered early coagulopathy was named the Acute Coagulopathy of Trauma-Shock (ACoTS) and designated as an endogenous precursor of Trauma-Induced Coagulopathy (TIC).\textsuperscript{68,69} Other ‘classic’ mediators or drivers such as hemodilution (due to resuscitation) inflammation, tissue trauma, hypothermia and acidosis (due to shock) may further contribute to TIC.
Figure 1. Diagram of the association of trauma with hemorrhage, shock, resuscitation and the ‘bloody vicious cycle’, consisting of acidosis, hypothermia and coagulopathy (curved arrows). The coincidence of traumatic hemorrhage and shock, which requires restoration of tissue perfusion and oxygenation by resuscitation, may result in the development of trauma-induced coagulopathy and/or acute coagulopathy of trauma shock (ACoTS). Both aggregate hemorrhage and thus may contribute to trauma-related mortality (Adapted from Hess et al.\textsuperscript{68} and Davenport et al.\textsuperscript{70}).

Meanwhile, it was shown in a randomized, placebo-controlled, multi-center trial that tranexamic acid, an antifibrinolytic drug, safely reduced the risk of death in bleeding trauma patients\textsuperscript{71} when given as early as possible.\textsuperscript{72} Realizing that early identification of ACoTS and/or TIC was crucial for effective treatment, it was acknowledged that the standard coagulation tests were of little help during the initial resuscitation (including massive transfusion of blood products) in hemorrhaging trauma patients, particularly due to the time-consuming nature of the procedure. Activated partial thromboplastin time (aPTT), prothrombin time (PT) and fibrinogen levels provided hardly any information on early clot formation, and the test results would only reflect the situation 45 minutes earlier, when the sample was taken.\textsuperscript{69,73} Furthermore, the apparent platelet dysfunction related to TIC could not be identified nor quantified by ‘simple’, numerical, platelet counts.\textsuperscript{69} Moreover, in the early 2000s the classic, cascade model of coagulation based on artificial segregation of an intrinsic and extrinsic pathway as reflected by the \textit{in vitro} laboratory tests aPTT and PT respectively, was replaced by a cell-based model of coagulation.\textsuperscript{73,74,75} In this new model of \textit{in vivo} coagulation, three overlapping stages of thrombin generation are defined. Binding of
FVIIa to tissue factor expressed on injured and/or activated cells leads to the production of small amounts of thrombin (*initiation*) that further activates platelets and platelet adhesion (*amplification*) resulting in massive production of thrombin at the platelet surfaces (*propagation*). This thrombin burst results in fibrin polymerization, which is required to form a stable, hemostatic clot.\textsuperscript{74}

Concurrently, given the need for a rapid and appropriate coagulation test for trauma patients with massive hemorrhage, thromboelastography (TEG) and thromboelastometry (TEM) re-emerged. This test had been developed in 1948 by Hartert and was primarily used as research tool. In the 1980s and 1990s it was mainly used during cardiac and liver transplant surgery.\textsuperscript{76,77} TEG and TEM are point-of-care tests that provide information on the actual processes of clot formation, clot stability and clot lysis, shortly (10-15 min) after the sample is taken.\textsuperscript{77,78} In TEG and TEM the viscoelastic properties of whole blood are shown graphically in real time and partly reflect the *in vivo* extracellular clotting process. In 1992, Mallett and Cox pointed out already that TEG and TEM would be useful in cases of massive blood loss to individualize treatment of hemostatic abnormalities and prevent dilutional coagulopathy resulting from empirical administration of blood products like fresh frozen plasma and platelets.\textsuperscript{76} Subsequently, the usefulness of TEG in the assessment of coagulation in trauma patients was confirmed by Kaufmann.\textsuperscript{77}

The test results of TEG and TEM can guide the clinician more directly and immediately while treating TIC during massive transfusion in trauma. These tests further allow for early and individualized goal-directed therapy with coagulation factor concentrates such as prothrombin complex concentrate (PCC) and fibrinogen concentrate. The clinical application of this ‘theragnostic concept’, using treatment algorithms based on TEM results, is promising. An observational study showed a favorable survival rate among major trauma patients that were treated using point-of-care coagulation testing.\textsuperscript{79} Another observational study showed that the theragnostic concept is associated with a significant reduction of the transfusion requirements for FFP, PRBC and PLTs, as well as with a reduced incidence of massive transfusion.\textsuperscript{80} Also, if rotational thromboelastometry is combined with functional platelet tests such as whole-blood impedance aggregometry, theragnostic algorithms can be extended to allow for the judicious administration of other coagulation factors such as FXIII and rFVIIa if required.\textsuperscript{80} Further research is warranted to investigate the efficacy, safety and cost-effectiveness of the theragnostic concept when compared to the empirical administration of reconstituted whole blood. Reducing the need for blood products such as FFP may also reduce the time to control/prevent TIC and reduce complications such as an increased risk for infections, ARDS and MODS, related to massive transfusion.
of blood products. Hemolytic transfusion reactions and viral and bacterial transmission may be reduced as well.\textsuperscript{75,81,82}

Re-examining the history of resuscitating patients with hemorrhagic shock reveals some interesting insights. The process of acquiring the current insight and advances in treatment was slow and lasted almost 100 years. Also, it appears that important leaps (forward and backward) in this process were made due to necessity created by wars. Resuscitation of exsanguinating trauma patients evolved from the administration of freeze-dried plasma and whole blood to infusion of large amounts of crystalloid fluids and packed red blood cells, hereby creating new phenomena such as ARDS, the abdominal compartment syndrome and traumatic coagulopathy. Subsequently, massive crystalloid infusion was abandoned and resuscitation with blood components, in a way that mimics transfusion of whole blood, was adapted. Interestingly, concepts that were described decades ago, such as permissive hypotension and damage control surgery, were reintroduced and incorporated in modern treatment. And freeze-dried plasma is in the picture again for pre-hospital resuscitation, while transfusion of whole blood has gained renewed attention. Goal-directed therapy also appears to be a promising means of countering trauma-induced coagulopathy at an early stage, and may lead to better survival and a reduction of the use of blood components.
The objective and outline of this thesis

The aim of this thesis was to evaluate several aspects of the management and treatment of trauma patients with life-threatening hemorrhage in order to delineate points of application for improvement of care and further research. Consequently, life-threatening hemorrhage in trauma was approached as a reversible disease that originates in the field and proceeds along the links of the trauma chain of survival, until the bleeding has been stopped and patient physiology has returned to normal. In particular, this thesis focuses on the evaluation of effects of current practice regarding volume support, massive transfusion and coagulation on hemorrhage control and patient outcome.

In Chapter 2, a typical case of exsanguinating trauma is dissected to evaluate the clinical course of life-threatening hemorrhage. The multidisciplinary treatment of the patient is co-ordinated by the trauma surgeon. The three mainstays of treatment are explained: hemorrhage control, volume support and coagulation management. In this anecdotal report, the challenges that are faced by the clinicians during this process are described.

In Chapter 3, in a narrative review, life-threatening hemorrhage in trauma is approached as a disease that can be cured. An overview is given of the state-of-the-art diagnostic and treatment options throughout the pre-clinical and clinical course of exsanguinating hemorrhage in trauma. All aspects of pre-hospital and in-hospital hemorrhage control, volume support and coagulation management are discussed.

As traumatic hemorrhage originates in the field, treatment starts in the pre-hospital setting. The best intravenous fluid resuscitation strategy in trauma is not known. We here hypothesized that the volume of pre-hospital intravenous fluid administration reduces the shock index upon emergency department admission, but increases allogeneic blood transfusion requirements. Therefore, in Chapter 4, the effects of intravenous fluid resuscitation, before and during transport to the hospital of hypotensive trauma patients, are investigated by regression analysis of a large cohort of patients presented at a level 1 trauma center.

After arrival in the emergency department, exsanguinating trauma patients will be subjected to empirical, massive transfusion of blood products. Decision-making and treatment are performed under hectic
circumstances while working against the clock. In Chapter 5, we hypothesized that ‘blind’ transfusion of blood products may deviate from the actual requirements of a patient. The practice of ‘blind’ transfusion of blood products is evaluated in a cohort of trauma patients who, despite all resuscitative efforts, including surgical procedures, died from exsanguinating hemorrhage in a level 1 trauma center.

Massive transfusion protocols (MTPs) are developed to facilitate the rapid availability and administration of blood products in exsanguinating trauma patients. MTPs are established using input from trauma surgery stakeholders, anesthesiology and blood banking, and should incorporate specific operating procedures to facilitate this process. In Chapter 6, the effect of the introduction of an MTP is evaluated in a before-and-after study in trauma patients who received massive transfusion in a level 1 trauma center. We hypothesized that MTP implementation is associated with improved outcome in trauma patients.

In Chapter 7, the role of coagulation factor recombinant FVIIa (Novoseven®) in blunt trauma patients with life-threatening hemorrhage is investigated. Since no surgical treatment options were left, these patients were about to exsanguinate from non-surgical bleeding (‘oozing’) due to traumatic coagulopathy. rFVIIa was administered as a last resort to stop bleeding, and it was hypothesized that rFVIIA administration is more effective in the reversal of life-threatening hemorrhage when compared to a baseline situation. The study was performed within the ICU-setting of a level 1 trauma center.

The main findings of this thesis are summarized and discussed in Chapter 8. Directions for future research are also indicated in this chapter.

In Chapter 9 a summary in Dutch-language is given.
References


64. Pragmatic, Randomized Optimal Platelets and Plasma ratios (PROPPR) www.clinicaltrials.gov/ NCT01227005; visited August 28, 2012

