The impact of ageing on trauma-related bleeding and coagulopathy

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University of Oxford

Trinity Term 2020

A thesis submitted for the Degree of Doctor of Philosophy

This thesis is dedicated to my parents and brother

Abstract

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The epidemiology of major injury is changing as the population ages, revealing gaps in our understanding of the management of older patients with trauma-related bleeding. Physiology and haemostasis alter with normal ageing and could attenuate the response to bleeding in an older person. The aim of this thesis was to explore the impact of the ageing trauma demographic on the presentation and management of bleeding and coagulopathy in trauma.

I conducted a systematic review to explore the evidence across age for the use of blood transfusion strategies in acute trauma haemorrhage. I identified 10 randomised controlled trials; older patients were not well represented. There were no randomised trials in older people or trials that evaluated interventions for different age groups.

A Delphi study was undertaken to develop a new consensus research definition for major bleeding in trauma. This definition was applied to the Trauma Audit Research Network registry to assess the effect of age on risk factors for major bleeding. I found older patients with bleeding were less likely to present with tachycardia than younger patients. Multivariable logistic regression using seven risk factors (age, male gender, penetrating injury, mechanism of injury, hypotension and tachycardia and unstable pelvis) showed all were independently significantly associated with bleeding. I also

identified a negative interaction between age and penetrating injury, and age and mechanism of injury. Multiple imputation was used to handle missing data and the significance of the risk factors in the imputation model was broadly similar to the complete case analysis model.

The effect of age on coagulation and fibrinolytic parameters was assessed in a multicentre cohort study. In patients who did not receive tranexamic acid, after adjusting for key covariates including presence of bleeding and injury severity, I found older age was associated with heightened fibrinolytic activity and fibrinogen levels compared with younger age.

The programme of work in this thesis has provided new data showing that age has a significant effect on the clinical presentation and risk factors for bleeding. Furthermore, coagulation and fibrinolytic parameters appear altered across age. These data are exploratory and hypothesis-generating. They inform future research areas to assess the effectiveness of different interventions including tranexamic acid across age, develop age-adapted transfusion protocols and prediction models for bleeding that take age into consideration.

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Statement of originality

All work in this thesis is my own unless otherwise stated.

I wrote the first draft of all published manuscripts arising from this thesis and then critically reviewed by senior co-authors. All publications were peer reviewed.

I performed all statistical analyses, which were critically appraised by my statistical supervisor.

I set up and conducted all stages of the Delphi study, leading the Delphi steering group.

I cleaned and analysed the TARN and ACIT data.

The laboratory assays in the ACIT study were performed by members of the Royal London Hospital research team.

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Abbreviations

AF	Atrial fibrillation
AIS	Abbreviated injury score
ACIT	Activation of Coagulation and Inflammation in Trauma
APTT	Activated partial thromboplastin time
ATC	Acute traumatic coagulopathy
bpm	Beats per minute
CA5	Clot amplitude after 5 minutes
CAT	Critical administration threshold
CCA	Complete case analysis
CCI	Charlston comorbidity index
CFT	Clot firmness time
CI	Confidence interval
CT	Clotting time
DCR	Damage control resuscitation
ED	Emergency Department
F	Factor
FFP	Fresh frozen plasma
FLyP	French lyophilised plasma
GCS	Glasgow coma score
Hb	Haemoglobin
HR	Heart rate
ICU	Intensive care unit
INR	International normalized ratio
IO	Intraosseous

IQR	Interquartile range
ISS	Injury severity score
ITT	Intention to treat
IV	Intravenous
LY30	Lysis index of the clot after 30 minutes
MCF	Maximum clot firmness
MHP	Major haemorrhage protocol
MICE	Multiple imputation by chained equations
MOI	Mechanism of injury
MTC	Major trauma centre
OR	Odds ratio
PAP	Plasmin-antiplasmin complex
PAI-1	Plasminogen activator inhibitor-1
PT	Prothrombin time
RBC	Red blood cell
RCT	Randomised controlled trial
RI	Resuscitation index
ROTEM	Rotational thromboelastometry
RTC	Road traffic collision
sFMC	Soluble fibrin monomer complex
SBP	Systolic blood pressure
SD	Standard deviation
TAFI	Thrombin activatable fibrinolysis inhibitor
TAFIa	Activated thrombin activatable fibrinolysis inhibitor
TARN	Trauma Audit Research Network
TBI	Traumatic brain injury

TEG	Thromboelastography
TIC	Trauma-induced coagulopathy
t-PA	Tissue plasminogen activator
TXA	Tranexamic acid
UK	United Kingdom
VHA	Viscoelastic haemostatic assay
VWF Ag	Von Willebrand factor antigen
WB	Whole blood

Chapter 1 Introduction

1.1 Trauma-related haemorrhage

Injuries account for approximately 4.6 million deaths worldwide with about 40% of these due to uncontrolled bleeding.[1] Trauma is now recognised to be a problem across a wide age demographic, particularly in older adults.[2,3] A historical perception that most major trauma patients are young and male is challenged by a recent report that shows that more than half of severely injured patients are now older with a lower degree of male preponderance.[4] This reflects changes in the cause of injury, imaging practices and to some degree the impact of an ageing population.[5] This change in the demographic landscape of trauma brings new challenges. Ageing-related physiological changes, particularly in the cardiovascular, pulmonary and haemostatic systems, and pre-existing medical conditions and/or medications may affect an older person's response to injury, susceptibility to bleeding and response to treatment.

Uncontrolled bleeding is the leading potentially preventable cause of death after injury.[6] Bleeding is exacerbated by acute traumatic coagulopathy (ATC), an endogenous impairment of haemostasis that occurs early after severe injury.[7–9] Ameliorating this coagulopathy is one of the key goals of the acute treatment of the bleeding patient.[7] In the past decade, improved understanding of the mechanisms of ATC has transformed resuscitation practice to target coagulopathy, moving away from large volumes of crystalloid infusion to upfront use of blood components.[10] These advances in resuscitation practice and overall improvements in care have led to reductions in death from trauma haemorrhage.[10] But there are uncertainties regarding ageing-related

factors and their impact on bleeding, particularly for the population of older patients where current evidence is limited.

This thesis explores the impact of the changing trauma demographic on the presentation and management of bleeding and coagulopathy. The purpose of this chapter is to describe the background to the main research questions addressed in this thesis. Firstly, I will describe major bleeding and coagulopathy in the general population, and then what is known about trauma haemorrhage in ageing and an older population. For the purpose of this thesis, I will use age 65 and above to define the ''older" population.

1.2 Importance of trauma-related bleeding and coagulopathy

In patients with critical bleeding, deaths occur either early within the first few hours from uncontrolled bleeding, or late deaths (>24 hours) usually from multiple organ failure, infection or sequelae of traumatic brain injury (TBI).[10–12] Approximately a quarter of patients with bleeding show signs of an early endogenous acute traumatic coagulopathy, due to injury itself, on arrival to hospital.[7,13] This coagulopathy occurs despite an upregulation in procoagulant pathways and increased thrombin-generating potential after injury,[14,15] and is strongly linked to higher injury severity and shock.[7,16] Compared with non-coagulopathic patients, coagulopathy is associated with poorer outcomes: higher blood transfusion requirements and risk of organ failure, longer intensive care stay and a fourfold higher mortality.[7,17]

1.3 Acute traumatic coagulopathy

Acute traumatic coagulopathy (ATC) is a multifactorial complex process primarily mediated by protein C activation and endothelial dysfunction, and characterised by hypofibrinogenaemia and activation of fibrinolysis.[18]

Some of the key coagulation changes include [18,19] :

- Normal to high levels of thrombin generation[20]
- Increased fibrinolysis due to the release of tissue plasminogen activator (tPA) from damaged endothelium or other cell surface receptors,[21] reflected in high tPA, high D-dimer
- Rapid reduction in fibrinogen levels[22]
- High levels of thrombin generation and tissue hypoxia, lead to activation of the endothelium.[19] This upregulates thrombomodulin (TM) and subsequent protein C activation. Activated protein C leads to inactivation of factor (F) Va and FVIIIa and depletion of fibrinogen,[23] as well as inhibition of plasminogen activator inhibitor-1 (PAI-1) which increases clot breakdown (fibrinolysis) through increased t-PA activity.[21,24]
- Platelet dysfunction (reduction in platelet aggregometry post injury)[25,26]

Patient factors such as age, co-morbidities and pre-morbid medications can also impact on the development of coagulopathy.[27] The endogenous ATC is further compounded by acidosis, hypothermia and dilution of clotting factors, leading to trauma-induced coagulopathy (Figure 1.1).

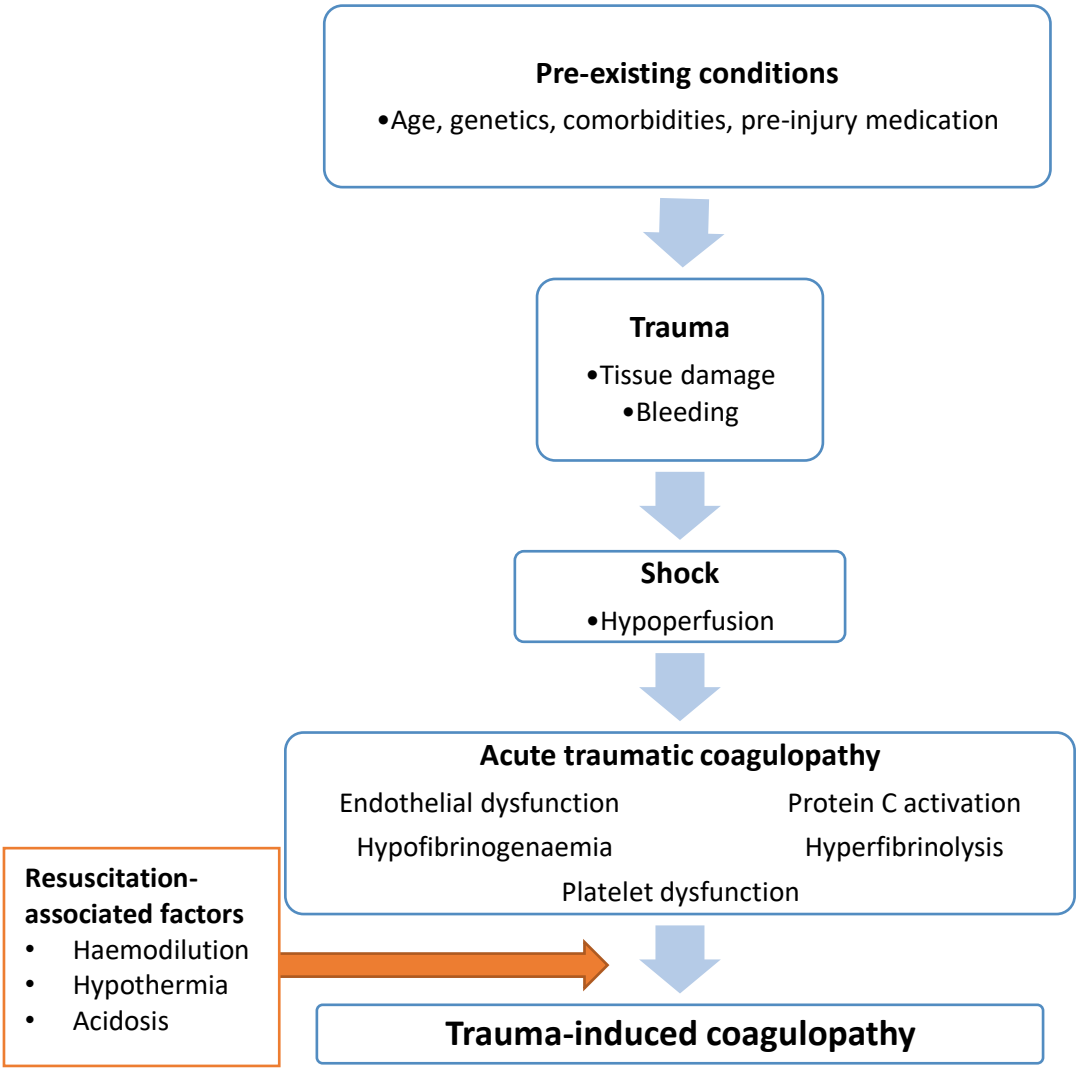


Figure 1.1 Pathways to acute traumatic coagulopathy and trauma-induced coagulopathy

Haemodynamic shock and tissue trauma initiate an early endogenous acute traumatic coagulopathy, driven by the protein C pathway. Early changes in coagulation are exacerbated by inadequate resuscitation resulting in trauma-induced coagulopathy. Adapted from Curry et al[19] Davenport et al.[19,27]

The identification of patients with coagulopathy is crucial in instituting timely and effective intervention, to maintain and/or rapidly regain haemostatic competence and reduce adverse sequelae of bleeding.[28] Improved understanding of the biology of ATC, has resulted in the introduction of management strategies, which include the rapid and consistent administration of transfusion therapy to specifically target this coagulopathy as part of the control of haemorrhage, a concept known as damage control resuscitation

(DCR).[29] The other principles of DCR are the early haemorrhage control through surgical or radiological intervention, permissive hypotension and the prevention of dilutional coagulopathy.[10] These have collectively led to improved mortality.[30,31] It is hoped that in the future, targeted or individualised management will lead to better outcomes, but this requires a deeper understanding of the mechanisms involved in ATC and effectiveness of different interventions on outcomes.[19] This is particularly important in light of the change in age demographics of trauma and population at risk of major bleeding.

1.4 Epidemiology of major bleeding in trauma

Major bleeding can be defined in many ways but most definitions use requirement for blood transfusion as a proxy for bleeding. To gain insight into the epidemiology of severe trauma haemorrhage, a prospective observational study was conducted in England and Wales between 2009-2011 in a sample of trauma-receiving hospitals (both Major Trauma Centres (MTCs) and trauma units).[29] One of the aims of the study was to examine the rate of severe bleeding following injury. In this study, major haemorrhage was defined as the requirement for four or more red blood cells (RBCs) within 24 hours of admission and massive haemorrhage as the requirement for 10 or more units of red cells within 24 hours. Data from the study were extrapolated to give a national incidence, based on data from Hospital Episode Statistics and Office of National Statistics.

A striking observation was that after major trauma, rates of bleeding appeared to be higher in older people. The extrapolated national likelihood of suffering injury with major bleeding was consistent across all age groups until the age of 65 years, after which it nearly doubled to 196 per million for major haemorrhage and 50 per million for

massive haemorrhage.[29] However, the reasons for this difference were not clear. The authors hypothesised that older people may be more likely to bleed for a similar 'type of injury' e.g. due to comorbidities or medications such as anticoagulants, or altered coagulation with ageing. But these and other contributory factors such as injury severity and type of injuries were not captured in this study.[29]

This thesis follows on from this study and explores the effect of ageing on bleeding and coagulopathy in trauma and evidence for age-adapted transfusion strategies.

1.4.1 Ageing and trauma

Increased longevity and a more active older population has contributed to a rise in injury rates among the older population.[32] In the 2017 UK national trauma database TARN (Trauma Audit Research Network) report on Trauma in Older People, over half of trauma admissions in the UK are now in people aged 60 and over.[4] The global community has seen similar trends in the incidence and prevalence of older trauma. This change in the demographics of trauma includes an increase in clinically vulnerable older trauma patients with compromised physiological reserve, co-morbidities, functional dependence, disability and frailty syndromes who may benefit from age-adapted protocols.[33–35] It is also recognised that for the same injury severity, older people have inferior outcomes and increased risk of death compared to younger patients.[36]

In response to this growing health concern, as well as the clinical and social burden associated with this trend, the trauma community has started to implement strategies to optimise the care of an ageing trauma population, for example through geriatric trauma units and protocols.[2,32,37–39] But most of our understanding of coagulopathy and

bleeding comes from studies in younger people and the military[40] and there are limited data to inform age-adapted protocols for the management of bleeding.

1.4.2 The ageing process

Ageing has been described as an increased inability over time to cope with biological stress leading to increased risk of disease and death.[41] Ageing is characterised by a progressive loss of physiological reserve and integrity that affects all body systems. However, how quickly an individual ages biologically is dependent on many factors. Diet, physical activity, lifestyle and genetics all play a role in influencing the ageing trajectory and a person's chronological age does not necessarily correspond to their physiological age.[41]

A recent report from the World Health Organisation (WHO)[42] gives us a balanced view of ageing and reminds us of the positive aspects:

> 'A longer life brings with it opportunities, not only for older people and their families, but also for societies as a whole. Additional years provide the chance to pursue new activities such as further education, a new career or pursuing a long neglected passion. Older people also contribute in many ways to their families and communities. Yet the extent of these opportunities and contributions depends heavily on one factor: health.'
>
> *WHO, 2018*

1.4.3 Potential ageing-related mechanisms for different outcomes in an older trauma population

With this in mind, although good outcomes can be achieved for older people suffering from major trauma, overall mortality is still higher in the older population compared to the young.[3] Studies that evaluated overall mortality (not specifically in bleeding), have

not established a clear cut-off for ageing but in general have described an increase in the mortality rate with increasing age, after 55, 65 and 70 years.[32,43–45] To enable comparisons with previous trauma epidemiology studies, for this thesis age 65 and above will be used to describe the older population.

There are several factors relating to the ageing process that may affect outcomes in trauma and these also apply to the patient with bleeding.

1.4.3.1 *Physiological and immune response*

Ageing is associated with a physiological decline in many systems including marked changes in the cardiovascular and respiratory systems. These systems particularly influence how a patient with major trauma-related bleeding presents, is able to tolerate blood loss and their response to treatment.

Table 1.1. Physiological changes in ageing

Adapted from [32,33]

Body system	Changes in ageing	Potential impact for older person
Cardiovascular	• Cardiac function declines with reduced adrenergic and baroreceptor sensitivity • Stiffness throughout the arterial vasculature increases left ventricular afterload, systolic blood pressure, and contributes to ventricular hypertrophy	• Typical cardiovascular response to hypovolaemia may be masked • May not be able to mount a compensatory tachycardic response or increase cardiac output. • Despite an apparently 'normal blood pressure and heart rate', patients still have evidence of tissue hypoperfusion • Admission vital signs may not be predictive of shock
Respiratory	• Loss of alveolar elastic recoil, stiffening of the chest wall and an increase in flow resistance	• Reduced oxygen exchange and decreased ventilation/perfusion ratio.
Immune	• Decline in immune function	• Increased susceptibility to stress of injury • Possible higher rate of systemic inflammatory response syndrome
Selected other systems	• Skin fragility, osteoporosis, dementia	• Increased risk of adverse outcomes, risk of falls

1.4.3.2 *Haemostasis in ageing*

Haemostatic integrity depends on maintaining the balance between prothrombotic and antithrombotic pathways. After vessel injury, the normal process of primary and secondary haemostasis results in the conversion of fibrinogen to fibrin to form a stable blood clot, which is then broken down over time (fibrinolysis) (Figure 1.2). In ageing, many of the components of haemostasis are altered. In particular, fibrinogen and fibrinolytic activity increase with age[46] and as these are two key components of acute

traumatic coagulopathy, it is hypothesised these may attenuate the profile of coagulopathy and fibrinolysis in an older person and potentially mask the severity of coagulopathy and how it is identified and treated.

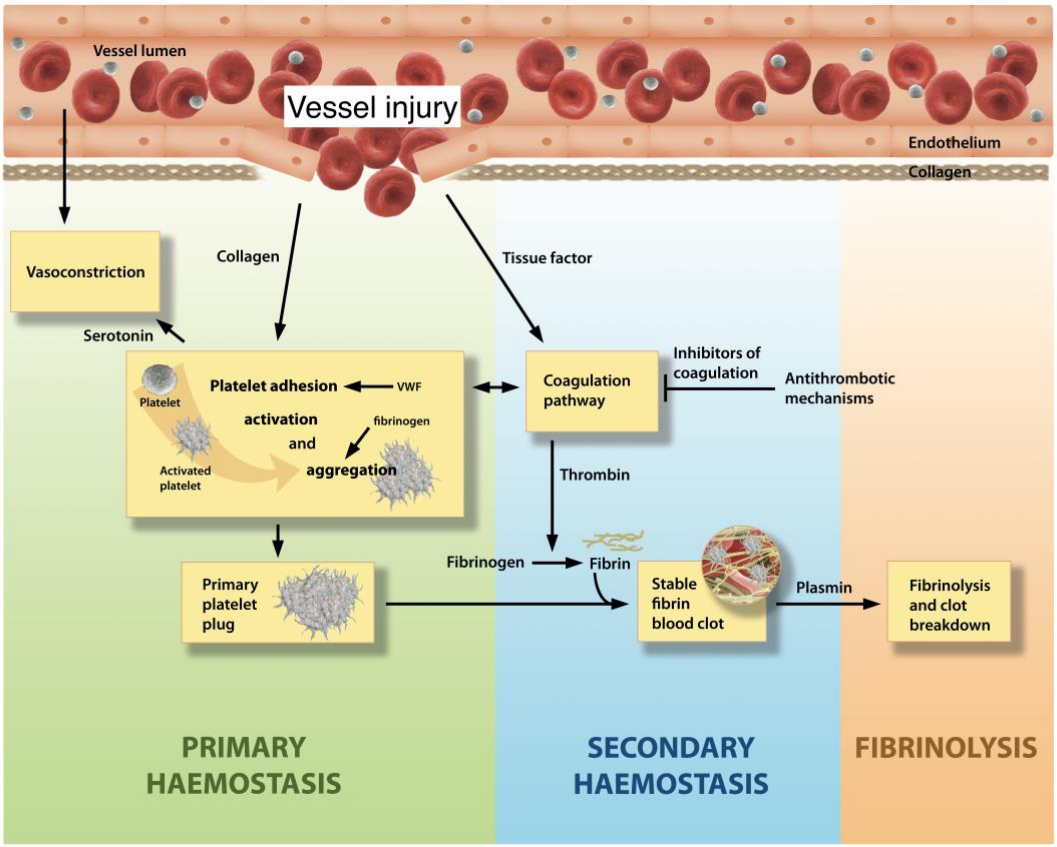


Figure 1.2. Overview of haemostasis

A vascular injury exposes collagen that allows platelets to adhere to the subendothelium via von willebrand factor (VWF). Activation of platelets occurs and platelets aggregate via VWF and fibrinogen. Primary haemostasis results in the formation of an initial platelet plug. Tissue factor activates the coagulation pathway in parallel to platelet activation with both pathways enhancing each other. Fibrinolysis prevents excessive thrombus formation, through the generation of plasmin followed by the breakdown of fibrin. Adapted from Kadir et al.[47]

1.4.3.3 *Frailty*

Frailty is a key concept underpinning health problems in later life. It is defined as a syndrome of decline in physiological reserve and resistance to stressors, which results in increased vulnerability to poor health outcomes and mortality.[48] Frailty has been

described in two models i) the phenotype model[49] and ii) the clinical deficit model.[50] The phenotype model describes a group of patient characteristics based on sarcopenia (unintentional weight loss, reduced muscle strength, reduced gait speed, self-reported exhaustion and low energy expenditure).[35,51] The clinical deficit model is based on a score of long-term conditions, where the higher the score the greater the risk of an adverse outcome. Frailty is now recognised as playing a key role in trauma outcomes and should be assessed for each patient on admission using a clinical frailty score or similar validated score.[39]

1.4.3.4 *Co-morbidities and medications*

Pre-existing medical conditions, particularly cardiovascular disorders, can also have a significant impact on an older person's clinical course, as these conditions can significantly compromise an older trauma patient's ability to compensate for, as well as to recover from, severe injury.[32]

The prevalence of hypertension is greater in older people, the prevalence increases from 27% in patients under the age of 60 to 74% in those aged older than 80 years.[52,53] Hypertension can mask the clinical presentation of shock, as a blood pressure acceptable in a young person may not apply to an older person, whose blood pressure may be usually higher and potentially lead to under-recognition of severe injury, inappropriate triage and suboptimal management.[54,55]

In addition, concurrent antithrombotic use is higher in older people. The prevalence of atrial fibrillation (AF) increases with age: 3.8% among those aged over 60 years and rising to 9.0% in those aged over 80 years.[35,56] Current guidance recommends anticoagulation for stroke prevention for patients over the age of 75 with AF or over 65

with additional risk factors. Studies show 40–66% of adults aged 75 years or older in the USA and Europe take one or more antiplatelet drugs with about half of these indicated for lifelong secondary prevention.[57] These antithrombotics interfere with either primary or secondary haemostasis. The heightened bleeding tendency resulting from antiplatelet or anticoagulant therapy could exacerbate coagulopathy and bleeding in trauma. Furthermore, older patients are more likely to be taking medications for arrhythmias to control heart rate such as beta-blockers, which could blunt the response to injury in haemodynamically compromised patients.

1.4.3.5 *Differences in treatment strategies*

Another factor that may influence the management and consequently outcomes is the problem of under-triage in the older population. This may relate to the type of injury as low-energy trauma may not flag as a high-risk mechanism for major trauma or bleeding but can cause significant injury in older people. As described earlier, altered physiological response may affect vital signs and identification of shock.[55] The response to resuscitative interventions may also be altered due to impaired cardiovascular function.[33]

1.4.3.6 *Injury-related factors*

Differences in the type, mechanism and pattern of injuries across age may play a role. Low level falls and non-penetrating injuries are more common in older age groups. The types of injuries sustained can also significantly affect the mortality rate of older patients.[32] In this regard, traumatic brain injury is the leading cause of death in older trauma patients.[58]

It has been reported that older patients with the same injury severity score (ISS) have poorer outcomes to younger patients with a similar ISS.[36] This may also be similar for the mechanism of injury. One study reported that falls accounted for a different injury severity and injury profile between younger and older patients. Older patients sustained more head/neck, chest, pelvic fracture/extremity injuries than younger patients with falls.[59] This is a concerning observation as falls are consistently among the leading causes of trauma in the older population and pelvic injuries in particular can be a cause of occult bleeding. The presence of occult injuries that are not diagnosable on primary survey and that were associated with major bleeding has also been demonstrated to be higher in older people (aged 65) compared with younger patients (aged <64).[60]

In conclusion, there is a multitude of factors that can potentially affect the clinical course of trauma and major bleeding in an ageing trauma population. Understanding the impact of these will help to inform future strategies and interventions in this vulnerable patient group.

1.4.4 Trauma-related bleeding and coagulopathy in an ageing population

Although this field is expanding, there are few studies that have specifically explored the impact of age on major bleeding or coagulopathy in trauma. Those that do tend to be single-centre observational studies that have mainly compared older patients with younger patients.

Coagulopathy and bleeding

The largest study of transfusion and coagulation in older patients comes from Mador et al in Ottawa, Canada.[43] 124 older patients (aged 55 and above) and 486 younger

patients were included in the analysis. Both groups were severely injured with ISS in the 20s. More older patients were coagulopathic on hospital admission according to elevated international normalized ratio (INR), 11% compared to 3% of controls had INR>1.5 (P-value=0.0008). However, 23% of the older patients with INR >1.5 were taking Vitamin K antagonists, which could account for the INR findings. Other markers such as platelet count, fibrinogen level (18.3% vs. 16.7%; P-value=0.69) and most thromboelastography (TEG) measurements (27% vs. 33%; P-value=0.18) were not statistically different between the groups.[43]

The need for blood transfusion within 24 hours was higher in older patients (43% vs. 30%; P-value=0.012) overall. Older patients received significantly more RBCs and FFP. However, after propensity-matched analysis, there was no difference in RBC transfusion or mortality. Despite similarly matched cohorts, trauma-associated coagulopathy as measured by TEG was less commonly observed in the older population. But the proportion of older patients with fibrinogen <2.0 g/L was significantly higher in the younger group compared with the older group (44% vs 33%, P-value=0.05).

Other studies of coagulation and fibrinogen in trauma and in massive bleeding

A study from Ohmori et al in Japan looked at coagulation markers including fibrinogen in severely injured patients (n=251).[61] There was no difference in the APTT (Activated partial thromboplastin time) or INR between both groups. However, for patients without massive transfusion, fewer older patients had a low fibrinogen level (<2.0 g/L) relative to the younger group (24% vs. 43%, OR 2.4, 95% CI (1.33–4.37), P-value=0.006).

The incidence of massive transfusion was equivalent at ~ 20% in both groups. In the massive transfusion group, whilst a significant difference was not observed in the older group compared to the younger group (44% vs. 75%, OR 3.5, 95% CI (0.98– 12.5), P-value=0.09), the trend was for older patients to have higher fibrinogen levels.[61] This could have clinical implications around the target for fibrinogen replacement in older people. Higher baseline fibrinogen levels in elderly patients could impact the level seen in trauma. Examining trends in fibrinogen may be more helpful as the initial fibrinogen level alone may not be a good early indicator of acute blood loss in older patients compared with younger patients.[61]

Another study of coagulation and transfusion in patients with massive transfusion did not detect any significant differences in the rate of ATC (defined as INR ≥1.5 or APTT >60 seconds) or any differences in INR between old and young patients (although the mean INR was elevated to ~1.7 in both groups).[62] It did not report on fibrinogen. Overall, there was also no difference in the numbers of red cell and FFP units transfused between both age groups at 4 hours and 24 hours.[62]

Coagulopathy associated with traumatic brain injury

There is also some evidence that traumatic brain injury (TBI) is associated with heightened fibrinolysis and this exacerbates intracranial haemorrhage and may exacerbate coagulopathy in patients with concurrent systemic injury.[63,64] The impact of older age on the coagulopathy of TBI has not been fully explored although one report suggested fibrinolysis may be higher in the older population.[65]

Summary

In summary, there is a suggestion that in patients with significant bleeding, fibrinogen may be higher in older trauma patients compared with younger patients. Other standard clotting parameters do not appear to demonstrate differences across age. However, it is difficult to draw firm conclusions from the relatively low numbers of patients. A broader assessment of coagulation and fibrinolysis is needed to examine the impact of age on bleeding and coagulopathy.

1.5 Transfusion management of bleeding

Deaths from uncontrolled bleeding frequently occur early with as many as 6 in 10 occurring within 3 hours.[12,19] Prompt recognition and effective treatment is the 'cornerstone' of modern trauma management and key to preventing further bleeding, coagulopathy and mortality.[66] This starts with initial assessment to determine the extent of trauma haemorrhage using a combination of patient physiology, anatomical injury pattern, mechanism of injury and the patient response to initial resuscitation.[27]

An improved understanding of the mechanisms that drive ATC has led to more focused resuscitation strategies to target the coagulopathy. Instead of large volumes of fluid resuscitation that can cause dilution of clotting factors and potentiate coagulopathy, there is now emphasis on early balanced transfusion therapy to mitigate coagulopathy (haemostatic resuscitation). Ideally, this commences as early as possible from time of injury and not just after hospital admission where the patient may already have developed significant coagulopathy and blood loss. This paradigm shift in practice has also brought about changes in pre-hospital care, where RBCs and fresh frozen plasma (FFP) are now carried on board by pre-hospital teams. This is accompanied by early

administration of the antifibrinolytic agent tranexamic acid (TXA), which has been shown to reduce mortality in patients with traumatic bleeding.[27,67]

After hospital arrival, blood components are then often delivered empirically in packs in proportions that approach the composition of whole blood, as part of a major haemorrhage protocol (MHP).[68] Laboratory and bedside tests of coagulation and haematological parameters guide the administration of on-going blood component therapy. The recommended targets are for haemoglobin >70-90 g/L, platelets >50 x 10^9/L (>100 x 10^9/L in TBI), APTT/PT 1.5 x normal and fibrinogen >1.5 g/L.[27] The MHP is activated if blood is transfused pre-hospital or on suspicion of active bleeding and/or haemorrhagic shock.

The goals of a MHP are to improve haemostasis, practical aspects of communication between members of the clinical team and transfusion laboratory, and patient outcomes through the timely and consistent delivery of blood components to the bedside. MHPs have been shown to improve mortality.[19,69,70]

Transfusion strategies of current MHPs are based on data from randomised and observational studies, but in general these studies have recruited mainly younger patients with trauma (mainly in the fourth-fifth decade) and older patients are not well represented.[12,71] The optimal transfusion strategy is uncertain and it is not known how appropriate or effective these strategies are for an ageing, older population in whom the signs of major bleeding may be masked.

1.5.1 The need for an age-adapted major haemorrhage protocol

There are limited data to guide the development of age-adapted major haemorrhage protocols in trauma. As described in earlier sections, triage criteria for activation of the MHP and the transfusion strategy used need to take into account the changes in vital signs. The older person may have a different haemodynamic response to bleeding than the younger adult patient. Patients with a higher baseline blood pressure, even with significant blood loss, hemodynamic instability may be slower to develop.[72] In addition, compensatory tachycardia may not occur. For these reasons, the traditional parameters for activation of the MHP may not be entirely valid for older people.[73]

This concept is supported by the results of a study in major trauma triage where substituting a systolic blood pressure (SBP) of less than 110 mmHg criterion for the current SBP of less than 90 mmHg criterion improved triage performance in older patients.[55] Older patients triaged under the new criteria had a risk of mortality similar to those under the current SBP criterion.[55]

1.5.2 Prediction of bleeding

A core principle of acute trauma care is the early identification of patients at risk of haemorrhagic shock to provide timely delivery of blood components and direct interventions to resuscitate and achieve haemostasis.[74] Early interventions can reduce the potentially devastating consequences of uncontrolled bleeding. But it can be challenging to identify the patient at risk of significant bleeding; this has led to the development of prediction models to help identify these patients. The choice of outcome variable to be used for these modelling studies is challenging due to the difficulty in identifying patients at risk of bleeding within trauma datasets, and often

results in the use of a surrogate marker of bleeding.[74] The most commonly studied surrogate is massive transfusion, defined as ≥10 units of RBC in 24 hours and roughly equivalent to replacement of a patient's blood volume within a 24-hour period.[75]

Several prediction scores have been developed for massive transfusion, which only takes the need for red cell transfusion up to 24 hours into consideration (Table 1.2). The majority of these scores, including the Trauma Associated Severe Haemorrhage (TASH) Score, and the Assessment of Blood Consumption (ABC) Score were developed prior to the modern era of balanced transfusion resuscitation (not solely RBC), were derived from a mainly younger age group and do not include age as a predictor.[76]

Table 1.2. Comparison of variables used in the most well-known prediction scores for massive transfusion

Modified from Burman et al.[77]

Variable	ABC score[78]	TASH score[79]	Schreiber et al.[80]	McLaughlin et al.[81]	ETS[82]	PWH[83]
Age					X	
Penetrating mechanism	X		X			
Tachycardia	X	X				X
Hypotension	X	X			X	X
(+) FAST examination	X	X				X
pH value				X		
Base deficit		X				X
PT/INR						
Haemoglobin/haematocrit		X	X	X		X
Pelvic fracture		X			X	X
GCS						X

FAST, focused assessment with sonography for trauma; PT, prothrombin time; INR, international normalised ratio; GCS, Glasgow coma scale.

Vital signs feature in the majority of these scores. But as older trauma patients may present with normal vital signs because of physiological differences compared with younger patients the validity of these scores for older people has been questioned.[84] Ohmori et al showed that the ABC, TASH and PWH scores were all less accurate in older

patients than in younger patients.[84] They also explored alternative risk factors for older people and found anatomical factors (unstable pelvic or limb injuries) and pre-injury anticoagulation/antiplatelet therapy and raised lactate were important factors in predicting the need for massive transfusion.[84]

Besides this study, there is little known about risk factors for major bleeding and the impact of age. One study suggested age was not a predictor of mortality after massive transfusion protocol activation but was limited by small numbers of participants (52 younger (under 65) and 14 older.[85]

Since the development of these models, trauma haemorrhage management has evolved markedly over the past 10-20 years with a current emphasis on early balanced transfusion and early interventions to stop the source of bleeding. Given these changes in practice, massive transfusion as a definition for major bleeding or as an endpoint in prediction models may be less clinically relevant today. This has led to a number of alternative definitions of major bleeding, which take this into account and also address some of the concerns with the risk of survivorship bias in the traditional definition, as many deaths from trauma occur in the first few hours after injury before the transfusion threshold was met.[12,86] (Survivorship bias would occur if a patient had substantial bleeding but died early before they reached their 10th unit of blood and was excluded from analysis).

1.6 Definitions of major bleeding

It is difficult to measure actual blood loss in trauma. Alternative definitions also use transfusion as a proxy for bleeding. In addition, they also consider the intensity and timing of transfusion of RBCs (and/or other intravenous fluids). Using these different

metrics better accounts for the earlier use of blood components and fluids that may be used during trauma resuscitation.[87] These include critical administration threshold,[88] resuscitation intensity,[89] critical bleeding,[90] and more recently the need for 4 units of RBC within 4 hours of admission.[91]

Others have proposed the need for composite definitions of major bleeding to include transfusion requirements, surgical/radiological intervention and death from bleeding.[74] Prediction models have also been developed for the pre-hospital setting, which can be applied at the scene and early on in the resuscitation pathway where it is thought they could have more of an impact.[92] This field is an area of active research, but there does not appear to be overall consensus on a definition for major bleeding in trauma.

Notwithstanding these research definitions, more pragmatic definitions of major bleeding are needed clinically in order to activate the MHP and these are usually based on presence of active bleeding, vital signs and/or rate of blood loss. The choice of definition also has implications for clinical trials in trauma haemorrhage, to define which patients are eligible for trial enrolment. Further studies are needed to work through some of these complexities and develop better agreement among the trauma community.

1.7 Trauma pathways

In this final section, I will describe the configuration of the trauma system and how the national system operates in England and Wales to deliver care for the injured patient. The national trauma system underwent substantial re-configuration in 2012 and is now divided into regional trauma networks (but still operates under national oversight). Centralised care for complex patients is provided by Major Trauma Centres (MTCs) with

specialist services for bleeding and surgery. The regional MTC forms a network with links to local trauma units. All trauma patients are triaged and those meeting the triage criteria for major trauma are taken to an MTC (Figure 1.3).

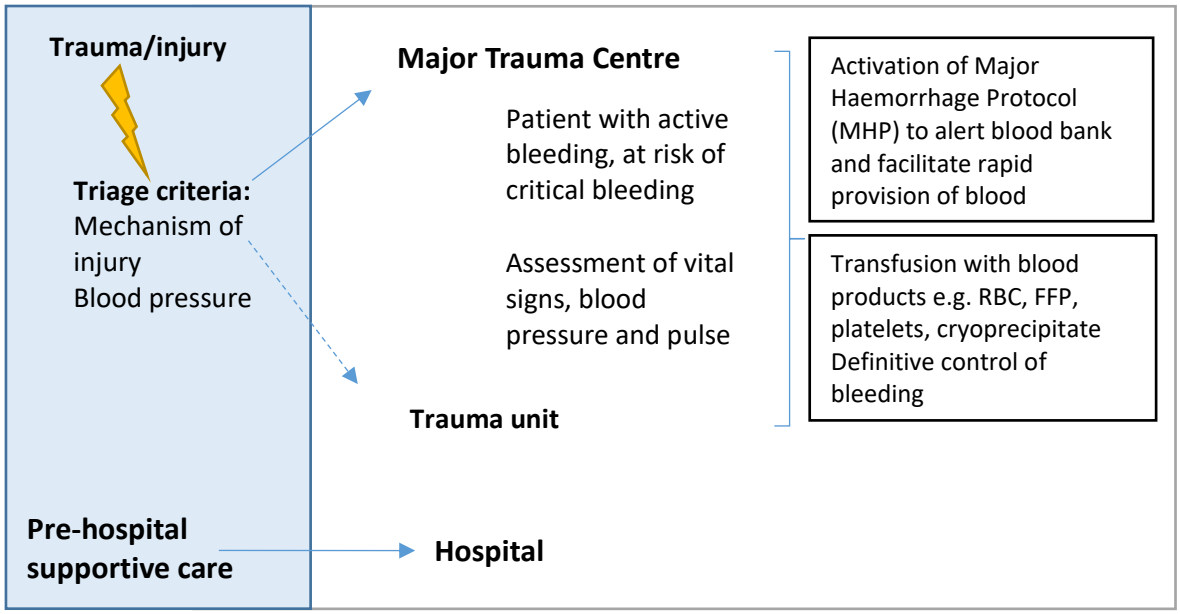


Figure 1.3. Trauma pathways and management of major bleeding in the UK

Patients are triaged at scene for admission to Major Trauma Centre if they meet appropriate criteria. Pre-hospital supportive care includes transfusion of blood products e.g. red cells (RBC) and/or fresh frozen plasma (FFP).

The advantages of a national trauma system have facilitated consistency of practice, organisation of services, audit through the national trauma audit research network (TARN) and implementation of national guidance. More recently, all major trauma centres have participated in a trauma haemorrhage RCT (CRYOSTAT-2), to evaluate the effectiveness of cryoprecipitate in major bleeding.[93] This represents a ground breaking step in collaborative research and the potential of a national clinical trial in trauma, especially for trauma haemorrhage where multi-centre participation is needed so that adequately powered trials can be performed.

Research needs

As data on all major trauma presentations to an MTC is captured, recent analyses have demonstrated that trauma in the older population is the fastest growing population affected by trauma.[3,4] A similar trend has been observed in other countries. The specific needs of an older and ageing trauma population have been recognised by a coalition for geriatric trauma, calling for research into this area.[2] Particularly for major bleeding, there is uncertainty about how ageing affects the clinical presentation and response to trauma-related bleeding and effectiveness of management in older patient groups. This may have implications on triage and MHPs in older people, who have altered physiological reserve and comorbidities to younger people, and may benefit from age-adapted protocols.

1.8 Summary

Uncontrolled bleeding in trauma is the leading cause of potentially preventable death from injury. Current practice for the identification and management of bleeding is based on studies where the majority of patients were in their younger years and few older people were included. However, the trauma population is ageing and the over 65s are the fastest growing group of patients suffering from injury in the UK. Ageing-related changes in haemostasis, physiological function, reserve and comorbidities can affect the signs of bleeding and question the effectiveness and safety of current management strategies for an older population.

Over the past two decades trauma haemorrhage management has changed almost beyond recognition through improved understanding of coagulopathy and the principles of damage control resuscitation. It is vital to continue improvements and address the

gaps in our knowledge as we consider the vulnerabilities and needs of an ageing trauma population.

1.9 Aims of this thesis

The overarching aim of this thesis is to investigate the impact of age on risk factors for major bleeding and coagulopathy in trauma, and to examine the evidence-base for transfusion strategies.

Specific aims

To investigate the impact of age on:

1) Transfusion management of trauma-related acute haemorrhage

2) Predictors of major bleeding in trauma

3) The laboratory profile of coagulation and coagulopathy in trauma.

Research questions and outline of proposed investigation

1. What is the evidence base for the use of blood for the acute management of trauma-related bleeding across age in trauma?

    - *Chapter 2: Systematic review of use of blood components in trauma haemorrhage*

2. Is there a consensus definition of major bleeding in trauma, and if not can a definition be developed?

    - *Chapter 3: Delphi study on a consensus definition for major bleeding in trauma*

3. What are the clinical characteristics of patients with major bleeding and do they vary with age?

    - *Chapter 4: Description of patients with major bleeding in TARN (Trauma Audit Research Network), the UK trauma database*

4. Which factors are associated with major bleeding and what is the impact of age on these factors?

    - *Chapter 5: Modelling risk factors associated with major bleeding in TARN*

    - *Chapter 6: Exploration and handling of missing data in modelling of risk factors for bleeding in TARN*

5. What is the haematological and coagulation profile of patients with major bleeding in trauma and does the profile differ across age groups?

    - *Chapter 7: Description and modelling of laboratory profile of adults with trauma and major bleeding in the ACIT (Activation of Coagulation and Inflammation in Trauma) study.*

Chapter 2 Systematic review of use of blood components for major bleeding in trauma

2.1 Introduction

After injury, derangements in blood clotting (acute traumatic coagulopathy (ATC) increase propensity to bleeding.[94]

2.2 Diagnosis of coagulopathy

ATC may be diagnosed by prolonged laboratory coagulation tests, such as prothrombin time (PT), international normalised ratio (INR), or activated partial thromboplastin time (APTT). Consensus on the laboratory definition of ATC is lacking; two different ranges are commonly used within the research and clinical literature: a PTr/INR ratio of ≥1.2,[13] and a PTr/INR ratio ≥1.5.[95] Viscoelastic haemostatic assays are alternative measures of haemostasis. Using rotational thromboelastometry (ROTEM), ATC has been defined as a reduction in clot strength (amplitude) at five minutes (A5 ≤40 mm).[96]

2.2.1 Management of coagulopathy and bleeding in trauma

The main goals of management of the bleeding patient are to (1) identify and stop on-going bleeding, and (2) support the circulation and oxygen delivery to tissues, by resuscitating the patient and optimising haemostasis by correcting coagulopathy.

Acute trauma resuscitation has shifted away from fluid-based resuscitation to one based on balanced blood component replacement. Many trauma services now have the capability to transfuse blood components in the pre-hospital phase.[40] Current approaches to resuscitation specify early delivery of blood components without waiting

for clotting results (empiric transfusion).[27] To facilitate empiric transfusion, hospitals use a major haemorrhage protocol (MHP), where a fixed ratio of blood components is delivered to the bedside in a 'major haemorrhage pack'. Further administration of individual components is guided by conventional hospital laboratory clotting tests or viscoelastic haemostatic assays. As part of the MHP, early tranexamic acid (TXA) (anti-fibrinolytic agent) is also recommended for patients with traumatic haemorrhage.[27,97,98]

Despite recent advances in the understanding of coagulopathy and the role of blood components to mitigate coagulopathy, it is uncertain how best to transfuse in trauma. Current guidelines recommend an FFP:RBC transfusion ratio of at least 1:2.[27] Despite this, questions remain over which ratios of red blood cells (RBCs) and fresh frozen plasma (FFP) to use, other types of blood components, laboratory or point of care guided transfusion and which haemoglobin or coagulation targets to aim for.

Some studies have explored more balanced FFP and RBC ratios and advocate a 1:1 ratio.[27,71] Furthermore, some advocate early platelet transfusion, as there is evidence of early platelet dysfunction in major trauma.[25,26] Other studies have tested early replacement of fibrinogen with cryoprecipitate and fibrinogen concentrate, as fibrinogen is the first clotting factor to decrease to critically low levels in major bleeding.[99,100]

In the acute setting, early intervention to control bleeding is critical. Logistical issues, such as blood product storage or shelf-life may hinder timely administration of blood products. These issues could be overcome by the use of lyophilised plasma and platelet products. Advantages of lyophilised products include a stable shelf-life, ease of use and storage, and a low volume for administration.

Alternatives to individual component transfusion such as whole blood have also been explored, as it has been shown that the use of individual blood components may not be optimally haemostatic.[101] Other transfusion strategies favour point-of-care haemostatic testing to guide component therapy rather than on conventional laboratory tests which take longer to process.

2.2.2 Risks associated with blood transfusion

Administration of blood components is not without risk. Achieving more balanced FFP:RBC ratios and upfront platelet transfusion risk adverse effects of administering higher volumes of FFP and platelet products.[102] Risks of high volume transfusion include fluid overload, multi-organ failure, sepsis, thrombosis and acute respiratory distress syndrome.[102]

2.2.3 Rationale for review

In summary, over recent years, our understanding of clotting derangements in ATC has led to therapeutic interventions to promote haemostasis and reduce bleeding. Studies evaluating the use of blood components have followed on from this, but despite the growing number of randomised trials, there is currently no consensus on the optimal use of blood components in the acute management of bleeding in trauma.

2.3 Aims

The main aim of this systematic review was to collate and appraise the evidence for the effect and safety of blood components in this setting. My secondary aim was to assess the evidence for different age groups e.g. older population vs younger population, as physiology and coagulation alter with age and to determine if there were any gaps in our understanding of the effectiveness of transfusion intervention across age.

2.4 Methods

I undertook a systematic review in accordance with Cochrane guidance, as it uses clearly-defined, systematic methods that minimise bias in the review process, thereby improving the reliability of findings and their interpretation.[103] To minimise bias, ensure transparency of reporting and reproducibility, I published a protocol a priori, which outlined the scope and methods of the search and analysis review.[104]

2.4.1 Eligibility criteria for considering studies for this review

2.4.1.1 *Types of studies*

Any type of randomised controlled trial (RCT) that was related to the early blood component management of haemorrhage (within the first 24 hours of injury) was considered. Only trials that were prospectively registered were included, unless the final report was published before 2010.

2.4.1.2 *Types of participants*

Adults and children (with no age restriction) with major bleeding in trauma were eligible for inclusion. Patients with major bleeding were defined as those with any of the following: had active bleeding and shock, required activation of the major haemorrhage protocol, predicted to bleed using a scoring system for haemorrhage in trauma, or as otherwise described by the study authors. Trials that assessed isolated burns injuries were excluded, due to the different mechanism of injury.

2.4.1.3 *Types of interventions*

Interventions examined different ways of using blood components (transfusion strategies). Each transfusion strategy needed to include at least one of the following

blood components: RBC, FFP, cryoprecipitate, whole blood, platelets, lyophilised or liquid plasma, or lyophilised platelets, and not contain only recombinant or plasma derived single factor, or multiple coagulation factor concentrates, such as fibrinogen concentrate, prothrombin complex concentrate, and recombinant FVIIa, since these interventions are covered in another review.[105]

I considered all trials that compared two transfusion strategies, including the following examples:

- Different ratios of blood products e.g. a transfusion strategy with fresh frozen plasma (FFP), platelets, and red blood cells in a 1:1:1 unit ratio compared to FFP, platelets, and red blood cells in a 1:1:2 ratio.
- Whole blood versus individual blood components
- Goal-directed strategy (viscoelastic haemostatic assay versus conventional laboratory clotting test-guided transfusion).

2.4.1.4 *Types of comparators*

- Placebo, another blood component (as defined in the trial or standard practice as defined in the trial).

I considered all trials, including placebo-controlled trials, where the comparator was a non-blood component (e.g. fluid resuscitation). An example of a placebo-controlled trial might be one that evaluated blood products that are not the current standard, e.g. early cryoprecipitate with empirical transfusion versus saline placebo and empirical transfusion. However, it was recognised that placebo-controlled trials could be challenging for studies of blood components.

2.4.2 Types of outcome measures

I chose the following outcomes based on their clinical relevance, as there is no core outcome set for trauma haemorrhage trials.

2.4.2.1 *Primary outcomes*

- All-cause mortality at 24 hours;
- All-cause mortality at 30 days.

2.4.2.2 *Secondary outcomes*

- Mortality due to haemorrhage within 24 hours.
- Time-to-anatomical haemostasis, as described in the study.
- Total thromboembolic events (arterial and venous) in the first 30 days after injury.
- Transfusion requirements (number of units or volume of red cells, FFP, cryoprecipitate, and platelets) in the first 24 hours.
- Degree of coagulopathy (defined as maximal change in prothrombin time or INR between baseline and post intervention). Post intervention was defined as up to one hour after the final blood product transfusion.
- Requirement for surgery or interventional procedure to control bleeding in the first 24 hours after injury.
- Length of stay in intensive care (ICU-free days).

2.4.3 Search strategy for the identification of studies

Full details of the search are described Appendix 1. I developed a comprehensive search at the protocol stage so as to try and capture 100% of eligible studies and ensure

completeness and validity of results. I devised the review search strategy with Dr Carolyn Doree (an experienced information specialist) who conducted the search. I also included other members of the review group, who included three subject experts and a methodologist.

The following databases were searched for RCTs:

- CENTRAL, *The Cochrane Library* (2019, issue 5)
- MEDLINE (OvidSP, 1946 onwards to 29 May 2019)
- Embase (OvidSP, 1974 onwards 29 May 2019)
- PubMed (epublications only to 29 May 2019)
- Transfusion Evidence Library (1950 onwards to 29 May 2019)
- Web of Science Conference Proceedings Citation Index – Science (CPCI-S, 1990 to 29 May 2019)

The following trial registries were searched for RCTs:

- ClinicalTrials.gov
- WHO International Clinical Trials Registry Platform (ICTRP)

The searches in MEDLINE and Embase were combined with adaptations of RCT filters as suggested in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions*.[106] Searches were not limited by language, year of publication, or publication type, to minimise loss of any eligible studies from publication bias and language bias. The final search was conducted on 29 May 2019.

2.4.3.1 *Searching other resources*

The reference lists of included studies were hand-searched to identify further relevant studies, and I contacted the lead authors of the included studies to identify any unpublished material or missing data.

2.4.4 Data collection and analysis

I uploaded all search results identified by the search strategy electronically into Covidence, an online systematic review platform (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org) for screening and analysis.

2.4.4.1 *Selection of studies*

I screened the citation and abstracts in duplicate with three other reviewers (Dr Nicola Curry, Dr Mike Desborough and Professor Simon Stanworth) to ensure consensus. Studies were excluded at this stage if they were clearly not within the remit of the review. For potentially relevant studies, full-text papers were reviewed in duplicate to determine their eligibility for inclusion in the review. Any disagreements were resolved by discussion between the reviewers. Reasons for study exclusion were recorded.

2.4.4.2 *Data extraction*

A data extraction form was piloted in Covidence. All extraction was performed independently by two reviewers (myself and Dr Desborough). The aim of duplicate data abstraction was to minimise errors and to ensure transparency reliability and validity.[107] Any disagreements were resolved by discussion between the reviewers. For two of the included trials, the authors responded to a request for unpublished outcome data relevant to the review outcomes.

The following data were abstracted:

- Trial details (trial design, setting, number of centres, recruitment dates, aim of study, length of follow-up, funding source)
- Participants (number of participants randomised, age, gender, mechanism of injury (blunt or penetrating), Injury Severity Score (ISS), anticoagulant/antiplatelet use, inclusion/exclusion criteria
- Definition of major bleeding (as defined by the study)
- Definition of coagulopathy (as defined by the study)
- Interventions (dose, route of administration and timing and co-intervention with TXA)
- Comparators (dose, route of administration and timing)
- Outcomes (mortality at 30 days and 24 hours, 24-hour mortality due to bleeding, time to haemostasis, thromboembolic events (arterial, venous and combined), RBC-, FFP-, platelet-, cryoprecipitate-, total blood component transfusion at 24 hours, change in coagulopathy, requirement for surgery or interventional procedure to control bleeding in the first 24 hours after injury ICU-free days).

2.4.5 Risk of bias assessment and grading the quality of evidence

Some features of the design, conduct and analysis of randomised studies can lead to bias, and some results are not disseminated because due to reporting bias. However, it is difficult to establish the extent to which biases have affected the results of a particular study or analysis.[108] For these reasons, assessment of whether a study is at risk of bias is an important part of grading overall quality of the evidence, as bias can compromise the confidence in results.

Bias may occur at the study level across several domains. The Cochrane risk of bias tool has been designed to assess a fixed set of domains of bias, focusing on different aspects of trial design, conduct and reporting:[108,109]

Selection bias

- Appropriate randomisation to prevent bias in selectively allocating interventions to participants. A method for allocating interventions should be specified and based on a random process. This incorporates both random sequence generation and allocation concealment.

Performance bias

- This refers to systematic differences between groups in the care that is received other than the intervention of interest. Blinding of participants and personnel may reduce the risk that it is the knowledge of which intervention was received, rather than the intervention itself, which affects outcomes. Non-blinding may also affect ancillary care, which may lead to 'catch-up' transfusion, which may be particularly relevant in transfusion trials.

Detection bias

- Blinding of the outcome assessor can reduce the risk that it is the knowledge of which intervention was received, rather than the intervention itself, which affects the measurement of the outcome. This may be particularly affected by outcomes where there may be more of a subjective element.

Attrition bias

- Systematic differences between groups in withdrawals from a study leads to incomplete outcome data. Intention to treat analysis can minimise this risk.

Reporting bias

- Results in analyses with statistically significant differences between intervention groups are more likely to be reported than non-significant differences resulting in selective reporting.

Other bias

- This may stem from a number of causes including imbalanced baseline characteristics or post hoc subgroup reporting.

Two independent reviewers (myself and another reviewer (MD)) assessed the risk of bias at the study level using the Cochrane risk of bias tool across the following domains:[108]

- Selection bias
- Performance bias
- Detection bias
- Attrition bias
- Reporting bias
- Other bias

Support for each judgement was recorded in Covidence.

I did not assess publication bias or small-study bias using funnel plots, as I did not perform any meta-analysis and there were fewer than 10 studies in any one outcome analysis.[110]

'Risk of bias' domains were assessed for the main outcomes, and where data allowed, for the secondary outcomes.

Individual studies were categorised as being at low, high, or unclear overall risk of bias according to the following:

- low risk of bias - all domains were at low risk of bias (plausible bias unlikely to seriously alter the results);
- unclear risk of bias - one or more domains had an unclear risk of bias (plausible bias that raises some doubt about the results); or
- high risk of bias - one or more domains were at high risk of bias (plausible bias that seriously weakens confidence in the results).

I anticipated that knowledge of the allocated intervention could be difficult to blind from clinicians and participants. However, it should be possible to blind knowledge of the allocated intervention from outcome assessors.

2.4.6 Measures of treatment effect

I calculated risk ratios (RR) for dichotomous data outcomes with 95% confidence intervals (CI). Where the number of observed events was small (less than 5% of sample per group), and where trials had balanced treatment groups, the Peto odds ratio (OR)

with 95% CI was reported.[111] Treatment effects for continuous data outcomes were planned to be reported as mean differences (MD) with 95% CI.

2.4.7 Data synthesis and analysis

2.4.7.1 *Assessment of heterogeneity and data analysis*

Analysis of the data was performed according to the guidance in chapter 9 of the Cochrane handbook for systematic reviews of interventions. I had planned to use a random-effects quantitative meta-analysis for clinically homogenous studies. But due to the heterogeneity of study populations, co-interventions and interventions, no meta-analysis was feasible and I analysed the studies narratively.[112]

It was apparent that the studies covered a broad range of interventions, and I categorised studies into groups (pre-hospital/in-hospital intervention and whether the intervention was trial-defined or standard of care) to enable similar trial comparisons. I conducted a narrative synthesis. This included simple vote counting and tabulating results to identify patterns within and across included trials to evaluate whether the treatment effect was consistent across all studies and to assess the reliability of the evidence.[112]

For the purposes of analysis, I grouped the studies into four groups, according to the study arms and setting of the intervention:

- Trial-defined intervention vs standard of care (pre-hospital)
- Trial-defined intervention vs standard of care (in-hospital)
- Trial-defined intervention vs trial-defined intervention (in-hospital)
- Viscoelastic haemostatic assay (VHA) vs conventional laboratory testing (in-hospital)

I had planned a number of sub-group analyses in the protocol:[104]

1. Children versus adults for patients treated with the same protocol (since different definitions of coagulopathy apply).
2. Studies of older adults (over 65 years of age) compared with younger adults, since older patients are more likely to have co-morbidities, such as cardiovascular disease or differences in coagulopathy that may affect the efficacy of transfusion interventions.
3. Studies of patients with traumatic brain injury, as brain injury alters coagulopathy, and the possible differences in efficacy of interventions in this group.

However, it was not possible to perform sub-group analyses, as individual patient data were not available for the studies included, and there were no published studies in children.

2.4.7.2 *Summary of findings*

I summarised the following five outcomes I considered to be most clinically important in a summary of findings table:

- All-cause mortality at 24 hours
- All-cause mortality at 30 days
- Time-to-anatomical haemostasis
- Transfusion requirements – total number of red cell units during first 24 hours
- Total thromboembolic events in the first 30 days.

I assessed the overall quality and certainty of the evidence at the outcome level for these five main outcomes using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and GRADEpro GDT software, as suggested in Chapters 11 and 12 of the Cochrane Handbook for Systematic Reviews of Interventions.[113–115] The following five GRADE domains were assessed:

- Risk of bias
- Inconsistency
- Indirectness
- Imprecision
- Publication bias

The quality of the evidence was assessed according to GRADE recommendations[116] and final assessments were agreed with another reviewer (Dr Desborough):

Grade	**Definition**
High	I am very confident that the true effect lies close to that of the estimate of the effect.
Moderate	I am moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	My confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	I have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

2.5 Results

2.5.1 Search results

Of 10,977 citations, 10,911 were excluded. Sixty-six full-text references were reviewed; ten completed trials were included and 13 on-going clinical trials were identified. A PRISMA flow chart illustrates the selection process (Figure 2.1).

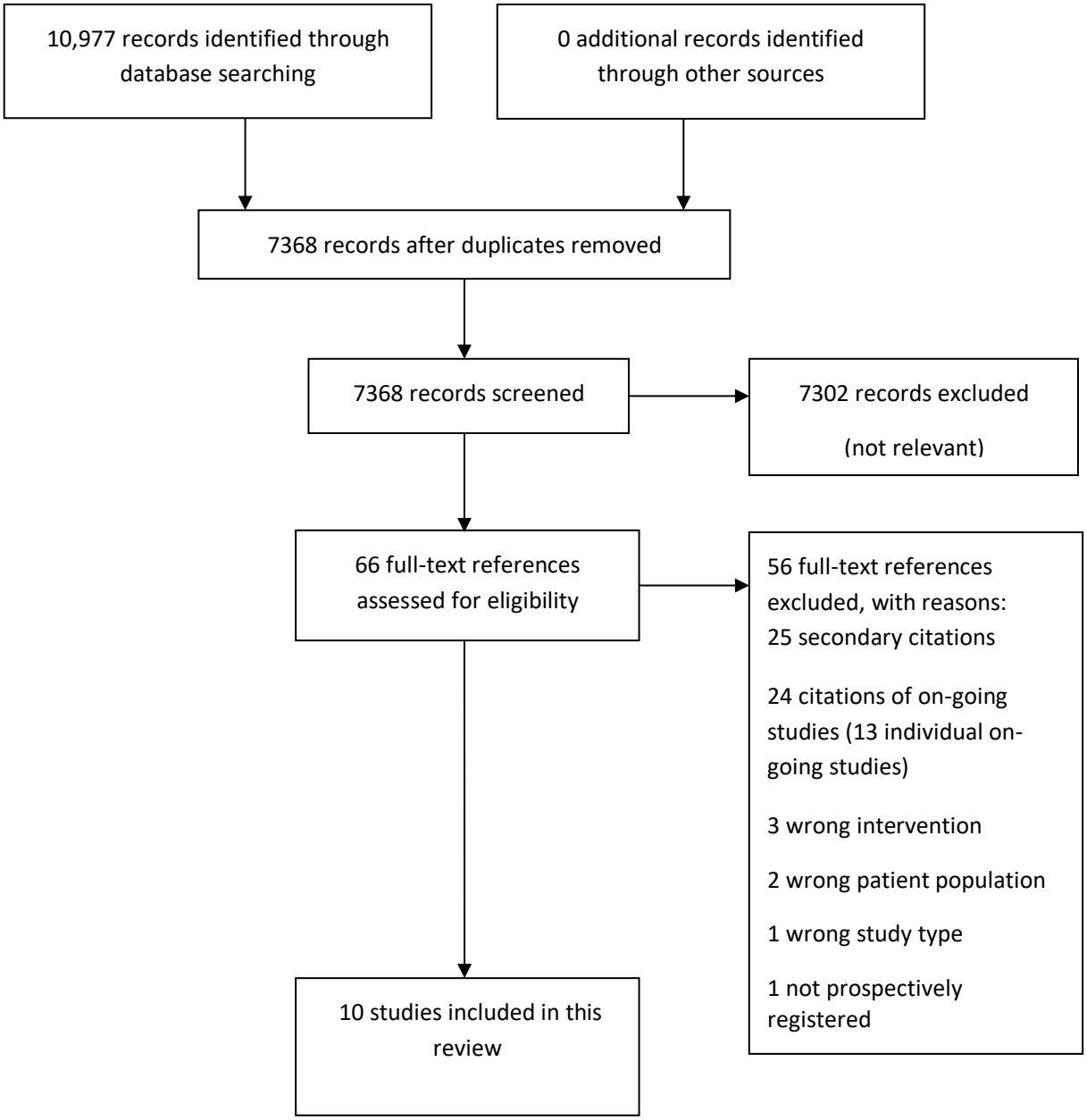


Figure 2.1. PRISMA flow diagram

2.5.2 Trial characteristics

The characteristics of the ten eligible studies are presented in Table 2.1. One study (published in 1986) was blinded to both participants and personnel and met the inclusion criteria but data were not available for any outcomes of interest in this review.[117] The other nine studies were open-label. There was one cluster-randomised trial[118] and two of the studies were feasibility studies.[99,119]

2.5.2.1 *Setting*

Of the ten included RCTs, there were two pre-hospital studies and eight in-hospital studies. Seven out of ten studies were single-centre studies[117,119–124] and three were multi-centre studies.[71,99,118] All studies were conducted in high-income countries in one or more major trauma centre(s) (Level 1 Trauma Centre equivalent).

2.5.2.2 *Participants*

A total of 1982 patients were randomised. Four studies included less than 100 people and the largest study was the PROPPR trial which included 680 participants.[71] Participants on average were aged in their 30s or 40s. Detailed descriptions of the trial characteristics are presented in Appendix 2 and a summary in Table 2.1. Overall, over 60% of trial participants were male, and the predominant mechanism of injury was blunt trauma. Trials did not evaluate specific age groups.

Table 2.1. Summary of included studies

Study	Arms	n	Age (median, IQR)	Tranexamic acid use %	Primary outcome(s)
Trial-defined intervention vs standard of care: pre-hospital					
Moore 2018 [124] **[USA]**	Pre-hospital plasma 2 units	65	33 (25 to 51)	6 (9%)	28-day mortality
	Standard of care resuscitation (saline)	60	32.5 (25.5 to 42)	8 (13%)	
Sperry 2018 [118] **[USA]**	Pre-hospital plasma 2 units	230	46 (28 to 60)	NR	30-day mortality
	Standard of care resuscitation	271	44 (31 to 59)	NR	
Trial-defined intervention vs standard of care: in-hospital					
Curry 2015 [99] **[UK]**	Early cryoprecipitate	20	31 (25 to 57)	20 (100%)	Feasibility
	Standard of care (MHP)	21	50 (29 to 59)	19 (95%)†	
Nascimento 2013 [119] **[Canada]**	Formula (1:1:1)	37	41 (23 to 58)	5 (13.5%)	Feasibility
	Laboratory guided standard of care (MHP)	32	34 (25 to 40)	6 (18.7%)	
Nathens 2006 [123] **[USA]**	Leucoreduced RBC	132	42.3 (19)^	NR	Infection within 28 days of randomisation
	Standard RBC	136	42.1 (18)^	NR	

Study	Arms	n	Age (median, IQR)	Tranexamic acid use %	Primary outcome(s)
Trial-defined intervention vs trial-defined intervention: in-hospital					
Cotton 2013 [121]	Modified whole blood	55	40 (29 to 56)	NR	24-hour blood product use
[USA]	Components	52	38 (25 to 56)	NR	
Garrigue 2018 [120]	French lyophilised plasma 4 units (+4 RBC)	23	48 (16.5)^	19 (82.6%)	Fibrinogen concentration at 45 minutes after randomisation
[France]	4 FFP (+4 RBC)	24	38 (15.6) ^	22 (91.7%)	
Holcomb 2015 [71]	1 FFP: 1 platelet: 1 RBC	338	34.5 (25 to 51)	64 (18.9%)	24-hour and 30-day mortality
[USA]	1 FFP: 1 platelet: 2 RBC	342	34 (24 to 50)	68 (19.9%)	
Reed 1986 [117]	Platelets	17	58 (19)^	NR	Unclear
[USA]	FFP	16	43 (22)^	NR	
VHA vs conventional laboratory testing (in-hospital)					
Gonzalez 2015 [122]	Transfusion guided by TEG	56	41 (28 to 54)	4 (7.1%)	28-day survival
[USA]	Transfusion guided by conventional lab tests	55	38 (25 to 53)	9 (16.4%)	

^ mean, SD. † missing for one patient. NR, not reported.

2.5.2.3 *Interventions and comparators*

The type of interventions differed across the trials. These included testing a blood component, ratio of components, VHA vs laboratory testing. Comparators and standard of care were not uniform.

Trial-defined intervention vs standard of care (pre-hospital) (n=2)

Setting

Two studies assessed the use of blood in a pre-hospital setting (both conducted in the USA). One study administered the intervention using ground transportation to a single centre and the other cluster randomised from 27 air medical bases to one of 9 major trauma centres.[118] The average transport time to hospital was 22 minutes in the ground transportation trial and 44 minutes in the air transport trial.

Population

The median age of participants was in the 30s for the ground transport trial and 40s for the air transport trial. The other baseline characteristics (injury severity, gender, mechanism of injury) were similar for both studies.

Intervention

Both studies assessed the effect of two units of thawed fresh frozen plasma. In the air transport trial, the plasma was given before any other resuscitative fluid, whereas this was not stipulated in the ground transport trial. The time to intervention was 20 minutes from injury in the ground transport trial and not reported in the air transport trial.

Comparator

The standard of care was different. In the ground transport trial, standard care comprised 0.9% saline only and no other blood components were available for pre-hospital transfusion. However, in the air transport trial, standard care was with crystalloid (+/- red cells).

Co-intervention

TXA use was 9-13% in the ground transport study and was not reported in the air transport study.

Trial-defined intervention vs standard of care (in-hospital) (n=3)

Setting

Out of the three studies, two were single-centre studies. There were two feasibility studies. Trials were conducted in the UK, Canada and US.

Population

The baseline injury severity, age and gender characteristics were similar across all three studies.

Intervention

The three studies evaluated different interventions (two pools of cryoprecipitate in addition to the standard MHP; 1:1:1 ratio of FFP:Platelet:RBC; leucoreduced RBC) against standard of care.

Comparison

One study compared leucoreduced RBC with standard RBC. In two studies, standard of care was defined as the MHP (which was specific to each trial).

- In the UK trial, the MHP was based on delivery of an empiric 'MHP pack (6 units RBC) and 4 units fresh frozen plasma (FFP)). TXA (1 g IV bolus, followed by 1 g 8-hour infusion) was part of the MHP protocol. If haemorrhage continued after completion of MHP pack 1, MHP pack 2 was transfused (6 units RBC, 4 units FFP, 2 pools cryoprecipitate and 1 adult pool of platelets (4 pooled buffy coat platelets or 1 single apheresis unit)). During active bleeding the targets for MHP therapy were: PTr ≤1.5; Clauss fibrinogen ≥1.5 g/L; platelet count >100×10^9/L; haemoglobin 80–100 g/L.
- The Canadian MHP was different to the UK MHP: red cell transfusions were administered to maintain euvolaemia and to maintain haemoglobin levels above 70 g/L. FFP was transfused in 3 units to 4 units aliquots if INR >1.8. Platelets were transfused one pool at a time to maintain the platelet count above 50 x 10^9/L. Cryoprecipitate was transfused 10 units at a time to keep fibrinogen above 1.0g/L.

Co-intervention

Two trials reported concomitant TXA use. Nearly 100% of patients in the UK trial received TXA, compared with less than 20% in the Canadian trial.

Trial-defined intervention vs trial-defined intervention (in-hospital) (n=4)

Setting

One of the studies was a multi-centre trial (USA). The other three studies were single-centre studies (two in the USA and one in France).

Population

The baseline characteristics for age, injury severity and gender were similar across all four trials. For the PROPPR study, the proportion of blunt trauma was lower than the other studies (~45% vs >80%).

Interventions

The interventions compared were different across all four studies:

- Modified whole blood vs blood components
- French lyophilised plasma 4 units (+4 RBC) vs 4 FFP (+4 RBC)
- 1 FFP: 1 platelet: 1 RBC vs 1 FFP: 1 platelet: 2 RBC
- Platelets vs FFP (this trial did not measure any of the outcomes relevant to this review).

Co-intervention

Two trials reported TXA use. A geographical imbalance was again observed where TXA use was lower in the US study (<20%) compared with nearly 100% in the European study.

Viscoelastic haemostatic assay vs conventional laboratory test (n=1)

One trial compared two methods of goal-directed use of blood (VHA vs conventional laboratory testing). This was a single-centre study in the US. The population characteristics for age, injury severity and gender were similar to the included trials for the previous comparisons.

The trial tested the use of TEG. The parameters for TEG-guided therapy are described in Appendix 2.4 (detailed study characteristics for Gonzalez *et al* trial). The comparator was defined as the MHP, in which goal-directed transfusion was guided by conventional coagulation assays (CCA). Upon activation of the MHP the blood bank delivered 4 units of RBCs and 2 units of plasma to the patient's bedside. This occurred regardless of randomisation group, and these were administered according to the treating clinicians' criteria while awaiting results of coagulation tests (CCA or TEG). In the CCA group, the following parameters triggered transfusions: INR ≥1.5 = 2 units of plasma; fibrinogen <1.5 g/L = 10-pack of cryoprecipitate; platelet count <100 x 10^9/L = 1 unit of apheresis platelets. TXA was administered on suspicion of fibrinolysis if D-dimer >0.5 mg/mL.

More patients received TXA co-intervention in the conventional coagulation arm (14%) compared with the VHA arm (7%).

2.5.2.4 *Outcomes*

No single study measured all outcomes of interest for this review. The pre-specified review outcomes included all-cause mortality at 30 days. Two trials measured 28-day mortality as a measure of short-term mortality.[122,124] For this review, 28-day mortality and 30-day mortality were classed as one outcome 'all-cause mortality within 30 days'.

The primary outcomes for each trial are listed in Table 2.1. The primary (and secondary outcomes) were unclear in one study and no outcome data were available for this study.[117] Out of the remaining seven studies, four of the studies measured mortality within 30 days as the primary outcome.

Both studies in the trial-defined intervention vs standard of care (pre-hospital) comparison measured 30-day mortality as the primary outcome. Two studies in the trial-defined intervention vs standard of care (in-hospital) tested feasibility as the primary outcome. However, the primary outcomes in the four studies that compared two trial-defined interventions were all different.

A summary of available trial outcome data against those of interest for the review is shown in Table 2.2. After contacting the authors, additional outcome data for 24-hour mortality and 24-hour mortality due to bleeding were obtained for two trials.[99,119] Intensive care unit (ICU) length of stay was defined as ICU-free days. On request, the study authors for one study that measured days in ICU provided this data as ICU-free days.[99]

Table 2.2. Outcome data available for each trial against outcomes specified for the review

For two studies (grey diagonal shading), the authors provided outcome data upon request (these were not the original trial outcomes). FgC, fibrinogen concentrate (instead of cryoprecipitate). PT, prothrombin time; INR, international normalised ratio; RBC, red blood cells; FFP, fresh frozen plasma; cryo, cryoprecipitate; ICU, intensive care unit; MHP, major haemorrhage protocol.

Study	Intervention and comparator	24 hr-mortality	30-day mortality	24-hour mortality due to haemorrhage	Time to haemostasis	Total thromboembolic events	Arterial thromboembolic events	Venous thrombotic events	Total transfusion in 24 hours	RBC in 24 hours	FFP in 24 hours	Platelet transfusion in 24 hours	Cryo in 24 hours	Change in PT	Change in INR	ICU-free days	Surgery to stop bleeding	Total available outcomes (out of possible 16 outcomes specified in review)
Trial-defined vs standard of care: pre-hospital																		
Moore 2018	Prehospital plasma 2 units vs Standard of care (saline)	✓	✓	×	×	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	×	12
Sperry 2018	Prehospital plasma 2 units vs Standard of	✓	✓	✓	×	×	×	×	✓	✓	✓	✓	×	×	×	×	×	6

Study	Intervention and comparator	24 hr-mortality	30-day mortality	24-hour mortality due to haemorrhage	Time to haemostasis	Total thromboembolic events	Arterial thromboembolic events	Venous thrombotic events	Total transfusion in 24 hours	RBC in 24 hours	FFP in 24 hours	Platelet transfusion in 24 hours	Cryo in 24 hours	Change in PT	Change in INR	ICU-free days	Surgery to stop bleeding	Total available outcomes (out of possible 16 outcomes specified in review)
	care resuscitation																	
Trial-defined intervention vs standard of care: in-hospital																		
Curry 2015	Early cryo vs Standard of care (MHP)	✓	✓	✓	×	✓	✓	✓	×	✓	✓	✓	✓	×	×	✓	×	11
Nascimento 2013	Formula (1:1:1) vs Laboratory guided standard of care (MHP)	✓	✓	✓	×	×	×	✓	×	✓	✓	✓	✓	×	✓	✓	×	10
Nathens 2006	Leucoreduced RBC vs Standard RBC	×	✓	×	×	×	×	×	×	×	×	×	×	×	×	×	×	1

Study	Intervention and comparator	24 hr-mortality	30-day mortality	24-hour mortality due to haemorrhage	Time to haemostasis	Total thromboembolic events	Arterial thromboembolic events	Venous thrombotic events	Total transfusion in 24 hours	RBC in 24 hours	FFP in 24 hours	Platelet transfusion in 24 hours	Cryo in 24 hours	Change in PT	Change in INR	ICU-free days	Surgery to stop bleeding	Total available outcomes (out of possible 16 outcomes specified in review)
Trial-defined intervention vs trial-defined intervention: in-hospital																		
Cotton 2013	Modified whole blood vs Component	✓	✓	×	×	×	✓	×	✓	✓	✓	✓	×	×	×	✓	×	8
Garrigue 2018	French lyophilised plasma 4 units (+4 RBC) vs 4 FFP (+4 RBC)	×	✓	×	×	×	×	×	×	✓	✓	✓	FgC ✓	×	×	×	×	5

Study	Intervention and comparator	24 hr-mortality	30-day mortality	24-hour mortality due to haemorrhage	Time to haemostasis	Total thromboembolic events	Arterial thromboembolic events	Venous thrombotic events	Total transfusion in 24 hours	RBC in 24 hours	FFP in 24 hours	Platelet transfusion in 24 hours	Cryo in 24 hours	Change in PT	Change in INR	ICU-free days	Surgery to stop bleeding	Total available outcomes (out of possible 16 outcomes specified in review)
Holcomb 2015	1 FFP: 1 platelet: 1 RBC vs 1 FFP: 1 platelet: 2 RBC	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	×	×	✓	✓	13
Reed 1986	Platelets vs FFP	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	0

Study	Intervention and comparator	24 hr-mortality	30-day mortality	24-hour mortality due to haemorrhage	Time to haemostasis	Total thromboembolic events	Arterial thromboembolic events	Venous thrombotic events	Total transfusion in 24 hours	RBC in 24 hours	FFP in 24 hours	Platelet transfusion in 24 hours	Cryo in 24 hours	Change in PT	Change in INR	ICU-free days	Surgery to stop bleeding	Total available outcomes (out of possible 16 outcomes specified in review)
VHA vs conventional laboratory testing: in-hospital																		
Gonzalez 2015	Transfusion guided by TEG vs Transfusion guided by conventional lab tests	×	✓	✓	×	✓	×	✓	×	✓	✓	✓	✓	×	×	✓	×	9

2.5.2.5 *Excluded studies*

Four studies were excluded (Table 2.3).

Table 2.3. Excluded studies

Study	Reason for exclusion
Ongoing	
FEISTY NCT02745041	Ineligible intervention: this study compares a factor concentrate (FgC) versus transfusion strategy.
Conventional Versus Point-of-care Based Coagulation Management NCT00997841	Ineligible population: cardiac surgery
Published	
Akbari 2018 [125]	Ineligible study registration: not prospectively registered
Schreiber 2015 [126]	Ineligible population: stable patients

2.5.2.6 *On-going trials*

There are 13 on-going trials. Six trials are comparing VHA with conventional laboratory test-guided transfusion. Two studies are evaluating a trial-defined intervention (cryoprecipitate in-hospital; modified whole blood in the pre-hospital setting) vs standard of care. Of the remaining five studies, two are assessing target haemoglobin thresholds and three are evaluating blood components in the pre-hospital setting. (On-going trials are listed in Appendix 3).

Assessment of heterogeneity

I observed diversity in the nature of the trial interventions. The nature of local practice and co-interventions also varied across studies and this could affect clinical outcomes (Table 2.4). In the two pre-hospital trials the transport time from scene to hospital was noticeably shorter in one study compared to the other (20 mins vs 40 mins). This imbalance could affect the timeliness of procedures to stop bleeding, especially in

trauma, where the initial resuscitation period is critical and delays could affect outcomes. This clinical heterogeneity precluded meta-analysis. Baseline characteristics of the study populations showed variation in the time from injury to hospital and randomisation, which could also impact on outcomes, although these timings were not always reported.

Furthermore, there was inter-trial variation in the use of TXA. For the two European studies,[99,120] TXA use was above 80%. But where reported by the four American/Canadian trials, it was less than 20%.

For the in-hospital trials, there was also a difference in the number of RBC units transfused pre-randomisation across trials. This ranged from zero to two units (Appendix 2:). Overall, I considered that differences in practice and co-intervention could impact on outcomes and clinical heterogeneity was deemed too high for meta-analysis.

Table 2.4. Trial characteristics of time to treatment and transport time

Time to randomisation reported from hospital arrival [71] and from injury.[120] NR, not reported. † one patient had missing data.

Study	Intervention and comparator	Time from injury to intervention (mins)	Time from injury to hospital (mins), median (IQR)	Transport time from scene to hospital (mins), median (IQR)	Time to randomisation (mins), median (IQR)
Trial-defined intervention vs standard of care: pre-hospital					
Moore 2018 [USA]	Pre-hospital plasma 2 units	First plasma unit 24 min (20 to 31) in the plasma group	28 (22 to 34)	19 (16 to 23)	NR
	Standard of care resuscitation (saline)	NR	24 (19 to 31)	16 (14 to 22)	NR
Sperry 2018 [USA]	Pre-hospital plasma 2 units	NR	NR	42 (34 to 53)	NR
	Standard of care resuscitation	NR	NR	40 (33 to 51)	NR
Trial-defined intervention vs standard of care: in-hospital					
Curry 2015 [UK]	Early cryo	NR	95 (76 to 119)	NR	NR
	Standard of care (MHP)	NR	96 (75 to 106)	NR	NR
Nascimento 2013 [Canada]	Formula (1:1:1)	NR	46 (30 to 59)	NR	NR
	Laboratory guided standard of care (MHP)	NR	45 (30 to 67)	NR	NR
Nathens 2006 [USA]	Leucoreduced RBC	NR	NR	NR	NR
	Standard RBC	NR	NR	NR	NR
Trial-defined intervention vs trial-defined intervention: in-hospital					
Cotton 2013 [USA]	Modified whole blood	NR	NR	NR	NR
	Component	NR	NR	NR	NR
Garrigue 2018 [France]	French lyophilised plasma 4 units (+4 RBC)	NR	NR	NR	122 (88 to 205)
	4 FFP (+4 RBC)	NR	NR	NR	117 (80 to 147)
Holcomb	1 FFP: 1 platelet: 1 RBC	NR	NR	NR	27.5

Study	Intervention and comparator	Time from injury to intervention (mins)	Time from injury to hospital (mins), median (IQR)	Transport time from scene to hospital (mins), median (IQR)	Time to randomisation (mins), median (IQR)
2015 [USA]	1 FFP: 1 platelet: 2 RBC	NR	NR	NR	(17 to 47) 25.5 (16 to 41)
Reed 1986 [USA]	Platelets	NR	NR	NR	NR
	FFP	NR	NR	NR	NR
VHA vs conventional laboratory testing: in-hospital					
Gonzalez 2015 [USA]	TEG	NR	35.5 (23 to 94)	NR	NR
	Conventional lab tests	NR	29 (21 to 72)	NR	NR

2.5.3 Risk of bias in included studies

Visual representations of the risk of bias assessments across all nine trials and for each item in the included trials are presented in Figure 2.2. More detailed information about the biases identified within the individual trials is presented in Figure 2.3. The outcomes for the study by Reed et al[117] were unclear; no risk of bias assessment could be made and I excluded it from the descriptions for risk of bias.

2.5.3.1 *Sequence generation*

Trial-defined intervention vs standard of care (pre-hospital) (n=2)

- One study was at low risk of bias because it used computer generated random numbers.[118]
- One study was at unclear risk of bias because the nature of the schedule for sequence generation was not specified.[124]

Trial-defined intervention vs standard of care (in-hospital) (n=3)

- All three studies were at low risk of bias because they used computer generated random numbers[99,119] or block permutation randomisation.[123]

Trial-defined intervention vs trial-defined intervention (in-hospital) (n=3)

- Two studies were at low risk of bias because they used computer generated random numbers.
- One study was at unclear risk of bias because the method of sequence generation was not specified.[121]

VHA vs conventional laboratory testing (n=1)

- The included study was at high risk of bias because there was weekly alternation of the two treatment modalities.

Figure 2.2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study

The study outcomes were unclear for the Reed study so risk of bias could not be assessed. Red=high risk of bias, yellow=unclear risk of bias, green= low risk of bias.

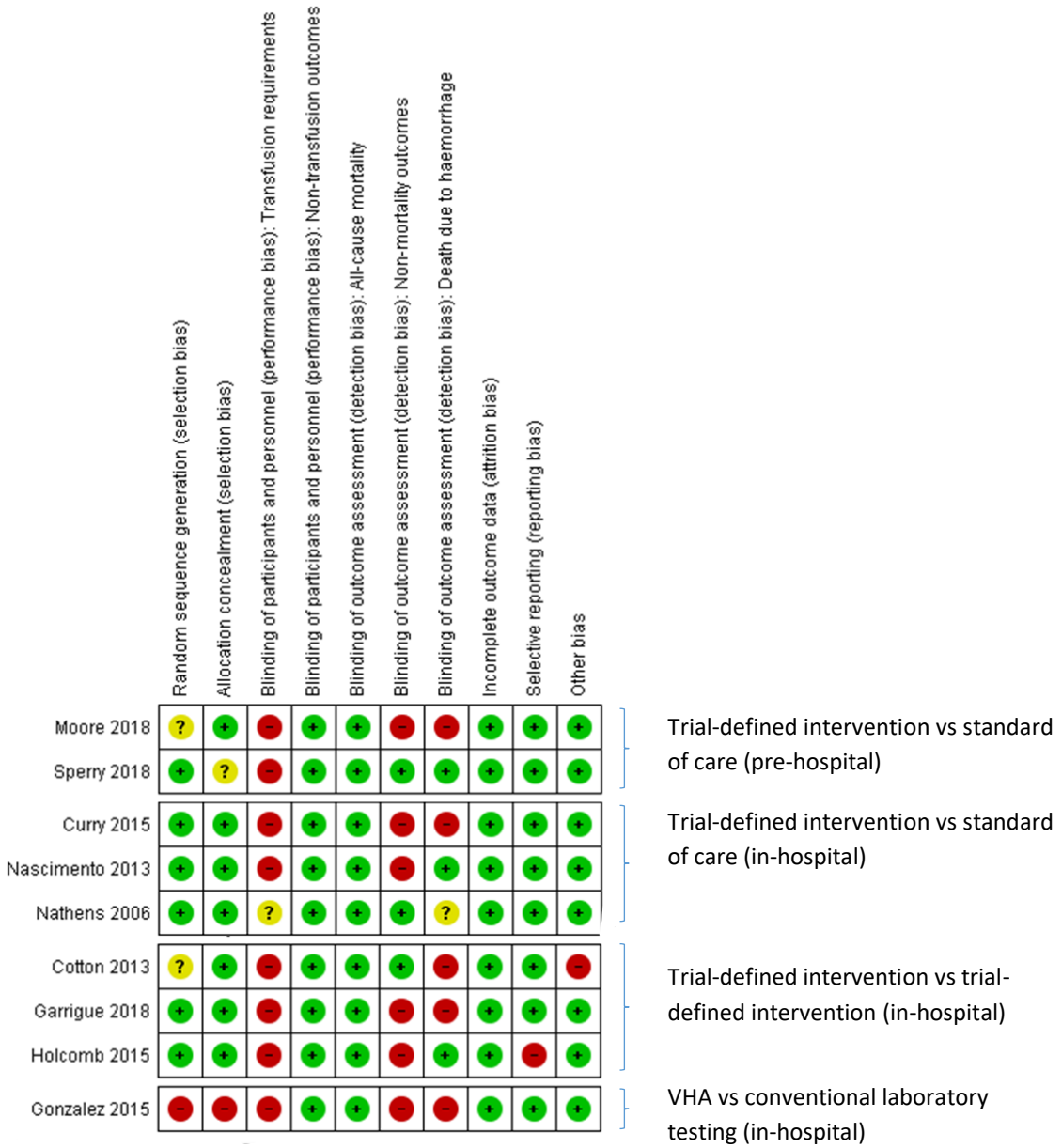
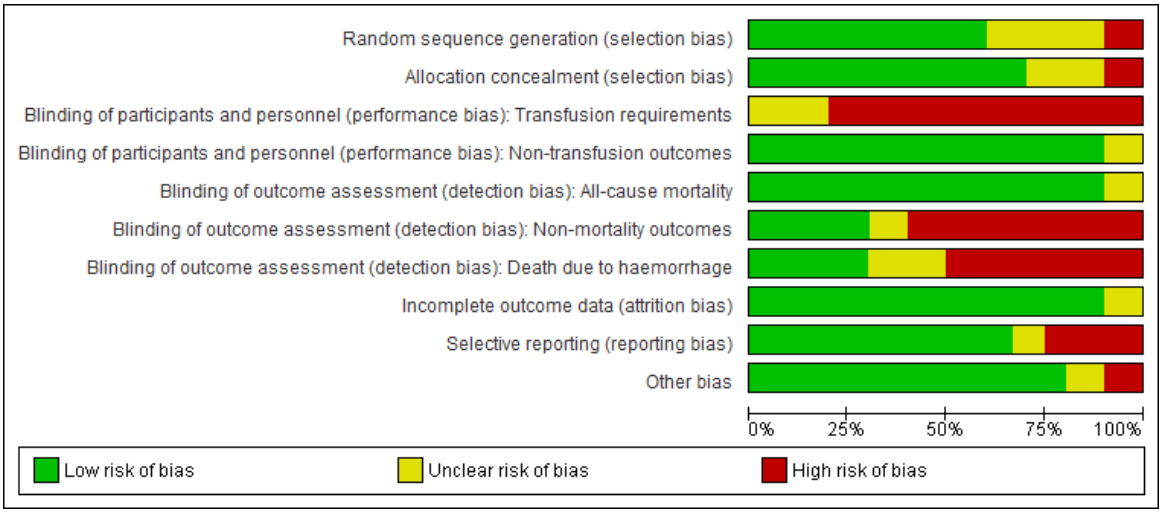


Figure 2.3 Risk of bias graph for included studies

Review authors' judgements about each risk of bias item presented as percentages across all included studies.



2.5.3.2 *Concealment of treatment allocation*

Trial-defined intervention vs standard of care (pre-hospital) (n=2)

- One study was at low risk of bias because the cassettes for treatment allocation were sealed.[124]
- One study was at unclear risk of bias because insufficient information was reported regarding treatment allocation.[118]

Trial-defined intervention vs standard of care (in-hospital) (n=3)

- All three studies were at low risk of bias because they used sealed opaque envelopes[99,119,123]

Trial-defined intervention vs trial-defined intervention (in-hospital) (n=3)

- All three studies were at low risk of bias because either:
    - they used sealed containers in the blood bank[71] or
    - they used sealed opaque envelopes.[120,121]

VHA vs conventional laboratory testing (n=1)

- The included study was considered to be at high risk of bias because allocation was not concealed.

2.5.3.3 *Blinding (performance bias and detection bias)*

Eight of the nine studies were open label studies. One was blinded to personnel, participants and outcome assessors.[123] I assessed performance and detection bias for different outcomes, as the risk of bias was considered to depend on the subjectivity/objectivity of the outcome. Performance bias was assessed for transfusion outcomes and non-transfusion outcomes. Detection bias was assessed for death due to bleeding, all-cause mortality and other non-mortality outcomes.

Performance bias: transfusion outcomes

For blinding of participants and personnel, eight studies were considered to be at high risk of bias for the transfusion outcomes because they were open label studies. Knowing which arm the patient was randomised to could affect how the patient was transfused. For one study in the trial-defined vs standard of care comparison,[123] the risk of bias for transfusion outcomes was unclear because the outcome was not reported.

Performance bias: non-transfusion outcomes

Studies were considered to be at low risk of bias for non-transfusion outcomes even though the majority of studies were open-label, as there was a low likelihood of these outcomes being affected by knowledge of the treatment arm. There were no patient reported outcomes and patient knowledge of their treatment arm was considered unlikely to have an effect on outcomes. For personnel, knowledge of intervention was considered unlikely to significantly affect management and subsequent non-transfusion outcomes.

Trial-defined intervention vs standard of care (pre-hospital) (n=2)

- Both studies were at low risk of bias for non-transfusion outcomes.

Trial-defined intervention vs standard of care (in-hospital) (n=3)

- All three studies were at low risk of bias for non-transfusion outcomes (one was blinded,[123] the other two were open-label).

Trial-defined intervention vs trial-defined intervention (in-hospital) (n=3)

- All three studies were at low risk of bias for non-transfusion outcomes.

VHA vs conventional laboratory testing (n=1)

- The study was at low risk of bias.

Detection bias: death due to bleeding

Trial-defined intervention vs standard of care (pre-hospital) (n=2)

- One study was at low risk of bias because the outcome assessors were blinded to group assignment.[118]
- One study was considered at unclear risk because this outcome was not measured.[124]

Trial-defined intervention vs standard of care (in-hospital) (n=3)

- One study was considered at low risk of bias because each death was adjudicated by a clinician blinded to group assignment.[119]
- One study was considered at high risk of bias because each death was adjudicated by a non-blinded outcome assessor.[99] (Data for this outcome was requested from the study authors and was not one of the original trial outcome measures).
- One study was considered at unclear risk because this outcome was not measured.[123]

Trial-defined intervention vs trial-defined intervention (in-hospital) (n=3)

- One study was considered at low risk of bias because each death was adjudicated by a clinician blinded to group assignment.[71]
- Two studies were considered at unclear risk because they did not measure this outcome.[120,121]

VHA vs conventional laboratory testing (n=1)

- One study was considered at high risk of bias because each death was adjudicated by a non-blinded outcome assessor.[122]

Detection bias: all-cause mortality

Trial-defined intervention vs standard of care (pre-hospital) (n=2)

- Both studies were at low risk of bias (one study because the outcome assessors were blinded to group assignment[118] and one because lack of blinding was not considered to affect judgment for all-cause mortality).[124]

Trial-defined intervention vs standard of care (in-hospital) (n=3)

- Three studies were considered at low risk of bias because each death was adjudicated by a clinician blinded to group assignment[119,123] or because lack of blinding was not considered to affect judgment for all-cause mortality.[99]

Trial-defined intervention vs trial-defined intervention (in-hospital) (n=3)

- Three studies were considered at low risk of bias because each death was adjudicated by a clinician blinded to group assignment[71] or because lack of blinding was not considered to affect judgment for all-cause mortality.[120,121]

VHA vs conventional laboratory testing (n=1)

- One study was considered at low risk of bias because lack of blinding was not considered to affect judgment for all-cause mortality.[122]

Detection bias: other non-mortality outcomes

- One study in the trial-defined intervention vs standard care comparison (pre-hospital) was considered at low risk of bias because outcome assessors were blinded to treatment assignment.[118]
- One study in the trial-defined intervention vs standard care comparison (in-hospital) was considered at unclear risk of bias because non-mortality outcomes were not reported.[123]
- The six remaining studies were considered to be at high risk of bias for non-mortality outcomes because the non-blinding of outcome assessors could affect judgment of the outcome.

2.5.3.4 *Incomplete outcome data (attrition bias)*

All nine studies were considered to be at low risk of bias because they performed intention to treat analysis.

2.5.3.5 *Selective reporting (reporting bias)*

Eight of the studies were at low risk of bias because they were prospectively registered and reported all pre-specified outcomes. One study in the trial-defined vs trial-defined comparison was considered to be at high risk of bias because not all outcomes were pre-specified (death due to bleeding was not a pre-specified outcome).[71]

2.5.3.6 *Other potential sources of bias*

Eight of the studies were at low risk of other potential sources of bias because of detailed methodological reporting. One study in the trial-defined intervention vs trial-defined intervention comparison was considered to be at high risk of bias because there

was a potential bias in study conduct. There was an amendment to study exclusion criteria after trial started (patients with TBI were added as an exclusion criterion) and there was a high proportion of patients not treated per protocol (19-29%).[121]

2.5.3.7 *Publication bias*

Although there were small numbers of trials in each comparison group, publication bias was not suspected because studies showing benefit and no effect were published and the search strategy was comprehensive.

2.5.4 Effects on outcomes

The five main outcomes for the summary of findings were:

- All-cause mortality at 24 hours
- All-cause mortality at 30 days
- Time-to-anatomical haemostasis
- Transfusion requirements – total number of red cell units during first 24 hours
- Total thromboembolic events in the first 30 days.

An overview of the results of these five main outcomes are shown in a vote-counting table (Table 2.5). One study showed a beneficial effect of the intervention on 24-hour mortality (with pre-hospital plasma). There was no clear effect of any of the interventions on number of units of RBC or thromboembolic events. Two studies showed a beneficial effect on 30-day mortality (one study of pre-hospital plasma vs standard of care and VHA vs conventional laboratory test guided transfusion); the others showed no effect. The single study that measured time to haemostasis showed a reduction in time to haemostasis.[71]

Summary of findings tables for each of the four comparisons and GRADE of evidence are presented in Table 2.6, Table 2.7, Table 2.8 and Table 2.9. Data for primary and secondary outcomes are presented in detail (sections 2.5.4.1, 2.5.4.3).

Table 2.5. Summary of study results for 5 main outcomes

(By vote-counting). a (trial-defined vs standard of care (pre-hospital); b (trial-defined vs standard of care (in-hospital)); c (trial-defined vs trial-defined (in-hospital)); d (VHA vs conventional laboratory testing (in-hospital)). ^Not pre-specified trial outcome (data provided by authors on request). *no thrombotic events in control arm.

	Number of studies reporting outcome	Studies showing harm	Studies showing neither benefit/harm	Studies showing benefit	Unclear
24-hour mortality	7	-	Moore[a] Curry[b]^ Nascimento[b] Cotton[c] Holcomb[c] Garrigue[c]	Sperry[a]	
Mortality within 30 days	9	-	Moore[a] Curry[b] Nascimento[b] Nathens[b] Cotton[c] Garrigue[c] Holcomb[c]	Sperry[a] Gonzalez[d]	-
Time to haemostasis	1	-	-	Holcomb[c]	-
RBC units in 24 hours	8	-	Moore[a] Sperry[a] Curry[b] Nascimento[b] Cotton[c] Garrigue[c] Holcomb[c] Gonzalez[d]	-	-
Total thromboembolic events in 30 days	4	-	Moore[a] Holcomb[c] Gonzalez[d]	-	Curry[b]*

Table 2.6. Summary of findings: Trial-defined intervention (plasma) compared to standard of care (pre-hospital)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard of care	**Risk with trial-defined intervention (plasma)**				
All-cause mortality at 24 hours	One study (n=501) showed a reduction in mortality with pre-hospital plasma (RR 0.63, 95% CI 0.42 to 0.93). The other study (n=125) showed no effect with pre-hospital plasma (RR 0.9, 95% CI 0.37 to 2.30).		-	626 (2 RCTs)	⨁⨁◯◯ LOW [a,b]	The smaller study was terminated early due to futility at interim analysis.
All-cause mortality within 30 days	One study (n=501) showed a reduction in mortality with pre-hospital plasma (RR 0.70, 95% CI 0.52 to 0.94). The other study (n=125) showed no clear effect (RR 1.54, 95% CI 0.60 to 3.98).		-	626 (2 RCTs)	⨁⨁◯◯ LOW [a,b]	
Time to haemostasis	Not estimable		-	(0 studies)	-	No studies reported outcome
24-hour RBC transfusion (units)	The median number of units ranged from 1.5 to 4 in the standard care arms. The median number of units ranged from 2 to 3 in the plasma arms.		-	626 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	
Total TE events	29 per 1,000	52 per 1,000 (11 to 218)	pOR 1.83 (0.36 to 9.36)	144 (1 RCT)	⨁⨁◯◯ LOW [b,d]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
TE: thromboembolic; CI: Confidence interval; RR: Risk ratio; pOR: Peto odds ratio.

Explanations: a. Heterogeneity of study populations; b.Small sample size; c. Open-label study; d. Only one study

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table 2.7. Summary of findings: Trial-defined intervention vs standard of care (in-hospital)

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
All-cause mortality at 24 hours	One study (n=41) showed no clear effect of early cryoprecipitate over standard of care on 24-hour mortality (RR 0.13, 95% CI 0.01 to 1.31). One study n=75 showed no clear effect of 1:1:1 RBC:FFP:Platelets over standard of care (RR 1.93, 95% CI 0.74 to 5.00).	(2 RCTs)	⊕⊕◯◯ LOW [a,b,c]
All-cause mortality within 30 days	One study (n=41) showed no clear effect of early cryoprecipitate over standard of care on 30-day mortality (RR 0.35, 95% CI 0.08 to 1.54). One study (n=268) showed no clear effect of leucoreduced red blood cells over standard RBC (RR 0.87, 95% CI 0.54 to 1.40). One study (n=75) showed no clear effect of 1:1:1 RBC:FFP:Platelets over standard of care (RR 2.27, 95% CI 0.90 to 5.74).	384 (3 RCTs)	⊕⊕◯◯ LOW [b,c]
Time to haemostasis	Not estimable	(0 RCTs)	-
24-hour RBC transfusion (units)	The median number of RBC units transfused in the standard care arms was 7 units. The median number of RBC units transfused in the intervention arms ranged from 7 to 8 units.	185 (2 RCTs)	⊕◯◯◯ VERY LOW [b,d,e]
Total thromboembolic events	One study (n=41) showed no clear effect of early cryoprecipitate and standard care on thrombotic events (Peto odds ratio 0.12, 95% CI 0.02 to 0.93). In one study n=75, the effect of the intervention was not estimable (the event rate in the standard arm was zero).	185 (2 RCTs)	⊕⊕◯◯ LOW [b,f]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; OR: Odds ratio

Explanations: a. Event rates vary across studies; b. Small sample size; c. Wide variation in effect estimates across studies; d. Open label study; e. heterogeneity of studies; f. Differing effects across studies.

Table 2.8. Summary of findings: Trial-defined intervention vs trial-defined intervention (in-hospital)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with trial-defined intervention 2	**Risk with trial-defined intervention 1**				
All-cause mortality at 24 hours	There was no clear effect between the interventions on 24-hour mortality. Whole blood vs component therapy, RR 1.13, 95% CI 0.37 to 3.49). Lyophilised plasma vs fresh frozen plasma, peto OR 1.04, 85% CI (0.06 to 17.2). 1:1:1 FFP:Platelet:RBC vs 1:1:2 FFP:Platelet:RBC RR 0.75, 95%CI (0.52 to 1.08).			834 (3 RCTs)	⨁⨁◯◯ LOW [a,b]	-
All-cause mortality within 30 days	There was no clear effect between the interventions on 30-day mortality. Whole blood vs component therapy RR 1.62, 95% CI 0.69 to 3.80). Lyophilised plasma vs fresh frozen plasma RR 0.75, 85% CI (0.28 to 2.02). 1:1:1 FFP:Platelet:RBC vs 1:1:2 FFP:Platelet:RBC RR 0.85, 95%CI (0.65 to 1.11).			834 (3 RCTs)	⨁⨁◯◯ LOW [a,b]	-
Time to haemostasis	In the group receiving 1:1:1 FFP:Platelet:RBC the median time to haemostasis was 105 minutes (IQR 64 to 179) (n=291). In the group receiving 1:1:2 FFP:Platelet:RBC the median time to haemostasis was 100 minutes (IQR 56 to 181) (n=267).			680 (1 RCT)	⨁◯◯◯ VERY LOW [c,d,e]	-

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with trial-defined intervention 2	**Risk with trial-defined intervention 1**				
24-hour RBC transfusion (units)	The median number of RBC units ranged from 6 to 9 units in the groups receiving the first trial-defined intervention. The median ranged from 4 to 9 units in the groups receiving the comparator intervention.			834 (3 RCTs)	⨁◯◯◯ VERY LOW [a,c,e]	
Total thromboembolic events	170 per 1,000	163 per 1,000 (117 to 226)	RR 0.96 (0.69 to 1.33)	680 (1 RCT)	⨁⨁◯◯ LOW [d,e]	For this outcome, trial-defined intervention 1 was 1:1:1 FFP:Platelet:RBC and trial-defined intervention 2 was 1:1:2 FFP:Platelet:RBC.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio.

Explanations: a. Heterogeneity of studies; b. Small sample size and wide confidence intervals c. Open label study; d. Only one study; e. Small sample size

Table 2.9. Summary of findings table: VHA vs conventional laboratory testing (in-hospital)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with conventional laboratory testing	**Risk with Viscoelastic haemostatic assay**				
All-cause mortality at 24 hours	Not estimable			(0 studies)	-	No study measured outcome
All-cause mortality within 30 days	364 per 1,000	196 per 1,000 (105 to 371)	RR 0.54 (0.29 to 1.02)	111 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	-
Time to haemostasis	Not estimable			(0 studies)	-	No study measured outcome
24-hour RBC transfusion (units)	The median number of RBC units was 11 (IQR 6 to 16) in the conventional laboratory arm. The median number of RBC units was 9 (IQR 5 to 16) in the viscoelastic haemostatic assay arm.			111 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	-
Total TE events	164 per 1,000	106 per 1,000 (41 to 281)	RR 0.65 (0.25 to 1.72)	111 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	-

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

TE: thromboembolic; CI: Confidence interval; RR: Risk ratio

Explanations: a. High risk of bias: allocation concealment and selection bias. b. Only one study c. Small sample size and wide confidence interval

2.5.4.1 *Primary outcomes*

Results for the two primary outcomes are presented in Table 2.10, Table 2.11, Figure 2.4, Figure 2.5.

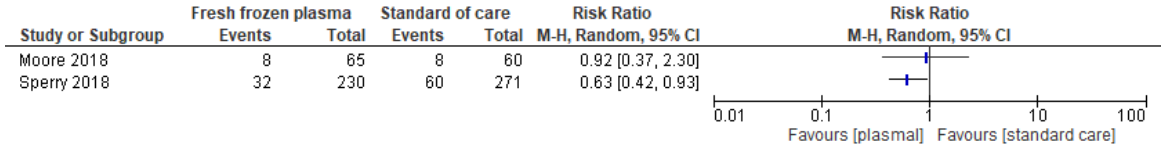
2.5.4.1.1 *All-cause mortality at 24 hours*

Table 2.10. Results for primary outcomes: all-cause mortality at 24 hours

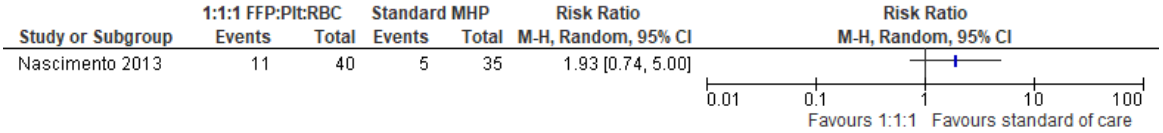
Study	Intervention	Comparator	Effect estimate (RR, 95% CI)	Comments
Trial-defined intervention vs standard of care: pre-hospital				
Sperry 2018	Pre-hospital plasma 2 units 32/230 (13.9%)	Standard of care resuscitation (crystalloid and some centres had RBC available) 60/271 (22.1%)	0.63 (0.42 to 0.93)	Beneficial effect of intervention
Moore 2018	Pre-hospital plasma 2 units 8/65 (12.3%)	Standard of care resuscitation (saline) 8/60 (13.3%)	0.92 (0.37 to 2.30)	-
In-hospital: trial-defined intervention vs standard of care				
Curry 2015	Early cryo 0/20 (0%)	Standard of care (MHP) 3/21 (14.3%)	0.13 (0.01 to 1.31)	Additional data received from authors. Not pre-specified outcome. Peto odds ratio
Nascimento 2013	Formula (1:1:1) 11/40 (27.5%)	Laboratory guided standard of care (MHP) 5/35 (14.3%)	1.93 (0.74 to 5.00)	Additional data received from authors. Not pre-specified outcome.
Trial-defined intervention vs trial-defined intervention: in-hospital				
Cotton 2013	Modified whole blood 6/55 (10.9%)	Blood components 5/52 (9.6%)	1.13 (0.37 to 3.49)	-
Garrigue 2018	French lyophilised plasma 4 units (+4 RBC) 1/23 (4.3%)	4 FFP (+4 RBC) 1/24 (4.2%)	1.04 (0.06 to 17.2)	Peto odds ratio
Holcomb 2015	1 FFP: 1 platelet: 1 RBC 43/338 (12.7%)	1 FFP: 1 platelet: 2 RBC 58/342 (17.0%)	0.75 (0.52 to 1.08)	-

Figure 2.4. Forest plot for 24-hour all-cause mortality

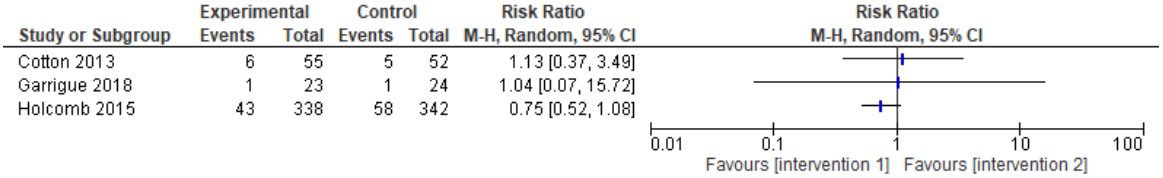
a) Trial-defined intervention vs standard of care: pre-hospital



b) Trial-defined intervention vs standard of care: in-hospital



c) Trial-defined intervention vs trial-defined intervention: in-hospital



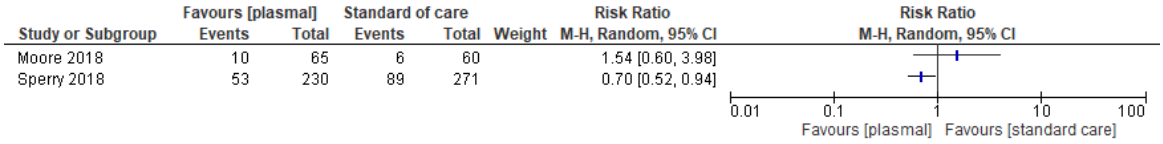
2.5.4.2 *All-cause mortality within 30 days*

Table 2.11. Results for primary outcomes: all-cause mortality within 30 days

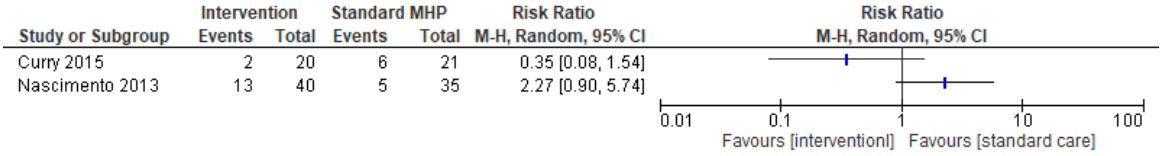
Study	Intervention	Comparator	Effect estimate (RR, 95% CI)
Trial-defined intervention vs standard of care: pre-hospital			
Moore 2018 (28-day mortality)	10/65 (15.4%)	6/60 (10.0%)	1.54 (0.60 to 3.98)
Sperry 2018	53/230 (23.0%)	89/271 (32.8%)	0.70 (0.52 to 0.94)
Trial-defined intervention vs standard of care: in-hospital			
Curry 2015 (28-day mortality)	2/20 (10.9%)	6/21 (28.6%)	0.35 (0.08 to 1.54)
Nathens 2006	Leucoreduced RBC 26/136 (19.1%)	Standard RBC 29/132 (22.0%)	 0.87 (0.54 to 1.40)
Nascimento 2013	13/40 (32.5%)	5/35 (14.3%)	2.27 (0.90 to 5.74)
Trial-defined intervention vs trial-defined intervention: in-hospital			
Cotton 2013	12/55 (21.8%)	7/52 (13.5%)	1.62 (0.69 to 3.80)
Garrigue 2018	5/23 (21.7%)	7/24 (29.2%)	0.75 (0.28 to 2.02)
Holcomb 2015	75/338 (22.2%)	89/342 (26.0%)	0.85 (0.65 to 1.11)
VHA vs conventional laboratory testing: in-hospital			
Gonzalez 2015 (28-day mortality)	11/56 (19.6%)	20/55 (36.4%)	0.54 (0.29 to 1.02)

Figure 2.5. Forest plot of 30-day mortality

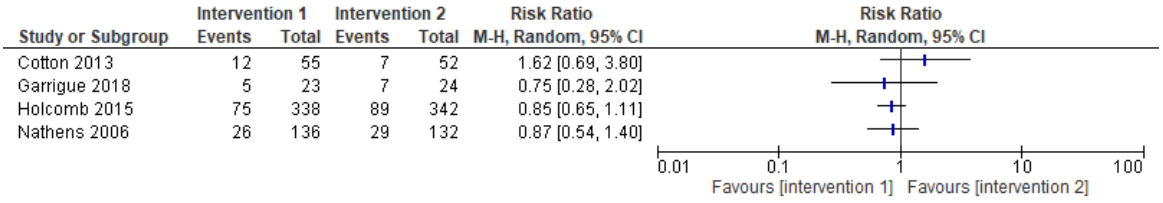
a) Trial-defined intervention vs standard of care: pre-hospital



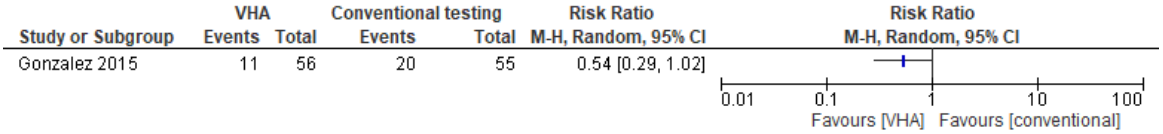
b) Trial-defined intervention vs standard of care: in-hospital



c) Trial-defined intervention vs trial-defined intervention: in-hospital



d) VHA vs conventional laboratory testing: in-hospital



2.5.4.3 *Secondary outcomes*

Results for the secondary outcomes are presented in Tables 2.12 to 2.24.

Table 2.12. Secondary outcome: 24-hour mortality due to bleeding

Study	Intervention	Comparator	Effect estimate RR (95% CI)	Comments
Trial-defined intervention vs standard of care: pre-hospital				
Sperry 2018	17/230 (7.4%)	26/271 (10.0%)	0.76 (0.40 to 1.41)	-
Trial-defined intervention vs standard of care: in-hospital				
Nascimento 2013	9/40 (22.5%)	3/45 (6.7%)	3.38 (0.98 to 11.61)	Study assessed overall mortality due to bleeding but the median time to death was ~3 hours in both arms. Data provided for 24-hour mortality by authors.
Curry 2015	0/20 (0%)	1/21 (4.8%)	0.14 (0.00 to 7.16)	Peto OR. Additional data provided by authors.
Trial-defined intervention vs trial-defined intervention: in-hospital				
Holcomb 2015	31/338 (9.2%)	50/342 (14.6%)	0.63 (0.41 to 0.96)	Beneficial effect of intervention
VHA vs conventional laboratory testing: in-hospital				
Gonzalez 2015	5/56 (8.9%)	11/55 (20.0%)	0.45 (0.17 to 1.20)	Reported not within 24 hours, but as overall mortality. The median time to death was 10.4 hr in the VHA arm and hr in the conventional lab testing arm.

2.5.4.3.1 *Time-to-anatomical haemostasis*

Table 2.13. Secondary outcome: time to haemostasis

Time-to-anatomical haemostasis, median (interquartile range (IQR))			
Study	Intervention	Comparator	Effect estimate
Trial-defined intervention vs trial-defined intervention: in-hospital			
Holcomb 2015	105 (64 to 179) minutes	100 (56 to 181) minutes	Unable to estimate

2.5.4.3.2 *Total thromboembolic events (arterial and venous) in the first 30 days after injury*

Table 2.14. Secondary outcome: total thromboembolic events

Total thromboembolic events				
Study	Intervention	Comparator	Effect estimate RR (95% CI)	Comments
Trial-defined intervention vs standard of care: pre-hospital				
Moore 2018	4/75	2/69	1.83 (0.36 to 9.36)	Peto OR
Trial-defined intervention vs standard of care: in-hospital				
Curry 2015	0/20	4/21	0.12 (0.02 to 0.93)	Peto OR
Nascimento 2013	3/40	0/35	Unable to estimate	-
Trial-defined intervention vs trial-defined intervention: in-hospital				
Holcomb 2015	58/338	61/342	0.96 (0.69 to 1.33)	-
VHA vs conventional laboratory testing: in-hospital				
Gonzalez 2015	6/56	9/55	0.65 (0.25 to 1.72)	-

Table 2.15. Secondary outcome: arterial thromboembolic events

Arterial thromboembolic events				
Study	Intervention	Comparator	Effect estimate RR (95% CI)	Comments
Trial-defined intervention vs standard of care: pre-hospital				
Moore 2018	0/75	0/75	Unable to estimate	-
Trial-defined intervention vs standard of care: in-hospital				
Curry 2015	0/20	1/21	0.14 (0.00 to 7.16)	Peto OR
Trial-defined intervention vs trial-defined intervention: in-hospital				
Cotton 2013	0/55	0/52	Unable to estimate	-
Holcomb 2015	8/338	13/342	0.62 (0.26 to 1.48)	Peto OR

Table 2.16. Secondary outcome: venous thromboembolic events

Venous thromboembolic events				
Study	Intervention	Comparator	Effect estimate RR (95% CI)	Comments
Trial-defined intervention vs standard of care: pre-hospital				
Moore 2018	4/75	2/69	1.83 (0.36 to 9.36)	Peto OR
Trial-defined intervention vs standard of care: in-hospital				
Curry 2015	0/20	3/21	0.13 (0.01 to 1.31)	Peto OR
Nascimento 2013	3/40	0/35	Unable to estimate	-
Trial-defined intervention vs trial-defined intervention: in-hospital				
Holcomb 2015	50/338	48/342	1.05 (0.73 to 1.52)	-
VHA vs conventional laboratory testing: in-hospital				
Gonzalez 2015	6/56	9/55	0.65 (0.25 to 1.72)	-

2.5.4.3.3 *Transfusion requirements (number of units or volume of red cells, FFP, Cryoprecipitate, and Platelets) in the first 24 hours*

Table 2.17. Secondary outcome: total transfusion requirements within 24 hours

Transfusion requirements within 24 hours (total), median (interquartile range (IQR))		
Study	**Intervention**	**Comparator**
Trial-defined intervention vs standard of care: pre-hospital		
Sperry 2018	3 (0 to 10)	4 (2 to 16)
Trial-defined intervention vs trial-defined intervention: in-hospital		
Cotton 2013	12 (6 to 24)	13 (5 to 29)

Table 2.18. Secondary outcome: RBC requirements within 24 hours

Transfusion requirements within 24 hours (RBC units), median (IQR)		
Study	**Intervention**	**Comparator**
Trial-defined intervention vs standard of care: pre-hospital		
Sperry 2018	3 (0 to 7)	4 (1 to 9)
Moore 2018	2 (0 to 9)	1.5 (0 to 9)
Trial-defined intervention vs standard of care: in-hospital		
Curry 2015	8 (5 to 11)	7 (6 to 9)
Nascimento 2013	7 (6 to 10)	7 (6 to 14)
Trial-defined intervention vs trial-defined intervention: in-hospital		
Cotton 2013	4 (2 to 8)	6 (2 to 11)
Garrigue 2018	6 (4 to 10)	7 (6 to 11.5)
Holcomb 2015	9 (5 to 15)	9 (6 to 16)
VHA vs conventional laboratory testing: in-hospital		
Gonzalez 2015	9 (5 to 16)	11 (6 to 16)

Table 2.19. Secondary outcome: FFP requirements within 24 hours

Transfusion requirements within 24 hours (FFP units), median (IQR)		
Study	**Intervention**	**Comparator**
Trial-defined intervention vs standard of care: pre-hospital		
Sperry 2018	0 (0 to 3) post hospital admission 2 pre-hospital	0 (0 to 4) post hospital admission 0 pre-hospital
Moore 2018	0 (0 to 4) post hospital 2 pre-hospital	0 (0 to 3) post hospital 0 pre-hospital
Trial-defined intervention vs standard of care: in-hospital		
Curry 2015	8 (5 to 11)	7 (6 to 9)
Nascimento 2013	6 (4 to 8)	4 (3 to 8)
Trial-defined intervention vs trial-defined intervention: in-hospital		
Cotton 2013	4 (2 to 8)	4 (2 to 10)
Garrigue 2018	4 (4 to 8)	6 (4 to 9)
Holcomb 2015	7 (3 to 13)	5 (2 to 10)
VHA vs conventional laboratory testing: in-hospital		
Gonzalez 2015	5 (3 to 9)	6 (4 to 9)

Table 2.20. Secondary outcome: Cryoprecipitate requirements within 24 hours

Transfusion requirements within 24 hours (cryoprecipitate pools), median (IQR)		
Study	**Intervention**	**Comparator**
Trial-defined intervention vs standard of care: pre-hospital		
Moore 2018	0 (0 to 0)	0 (0 to 0)
Trial-defined intervention vs standard of care: in-hospital		
Curry 2015	2 (2 to 4)	2 (0 to 2)
Nascimento 2013	0 (0 to 0)	0 (0 to 10)
Trial-defined intervention vs trial-defined intervention: in-hospital		
Garrigue 2018 (FgC)	2 (0 to 3)	3 (2 to 4)
Holcomb 2015	0 (0 to 0)	0 (0 to 9)
VHA vs conventional laboratory testing: in-hospital		
Gonzalez 2015	0 (0 to 2)	1 (0 to 2)

Table 2.21. Secondary outcome: Platelet requirements within 24 hours.

Transfusion requirements within 24 hours (platelet doses), median (IQR)			
Study	**Intervention**	**Comparator**	**Comments**
Trial-defined intervention vs standard of care: pre-hospital			
Sperry 2018	0 (0 to 1)	0 (0 to 1)	-
Moore 2018	0 (0 to 0)	0 (0 to 0)	-
Trial-defined intervention vs standard of care: in-hospital			
Curry 2015	1 (0 to 2)	1 (1 to 2)	-
Nascimento 2013	8 (4 to 8)	4 (0 to 8)	4 units platelets equivalent to 1 apheresis pool
Trial-defined intervention vs trial-defined intervention: in-hospital			
Cotton 2013	0 (0 to 1)	0 (0 to 2)	-
Garrigue 2018	0 (0 to 1)	1 (0 to 2)	-
Holcomb 2015	12 (6 to 18)	6 (0 to 12)	6 units platelets equivalent to 1 apheresis pool
VHA vs conventional laboratory testing: in-hospital			
Gonzalez 2015	1 (0 to 2)	1 (0 to 2)	-

2.5.4.3.4 *Degree of coagulopathy*

This was defined as maximal change in prothrombin time (PT) or INR between baseline and post intervention.

Table 2.22. Secondary outcome: change in coagulopathy

Change in coagulopathy (INR)				
Study	**Intervention**	**Comparator**	**Effect estimate**	**Comments**
Trial-defined intervention vs standard of care: pre-hospital				
Moore 2018	INR 1.27 (1.11 to 1.4)	INR 1.15 (1.08 to 1.29)	Unable to estimate	INR on arrival at hospital, not change from baseline
Trial-defined intervention vs standard of care: in-hospital				
Nascimento 2013	INR post-treatment reported as median (IQR): 1.19 (1.1 to 1.3)	INR post-treatment reported as median (IQR): 1.34 (1.2 to 1.5)	Unable to estimate	-
Trial-defined intervention vs trial-defined intervention: in-hospital				
Garrigue 2018	-	-	-	Overall summary statistic reported but not for individual arms. Mean difference from baseline -0.28 (-0.43 to -0.13) at 6 hours post randomisation

2.5.4.3.5 *Requirement for surgery or interventional procedure to control bleeding in the first 24 hours after injury*

Table 2.23. Secondary outcome: requirement for intervention to stop bleeding

Requirement for intervention to stop bleeding				
Study	**Intervention**	**Comparator**	**Effect estimate Peto OR, 95% CI**	**Comments**
Holcomb 2015	13/338	16/342	0.82 (0.39 to 1.72)	Study defined outcome as requirement for surgical or radiological intervention to control bleeding after haemostasis achieved

2.5.4.3.6 *Length of stay in intensive care*

Table 2.24. Secondary outcome: Length of stay in intensive care (ICU-free days).

ICU-free days (median, IQR)				
Study	**Intervention**	**Comparator**	**Effect estimate**	**Comments**
Trial-defined intervention vs standard of care: pre-hospital				
Moore 2018	23 (7 to 26)	24 (17 to 26)	Unable to estimate	-
Trial-defined intervention vs standard of care: in-hospital				
Curry 2015	16 (4.5 to 24)	8 (0 to 13)	Unable to estimate	Data provided by authors
Nascimento 2013	23 (12 to 26)	20 (5 to 24)	Unable to estimate	
Trial-defined intervention vs trial-defined intervention: in-hospital				
Cotton 2013	30 (11 to 30)	29 (17 to 30)	Unable to estimate	
Holcomb 2015	5 (0 to 11)	4 (0 to 10)	Unable to estimate	
VHA vs conventional laboratory testing: in-hospital				
Gonzalez 2015	16 (0 to 22)	9 (0 to 19.5)	Unable to estimate	

2.5.4.4 *GRADE quality of the evidence*

For the five main outcomes, the overall certainty of evidence (GRADE assessment) was very low or low. Most of the downgrading was for imprecision (wide CIs, small sample sizes), inconsistency (only one study for some comparisons) and high risk of bias.

2.6 Discussion

2.6.1 Summary of key results

This systematic review identified 10 RCTs with 1982 participants that assessed the effects of blood transfusion in trauma-related major bleeding; outcome data relevant to this review was available from nine studies (n=1949). Study interventions were heterogeneous and all studies involved adult patients with injury. No studies were identified that specifically evaluated interventions for older or younger age groups.

Across these nine studies:

- The overall quality was assessed to be low or very low as assessed by GRADE.
- There was marked clinical heterogeneity, as the trials were conducted in a variety of pre-hospital and in-hospital clinical settings with different local practice and standard of care.
- There was diversity in the size, methodology and reporting of primary outcomes – from the PROPPR trial[71] which recruited 680 participants and reported on short-term mortality to smaller trials, which evaluated feasibility[99,119] or change in coagulopathy.[120]

The heterogeneous nature of the data meant that I was unable to pool estimates across study types. Across all outcomes, available data on overall mortality and adverse events

due to thromboembolic events were insufficient to clearly demonstrate whether an increase, or a decrease in events was associated with a specific blood component intervention initiated in the pre-hospital or in-hospital setting.

Summary of the main findings for the four comparisons:

- Trial-defined intervention vs standard of care (pre-hospital)

Two trials with 626 participants compared pre-hospital plasma with standard of care. One trial showed a reduction in mortality at 24 hours and 30 days with pre-hospital plasma (but no effect on 24-hour mortality due to bleeding). The other trial showed no effect on the mortality outcomes and the trial was stopped early due to futility.

- Trial-defined intervention vs standard of care (in-hospital)

Three studies with 378 participants compared an intervention with standard of care. In all three studies, there was no significant difference in risk of mortality between the intervention and comparator.

- Trial-defined intervention vs trial-defined intervention (in-hospital)

Three studies with 804 participants compared two different interventions. There was no significant difference in risk of all-cause mortality between the arms. However, for the largest trial (n=642), there was a significant reduction in death due to bleeding at 24 hours.

- Viscoelastic haemostatic assay vs conventional laboratory testing (in-hospital)

One study assessed this comparison (n=111) and showed a significant difference in 30-day mortality and death due to bleeding.

I found there was no significant difference in the risk of thromboembolic events between any of the comparisons. For the secondary outcome of total number of RBCs transfused over 24 hours, there was a marked difference between the pre-hospital and in-hospital studies. Patients in the pre-hospital studies received on average half the total number of RBCs as those in the in-hospital studies (4 vs 8). Similar trends were observed for other blood components with the pre-hospital study participants requiring fewer components.

Risk of bias

In general, methodology and reporting was sufficient for risk of bias assessment (unclear for random sequence generation in two studies). The majority of studies were open-label, only one was double-blind. Although trial design and blinding for trauma haemorrhage trials using blood components is challenging, and the majority of studies are open-label, it should be possible to ensure outcome assessors are blinded to minimise bias. This is particularly important for outcomes such as death from bleeding that could be subjective. In only three out of the five trials reporting this outcome were outcome assessors blinded.

Eight trials were considered at high risk of performance bias for transfusion requirements (due to the open-label nature of the studies) and the majority of trials were judged at high risk of detection bias for non-mortality outcomes (e.g. thromboembolic events, ICU-free days).

Overall certainty of evidence

For all four comparisons, the overall certainty of the evidence for the use of blood components in trauma-related bleeding was low or very low (by GRADE assessment). The downgrading was mainly for risk of bias, imprecision, and inconsistency.

2.6.2 Overall completeness and applicability of the evidence

All the studies included in this review recruited adult patients (including those aged 16 and above). The median age of participants was in their 30s-40s. There were no studies that evaluated specific age groups of patients such as older patients or children. Although many different types of blood component intervention were evaluated, there were limited outcome data relevant for this review, as the choice of study outcomes varied across trials. The review outcomes in this review were based on those that were considered clinically relevant, but there is no universally agreed core outcome set for trials in trauma haemorrhage. The majority of included studies measured and reported outcome data for mortality within 24 hours and 30 days but the other non-mortality outcomes were less consistently measured. Only one trial reported time to haemostasis.

Applicability of evidence:

All included trials were conducted in high-income countries. The results may not be generalisable to other settings with less developed trauma systems. The nine trials that provided outcome data were published in the past six years. Even within this timeframe, there have been advances in trauma haemorrhage management, particularly in the provision of pre-hospital blood components, which may affect the applicability of these findings. For current 'standard of care', there is regional, intra- and inter-country

variation in transfusion practice including TXA administration. One could postulate that studies with high proportion of patients receiving early TXA administration may have had an attenuated baseline risk of mortality as demonstrated in the CRASH-2 trial.[127] It is important to consider the review evidence in the context of local practice, geographical proximity to a trauma centre and set-up of trauma services. These could all impact on the applicability and generalizability of the review interventions and how quickly the intervention can be delivered after injury.

The heterogeneity of the studies limited meta-analysis. Additional data relating to trial characteristics were not always reported. If these were available, I could have refined the assessment and grouping of studies. For example, I could have stratified studies according to time to intervention and co-interventions and combined study estimates.

2.6.3 Quality of the data

The included studies do address the question of use of blood components in trauma resuscitation but the data are limited to adults, mostly in the age group 30-40. The combined total number of patients in this body of evidence is 1982 and the studies were mostly small studies. Two of the studies are feasibility studies and it is possible that some studies that have been registered but not yet published may have had 'non-significant' results. For the four comparisons, the overall quality was judged to be low or very low due to limitations with risk of bias (mainly performance and detection bias), inconsistency and imprecision.

The sample size of each trial in this review was small and likely to be underpowered. I observed that the baseline risk of mortality used for power calculations and actual trial-reported mortality differed across studies; underpowering could have an impact on the

accuracy of trial estimates and consistency of results. Furthermore, mortality differed in the comparator groups across studies. For example, 30-day mortality in the comparator group for the pre-hospital trials ranged from 13.5-36.4% and 10.0-32.8% in the in-hospital trials. Such wide ranges could not be fully explained by differences in patients characteristics but suggest that local practice and standard of care may have a significant impact on outcomes.

2.6.4 Potential biases in the review process

I did not pre-specify extraction of potential effect modifiers (such as time from injury to trial intervention or TXA co-administration) in the initial protocol. However, during study screening and extraction, the clinical heterogeneity of the studies became apparent and I thought these were important data to capture.

I did not include trials of fibrinogen concentrate as already these were part of another systematic review[105] but these could be included in future reviews for a comprehensive assessment of use of blood products in acute trauma transfusion.

2.6.5 Comparison with other reviews

I found a lack of high quality evidence for a beneficial effect of one blood component strategy over another in trauma-related major bleeding. This is in keeping with another systematic review in patients with critical bleeding requiring massive transfusion, which found low-quality evidence of no difference in mortality with a 1:1:1 (FFP:Platelet:RBC) compared with a 1:1:2 transfusion ratio.[128]

2.6.6 Future work

This systematic review showed that the nature and timing of transfusion interventions were diverse, even within 24 hours of injury. The ongoing trials are also heterogeneous but will add to the available evidence and may enable pooling of data.

Going forwards, future reviews could stratify the interventions by more specific definitions e.g. ratio of blood components or types of fibrinogen replacement and take into account the setting and time from injury.

For future studies, more progress could be made through a collaborative and international approach to prioritise research questions. The quality of the RCT evidence base could be strengthened through the development of a core outcome set for trauma haemorrhage RCTs using agreed internationally clinically meaningful outcomes to aid interpretation and comparison of trials. To this end, the use of all-cause mortality as an outcome in trials of major bleeding (all types of bleeding not just trauma) has been questioned and cause-specific mortality may be a more appropriate endpoint.[129] Furthermore, consistent reporting of trial characteristics would enable assessment of heterogeneity and facilitate pooling of data where appropriate. Other areas for potential development arising from this review are shown in Table 2.25.

Table 2.25. Areas for future work

Problem identified	Suggestion for further work
Heterogeneous trial outcomes	Development of CORE outcome set for trauma haemorrhage RCTs
Inconsistent reporting of trial characteristics and time of administration of interventions from injury	Development of consensus for trauma RCT reporting
Small numbers of participants/inconsistency	Multi-centre trials to enable appropriately powered trials
Risk of bias	Blinding of outcome assessors (and clinicians if possible)
Applicability of data	Trials for young and older populations Trials in low- and middle-income countries

2.6.7 Conclusion

The purpose of this chapter was to assess the effect and safety of blood components for patients with major bleeding in trauma. This review shows that there is inconclusive evidence to support the use of one blood component strategy over another in trauma haemorrhage and overall certainty of evidence was low or very low. A secondary objective was to assess the evidence for different age groups. Evidence was insufficient; trials were limited to adults, median age 30-40 with few older patients represented.

Future trials need to address the uncertainty regarding the use of blood components in older and younger age groups. Trials need to be robust in design and reporting to facilitate analysis and assessment of results, taking into account the time-sensitive nature of resuscitation in trauma.

Chapter 3 A Delphi study to establish consensus on a definition of major bleeding in adult trauma

3.1 Introduction

Agreeing a common definition for major bleeding in trauma is fundamental to the conduct and interpretation of practice and research. Prognostic studies and risk scores for outcomes following major traumatic bleeding require clear and accepted definitions of haemorrhage. A standardised approach to classification of major bleeding is also integral to support a comparison of findings in trauma registries and observational datasets.[90]

The traditional definition of major bleeding in trauma has been based on the need for ≥10 units of red blood cells (RBC) over 24 hours, using blood transfusion as a proxy for bleeding. However, there has been a paradigm shift in the management of major traumatic bleeding, with increased emphasis on early empiric transfusion support using balanced ratios of red cells and plasma. Many potentially preventable deaths in trauma are due to uncontrolled haemorrhage which occur in the first few hours after injury.[130] More recently, clinical studies have started to explore the role of pre-hospital transfusion of not just RBC but also other blood components, such as plasma (FFP), beginning prehospital or early after admission.[29,131]

The clinical validity of the traditional definition of massive transfusion has also been questioned.[88,132] This definition is based on retrospective analysis of transfusion needs over a period of up to 24 hours, often after a patient has been discharged from the emergency department and into areas such as intensive care units. The definition is

prone to survivorship bias as patients may die before reaching this threshold.[88,133] This has led to the development and reporting of other transfusion endpoints. These include critical administration threshold (CAT (≥3 units RBC during any 1-hour period in the first 24 hours after arrival), critical bleeding (≥5 units RBC in 4 hours)) and resuscitation intensity (blood and fluid administration within 30 minutes of hospital arrival), which mitigate some of the survivorship limitations with the historical definition.[90,132,134,135] However, these alternative definitions have not been widely applied internationally in the trauma literature.

With this in mind, the aim of this Delphi study was to develop a consensus definition of major bleeding. The Delphi technique uses an iterative process of group voting over several rounds to determine expert group consensus. The value of continuing to use transfusion as a surrogate marker of bleeding was recognised, given the challenges of documenting blood loss in the setting of trauma.

3.2 Methods

3.2.1 Delphi technique

A Delphi survey was conducted to reach a transfusion-based definition of major bleeding in adult trauma. This methodology was chosen as it allows for a large number of participants from geographically diverse regions to participate and provides the greatest degree of anonymity compared to other consensus methods; it has been used in trauma and other healthcare settings to develop consensus for other topics.[136,137,138]

3.2.2 Participant selection

The expert panel was recruited from three international research groups with an active interest in trauma haemorrhage (including specialists in trauma, emergency medicine, intensive care, anaesthesia, haematology and epidemiology):

- Chicheley Hall Trauma Colloquium (international group)
- Traumatic Haemostasis and Oxygenation Research (THOR) steering committee (international group)
- Principle investigators on the CRYOSTAT-2 trial (a randomised controlled trial (RCT) evaluating early cryoprecipitate in trauma, currently recruiting in all of the 26 major trauma centres in England and Wales).

3.2.3 Delphi steering group

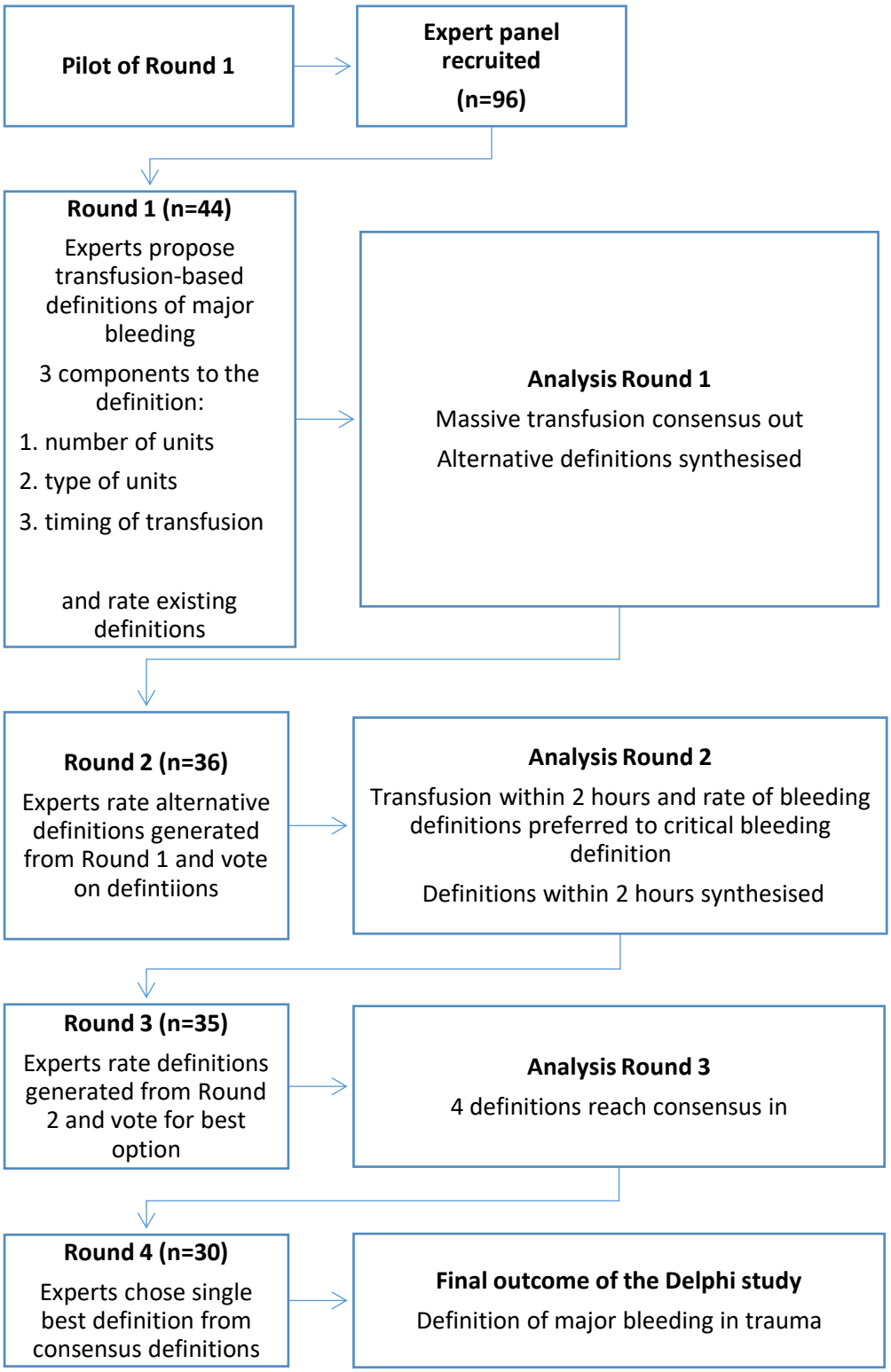
I led the 5-member steering group (HW, Nicola Curry, Simon Stanworth, Ly-Mee Yu, Ross Davenport) and prepared, analysed, supervised and monitored all Delphi rounds.

3.2.4 Conducting the Delphi survey

A Delphi survey was conducted over four rounds between April and November 2018 (Figure 3.1). After testing the first round in a pilot, an invitation email was sent to 96 eligible participants from the three expert groups. Questionnaires were designed using a web-based application, Online surveys (formerly Bristol Online Surveys).[139] The questionnaires took the format of open questions with free-text response boxes, or questions asking for agreement with a statement using 6-point Likert scale: 1=strongly agree, 2=agree, 3=somewhat agree, 4=somewhat disagree, 5=disagree, 6=strongly disagree.[140] Questions also included single best option questions. Comments and definitions proposed by participants in each round were considered by the steering

group and used to inform subsequent rounds of the survey.[141] Reminder emails were sent to non-responders. Non-participation in one round precluded further participation in subsequent rounds and no new participants were invited after the first round.

Figure 3.1. Participant flow through the four rounds of the Delphi study



In Round 1, participants were firstly asked how major bleeding should be defined; the definition was composed of 3 components: i) number of units, ii) type of blood component (RBC-based definition or transfusion inclusive of multiple blood components) and iii) timing of transfusion after injury. For each component of the definition, participants voted either by choosing one of the options given or suggesting an alternative as free text. Finally, participants were also asked to rate their level of agreement with the existing massive transfusion (≥10 units of RBC over 24 hours) and critical bleeding definitions (≥5 units RBC in 4 hours).[90]

As part of the iterative process, at the start of Rounds 2 and 3, participants were provided with the overall quantitative response of the group (descriptive statistics illustrating the group opinion), as well as categorised group comments and whether consensus had been reached. Based on the results from the first round, the questions in Round 2 expanded on two aspects of the timing of transfusion: i) rate of transfusion and ii) transfusion requirements up to a specific time point after injury (participants were asked to give a time point after injury when the cumulative transfusion total would be calculated e.g. if a participant voted for 4 hours after injury, this would include all units transfused up to that point). Participants were also asked to rate their level of agreement with, and select a best definition out of the amalgamated definitions that were synthesised from Round 1. At the end of Round 2, as the majority of responses indicated the best definition was within 2 hours of injury, a third round was conducted to clarify opinion on these definitions. Voting using similar methods to the previous rounds took place to reach consensus. At the end of the third round, there were 4

definitions that reached agreement and so to narrow down further, the fourth round asked for a single best definition.

3.2.5 Analysis

Consensus 'in' for each statement was set at ≥75% agreement (defined as somewhat agree-strongly agree (score 4-6)) and <15% disagreement (strongly disagree-disagree (score 1-2), modified from previous reports).[142,143] Consensus 'out' was set at ≥75% disagreement (somewhat disagree-strongly disagree (score 1-3)) and <15% agreement (strongly agree-agree (score 1-2)). Data from each round were analysed using Stata 15.1 (StataCorp. 2017. *Stata Statistical Software: Release 15.* College Station, TC: StataCorp LLC). Qualitative responses from Round 1 were categorised and analysed using framework analysis (NC and I coded independently and resolved any discrepancies with the steering group).

3.2.6 Ethics

The study was discussed with the University of Oxford Research Office. No formal research ethics approval was required for this study as it was a survey of healthcare professionals identified through networks. Completion of the survey was deemed as consent.

3.3 Results

Forty four of the 96 (46%) experts accepted the invitation to take part in Round 1. The majority of respondents (>80%) were from the UK and North America. The distribution of specialties and regions remained consistent from Round 1-4 (Table 3.1).

Table 3.1. Participant specialty and region

	Round 1 N=44 (%)	Round 2 N=36 (%)	Round 3 N=35 (%)	Round 4 N=30 (%)
Response rate (%)*	44/96 (45)	36/44 (82)	35/36 (97)	30/35 (86)
Specialty				
EM	11 (25)	9 (25)	9 (26)	7 (23)
Trauma	13 (30)	10 (28)	9 (26)	7 (23)
Anaesthesia	4 (9)	3 (8)	3 (9)	3 (10)
Haematology/Transfusion	3 (7)	3 (8)	3 (9)	3 (10)
Intensive care	4 (9)	4 (11)	4 (11)	4 (13)
Anaesthesia/intensive care	1 (2)	1 (3)	1 (3)	1 (3)
Trauma/intensive care	3 (7)	3 (8)	3 (9)	3 (10)
EM/intensive care	1 (2)	1 (3)	1 (3)	1 (3)
General surgery/trauma	1(2)	1 (3)	1 (3)	-
Other	1(2)	1 (3)	1 (3)	1 (3)
Region				
North America	14 (32)	11 (31)	10 (28)	9 (31)
Continental Europe	5 (11)	4 (11)	4 (11)	4 (14)
UK	24 (55)	20 (56)	20 (56)	16 (55)
Other	1 (2)	1 (3)	1 (3)	-

*Response rate = participants who responded out of eligible respondents. No new participants were recruited after round 1. Participants needed to have completed the previous round(s) in order to be eligible to continue to the next round. EM, Emergency Medicine.

3.3.1 Round 1

The results from Round 1 show how the expert panel voted on the three components of the transfusion definition: i) number of units, ii) type of component and iii) timing of transfusion (Table 3.2). Over 70% of the expert panel voted for timing of 1 or 2 hours (39% 1 hour; 36% 2 hours).

Table 3.2. Round 1 (n=44): results for timing, type of blood product and number of units

Timing (hours)	N (%)
1	17 (39)
2	16 (36)
3	6 (14)
4	3 (6.8)
6	1 (2)
Other	1 (2)
Type of blood component	
RBC only	26 (59)
Multiple blood component or other	18 (41)
Number of units	
≥ 2	8 (18)
≥ 3	7 (15)
≥ 4	15 (34)
≥ 5	5 (11)
≥ 6	5 (11)
Other*	4 (9)

RBC, red blood cell. * ≥ 3 units per hour, > 3 units/hour, >7, administration of blood components either pre-hospital or within 1 hr of arrival in ED

As each component had been addressed in separate questions, the three parts were synthesised into an overall combined definition. This was conducted by participant and yielded 30 different transfusion definitions for the next round (Table 3.3).

There was a diverse range of opinions with the two single most commonly proposed definitions ≥3 units RBC in 1 hour (N=5, 11%) and ≥ 4 units RBC in 2 hours (N=5, 11%). 41% of definitions included a definition of more than one type of blood component (non-RBC alone).

Table 3.3. Transfusion definitions proposed by participants at the end of Round 1

Definition			Number of participants	% of votes
Number of units	**Timing**	**Type of blood component**		
≥ 2	1 hour	RBC	2	5%
≥ 2	1 hour	RBC and FFP	1	2%
≥ 2	1 hour	(1:1:2 RBC/FFP/Platelet)	1	2%
≥ 2	2 hours	RBC	1	2%
≥ 2	2 hours	Any of RBC, FFP, Platelet	1	2%
≥ 2	2 hours	Any	1	2%
≥ 2	6 hours	RBC	1	2%
≥ 3	1 hour	RBC	5	11%
≥ 3	1 hour	Any of RBC, FFP, Platelet	1	2%
≥ 3	1 hour	Any	1	2%
≥ 3	2 hours	RBC	2	5%
≥ 4	1 hour	RBC	1	2%
≥ 4	1 hour	1:1:1 RBC:FFP:cryoprecipitate	1	2%
≥ 4	1 hour	Any	1	2%
≥ 4	1 hour	RBC, FFP	1	2%
≥ 4	2 hours	RBC	5	11%
≥ 4	2 hours	FFP, RBC	1	2%
≥ 4	2 hours	Any	2	5%
≥ 4	2 hours	At least 1 RBC and 1 FFP	1	2%
≥ 4	3 hours	RBC	2	5%
≥ 5	1 hour	RBC	2	5%
≥ 5	2 hours	RBC	1	2%
≥ 5	3 hours	RBC	1	2%
≥ 5	4 hours	RBC	1	2%
≥ 6	2 hours	RBC	1	2%
≥ 6	3 hours	RBC	1	2%
≥ 6	3 hours	RBC and FFP	1	2%
≥ 6	3 hours	Any and at least 2 RBC and 2 FFP	1	2%
≥ 6	4 hours	6 RBC or (3 RBC and 3 FFP)	1	2%
≥ 7	4 hours	3 RBC and 3 FFP	1	2%
Other	Other	TXA prehospital	1	2%

RBC, red blood cell; FFP, fresh frozen plasma

In addition to voting on components of a definition, the rating of existing definitions showed the massive transfusion definition (≥10 units RBC in 24 hours) reached consensus 'out' criteria (breakdown of the rating showed 34/44 (77%) disagreed with the definition (score 1-3) and 4/44 (9%) agreed (score 5-6). The critical bleeding definition (≥5 units RBC within 4 hours of injury) neither reached consensus 'in' nor 'out'. Three themes, each with their own categories, emerged from the framework analysis of the qualitative data:

i) type of components (RBC only, all types of blood components, specific combinations e.g. RBC and FFP)

ii) number of components (ratios of components, range of number of units)

iii) timing of transfusion (rate of transfusion, location: pre-hospital/emergency department).

3.3.2 Round 2

3.3.2.1 *Timing of transfusion and type of blood component*

When asked whether bleeding should be defined by rate of bleeding or transfusion at a certain time-point, neither option reached consensus. Within the sub-questions for rate of bleeding 42% voted for 3 units RBC/hour and 44% for 3 units any blood component/hour with the remainder voting other (Table 3.4). But within the sub-questions for definitions at a certain time-point, consensus 'in' was reached on 2 definitions: ≥3 units RBC in 1 hour and ≥4 units RBC in 2 hours (Table 3.5). Regarding the type of blood component, multiple blood components reached consensus, whereas an RBC-only definition did not (Table 3.5).

Table 3.4. Round 2 (n=36): Timing of transfusion: rate or time-point

Definition	Agree (score 4-6)	Disagree (score 1-2)	Consensus in
Major bleeding should be defined by rate of bleeding	75%	19%	N
Major bleeding should be defined by bleeding at a certain time-point	72%	17%	N

Timing of transfusion

Concerning the timing of a transfusion definition for research- if major bleeding were to be defined by rate of bleeding, how would you define it?	
3 units RBC/hour	42%
3 units any blood component/hour	44%
Other	14%

Concerning the timing of a transfusion definition for research- if major bleeding were to be defined at a certain time-point, what would it be?			
Definition	**Agree (score 4-6)**	**Disagree (score 1-2)**	**Consensus in**
Major bleeding should be defined within:			
1 hour of injury	53%	33%	N
2 hours of injury	78%	6%	**Y**
4 hours of injury	64%	19%	N

Table 3.5. Round 2 (n=36): Type of blood component and combined definitions

Type of blood component

Concerning the type of blood component in a definition of major bleeding – please indicate your level of agreement with the following:			
Definition	**Agree (score 4-6)**	**Disagree (score 1-2)**	**Consensus in**
Major bleeding should be based on RBC transfusion only	33 %	50%	N
Major bleeding should include all types of blood components (multiple blood components)	89%	6%	**Y**

Combined definitions

If you were to interrogate a database to capture patients with major bleeding in acute trauma (e.g. that could be used to develop a prediction score), how would you define major bleeding? Please indicate your level of agreement with the following:			
Definition	**Agree (score 4-6)**	**Disagree (score 1-2)**	**Consensus in**
≥ 3 units RBC in 1 hour	86%	3%	**Y**
≥ 4 units any blood component in 4 hours	67%	22%	N
≥ 4 units RBC in 2 hours	78%	11%	**Y**
≥ 5 units RBC in 4 hours	53%	19%	N

3.3.2.2 *Single best definition*

The final question of the second round asked participants to choose a single best definition out of the 30 transfusion definitions (listed in Table 3.3) derived from the previous round. Only 9/36 (25%) of participants selected either of the consensus options (i.e. ≥3 units RBC in 1 hour and ≥4 units RBC in 2 hours) (Table 3.6). The majority of responses indicated a definition within 2 hours of injury.

Table 3.6. Round 2 (n=36): Single best definition

Choose one definition from the definitions suggested by the group in Round 1				
Number of units	**Timing**	**Type of blood component**	**Frequency**	**%**
≥ 2	1 hour	1:1:2 RBC/FFP/Platelet	1	3%
≥ 2	2 hours	RBC	1	3%
≥ 3	1 hour	RBC	5	14%
≥ 3	1 hour	Any of RBC, FFP, Platelet	4	11%
≥ 4	1 hour	RBC	1	3%
≥ 4	1 hour	1:1:1 RBC:FFP:cryoprecipitate	2	6%
≥ 4	1 hour	Any	4	11%
≥ 4	2 hours	RBC	4	11%
≥ 4	2 hours	FFP, RBC	3	8%
≥ 4	2 hours	Any	4	11%
≥ 4	2 hours	At least 1 RBC and 1 FFP	3	8%
≥ 4	3 hours	RBC	2	6%
≥ 5	2 hours	RBC	1	3%
≥ 5	3 hours	RBC	1	3%
Total			36	100%

3.3.3 Round 3

In Round 3 there was broad endorsement of the definitions within 2 hours. Four definitions reached consensus 'in' (Table 3.7). For the 4 definitions that reached consensus: 18 participants (51%) agreed with all definitions that reached consensus and 22 (63%) agreed with all of the 2 hour options. The rate-based definitions approached, but did not reach the criteria for consensus 'in.' Distilling down the definitions further, the most voted for single best definition was ≥4 units of multiple blood components within 2 hours of injury (42%) (Table 3.7). Some participants commented that a short duration may exclude patients where prehospital blood may not be available and patients with a longer transport time and a rate-based definition may be more appropriate.

3.3.4 Round 4

In the final round, 20/30 (67%) participants voted for ≥4 units of multiple blood components within 2 hours of injury as the best definition (out of the 4 definitions that had reached consensus in Round 3) (Table 3.7).

Table 3.7. Round 3 (n=35) and Round 4 (n=30): Definitions reaching consensus

Definition	**Round 3**			**Round 4 best option**
	Agree (score 4-6)	**Disagree (score 1-2)**	**Consensus in**	
≥ 3 units RBC within 1 hour of injury	57%	20%	N	-
≥ 3 units any of RBC, FFP, Plt and whole blood within 1 hour of injury	69%	23%	N	-
≥ 4 units RBC within 1 hour of injury	60%	29%	N	-
≥ 4 units any of RBC, FFP, Plt and whole blood within 1 hour of injury	80% (16/28, 57% UK)	11%	Y	**27 %**
≥ 4 units RBC within 2 hours of injury	74% (13/26, 50% UK)	11%	Y	**3%**
≥ 4 units at least 1 RBC and 1 FFP within 2 hours of injury	77% (14/25, 56% UK)	11%	Y	**3%**
≥ 4 units any (including whole blood) within 2 hours of injury	86% (16/30, 53% UK)	6%	Y	**67%**
Rate-based definitions				
Need for 3 units of RBC/hour within the first 2 hours of injury	69%	14%	N	-
Need for 3 units of any blood component within the first 2 hours of injury	69%	11%	N	-

3.4 Discussion

In this Delphi survey, the consensus opinion of the expert panel was not to use the traditional definition of massive transfusion as a definition of bleeding in trauma for research purposes. Instead, consensus for a new definition of major bleeding in trauma was reached; this is defined as 4 units or more of multiple (any) blood components within 2 hours of injury. The findings of this Delphi survey are in keeping with the evolution of trauma transfusion practice which now emphasises the role of multiple types of blood components and timely administration within a few hours after injury, and not solely after hospital arrival.

Unlike previous definitions, of the four definitions submitted for the final consensus round, three were based on transfusion of multiple types of blood component (not just RBC). This differs to previously described definitions (massive transfusion, critical bleeding, CAT) that are based on RBC only. The only metric of bleeding severity that includes other blood components is the resuscitation intensity (RI).[89] This metric is composed of resuscitation fluids that include RBC, FFP, platelet and fluid administration within 30 minutes of hospital arrival. Including fluids in the definition was not part of this Delphi process and did not feature in the qualitative comments, although it could be explored in further work to develop a composite definition of bleeding.

The International Society on Thrombosis and Haemostasis published a recommended uniform definition of major bleeding for the evaluation of anti-haemostatic agents in 2005.[144] This definition encompasses red cell transfusion and critical sites of bleeding and mortality, but was not designed specifically with the types of bleeding encountered in acute trauma in mind.

Another difference in our consensus definition is that it is based on transfusion requirement from the time of injury, whereas other previously described definitions commence after hospital admission. This earlier time point encompasses a critical period after injury where key decisions on triage and management are made and may have significant impact on outcome after traumatic haemorrhage. This critical early phase after injury shows the importance and feasibility of early transfusion. This has been the focus of intervention in trauma haemorrhage trials e.g. PROPPR,[71] PAMPer,[118] CRYOSTAT-1[99] and other ongoing trials CRYOSTAT-2 (ISRCTN 14998314), RePHILL.[145]

In the study of trauma haemorrhage, the population captured by any definitions of major bleeding will depend on the metrics used to define bleeding. Clinically relevant definitions that best capture the at risk population are essential in the development of any prediction models for bleeding outcomes. Consequently, the validity of any prediction model to predict mortality may depend on the definition used. Meyer et al recently explored different transfusion based definitions of major bleeding and their validity in predicting early death in trauma in the PROPPR RCT.[87] They assessed the validity of two surrogate metrics (CAT+ and RI) for early mortality in severe trauma in the PROPPR RCT and compared them to the traditional definition of massive transfusion.[87] (CAT+ was defined as ≥3 RBC in the first hour after admission). RI was also assessed as a categorical variable RI4+ (≥4 units in 30 minutes). The results showed both CAT+ and RI4+ were superior predictors to massive transfusion, capturing patients omitted by the massive transfusion definition. They showed that while CAT+ may be suited for patients receiving an RBC-dominant resuscitation, RI4+ is more comprehensive. It is important to note that the work was in the context of clinical trial

data and based on definitions that did not include prehospital transfusion. However, it does show that massive transfusion is an inferior predictor of mortality and further evidence to suggest a move away from the traditional definition of massive transfusion in research.

3.4.1 Applicability of consensus definition

This Delphi process has yielded a pragmatic transfusion-based definition that could help groups doing research in this field. The consensus definition reached by the panel incorporates the transfusion of multiple blood components early after injury, using a cut-off at a specific time-point. It is acknowledged that this may not wholly reflect the intensity of transfusion and therefore the overall degree of blood loss in the same way that a rate-based definition (units per hour) may. The CAT is an example of a rate-based definition, but at the time it was developed, it did not include transfusion pre-admission. Data on hourly transfusion rate may not be readily extractable from registry data.

There are caveats to the applicability of the consensus definitions. Even within mature trauma systems, there are regional differences in practice that may affect the generalisability of the definitions e.g. i) location (proximity/transport times from injury to hospital) ii) prehospital transfusion availability/practice. There are also limitations with the use of a short time-frame in the definition (within 2 hours of injury); patients with delays in transport might not be captured due to the timing issue and/or access to blood components. These limitations were described by a small number of Delphi participants. However, the alternative rate-based definitions approached, but did not reach consensus ‘in’.

3.4.2 Strengths

This is the first report of a Delphi process to appraise how major traumatic bleeding is defined for research purposes. There was a good level of participation throughout the survey, particularly rounds 2-4. The international panel of experts who took part in the study reflected the multidisciplinary nature of trauma care and there was consistent representation from specialities in each round.

3.4.3 Limitations

Although there was good international representation, half of the participants in our Delphi survey were from the UK and there were relatively few participants outside of the UK and North America. One of the proposed definitions reflected NICE (National Institute for Healthcare Excellence) guidelines in UK on transfusion in trauma (2 FFP and 2 RBC empirical transfusion),[146] although the final definition for consensus was more generalisable to include any blood component. It may be that the Delphi definition may be more suited to countries with similar transfusion practice to the UK. There are also limitations in the breadth of participants in the panel. I recognise that a more diverse panel that included patients and other stakeholders may have had an impact on the development and choice of definition.

The use of factor concentrates was not specifically explored in this study, rather the definitions were comprised of blood components and it was not known whether participants considered concentrates interchangeable with conventional blood products. In summary, one definition may not fit all as practice does differ even within Europe/North America. A particular challenge is to find an outcome or more global definition that could be applied to different settings.

Finally, the definition of major bleeding in this study is based on a transfusion outcome. The steering group of this Delphi study and others acknowledge that significant traumatic haemorrhage may also occur without meeting the transfusion parameters for major bleeding especially if interventions such as surgery or angiography are employed to rapidly control bleeding.[66] A composite outcome comprising transfusion, surgery for haemostasis, or angiography with embolization has been proposed,[66,74] but might be more complex to apply in practice. Further work leading on from this Delphi Study could explore combined definitions.

In order to be able to accurately predict bleeding, the definitions have implications for how transfusion data are captured and recorded in trauma registries and in observational studies. Of particular importance is the capture of detailed data on specific timings and type of component transfused both in the prehospital and hospital settings. Moving away from the definition of the massive transfusion, future work could use this consensus definition to identify characteristics of patients with traumatic haemorrhage both retrospectively and prospectively. To test its general applicability, further work could compare populations identified by this definition in different settings and countries and exploring consensus on composite definitions of bleeding.

3.5 Conclusion

In this Delphi study, the expert panel reached consensus on a transfusion-based definition of major bleeding in trauma for use in clinical research. This differs from previous definitions of massive haemorrhage: a shorter timeframe (within 2 hours) to reflect the acuity of traumatic bleeding and the option for multiple blood components in keeping with balanced approach to blood component resuscitation. This consensus

definition could be used in further work to guide the recording of transfusion data in trauma registries, and in research to characterise patients at risk of major bleeding.

3.6 Acknowledgements

I am very grateful to all the experts who participated in the Delphi consensus process, including Dr Adam Brooks, UK; Dr Heidi Doughty, UK; Dr Beverley Hunt, UK; Dr Daniel Horner, UK; Dr Donald Jenkins, USA; Dr Nicole Juffermans, Netherlands; Dr Lucy Kornblith, USA; Dr Marc Maegele, Germany; Dr Max Marsden, UK; Dr Phil Moss, UK; Dr Matthew Neal, USA; Dr Phil Spinella, USA; Dr Martin Schreiber, USA; Dr Susanne Kellett, UK; Dr Tom Woolley, UK; Dr Tony Kehoe, UK; Dr Mark Yazer, USA and others on the panel (who wished to retain anonymity).

Chapter 4 Characteristics of older and younger adults with major bleeding in the UK trauma registry

4.1 Introduction

Although advances in trauma care and a better understanding of coagulopathy have improved outcomes for patients with injury, uncontrolled bleeding continues to be a significant cause of morbidity and mortality in trauma.[29] Over recent years, the age demographic of trauma has changed with a greater proportion of older people affected by severe injury than before.[3,4] The impact of age and patient factors on bleeding is an area of uncertainty, particularly for the population of older patients where current evidence is limited and yet physiological responses to shock and bleeding may be different to younger patients.

Early identification of patients with major bleeding is essential for appropriate triage and management. It is possible that factors such as age-related decline in baseline cardiovascular function, pattern of injury and response to bleeding are different in older people and may alter their clinical presentation with bleeding. However, data comparing characteristics of older people with their younger counterparts are limited. A better knowledge of the population at risk and understanding differences between older and younger people could provide a foundation upon which to develop an age-appropriate approach to diagnosis and treatment of bleeding.

The Delphi process for developing a consensus definition of major bleeding was described in the previous chapter. In this chapter, the definition was applied to the UK

trauma registry (Trauma Audit Research Network (TARN)). Patient characteristics were compared with those reported for existing definitions of major bleeding.

4.2 Aims

The aims of this chapter were to describe:

i) the characteristics

ii) transfusion requirements

iii) mortality

in older (aged ≥65 years) and younger patients (<65 years of age) with major bleeding in the TARN database.

4.3 Methods

4.3.1 Study design and the TARN database

A retrospective analysis was performed on a cohort of adult trauma patients (aged 16 and above) in the TARN database. TARN is the national clinical audit and quality assurance programme for injury in the UK.[147,148] It has grown, since its inception in 1989, to be the largest trauma registry in Europe. The aim of TARN is to collect and analyse clinical and epidemiological data, to aid the development of trauma services and to inform the research agenda.

Data are collected prospectively on patients suffering trauma in England and Wales who meet the following criteria:[149]

Inclusion criteria

A patient with trauma who:

- Is admitted for 72 hours or more, or
- Is admitted to intensive care, or
- Died at the hospital
- Was transferred into the hospital for specialist care
- Was transferred to another hospital for specialist care or an intensive care bed.

AND

- Whose isolated injuries meet a set of severity criteria

Exclusion criteria

- Patients who die at scene or en route to hospital.
- Patients over 65 with isolated hip or pubic ramus fracture
- Patients with isolated closed limb injuries other than to the femoral shaft.

For each patient meeting the TARN inclusion criteria, trained coordinators from each participating hospital collect data on patient demographics, injury, intervention, investigation and outcomes. These data are entered into the central TARN database, according to guidance in the TARN procedures manual.[149] TARN analysts in the central office code injuries and check each submission. Data quality standards and monitoring are key aspects in the conduct of the TARN database (Table 4.1).

Table 4.1. TARN data quality methods according to Wang and Strong's conceptual model for measuring data quality

Domain[150]	Description	TARN methods
Completeness	All necessary data are provided	Accreditation check hospital level.
Accuracy	Data conform with a verifiable source	Checked at source
Precision	Data value is specific	Checked centrally and at source.
Correctness	Data are within specified value domains	Flags are raised for some vital sign parameters. All reports submitted are checked and any queries are raised centrally within one week of submission.
Consistency	Data are logical across data points	In-built
Timeliness	Trauma registry data are available when needed	TARN reports are submitted within 30 days of admission.

TARN monitors data and feedbacks data accreditation measures to participating hospitals including:

- Hospital data accreditation % - a measure of how often core fields are completed in every submission including for the following:
    - Glasgow coma score (GCS)/intubation
    - Incident or 999 call date and time
    - Arrival time
    - Transfer reason, request date and hospital
    - Computed tomography scan time
    - Operation times, grades, specialty
    - Doctors in the emergency department (ED): times, grades, specialities
    - Injury detail
    - Pre-existing medical conditions
    - Pupils reactivity for severe head injury (abbreviated injury score (AIS) 3+).

As a check of data completeness, the number of submissions made to TARN is compared to the number that appear to meet criteria for TARN inclusion in the Hospital Episode Statistics dataset.

4.3.2 Eligibility criteria for study on major bleeding

TARN-eligible adults aged 16 and above, who were admitted directly to an MTC between 1 January 2012 and 31 December 2017, were included in the study.

In April 2012, major trauma services across England were organised into trauma networks. Within these networks, severely injured patients are triaged directly to a regional MTC. These major centres have the facilities to provide specialised trauma care including pre-hospital blood support and one of the requirements of an MTC is to submit detailed individual patient data for injured patients to TARN.

I decided to focus this study on patients admitted directly to MTCs, rather than Trauma Units because:

- Patients with severe injury or suspected major bleeding would be more likely to be triaged to an MTC where there is specialist expertise to control haemorrhage and provision of pre-hospital blood (trauma units are not set up to provide blood pre-hospital).
- Data completeness, particularly of transfusion data is higher for MTCs compared with Trauma Units.

4.3.3 Definition of major bleeding: transfusion outcome

The outcome of interest was major bleeding. *A priori*, this was defined as the need for ≥4 units red blood cells (RBCs) in 24 hours (based on the definition used by Stanworth et al).[29] This definition is dependent on knowing the timing and volume of each blood component. However, after the initial data extraction from the TARN database in 2017, it was noted that there was a multi-recording problem where not all blood component transfusions were recorded individually, but rather as an overall total. To address this, the bug was fixed in the TARN database for prospective cases and TARN contacted hospitals to try and retrieve the missing data.

Previous models for massive bleeding in trauma traditionally predict for massive transfusion (≥10 units within 24 hours of admission). However, the first few hours after injury are particularly crucial; death from bleeding occurs early and recent studies show the median time to death from haemorrhage is 2-3 hours after admission.[12,71] As there is no firm consensus on a definition of major bleeding in trauma, a Delphi study was undertaken to re-appraise the definition (see Chapter 3).

The outcome of the Delphi study was a consensus transfusion-based definition of major haemorrhage: the need for ≥4 units of any blood product (RBC, fresh frozen plasma (FFP), cryoprecipitate, platelets) within 2 hours of injury. This consensus definition was used as the outcome for the TARN study on major bleeding.

In order to generate this outcome in the TARN dataset, the following data were required:

1. Time of injury
2. Number of units of each blood component transfused (within 2 hours of injury)

4.3.4 Selection of risk factors

The TARN dataset was interrogated for variables of interest relevant to traumatic haemorrhage. These variables were chosen because they were of importance in previous prediction scores and/or clinically relevant factors that could differ in young and older populations presenting with early bleeding. Data on the following presenting characteristics and outcomes were also obtained.

Presenting characteristics:

Age; gender; penetrating (vs blunt) injury; mechanism of injury; ISS; body region and severity of injury by body region; charlston comorbidity index (CCI); atrial fibrillation (AF); ischaemic heart disease (IHD); hypertension; anticoagulation and antiplatelet therapy; vital signs (pre-hospital and in ED) for systolic blood pressure (SBP), heart rate (HR), GCS; use of tranexamic acid (TXA); pre-hospital arrest.

Outcomes:

Transfusion requirements within the first 2 hours (h) of injury; 6-h, 24-h and 28-day all-cause mortality (after admission).

4.3.5 Subgroup analysis

A post-hoc subgroup analysis was performed for patients with blunt injuries, as the presenting characteristics of patients and vital signs could be affected by the type of injury.

4.3.6 Statistical analysis

Patients were divided into two groups: younger (aged 16-64) and older (aged 65 and above). The characteristics of older and younger patients were examined using descriptive statistics. I examined the overall TARN cohort admitted directly to an MTC and the cohort with major bleeding. Continuous variables were described as mean and standard deviation if normally distributed and median and interquartile range (IQR) if skewed (normality assessed using histograms). Dichotomous variables were presented using percentages. Comparisons of continuous data were performed with t-test for normally distributed continuous data, Mann-Whitney's U test for skewed data, and chi-squared or 2-sided Fisher's exact test for categorical data. Data analyses were carried out in Stata version 15.1 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

4.3.7 Ethics

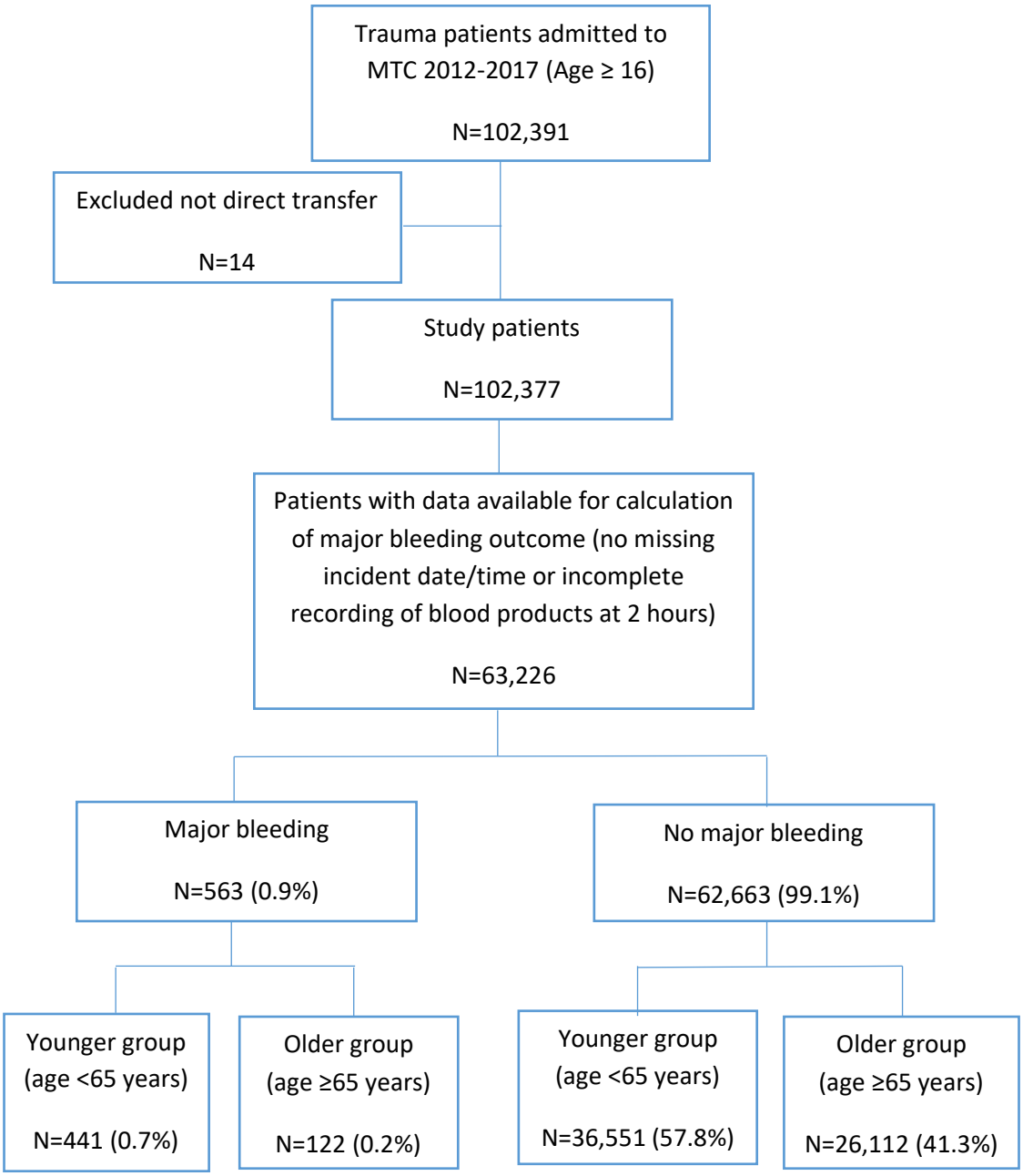
This work was in collaboration with TARN and all data were analysed anonymously. TARN has been granted ethical approval for research on anonymised data that it holds (PIAG Section 60).

4.4 Results

4.4.1 Baseline characteristics

A flow diagram of the derivation of the study population is shown in Figure 4.1.

Figure 4.1. Derivation of study population



Between 1 January 2012 and 31 December 2017, a total of 102,391 adult patients were enrolled in the TARN database. 14 patients not directly admitted to an MTC were excluded. Of the remaining 102,377 patients, there were 62,223 patients with a known bleeding outcome. There were 563 patients (0.9%) who met the definition of major bleeding (441 younger patients (0.7%) and 122 older patients (0.2%)).

4.4.1.1 *Baseline characteristics of overall cohort*

The baseline characteristics of the overall cohort (n=102,377) are shown in

Table 4.2. The group of young patients (age <65) were predominantly male (73.6%), with over 75% of injuries due to RTC or falls. However, for the older group (age ≥65 years) less than half the patients were male (43.3%) and the majority of injuries were due to falls <2m (71.5%). The median (IQR) ISS was higher in the young group 13 (9-25) vs 9 (9-20) in the young group, P-value <0.001. Pre-existing hypertension was more common in older patients compared with younger patients (40.1% vs 7.1%).

Table 4.2. Baseline characteristics of overall cohort (TARN)

	Young <65 N=60,220	Older ≥65 N=42,157	P-value	Total N=102,377
Age, mean (SD)	41 (15)	80 (9)		57 (23)
Range	16 to 64	65 to 114		65 to 114
Male	44,314 (73.6%)	18,234 (43.3%)	<0.001	62,548 (61.1%)
Penetrating injury	4,730 (7.9%)	264 (0.6%)	<0.001	4,994 (4.9%)
Mechanism of injury			<0.001	
RTC	24,752 (41.1%)	5,182 (12.3%)		29,934 (29.2%)
Fall≥2m	10,324 (17.1%)	5,836 (13.8%)		16,160 (15.8%)
Fall<2m	13,880 (23.0%)	30,156 (71.5%)		44,036 (43.0%)
Shooting/stabbing	4,248 (7.1%)	164 (0.4%)		4,412 (4.3%)
Blow(s)	4,589 (7.6%)	403 (1.0%)		4,992 (4.9%)
Other	2,427 (4.0%)	416 (1.0%)		2,843 (2.8%)
ISS, median (IQR)	13 (9-25)	9 (9-20)	<0.001	12 (9-22)
CCI Band			<0.001	
Minor/none	36,716 (61.0%)	12,775 (30.3%)		49,491 (48.3%)
Mild	15,311 (25.4%)	18,605 (44.1%)		33,916 (33.1%)
Moderate	1,747 (2.9%)	7,211 (17.1%)		8,958 (8.8%)
Severe	933 (1.5%)	1,472 (3.5%)		2,405 (2.3%)
Missing, n(%)	*5,513 (9.2%)*	*2,094 (5.0%)*		*7,607 (7.4%)*
Anticoagulation	80 (0.1%)	550 (1.3%)	<0.001	630 (0.6%)
Antiplatelet	114 (0.2%)	652 (1.5%)	<0.001	766 (0.7%)
Warfarin	78 (0.1%)	539 (1.3%)	<0.001	617 (0.6%)
Pre-hospital arrest	764 (1.3%)	185 (0.4%)	<0.001	949 (0.9%)
TXA	14,126 (23.5%)	3,326 (7.9%)	<0.001	17,452 (17.0%)
MHP	3,469 (5.8%)	661 (1.6%)	<0.001	4,130 (4.0%)
Hypertension	4,260 (7.1%)	16,900 (40.1%)	<0.001	21,160 (20.7%)
Ischaemic heart disease	448 (0.7%)	3,170 (7.5%)	<0.001	3,618 (3.5%)
Atrial fibrillation	283 (0.5%)	3,957 (9.4%)	<0.001	4,240 (4.1%)

ISS, injury severity score; CCI, charlston comorbidity index: minor/none=0, mild 1-5, moderate 6-10, severe >10; MHP, major haemorrhage protocol

The distribution and severity of injuries are shown in Table 4.3. Younger patients were twice as likely to have polytrauma compared to the older group (21.5% vs 10.7%). The distribution of injuries was broadly similar between the two age groups, except in the younger group where there was a higher proportion of abdominal injuries, unstable pelvic fracture and open fractures. Nearly a third of younger patients had a severe thoracic injury compared with 20.2% in the older group.

Table 4.3. Injury characteristics of patients: overall cohort

	Young <65 N=60,220	Older ≥65 N=42,157	P-value	Total N=102,377
Polytrauma	12,921 (21.5%)	4,492 (10.7%)	<0.001	17,413 (17.0%)
Body region injured				
TBI	16,162 (26.8%)	12,432 (29.5%)	<0.001	28,594 (27.9%)
Facial	1,698 (2.8%)	808 (1.9%)	<0.001	2,506 (2.4%)
Thoracic	15,203 (25.2%)	10,244 (24.3%)	<0.001	25,447 (24.9%)
Abdominal	5,133 (8.5%)	824 (2.0%)	<0.001	5,957 (5.8%)
Extremity	9,041 (15.0%)	6,288 (14.9%)	0.67	15,329 (15.0%)
Pelvis Stable	4,578 (7.6%)	4,979 (11.8%)	<0.001	9,557 (9.3%)
Pelvis Unstable	3,603 (6.0%)	1,193 (2.8%)	<0.001	4,796 (4.7%)
Open femur	1,063 (1.8%)	150 (0.4%)	<0.001	1,213 (1.2%)
Open fracture	5,686 (9.4%)	1,549 (3.7%)	<0.001	7,235 (7.1%)
Severe injury (AIS 3+)				
Head	16,748 (27.8%)	12,957 (30.7%)	<0.001	29,705 (29.0%)
Thorax	19,059 (31.6%)	8,495 (20.2%)	<0.001	27,554 (26.9%)
Abdomen	4,716 (7.8%)	657 (1.6%)	<0.001	5,373 (5.2%)
Spine	5,232 (8.7%)	4,073 (9.7%)	<0.001	9,305 (9.1%)
Pelvis	3,608 (6.0%)	1,196 (2.8%)	<0.001	4,804 (4.7%)
Limbs	17,500 (29.1%)	10,519 (25.0%)	<0.001	28,019 (27.4%)
Other	1,523 (2.5%)	244 (0.6%)	<0.001	1,767 (1.7%)

TBI, traumatic brain injury; AIS, abbreviated injury scale

Vital signs are shown in Table 4.4. Older patients presented with a higher pre-hospital blood pressure compared to younger patients (mean (sd) 146 (32) vs 129 (28)). There was no difference in the mean pre-hospital pulse between old and young, however the proportion of young patients with pre-hospital heart rate ≥100 bpm was higher in the young group (23.7% vs 14.5%).

Table 4.4. Vital signs of patients: overall cohort

	Young <65 N=60,220	Older ≥65 N=42,157	P-value	Total N=102,377
Pre-hospital SBP (mmHg)				
Mean (SD)	129 (28)	146 (32)	<0.001	136 (31)
Missing, n(%)	*14,940 (24.8%)*	*10,130 (24.0%)*		*25,070 (24.5%)*
Pre-hospital pulse (bpm)				
Mean (SD)	89 (24)	83 (20)	<0.001	87 (23)
Missing, n(%)	*13,128 (21.8%)*	*9,506 (22.5%)*		*22,634 (22.1%)*
Pre-hospital GCS				
Median (IQR)	15 (14-15)	15 (14-15)	<0.001	15 (14-15)
Missing, n(%)	*11,920 (19.8%)*	*9,147 (21.7%)*		*21,067 (20.6%)*
ED systolic BP (mmHg)				
Mean (SD)	132 (26)	146 (31)	<0.001	137 (29)
Missing, n(%)	*4,055 (6.7%)*	*3,148 (7.5%)*		*7,203 (7.0%)*
ED pulse (bpm)				
Mean (SD)	87 (22)	82 (18)	<0.001	85 (21)
Missing, n(%)	*3,520 (5.8%)*	*3,008 (7.1%)*		*6,528 6.4%)*
ED GCS				
Median (IQR)	15 (15-15)	15 (14-15)	0.037	15 (15-15)
Missing, n(%)	*7,921 (13.2%)*	*4,004 (9.5%)*		*11,925 (11.6%)*
Pre-hospital SBP ≤90 mmHg	3,152 (5.2%)	1,373 (3.3%)	<0.001	4,525 (4.4%)
Missing, n(%)	*14,940 (24.8%)*	*10,130 (24.0%)*		*25,070 (24.5%)*
Pre-hospital pulse ≥100 bpm	14,290 (23.7%)	6,098 (14.5%)	<0.001	20,388 (19.9%)
Missing, n(%)	*13,128 (21.8%)*	*9,506 (22.5%)*		*22,634 (22.1%)*

GCS, Glasgow Coma Scale; SBP, systolic blood pressure; bpm, beats per minute

Transfusion requirements

Blood transfusion requirement in the first two hours of injury was low; approximately 99% of both young and older patients did not receive any blood component (Table 4.5).

Although the proportion of patients requiring transfusion was low, younger patients were more likely to receive transfusion than older adults, particularly for red blood cell transfusion (Table 4.5).

Table 4.5. Transfusion requirements within 2 hours of injury: overall cohort

	Young <65 (N = 60,220)	Older ≥65 (N = 42,157)	P-value	Total (N = 102,377)
RBC within 2 hours (units)			<0.001	
0	58,176 (96.6%)	41,769 (99.1%)		99,945 (97.6%)
>0 and <3	751 (1.3%)	154 (0.4%)		905 (0.9%)
3-4	389 (0.7%)	113 (0.3%)		502 (0.5%)
>4	251 (0.4%)	64 (0.2%)		315 (0.3%)
Missing, n (%)	653 (1.1%)	57 (0.1%)		710 (0.7%)
FFP within 2 hours (units)			<0.001	
0	59,291 (98.5%)	41,980 (99.6%)		101,271 (98.9%)
1-2	154 (0.3%)	64 (0.2%)		218 (0.2%)
3-4	120 (0.2%)	43 (0.1%)		163 (0.2%)
>4	31 (0.05%)	16 (0.04%)		47 (0.05%)
Missing, n (%)	624 (1.0%)	54 (0.1%)		678 (0.7%)
Cryoprecipitate within 2 hours (units)			0.439	
0	60,079 (99.8%)	42,138 (99.95%)		102,217 (99.8%)
1-2	19 (0.03%)	11 (0.03%)		30 (0.03%)
3-4	10 (0.02%)	5 (0.01%)		15 (0.01%)
Missing, n (%)	112 (0.19%)	3 (0.01%)		115 (0.11%)
Platelets within 2 hours (pools)			0.588	
0	59,980 (99.6%)	42,113 (99.9%)		102,093 (99.7%)
1-2	52 (0.09%)	31 (0.07%)		83 (0.08%)
3-4	1*	1*		2*
>4	0*	1*		1*
Missing, n (%)	187 (0.31%)	11 (0.03%)		198 (0.19%)
Total within 2 hours (units)			0.588	
<4	59,626 (99.0%)	41,993 (99.6%)		101,619 (99.3%)
4	221 (0.4%)	44 (0.1%)		265 (0.3%)
5-6	163 (0.3%)	44 (0.1%)		207 (0.2%)
7-8	99 (0.2%)	32 (0.1%)		131 (0.1%)
>8	111 (0.2%)	44 (0.1%)		155 (0.2%)

*% not presented

Overall mortality was higher in the older group compared with the younger group (14.7% vs 5.6%) (Table 4.6). Mortality across both age groups was fairly similar up to 24 hours. However, by 28 days the increased mortality in the older group became more apparent (11.3% vs 4.8% in the young) (Table 4.6).

Table 4.6. All-cause mortality of patients: overall cohort

	Young <65 (N = 60,220)	Older ≥65 (N = 42,157)	P-value	Total N=102,377
Known outcome	57,528 (95.5%)	40,506 (96.1%)	<0.001	98,034 (95.8%)
Within 6-hr mortality	738 (1.2%)	439 (1.0%)	0.007	1,177 (1.1%)
Within 24-hr mortality	1,257 (2.1%)	1,079 (2.6%)	<0.001	2,336 (2.3%)
Within 28-day mortality	2,862 (4.8%)	4,746 (11.3%)	<0.001	7,608 (7.4%)
Within 30 days or discharge*	3,364 (5.6%)	6,199 (14.7%)	<0.001	9,563 (9.3%)

*whichever occurred earliest

4.4.1.2 *Baseline characteristics of patients with major bleeding*

The baseline characteristics of the patients with bleeding are shown in Table 4.7. Demographics of patients with major bleeding (TARN) . The older group were mostly male (61.5%), mean (SD) age of 77 (7), were severely injured and suffered mostly blunt injury (98%). The two leading causes of injury were RTC (67%) and falls ≥2 m (19.7%).

The younger group had a mean age of 34 and had similar injury severity to the older group. However, there was a larger proportion of males (83.3% vs 61.5%, P-value <0.001) and a higher proportion of penetrating injury (29% vs 2%, P-value <0.001) in the young group compared with the older group. The mechanism of injury was different in the younger group with RTC and shooting/stabbing injury accounting for the majority of injuries (50% and 30% respectively).

Table 4.7. Demographics of patients with major bleeding (TARN)

Definition of major bleeding = ≥4 units of blood components (RBC, FFP, cryoprecipitate, platelets) within 2 hours of injury.

	Young <65 (N = 441)	Older ≥65 (N = 122)	P-value	Total (N = 563)
Age, mean (SD)	34 (14)	77 (7)	-	44 (22)
Range	16 to 64	65 to 93		
Male	368 (83.4%)	75 (61.5%)	<0.001	443 (78.7%)
Penetrating injury	132 (29.9%)	2 (1.6%)	<0.001	134 (23.8%)
Mechanism of injury			<0.001	
RTC	237 (53.7%)	82 (67.2%)		319 (56.7%)
Fall ≥2 m	56 (12.7%)	24 (19.7%)		80 (14.2%)
Fall <2 m	1 (0.2%)	7 (5.7%)		8 (1.4%)
Shooting/stabbing	126 (28.6%)	2 (1.6%)		128 (22.7%)
Blow(s)	7 (1.6%)	2 (1.6%)		9 (1.6%)
Other	14 (3.2%)	5 (4.1%)		19 (3.4%)
ISS, mean (SD)	34 (17)	37 (14)	0.061	34 (16)
CCI band			<0.001	
Minor/none	262 (72.0%)	41 (43.2%)		303 (66.0%)
Mild	88 (24.2%)	39 (41.1%)		127 (27.7%)
Moderate	8 (2.2%)	13 (13.7%)		21 (4.6%)
Severe	6 (1.6%)	2 (2.1%)		8 (1.7%)
Missing, n (%)	*77 (17.5%)*	*27 (22.1%)*		*104 (18.5%)*
Anticoagulation	0 (0.0%)	3 (2.5%)	-	3 (0.5%)
Antiplatelet	1 (0.2%)	0 (0.0%)	-	1 (0.2%)
Pre-hospital arrest	50 (11.3%)	14 (11.5%)	0.966	64 (11.4%)
TXA	420 (95.2%)	110 (90.2%)	0.035	530 (94.1%)
MHP activation	318 (72.1%)	78 (63.9%)	0.080	396 (70.3%)
Hypertension	16 (3.6%)	32 (26.2%)	<0.001	48 (8.5%)
IHD	3 (0.7%)	11 (9.0%)	<0.001	14 (2.5%)
AF	2 (0.5%)	2 (1.6%)	0.206	4 (0.7%)

CCI band scoring: minor/none = 0, mild 1-5, moderate 6-10, severe >10; MHP, major haemorrhage protocol

The major haemorrhage protocol (MHP) was activated less frequently in the older group (63.9% vs 71.9%, although this was not statistically significant, P-value=0.088). TXA use was above 90% in both groups, although lower in the older group (90% vs 95%, P-value=0.037). Overall, across both age groups, anticoagulation and antiplatelet use was low. There were notable differences in the pattern and severity of injury with more polytrauma, head injury and thoracic injury in the older group (Table 4.8). There were significant differences between young and older in the severity of injuries with a greater proportion of severe head, abdominal and pelvic injuries (AIS 3+) in older patients (Table 4.8).

Table 4.8. Injury characteristics of patients with major bleeding

	Young <65 (N = 441)	Older ≥65 (N = 122)	P-value	Total (N = 563)
Polytrauma	301 (68.3%)	98 (80.3%)	0.009	399 (70.9%)
Body region injured				
TBI	166 (37.6%)	64 (52.5%)	0.003	230 (40.9%)
Facial	23 (5.2%)	3 (2.5%)	0.327	26 (4.6%)
Thoracic	220 (49.9%)	92 (75.4%)	<0.001	312 (55.4%)
Abdominal	151 (34.2%)	29 (23.8%)	0.028	180 (32.0%)
Extremity	166 (37.6%)	70 (57.4%)	<0.001	236 (41.9%)
Pelvis Stable	47 (10.7%)	27 (22.1%)	0.001	74 (13.1%)
Pelvis Unstable	109 (24.7%)	41 (33.6%)	0.049	150 (26.6%)
Open femur	21 (4.8%)	7 (5.7%)	0.661	28 (5.0%)
Open fracture	62 (14.1%)	22 (18.0%)	0.289	84 (14.9%)
Severe injury (AIS 3+)				
Head	179 (40.9%)	64 (52.5%)	0.019	243 (43.4%)
Thorax	331 (75.1%)	96 (78.7%)	0.407	427 (75.8%)
Abdomen	156 (35.4%)	31 (25.4%)	0.039	187 (33.2%)
Spine	58 (13.2%)	15 (12.3%)	0.803	73 (13.0%)
Pelvis	109 (24.7%)	41 (33.6%)	0.049	150 (26.6%)
Limbs	160 (36.3%)	40 (32.8%)	0.475	200 (35.5%)
Other	31 (7.0%)	5 (4.1%)	0.242	36 (6.4%)

TBI, traumatic brain injury; AIS, abbreviated injury scale

Pre-hospital and ED vital signs are presented in Table 4.9. Young patients were tachycardic in the pre-hospital setting and in ED. This contrasted with older patients, who were not tachycardic. Systolic BP in both pre-hospital and ED were similar for both age groups with bleeding.

Table 4.9. Vital signs of patients with major bleeding

	Young (N =441)	Older (N= 122)	P-value	Total (N=563)
Pre-hospital SBP (mmHg)				
Mean (SD)	99 (40)	103 (44)	0.455	100 (41)
Missing, n (%)	*106 (24.0%)*	*16 (13.1%)*		*122 (21.7%)*
Pre-hospital pulse (bpm)				
Mean (SD)	102 (41)	89 (31)	0.001	99 (39)
Missing, n (%)	*51 (11.6%)*	*10 (8.2%)*		*61 (10.8%)*
Pre-hospital GCS				
Median (IQR)	11 (3 to 15)	11 (3 to 5)	0.695	11 (3 to 15)
Missing, n (%)	*27 (6.1%)*	*4 (3.3%)*		*31 (5.5%)*
ED systolic BP (mmHg)				
Mean (SD)	105 (40)	105 (38)	0.985	105 (40)
Missing, n (%)	*83 (18.8%)*	*13 (10.7%)*		*96 (17.1%)*
ED pulse (bpm)				
Mean (SD)	108 (35)	91 (29)	<0.001	104 (34)
Missing, n (%)	*50 (11.4%)*	*31 (25.4%)*		*60 (10.7%)*
ED GCS				
Median (IQR)	14 (8 to 15)	13 (6 to 15)	0.027	14 (7 to 15)
Missing, n (%)	*173 (39.2%)*	*48 (39.3%)*		*221 (39.3%)*
Pre-hospital SBP ≤90 mmHg (n, %)	120 (35.8%)	41 (38.7%)	0.594	161 (36.5%)
Missing, n (%)	*106 (24.0%)*	*16 (13.1%)*		*122 (21.7%)*
Pre-hospital pulse ≥100 bpm (n, %)	229 (58.7%)	42 (37.5%)	<0.001	271 (54.0%)
Missing, n (%)	*51 (11.6%)*	*10 (8.2%)*		*61 (10.8%)*

GCS, Glasgow Coma Scale; SBP, systolic blood pressure; bpm, beats per minute

Patients with shock typically present with hypotension and tachycardia. Commonly used shock parameters were applied to the TARN data. This showed 35.8% of young patients and 38.7% of older patients with bleeding had a pre-hospital SBP ≤90 mmHg,

P-value=0.623. This contrasted with tachycardia where there was a significant difference between young and old; 58.7% of younger patients had pre-hospital HR ≥100 bpm compared with 37.5% in older patients, P-value <0.001. The mean (SD) pre-hospital HR was significantly higher in younger patients compared with older patients 102 bpm (41) vs 89 bpm (31), P-value=0.001.

Transfusion requirements

The transfusion requirements for RBC, FFP, cryoprecipitate and platelets within 2 hours of injury are shown in Table 4.10, Table 4.11 and as a box plot in Figure 4.2. In both age groups, RBCs were the main type of blood component transfused. In the younger group transfusion was unbalanced in this early period, who tended to receive RBC only and half received zero units of FFP. The ratio of FFP:RBC was in the region of 1:2 in older patients. Few patients received cryoprecipitate or platelets within 2 hours of injury. There was a significant difference observed in FFP transfusion, platelet transfusion and total transfusion. Young patients received a median of zero FFP units (IQR 0 to 2) compared with a median of two (IQR 0 to 4) in the older group, P-value <0.0001. The proportion of older patients receiving 1-2 pools of platelets was higher than in the younger group (17.2% vs 7.5%). Older patients received a higher total number of units than younger patients (median (IQR) 6 (4 to 9) vs 5 (4 to 8) units, P-value=0.004).

Table 4.10. Transfusion requirements within 2 hours of injury

	Young <65 (N = 441)	Older ≥65 (N = 122)	P-value	Total (N = 563)
RBC within 2 hours (units)			0.933	
0	10 (2.3%)	0 (0.0%)		10 (1.8%)
>0 and <3	50 (11.4%)	9 (7.4%)		59 (10.5%)
3-4	200 (45.5%)	64 (52.5%)		264 (47.0%)
0	180 (40.9%)	49 (40.2%)		229 (40.7%)
Missing, n (%)	1 (0.2%)	0 (0.0%)		1 (0.2%)
FFP within 2 hours (units)			<0.001	
0	241 (54.6%)	37 (30.3%)		278 (49.4%)
1-2	90 (20.4%)	42 (34.4%)		132 (23.4%)
3-4	84 (19.0%)	31 (25.4%)		115 (20.4%)
>4	26 (5.9%)	12 (9.8%)		38 (6.7%)
Cryoprecipitate within 2 hours (units)			0.059	
0	415 (94.7%)	110(90.2%)		525 (93.8%)
1-2	15 (3.4%)	7 (5.7%)		22 (3.9%)
3-4	8 (1.8%)	5 (4.1%)		13 (2.3%)
Missing, n (%)	3 (0.7%)	0 (0.0%)		3 (0.5%)
Platelets within 2 hours (pools)			<0.001	
0	404 (92.2%)	99 (81.1%)		503 (89.8%)
1-2	33 (7.5%)	21 (17.2%)		54 (9.6%)
3-4	1 (0.2%)	1 (0.8%)		2 (0.4%)
>4	0 (0.0%)	1 (0.8%)		1 (0.2%)
Missing, n (%)	3 (0.7%)	0 (0.0%)		3 (0.5%)
Total within 2 hours (units)			0.004	
4	167 (37.9%)	31 (25.4%)		198 (35.2%)
5-6	115 (26.1%)	34 (27.9%)		149 (26.5%)
7-8	73 (16.6%)	24 (19.7%)		97 (17.2%)
>8	86 (19.5%)	33 (27.0%)		119 (21.1%)

RBC, red blood cells; FFP, fresh frozen plasma

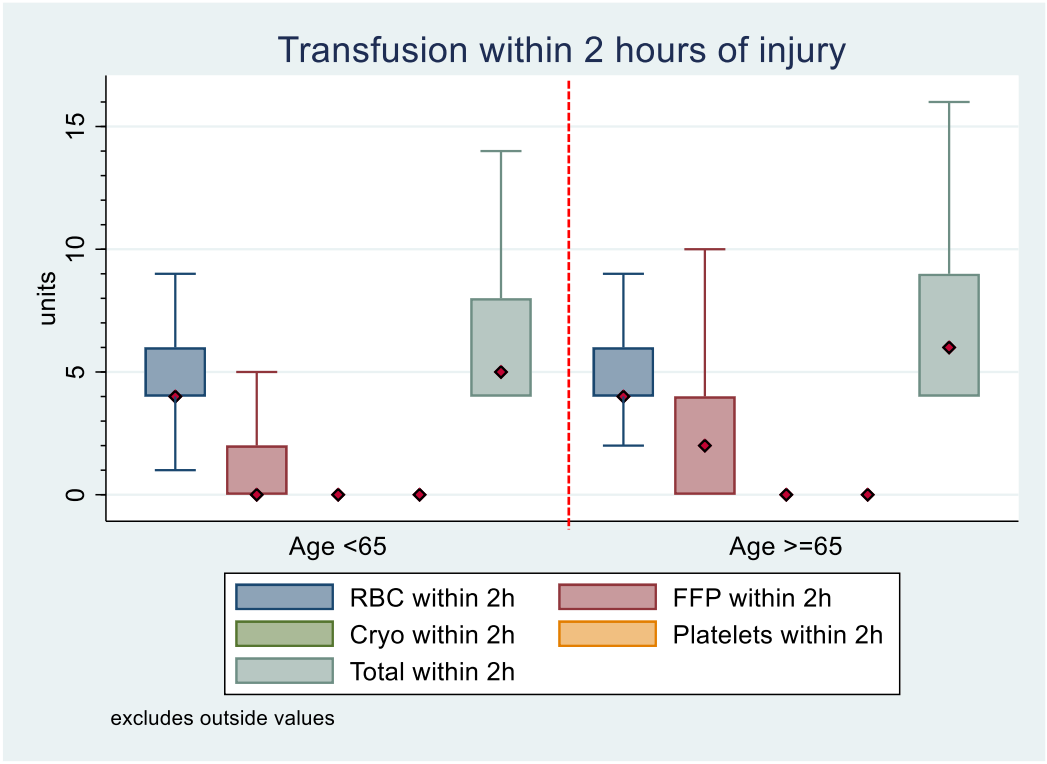
Table 4.11. Median units transfused within 2 hours of injury

	Young <65 (N = 441)	Older ≥65 (N = 122)	P-value	Total (N = 563)
RBC within 2 hours (units), median (IQR)	4 (4 to 6)	4 (4 to 6)	0.933	4 (4 to 6)
Missing, n (%)	1	0		1
FFP within 2 hours (units), median (IQR)	0 (0 to 2)	2 (0 to 4)	<0.001	1 (0 to 3)
Missing, n (%)	0	0		0
Cryoprecipitate within 2 hours (units), median (IQR)	0 (0 to 0)	0 (0 to 0)	0.059	0 (0 to 0)
Missing, n (%)	3	0		3
Platelets within 2 hours (pools), median (IQR)	0 (0 to 0)	0 (0 to 0)	<0.001	0 (0 to 0)
Missing, n (%)	3	0		3
Total within 2 hours (units)*, median (IQR)	5 (4 to 8)	6 (4 to 9)	0.004	6 (4 to 8)

*total calculated as sum of RBC, FFP, cryoprecipitate and platelets. RBC, red blood cells; FFP, fresh frozen plasma

Figure 4.2. Box plot of transfusion requirements within 2 hours of injury by age group

(563 patients with major bleeding). Median and IQR.



RBC, red blood cells; FFP, fresh frozen plasma; Cryo, cryoprecipitate

The total number of units transfused at 2 and 4 hours was similar for both age groups (Table 4.12). Data are also presented for totals up to 24 hours; this shows the majority of transfusions occurred early, within 4 hours of injury (Table 4.12).

Table 4.12. Total transfused units for patients with major bleeding (as recorded in the TARN database)

Overall total at 2, 4 and 24 hours after injury (different to sum of individual components in Table 4.12).

	Young <65 (N = 441)	Older ≥65 (N = 122)	P-value	Total (N = 563)
Total within 2 hours, median (IQR)	5 (4 to 8)	6 (5 to 9)	0.001	6 (4 to 8)
Total within 4 hours, median (IQR)	7 (4 to 10)	8 (5 to 11)	0.012	7 (4 to 10)
Total within 24 hours, median (IQR)	7 (4 to 10)	8 (5 to 12)	0.038	7 (5 to 11)

4.4.2 Mortality

Mortality was high in the cohort of patients with major bleeding. Overall all-cause mortality reached nearly 40% (Table 4.13). Mortality in both young and older patients was fairly similar up to 6 hours after admission but the rise thereafter was notably greater in the older population. 28-day mortality was nearly twice as high in the older group than in the younger group (58.2% vs 32.7%, P-value <0.001).

Table 4.13. All-cause mortality in patients with major bleeding

	Young <65 (N = 441)	Older ≥65 (N = 122)	P-value	Total (N = 563)
Outcome known	409 (92.7%)	110 (90.2%)	-	519 (92.2%)
Within 6-hr mortality	72 (16.3%)	27 (22.1%)	0.136	99 (17.6%)
Within 24-hr mortality	95 (21.5%)	42 (34.4%)	0.003	137 (24.3%)
Within 28-day mortality	144 (32.7%)	71 (58.2%)	<0.001	215 (38.2%)
Within 30 days or discharge*	147 (33.3%)	75 (61.5%)	<0.001	222 (39.4%)

* (whichever occurred earliest)

4.4.3 Comparison of overall cohort and bleeding cohort

Compared with the overall cohort, patients with bleeding were more severely injured with ISS >30 vs <16 in the overall cohort. There were differences in the type of injury; penetrating injuries were more common in patients with bleeding, particularly in the young. In the older group with bleeding, the main mechanism of injury was RTC compared with low level falls in the overall cohort. Patients with bleeding had different patterns and severity of injuries, notably with more polytrauma, TBI and thoracic injuries.

There were differences in the vital signs of injured patients. In the older group, ~ 40% of patients had pre-existing hypertension. In older patients, the mean (SD) pre-hospital SBP was higher in the overall cohort compared with the bleeding group (146 (32) mmHg vs 103 (44)) mmHg. In young patients, the pre-hospital SBP was 129 (28) mmHg in the overall group vs 99 (40) mmHg in the bleeding group. In the young group, bleeding patients were more tachycardic than young patients in the overall cohort (mean pre-hospital heart rate 102 (41) vs 89 (24). This contrasted with older patients where the mean (SD) pre-hospital heart rate in bleeders was similar to the overall older group (83 (20) vs 89(31)). The percentage of older patients with tachycardia (pulse ≥100) was higher in the bleeding group compared with the overall cohort (37.5% vs 14.5%). A similar trend was observed in the young, however the percentage of tachycardic patients was higher (58.7% vs 23.7%).

In the overall cohort transfusion use was low and the majority of patients (approximately 99%) did not require red cell transfusion. Mortality was increased 4-fold

in older patients with bleeding compared with the older overall cohort. This rose to a 6-fold increase in younger patients with bleeding.

4.4.4 Characteristics of patients with blunt injuries

There were a total of 429 patients in the subgroup analysis with blunt injury and major bleeding. The baseline characteristics of patients with blunt injury are presented in Table 4.14 and were similar to the overall cohort that included both patients with blunt and penetrating injury.

Table 4.14. Characteristics of patients with major bleeding and blunt trauma

	Young <65 (N = 309)	Older ≥65 (N = 120)	P-value	Total (N = 429)
Age, mean (SD) **Range**	36 (14) 16 to 64	77 (7) 65 to 93	-	48 (22)
Male	243 (78.6%)	73 (60.8%)	<0.001	316 (73.7%)
Mechanism of injury			0.009	
RTC	233 (75.4%)	82 (68.3%)		315 (73.4%)
Fall ≥2m	56 (18.1%)	24 (20.0%)		80 (18.6%)
Fall <2m	1 (0.3%)	7 (5.8%)		8 (1.9%)
Shooting/stabbing	1 (0.3%)	0 (0.0%)		1 (0.2%)
Blow(s)	6 (1.9%)	2 (1.7%)		8 (1.9%)
Other	12 (3.9%)	5 (4.2%)		17 (4.0%)
ISS, mean (SD)	40 (15)	37 (13)	0.127	39 (15)
CCI band			<0.001	
Minor/none	171 (69.2%)	41 (44.1%)		212 (62.4%)
Mild	63 (25.5%)	39 (41.9%)		102 (30.0%)
Moderate	7 (2.8%)	12 (12.9%)		19 (5.6%)
Severe	6 (2.4%)	1 (1.1%)		7 (2.1%)
Missing, n (%)	*62 (20.1%)*	*27 (22.5%)*		*89 (20.7%)*
Pre-hospital arrest	41 (13.4%)	14 (11.7%)	0.656	55 (12.8%)
TXA	298 (96.4%)	108 (90.0%)	0.008	406 (94.6%)
MHP activation	217 (70.7%)	77 (64.2%)	0.178	294 (68.9%)
Hypertension	16 (5.2%)	30 (25.0%)	<0.001	45 (10.7%)
IHD	3 (1.0%)	11 (9.2%)	<0.001	14 (3.3%)
AF	2 (0.7%)	2 (1.7%)	0.312	4 (0.9%)

ISS, injury severity score; CCI, charlston comorbidity index; TXA, tranexamic acid; MHP, major haemorrhage activation; IHD, ischaemic heart disease; AF, atrial fibrillation

The significantly higher heart rate in younger patients was again observed; younger patients had higher pre-hospital pulse than older patients but there was no difference in systolic blood pressure (SBP); mean (SD) pulse 102 bpm (42) in younger group vs 88 (31) in older patients, P-value <0.001 (Table 4.15).

Table 4.15. Vital signs of patients with major bleeding and blunt trauma

	Young (N = 309)	Older (N = 120)	P-value	Total (N = 429)
Pre-hospital SBP (mmHg)				
Mean (SD)	100 (42)	103 (44)	0.544	101 (43)
Missing, n (%)	*76 (24.6%)*	*16 (13.3%)*		*92 (21.4%)*
Pre-hospital pulse (bpm)				
Mean (SD)	102 (42)	88 (31)	<0.001	98 (39)
Missing, n (%)	*34 (11.0%)*	*10 (8.3%)*		*44 (10.3%)*
Pre-hospital GCS				
Median (IQR)	8 (3 to 14)	10 (3 to 15)	0.296	10 (3 to 14)
Missing, n (%)	*15 (4.9%)*	*4 (3.3%)*		*19 (4.4%)*
ED SBP (mmHg)				
Mean (SD)	107 (41%)	104 (39%)	0.513	106 (40%)
Missing, n (%)	*64 (20.7%)*	*13 (10.8%)*		*77 (17.9%)*
ED pulse (bpm)				
Mean (SD)	109 (35%)	91 (29)	<0.001	104 (34%)
Missing, n (%)	*35 (11.3%)*	*10 (8.3%)*		*45 (10.5%)*
ED GCS				
Median (IQR)	13 (5 to 15)	13 (6 to 15)	0.656	13 (5 to 15)
Missing, n (%)	*149 (48.2%)*	*48 (40.0%)*		*197 (45.9%)*
Pre-hospital SBP <90 mmHg (n, %)	83 (35.6%)	40 (33.3%)	0.617	123 (36.5%)
Missing, n (%)	*76 (25.0%)*	*16 (13.3%)*		*92 (21.4%)*
Pre-hospital pulse ≥100 bpm (n, %)	163 (59.3%)	40 (36.4%)	<0.001	203 (52.7%)
Missing, n (%)	*34 (11.0%)*	*10 (8.3%)*		*44 (10.3%)*

SBP, systolic blood pressure; ED, emergency department; bpm, beats per minute; GCS, glasgow coma score

4.4.5 Missing data

Data were complete for the majority of variables with the exception of CCI band and vital signs. There were more missing data for pre-hospital SBP and pulse compared with the corresponding ED vital signs. Mortality outcomes were known for more than 90% of patients with major bleeding. The percentage of missing vital signs was similar across young and older age groups. Up to a quarter of pre-hospital blood pressure or pulse data were missing. The percentage of missing emergency department vital signs was low (<8%). Nearly 40% of bleeding outcomes were missing.

The elements required to generate the outcome were not available in all cases. In 38,562/102,377 (37.7%) of cases, the date/time of injury was not documented. Out of the 102,377 cases, there were 596 cases (0.6%) where the total, but not individual number of units transfused within 2 hours was available. Overall, the outcome was missing in 39,154 cases (38.2%).

4.5 Discussion

The landscape of trauma has changed over the past decade. The number of elderly patients with major injury is rising and will continue to rise with the ageing population.[4] There is increasing recognition of the importance of considering age-specific needs and demographic change in patient management.[2,4] This also applies to acute resuscitation and haemorrhage where physiological and pharmacological factors (e.g. anticoagulation) associated with bleeding may differ in older patients compared to younger patients. Understanding the presenting characteristics and features of the older population is important as differences in presentation could impact on how patients are identified and managed.

4.5.1 Key findings

This study of TARN data shows there are differences across young and older people. In this study, both old and young patients with major bleeding were severely injured with similar ISS. However, differences were observed in the characteristics, transfusion use and outcomes of older patients that could have potential clinical and research implications.

In the overall study group, a 'typical' older patient could be described as female who suffered injury through a low-level fall. Younger patients were more likely to be male and suffer high energy trauma. However, the characteristics and presenting features of the bleeding cohort was different.

In patients with bleeding, the proportion of female patients was higher in the older group compared with younger groups. Penetrating injury and shooting/stabbing injuries were infrequent (<2%) in older people in contrast to the younger population where they accounted for a third of injuries. Although falls contribute to a larger proportion of cases in the elderly than in the young, RTC is still the predominant mechanism of injury. The differences in demographics could have implications for injury prevention strategies.

The pattern of injury showed the proportion of TBI, thoracic and pelvic injuries to be higher in older patients compared with younger patients. Older patients were more likely to have polytrauma. These findings could be useful in initial triage or trauma survey where the body region injured could help identify patients at high risk of bleeding.

Vital signs play a particularly important role in triage. It is known that blood pressure rises with age in the normal population, but it is not clear whether this is seen in patients with bleeding. Data from this TARN study showed the SBP in patients with bleeding was similar across both age groups. Both young and old had similar mean SBP and were not hypotensive as might be expected if a patient had severe bleeding. This contrasts with previous observational studies of massive bleeding (mainly including younger patients) that have shown hypotension to be a feature (Table 4.16). Although the definition for bleeding is unique to the TARN database and different from the other studies, it is not clear why SBP appeared to be preserved in the TARN patients. For the older patients, there was a higher proportion of patients with a pre-morbid diagnosis of hypertension (29.2% vs 3.6% in the young), which may have meant their pre-injury baseline SBP was higher. It is unlikely to be due to the type of injury because a similar pattern across age was observed for patients with blunt injury.

Table 4.16. Comparison of baseline characteristics with alternative definitions of major bleeding in three other observational studies

Baseline characteristics	Delphi bleeding definition, TARN cohort	Massive transfusion, ABC score derivation [78]	CAT, original [88]	CAT applied [86]	Massive transfusion applied [86]
	N = 563	**N = 76**	**N = 77**	**N =145**	**N = 48**
	Multi-centre, UK	Single-centre USA	Single-centre, USA	Single-centre, Canada	Single-centre, Canada
	2012-2017	2005-2006	2006-2009	2014-2017	2014-2017
Age	44 (22)	40 (18)	40.5 (16.1)	53 (31)	40.5 (31.5)
Male (%)	78.7%	73%	84.4%	76.5%	83.3%
Blunt (%)	76.2%	72%	64.9%	66.9%	60.5%
ISS	34 (16)	34 (22 to 41)	NISS 24 (12)	29 (18 to 38)	33 (21 to 48)
SBP at scene	100^ (41)	NR	NR	NR	NR
HR at scene	99^ (39)	NR	NR	NR	NR
ED SBP	105^ (40)	89 (34)	99 (36)	90 (75 to 120)	84 (64 to 95)
ED HR	104^ (34)	111 (28)	105 (34)	110 (95 to 129)	115 (109 to 130)
Mortality					
6-h	17.6%	NR	NR	NR	NR
24-h	24.3%	NR	NR	NR	NR
30-day	38.2%*	NR	NR	22.1%	33%
Overall mortality (%)	39.5%	45%	NR	NR	NR

h, hours; CAT, Critical administration threshold; NR, not recorded. ^Missing data present, see Table 4.9. *For TARN, mortality within 28 days.

Although the absolute SBP in young and old was similar, compared to the overall cohort the relative drop in SBP was higher in the older group who generally had a higher baseline blood pressure. This is reflected in a closer examination of the older group that shows a difference in the SBP between bleeding and non-bleeding patients (Table 4.17). In the older cohort, the mean (SD) SBP at scene was 147 (32) mmHg in the non-bleeding group compared with 99 (40) mmHg in the group with bleeding. From this, it could be inferred that a relative drop in blood pressure, and not just the absolute value is an important factor to consider when interpreting the blood pressure reading. Traditional

thresholds for blood pressure may need to be modified for older people to reduce the risk of undertriage.

Table 4.17. Comparison of baseline characteristics of older group patients with bleeding in TARN with another published cohort

Baseline characteristics	Bleeding TARN cohort (Delphi bleeding definition) N = 122	Bleeding Ohmori et al [84] (MT definition) N = 74	No bleeding TARN (No Delphi bleeding) N = 26,112	No bleeding Ohmori et al [84] (No MT) N = 306
Location	Multi-centre, UK	Single-centre, Japan	Multi-centre, UK	Single-centre, Japan
Year	2012-2017	2007-2015	2012-2017	2007-2015
Age	77 (7)	78 (73 to 83)	80 (9)	77 (70 to 81)
Male (%)	61.5%	73%	42.7%	66%
Blunt (%)	98.4%	NR	99.4%	NR
ISS	37 (14)	34 (26 to 43)	9* (9 to 20)	22 (17 to 27)
SBP at scene	n=112	n=74	n=22,487	n=306
Median, IQR Mean, SD	105 (75 to 128) 99 (40)	NR -	146 (127 to 168) 147 (32)	NR -
HR at scene	n=106	n=74	n=22,109	n=306
Median, IQR Mean, SD	89 (70 to 110) 89 (31)	NR -	81 (70 to 94) 83(20)	NR -
ED SBP	n=112	n=74	n=24,591	n=306
Median, IQR Mean, SD	100 (78 to 130) 105 (38)	109 (92 to 133) -	146 (127 to 166) 147 (31)	130 (109 to 159) -
ED HR	n=112	n=74	n=24,690	n=306
Median, IQR Mean, SD	90 (74 to 109) 91 (29)	90 (77 to 110) -	80 (69 to 92) 82 (18)	81 (68 to 95) -
Overall mortality (%)	61.5%	21%	14.8%	0%

MT, massive transfusion; NR, not reported, ISS, injury severity score; SBP, systolic blood pressure; HR, heart rate; ED, emergency department. *ISS skewed in non-bleeding group. The single-centre study by Ohmori et al included severely injured patients with ISS ≥16 from Jan 2007-March 2015.[84]

Concern with undertriage of older people has led to exploration of a higher threshold for hypotension in older people, not specifically in bleeding patients but as a criterion for triage. In the United States, Brown *et al* showed that shifting the threshold from 90

mmHg to 110 mmHg increased sensitivity of the triage criterion for transfer to a trauma centre.[55] The importance of age-appropriate triage and pathways has also been recognised as an area for development for older people with trauma in the UK.[4]

The assessment of HR is an important component at triage; one of the earliest compensatory responses to shock is increased sympathetic tone resulting in tachycardia. The data from TARN showed younger people with bleeding were tachycardic, consistent with previous observational data (Table 4.9). However, older people did not present with tachycardia. Although there are few published reports of older people with major bleeding, the TARN results are in keeping with a study of older patients with massive transfusion in Japan.[84] Ohmori et al showed that older people with massive transfusion did not present to ED with tachycardia, and similar to the TARN data, also did not present with hypotension.[84] It is possible that for older people, tachycardia is blunted due to changes in cardiovascular function that occur with ageing, so older people do not mount the same compensatory response to bleeding as in younger people.

In summary, older people with bleeding did not seem to present with classical signs of shock; vital signs appeared attenuated. It is recognised that hypotension and tachycardia are not the only markers of shock (acidosis is not routinely measured pre-hospital), and there are other factors that might have influenced these parameters such as medication use, hypovolaemia, pain, tension pneumothorax and cardiac tamponade. Nevertheless, these differences are notable. They suggest that a one-size fits all approach is not suitable and triage criteria should be modified for age.

The main difference in transfusion use was that younger patients received less FFP than older patients at 2 hours; half of younger patients received no FFP which would be

considered suboptimal as guidelines recommend balanced transfusion of FFP:RBC ratio of at least 1:2. RBCs were the first blood components to be carried on board by paramedics and pre-hospital care providers. This has been followed by FFP more recently. The reasons for the difference in FFP across age are not clear and do not appear to be related to the year of recruitment, which was similar for young and old (Appendix 4:). The difference may not be related to clinical practice but rather a methodological issue due to the problem with multi-recording of blood components. It was not possible to describe the pattern of transfusion for each component at other time points in more detail, due to multi-recording. It is difficult to compare with other data due to the paucity of published data on transfusion use in older people with major bleeding.

Outcomes were poorer for older people, with a disparate rise in mortality particularly noted after 6 hours. Late mortality has been observed in other studies of trauma haemorrhage.[29] The particularly high late mortality in older people is notable in this study. Mortality within 30 days or discharge reached 61.5% in older people, double that of younger people (33.3%). Reasons for this are uncertain. It could be due to factors related to the injury itself and the host response to injury or external factors relating to care of the older person. This is an area where further research is needed.

As this study uses a novel definition of major bleeding, it is difficult to compare directly with other studies. The baseline demographics of the patients in this study would appear to be broadly similar to other studies of bleeding including the population with massive transfusion from which the ABC score was derived, and the population for the CAT definition of bleeding. However, the main difference is in the ED SBP, which was

higher in the TARN cohort; the trend in tachycardia was similar across all studies (Table 4.16). The high mortality of the older patients in TARN (compared with the study by Ohmori et al)[84] would suggest the TARN study population reflects the severe end of the prognostic spectrum of patients with major bleeding.

Missing data in trauma

In this TARN study, data completion for demographic and injury data in the overall study cohort was excellent. The fields where data were missing were in CCI and in the vital signs. The bleeding outcome was a novel definition of bleeding and not routinely collected, and was missing in 40% of cases.

The problem of missing data is not a new issue, and has been raised as a concern for researchers in the trauma community.[151] Trauma data collection is challenging for several reasons including the potential for data to be lost or incompletely recorded due to the time critical nature of care, transfer from pre-hospital to hospital setting where data can be lost in handover, different electronic patient records that do not necessarily communicate with each other and the detailed level of often complex data that is relevant to trauma outcomes.

Despite the challenges with missing data, data contained within trauma registries have driven improvements in the delivery of trauma care through recording data on outcomes and processes of the trauma management pathway.[152] Registries require careful curation and their quality is testament to the attention to detail and effort from all parties in submitting and checking data. Registry data are powerful and valuable tools that have driven improvements in patient care and outcomes, especially in trauma

where clinical trials are not always feasible. Examples of this in TARN include the development of a model to predict expected survival for each patient, which is used as a performance indicator for hospitals to review performance and identify outliers where improvements can be made.[153] Another example from TARN is where analysis of registry data has led to a change in practice in severe brain injury; triage of patients with severe brain injury to neuroscience specialist centres has halved mortality in this group of patients.[154] However, these rigour of such analyses and work is dependent on data quality in terms of both completeness and accuracy.[155] Incomplete or inaccurate data can limit capacity for comparing and benchmarking different systems of trauma care and potentially compromise research outputs.[152] Challenges arise with the presence of incomplete registry data or level of detailed data that is needed for research studies. These may be more of an issue with retrospective studies rather than prospective studies. Understanding missing data is important as the way in which data are missing and handled in the analysis can lead to bias and incorrect inferences.

Porgo *et al* systematically appraised data quality in trauma registry data in studies up until 25 November 2015.[156] Fields relating to six domains of data quality were evaluated: data completeness, accuracy, precision, correctness, consistency, and timeliness of data.[156] Ten studies that assessed data quality in trauma registries were included (TARN was not included, as no TARN report met the criteria of the review). The review found that most studies assessed data quality based on data completeness. Within the trauma datasets, the following characteristics were most commonly assessed: age, SBP, GCS score, respiratory rate, and gender. Between studies, there were large differences in the completeness of SBP, Glasgow coma score (GCS), respiratory rate, and MOI (in the study

it was not reported whether these were pre-hospital or ED vital signs). Less variation was found for data accuracy; accuracy for data on intensive care unit and hospital length of stay, age, gender, GCS score, and intubation attempts was close to 100%. When stratifying analyses by decade of data collection (1990-1999, 2000-2009, and 2010-2015) and by years since the registry was implemented, no changes or improvements in data quality were observed. The authors of the review recommended the development of a standardised and reproducible method to measure data quality in trauma[156] and this would be a step forward in setting standards for data quality.

The impact of missing data on prediction models of massive transfusion was explored by Trickey *et al* using data from the PROMMT (Prospective, Observational, Multicenter, Major Trauma Transfusion) study, a transfusion study in trauma in the United States.[151] The study conducted a sensitivity analysis to evaluate the impact of incomplete data on three published clinical risk prediction algorithms. The results showed there was more missing data for patients with massive transfusion compared to those without massive transfusion.[151] Percentages of missing data ranged from 2.2% (heart rate) to 45% (respiratory rate). When three different prediction models for massive transfusion were applied to the PROMMT data, all models demonstrated lower predictive accuracy compared with the original published results using CCA.[151]

Although the primary focus of the study was on the impact of missing data on assessments of model predictive accuracy, the authors also acknowledged that it is important to consider missing data during the development of prediction scores. The likelihood of missing data fields in a real-world clinical setting is important to consider. Furthermore, the overall degree of missing data for a model is dependent not only on

the choice of variables in the model but also on the number of variables necessary to fulfil the model calculations.[151] Some have suggested that future prediction models may incorporate some flexibility within the score, such as substituting other available parameters e.g. the Larson score which requires two of four available positively coded variables or three of four available negatively coded variables to calculate the probability of massive transfusion.[151,157]

To improve trauma data quality, strategies to reduce missing data and maximise data quality at source are important areas to address. Although analytical methods can be used to handle missing data, reduction in the amount of missing data is preferable. To improve data flow, the integration of electronic patient records and linkage with GP records can provide baseline data on pre-existing comorbidity and medication data and be linked to outcomes. When designing prospective studies, another useful strategy may be to maintain a focussed research area and limit information collected only to essential variables.[151]

A global strategy has been suggested to standardise trauma registry data, including a global minimum dataset and dictionary, uniform approaches to risk adjustment and the standardisation of data quality monitoring and reporting.[152] European trauma registries have agreed a list of 40 key variables to assess quality of trauma care (the Utstein template).[158] One of the challenges is how trauma registries can be developed to capture valuable data relevant to the changing needs of the population, demographic change and pertinent clinical issues. For example, collecting data on frailty is more relevant now as we have an ageing population and this is known to affect outcomes in trauma. Furthermore, the management of trauma haemorrhage and transfusion has

evolved and it may be an opportunity to reconsider how our existing databases capture information in this complex area. This is challenging, particularly in haemorrhage where composite outcomes are dependent on a high level of detail with accurate timing and location of parameters relative to the time of injury. One of the major barriers to the maintenance and improvement in quality of the source data is financial cost. High quality trauma registry data require considerable investment of both infrastructure and human resources.[156,159]

4.5.2 Strengths and limitations

The strengths of this study are that a large number of patients, including many older patients with significant bleeding were included in this study. Demographic data were complete for all ISS, gender and injury types.

However, there are limitations. Limitations relating to the Delphi survey definition of major bleeding are discussed in chapter 3. Aside from these, one of the particular challenges working with registry data is that the data collected are not necessarily the precise data required for a research study. As the Delphi definition was applied to the TARN data, it became apparent that critical information on time of injury was missing in a significant number of cases. In 40% of cases, this was not recorded and meant that transfusion totals could not be calculated at the 2-hour time-point and the outcome was classified as 'missing'. Although we sought to retrieve data where there was multi-recording of transfusion, this could not be completed for all cases. It is possible that for both these reasons, the population captured by the definition may not reflect the true population. As this definition is newly developed, it has not been applied to external populations outside of the UK.

The potential usefulness of the definition in capturing patients with bleeding could be limited if there is a high proportion of cases missing the time of injury. Only the first SBP or HR measurement was recorded. Patient parameters are in flux and it is possible that if serial measurements were available, they may have demonstrated different trends in blood pressure or pulse. The proportion of missing data for observations was greater in the pre-hospital setting compared with ED setting, and in the younger population compared with the older population. This is explored further in chapter 5 in the TARN study to identify factors associated with major bleeding.

The percentage of older patients with AF or IHD who were prescribed antiplatelet or anticoagulation therapy was lower than expected. As older patients with AF are at higher risk of thrombosis, unless there are significant contra-indications, it would be expected that all should be on some form of anti-thrombotic and/or antiplatelet. Irrespective of comorbidities, the overall proportion of patients taking anti-thrombotic and/or antiplatelet therapy was low. These data may be difficult to extract from source data and may contribute to the low numbers recorded in the TARN cohort and may not reflect the true at risk population.

Whether the patient is actively bleeding or at significant risk of bleeding is seldom documented in patient records. Other factors alluded to previously such as pain and tension pneumothorax can contribute to tachycardia and hypotension. It is possible that these other factors contributed in part to the differences seen in young and old. The concomitant use of beta-blocker medication or other heart rate-controlling mediation could have modified heart rate and led to the blunted response in older people, but these data were not captured in the TARN database.

Another limitation of this study is that it was restricted to patients admitted directly to an MTC. The results may not be generalizable to the wider population, as there have been concerns that there is under-triage of older patients to MTCs.[4] However, including all patients admitted to trauma units could dilute the number of potentially eligible patients and cloud any findings.

4.6 Conclusion

This study shows baseline differences in the characteristics of older patients with major bleeding, compared with younger patients. This could impact on how patients are identified and managed. Differences in presenting heart rate could be particularly important in how patients are triaged at scene; older patients appear to have a blunted tachycardic response and may not mount the same response in bleeding as younger people. Overall, this cohort of patients with major bleeding had poor outcomes, with particularly high mortality after 6 hours in the older group. The reasons for this peak in later mortality are uncertain and are important areas to address in future work. There is an opportunity to improve outcomes for all patients, particularly in the older group who may benefit from more age-relevant clinical decision aids to recognise and treat major bleeding.

Chapter 5 The impact of age on risk factors associated with major bleeding

5.1 Introduction

Haemorrhagic shock is the leading potentially preventable cause of early mortality in severe injury. Key to improving outcomes are early recognition and control of haemorrhage.[92] In order to improve the identification of patients at risk of significant bleeding and who require aggressive haemostatic resuscitation, a number of scoring systems have been developed.[160] Identifying patients at risk could assist the attending clinician in treatment and triage decision-making. Historically, these scores for major bleeding predict the need for massive transfusion (≥10 units of RBC within 24 hours of admission) and were designed to be used on arrival to hospital. However, if patients at high risk of bleeding can be identified early on, in the pre-hospital phase, this could aid appropriate triage and initiation of interventions by the multidisciplinary trauma team and reduce delay in the management of bleeding.

There are three main stages in the development of a clinical prediction score: model development, validation and impact assessment. It was not possible to accomplish all stages within the timeframe of the thesis. In this thesis, I undertook the first step towards developing a pre-hospital prediction model: to explore potential pre-hospital factors associated with large volume transfusion.

The aim of this chapter was to identify factors for major bleeding using large volume blood transfusion as a surrogate marker of bleeding (the new Delphi definition). Because the Delphi definition applies to the acute phase after injury (within 2 hours), the aim of

this chapter was to identify early risk factors, known at the time of injury. Even within existing prediction scores for massive transfusion, the populations included have been mainly younger people with a relatively small proportion of older people and there is little published on the effectiveness of these scoring systems in older people, or how they compare with a younger population. One study applied three well-known scores (ABC, TASH and Prince of Wales scores) to an older population and demonstrated that the scores were less sensitive at predicting haemorrhage in the older group than for the younger population.[84] None of these three scores that have been developed include age as a variable nor age as an effect modifier.

In Chapter 4, the descriptive characteristics of the TARN cohort with major bleeding showed baseline differences in the characteristics of older and younger patients with injury, particularly for mechanism of injury, type of injury (blunt vs penetrating) and vital signs. Potentially, age could have an impact on the risk of bleeding either as an independent risk factor and/or by interacting with other factors. This could affect how patients of different ages with bleeding are identified and their subsequent management. This could be particularly relevant for the group of older patients who may be missing from previous study populations from which prediction scores were derived.

5.2 Aims

The overall aim was to understand candidate factors for major bleeding across age.

- To identify factors, known at the time of injury, associated with major bleeding in trauma (≥4 units of any blood component within 2 hours of injury), using transfusion as a surrogate marker of bleeding

- To explore the interaction between age and factors associated with major bleeding.

5.3 Methods

5.3.1 Study setting and design

A retrospective analysis of the UK national trauma database from the Trauma Audit & Research Network (TARN) was undertaken. Details about the TARN database and derivation of the study population are described in Chapter 4. Briefly, TARN-eligible adult patients who were admitted directly to a Major Trauma Centre (MTC) between 1 Jan 2012 and 31 December 2017 were included in the study.

The analysis of factors associated with bleeding (defined from the Delphi study as ≥4 units of any blood component within 2 hours of injury) was carried out in several steps. Firstly, I described the characteristics of the cohort with major bleeding and no major bleeding. Candidate variables were then selected and fitted to a logistic regression model to assess the association with bleeding. The impact of missing data will be explored in Chapter 6.

5.3.2 Selection of Risk Factors

Categorical data were presented as frequency and percentage and continuous data as mean (standard deviation, SD) for normal data, and median (IQR) for skewed data. As the definition for haemorrhage encompassed bleeding early after injury, the candidate factors were first selected based on their clinical relevance and whether they were likely to be known at the scene of injury. Potential variables had to be part of the data that is available in the TARN database. The selection of variables and physical parameters

known at scene, rather than laboratory tests, would be useful in the identifying patients with bleeding early and prior to ED (Emergency Department) arrival. FAST (focused assessment with sonography for trauma) scan positivity was not chosen as this has shown to be associated with inter-observer variability and concerns with sensitivity, specificity and its performance in a pre-hospital setting.[161,162]

5.3.3 Logistic regression: univariable analysis

Each factor was assessed individually using logistic regression to evaluate the association with major bleeding. Age was included as a continuous variable in the model. Pulse and systolic blood pressure were dichotomised into clinically relevant categories to delineate shock (pulse ≥100 bpm (beats per minute) and systolic blood pressure (SBP) ≤90 mmHg). Correlation between the independent variables was assessed using the Spearman correlation coefficient. If variables were highly correlated (i.e. r >0.8), then the plan *a priori* was to choose the most clinically relevant variable.

5.3.4 Logistic regression: multivariable analysis

Candidate factors with P-value <0.2 were included into a multivariable logistic regression model to explore the main effects which were significantly associated with bleeding. Odds ratios and 95% confidence intervals (CI) were determined.

I then explored the interaction between age and each factor in the multivariable model. I initially explored the interactions by separate age group (younger, aged <65 and older ≥65) to help investigate and interpret the age-variable interaction.

Stepwise backwards elimination was performed to identify the best 'subset' (i.e. the best combination of clinical variables that explained the model, using variables available

at the scene of injury). I manually eliminated variables by P-value, with the highest P-value eliminated first. A two-sided P-value of <0.05 was considered to be statistically significant. At the end of the elimination process, this yielded the best subset of the main effects in a multivariable model. I then explored the age-interaction effect by adding each interaction to the multivariable model. All analyses were performed in Stata version 15.1 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

5.3.5 Sample size

For the development of a multivariable prediction model using binary logistic regression, the rule of thumb for the sample size required and maximum number of candidate predictors has been considered to be ten events per variable.[163,164] However, there is debate over this rule. Recent studies have instead suggested alternative methods such as an out-of-sample predictive performance scale, such as the rMPSE (root mean square prediction error) and MAPE (mean absolute prediction error) or alternative criteria, described by Riley et al.[165,166] As the aim of this work was exploratory and the TARN study is a large observational study with only a few variables being considered, these criteria were not applied to this study.

5.3.6 Assessment of percentage and pattern of missing data

The percentage and pattern of missing co-variate and outcome data were assessed by age group (young and old) and for the overall cohort.

5.3.7 Assessment of mechanisms of missingness

By default, many statistical packages restrict analyses to complete data i.e. include cases with no missing data (complete case analysis, CCA). However, individuals with complete

data may not be representative of the entire sample, and CCA can lead to biased results and a loss of efficiency.[167,168]

The type of missing data determines the appropriate approach to handle incomplete data and depends on the reasons for missingness (mechanism of missingness).[169–171] Multiple imputation, an approach to handle missing data, was first introduced in the 1970s by Rubin et al[171,172] and has been widely adopted in the medical literature as a method to handle the problem of missing data.[173] Multiple imputation operates under the assumption that the mechanism of missingness is at least MAR, and can also operate if data are MCAR.

Multiple imputation creates multiple (*m*) copies of the dataset and replaces the missing values in each replicate with independent random draws from a model of the distribution of variables that have missing observations (the imputation model).[167] The analysis model is then fitted to each imputed data set. The multiple estimates of interest and corresponding standard errors are combined into one estimation using Rubin's rules, that allow for the uncertainty of missing data.[167,171] The inclusion of additional (auxiliary) variables in the imputation model provides information about the missing values and can make the MAR assumption more plausible.[167,174]

The three types of mechanisms of missingness are:

1) Missing completely at random (MCAR) – where missingness is not related to any observed or unobserved variables;

2) Missing at random (MAR) – when other variables (but not the variable itself) in the dataset can be used to predict missingness for a given variable;

3) Missing not at random (MNAR) – the value of the unobserved variable itself predicts missingness, conditional on the observed data. It is not possible to test for MAR and MNAR from the observed data alone. Identifying observed predictors of the missingness mechanism can refute MCAR.

The mechanism of missing data was assessed by examining the pattern of missing data and investigating whether the variables with missing data were associated with other observed variables. I assessed the plausibility of MCAR by examining differences between variables for the group with complete and missing outcome data. A logistic regression model identified factors that were associated with the missingness of the variable with missing data. This was used to inform the choice of auxiliary variables for the imputation model.

5.3.8 Multiple imputation to handle missing data

Variables with missing data were all assessed using multiple imputation. In the imputation models, I included all variables that appeared in the analytical model, auxiliary variables and the interaction terms to preserve the relationships between variables of interest.[175] The imputation was performed separately for the two models that included different interaction terms.

Imputations were generated by multiple imputation by chained equations (MICE). MICE is an iterative method that imputes multiple variables by using chained equations, iteratively for each variable with missing values.[176] The imputations are produced by fitting a sequence of regression models and drawing values from the corresponding predictive distributions.[177] It is also known as fully conditional specification (FCS)[178] and sequential regression multivariate imputation.[177] MICE operates under the assumption

that missing data are MAR. MICE has no formal theoretical justification, rather has been based on empirical studies[179] and has been used in handling missing data in transfusion.[180] The MICE method was chosen as it can handle different types of variable (including continuous, binary, unordered categorical) because each variable is imputed using its own imputation model[179] (the joint modelling method is less suited for imputing categorical variables since it assumes normality and linearity).[180] Another reason for choosing MICE was because of the non-monotone pattern of missing values occurring in several variables (see Results section).

The *mi impute chained regress* function was used to impute missing continuous data (pre-hospital SBP and pulse) and mi impute chained logit was used to impute missing binary data (outcome). The imputation model included all variables in the original model (including the outcome), as well as eight auxiliary variables: Emergency Department (ED) pulse, ED SBP, whether the incident date and time was substituted with the time of the 999 call, ISS, pre-hospital arrest, open fracture, limb injury and tranexamic acid (TXA). The auxiliary variables were either associated with the value of the incomplete variable, or associated with missingness to make the MAR assumption more plausible.[167] Twenty imputations were generated according to the percentage of missing data.[179]

Predictive mean matching (PMM) is an alternative method for imputing missing continuous data. It is a partially parametric method that matches the missing value to the observed value with closest predicted mean.[181] One of the main attractions of this method is that as only observed values are used, the distribution and range of data are maintained, only generating plausible imputed values, and has been demonstrated to be a valid method in simulation studies and may be slightly better at dealing with non-

normally distributed variables.[169,182] However, as the variables with missing data were normally distributed, PMM was not used.

Variables in original model	Auxiliary variables
• Age • Penetrating injury • Male gender • Pre-hospital systolic blood pressure (SBP) category • Pre-hospital pulse category • Mechanism of injury • Unstable pelvic injury • Penetrating-age interaction or mechanism of injury-age interaction	• Emergency department pulse • Emergency department systolic blood pressure • Whether the incident date and time was substituted with the time of the 999 call • Injury severity score • Pre-hospital arrest • Open fracture • Limb injury (Abbreviated Injury Score (AIS) 3+) • Tranexamic acid use

After each imputed dataset was generated, the continuous pulse and SBP data were categorised into binary variables, using the same categories as in the analytical model. For the imputed variables, the distribution of imputed data in each dataset was checked with the CCA data.

Finally, the analytical model was fitted to each imputed dataset (following Rubin's rules) and the combined inference was compared with the CCA model. Multiple imputation analyses were performed in Stata 15.1 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) (Stata code is documented in Appendix 5.1).

5.4 Results

Of the 102,377 patients admitted directly to an MTC, 63,226 patients had a known bleeding outcome. Out of the 63,226 patients with known outcome, 563 (0.9%) had

major bleeding, of which 441 (0.7%) were young (aged <65) and 122 (0.2%) were older (aged ≥65)).

5.4.1 Baseline characteristics

The characteristics of patients with and without major bleeding, their vital signs and pattern of injuries are described below and shown in, Table 5.2, Table 5.3.

Overall cohort

The mean (SD) age of patients with bleeding was 44 (22), with ages ranging from 16 to 93 years; the majority of patients were male (78.7%), and 75% of injuries were non-penetrating (Table 5.1). Over 90% of injuries were due to Road Traffic Collision (RTC), shooting/stabbing or fall from ≥2 m. In the group with bleeding, 54% had pre-hospital heart rate ≥100 bpm and 36.5% had pre-hospital systolic blood pressure ≤90 mmHg (Table 5.2). In contrast, the non-bleeding group was older, mean (SD) age 57 (23); the proportion of females was higher (40%) there were fewer penetrating injuries (Table 5.1).

Table 5.1. Characteristics of patients by major bleeding status

	Bleeding			No bleeding		
	Young	**Old**	**Total**	**Young**	**Old**	**Total**
	(N =441)	(N =122)	(N =563)	(N=36,551)	(N =26,112)	(N=62,663)
Age, mean (SD)	34 (14)	77 (7)	44 (22)	41 (15)	80 (9)	57 (23)
Male	368 (83.4%)	75 (61.5%)	443 (78.7%)	26,643 (72.9%)	11,157 (42.7%)	37,800 (60.3%)
Penetrating	132 (29.9%)	2 (1.6%)	134 (23.8%)	2484 (6.8%)	160 (0.6%)	2644 (4.2%)
Mechanism of injury						
RTC	237 (53.7%)	82 (67.2%)	319 (56.7%)	15,732 (43.0%)	3398 (13.0%)	19,130 (30.5%)
Fall ≥2 m	56 (12.7%)	24 (19.7%)	80 (14.2%)	6505 (17.8%)	3854 (14.8%)	10,359 (16.5%)
Fall <2 m	1 (0.2%)	7 (5.7%)	8 (1.4%)	8133 (22.3%)	18,290 (70.0%)	26,423 (42.2%)
Shooting/ stabbing	126 (28.6%)	2 (1.6%)	128 (22.7%)	2209 (6.0%)	94 (0.4%)	2303 (3.7%)
Blow(s)	7 (1.6%)	2 (1.6%)	9 (1.6%)	2584 (7.1%)	232 (0.9%)	2816 (4.5%)
Other	14 (3.2%)	5 (4.1%)	19 (3.4%)	1388 (3.8%)	244 (0.9%)	1632 (2.6%)
ISS, median (IQR)	34 (19 to 45)	35 (29 to 45)	34 (22 to 45)	13 (9 to 25)	9 (9 to 20)	13 (9 to 22)
CCI band						
Minor/none	262 (72.0%)	41 (43.2%)	303 (66.0%)	22,808 (67.1%)	7851 (31.2%)	30,659 (51.9%)
Mild	88 (24.2%)	39 (41.1%)	127 (27.7%)	9587 (28.2%)	11,850 (47.2%)	21,437 (36.3%)
Moderate	8 (2.2%)	13 (13.7%)	21 (4.6%)	1056 (3.1%)	4527 (18.0%)	5583 (9.4%)
Severe	6 (1.6%)	2 (2.1%)	8 (1.7%)	516 (1.5%)	902 (3.6%)	1418 (2.4%)
Missing, n (%)	77 (17.5%)	27 (22.1%)	104 (18.5%)	2584 (7.6%)	982 (3.9%)	3566 (6.0%)
Anticoagulation	0 (0.0%)	3 (2.5%)	3 (0.5%)	55 (0.2%)	338 (1.3%)	393 (0.6%)
Antiplatelet	1 (0.2%)	0 (0.0%)	1 (0.2%)	76 (0.2%)	486 (1.9%)	562 (0.9%)
Warfarin	0 (0.0%)	3 (2.5%)	3 (0.5%)	54 (0.1%)	335 (1.3%)	389 (0.6%)
Pre-hospital arrest	50 (11.3%)	14 (11.5%)	64 (11.4%)	413 (1.1%)	124 (0.5%)	537 (0.9%)

	Bleeding			No bleeding		
	Young	**Old**	**Total**	**Young**	**Old**	**Total**
TXA	420 (95.2%)	110 (90.2%)	530 (94.1%)	9130 (25.0%)	2288 (8.8%)	11,418 (18.2%)
MHP activation	318 (72.1%)	78 (63.9%)	396 (70.3%)	1726 (4.7%)	360 (1.4%)	2086 (3.3%)
Hypertension	16 (3.6%)	32 (26.2%)	48 (8.5%)	2695 (7.4%)	10,625 (40.7%)	13,320 (21.3%)

RTC, road traffic collision; ISS, injury severity score; CCI, charlston comorbidity index; TXA, tranexamic acid; MHP, major haemorrhage protocol

Table 5.2. Vital signs in patients by major bleeding status

	Bleeding			No bleeding		
	Young	**Old**	**Total**	**Young**	**Old**	**Total**
	(N =441)	(N =122)	(N =563)	(N =36,551)	(N =26,112)	(N =62,663)
Pre-hospital SBP (mmHg) Mean (SD)	99 (40)	103 (44)	100 (41)	130 (27)	147 (32)	137 (30)
Missing, n (%)	106 (24.0%)	16 (13.1%)	122 (21.7%)	5773 (15.8%)	4003 (15.3%)	9776 (15.6%)
Pre-hospital pulse (bpm) Mean (SD)	102 (41)	89 (31)	99 (39)	88 (23)	83 (20)	86 (22)
Missing, n (%)	51 (11.6%)	10 (8.2%)	61 (10.8%)	4716 (12.9%)	3625 (13.9%)	8341 (13.3%)
Pre-hospital GCS Median (IQR)	11 (3 to 15)	11 (3 to 15)	11 (3 to 15)	15 (14 to 15)	15 (14 to 15)	15 (14 to 15)
Missing, n (%)	27 (6.1%)	4 (3.3%)	31 (5.5%)	4115 (11.3%)	3449 (13.2%)	7564 (12.1%)
Pre-hospital SBP ≤90 mmHg	120 (35.8%)	41 (38.7%)	161 (36.5%)	1888 (6.1%)	902 (4.1%)	2790 (5.3%)
Missing, n (%)	106 (24.0%)	16 (13.1%)	122 (21.7%)	5773 (18.8%)	4003 (18.1%)	9776 (18.5%)
Pre-hospital pulse ≥100 bpm	229 (58.7%)	42 (37.5%)	271 (54.0%)	9239 (29.0%)	4097 (18.2%)	13,336 (24.5%)
Missing, n (%)	51 (11.6%)	10 (8.2%)	61 (10.8%)	4716 (14.8%)	3625 (16.1%)	8341 (15.4%)

Table 5.3. Body region injured by bleeding status

	Bleeding			No bleeding		
	Young	**Old**	**Total**	**Young**	**Old**	**Total**
	(N =441)	(N =122)	(N =563)	(N =36,551)	(N =26,112)	(N =62,663)
Polytrauma	301 (68.3%)	98 (80.3%)	399 (70.9%)	7931 (21.7%)	2840 (10.9%)	10771 (17.2%)
TBI	166 (37.6%)	64 (52.5%)	230 (40.9%)	9883 (27.0%)	7611 (29.1%)	17494 (27.9%)
Facial	23 (5.2%)	3 (2.5%)	26 (4.6%)	1016 (2.8%)	502 (1.9%)	1518 (2.4%)
Thoracic	220 (49.9%)	92 (75.4%)	312 (55.4%)	9269 (25.4%)	6242 (23.9%)	15511 (24.8%)
Abdominal	151 (34.2%)	29 (23.8%)	180 (32.0%)	2985 (8.2%)	509 (1.9%)	3494 (5.6%)
Extremity	166 (37.6%)	70 (57.4%)	236 (41.9%)	5485 (15.0%)	3897 (14.9%)	9382 (15.0%)
Stable pelvis	47 (10.7%)	27 (22.1%)	74 (13.1%)	2805 (7.7%)	3067 (11.7%)	5872 (9.4%)
Unstable pelvis	109 (24.7%)	41 (33.6%)	150 (26.6%)	2136 (5.8%)	749 (2.9%)	2885 (4.6%)
Open femoral fracture	21 (4.8%)	7 (5.7%)	28 (5.0%)	646 (1.8%)	97 (0.4%)	743 (1.2%)
Open fracture	62 (14.1%)	22 (18.0%)	84 (14.9%)	3649 (10.0%)	1076 (4.1%)	4725 (7.5%)

TBI, traumatic brain injury

Younger cohort (aged <65)

The mean (SD) age of patients with bleeding was 33 (14); the majority (83.4%) were male and nearly a third of injuries were penetrating (30%) (Table 5.1). In comparison, patients without major bleeding were older (mean (SD) age 41 (15)) and there was a greater proportion of females. RTC accounted for approximately half of injuries in bleeding and non-major bleeding groups (53.7% vs 43.0% respectively). However, penetrating injury was more common in the bleeding group (29.9% vs 6.8%). The injury severity score (ISS) was higher in the group with bleeding, (median 34, IQR (22 to 45) compared with ISS median 13, IQR (9 to 25) in the group without major bleeding.

Patients with bleeding were more shocked than the non-bleeders (58.7% vs 29.0% had pre-hospital pulse ≥100 bpm, and 35.8% vs 6.1% had pre-hospital systolic blood pressure (BP) ≤90 mmHg) (Table 5.2). Patients with bleeding were more tachycardic and hypotensive compared to the non-bleeders (mean (SD) pre-hospital heart rate was 102 bpm (41) vs 88 (23), and mean (SD) pre-hospital SBP 99 mmHg (40) vs 130 (27), respectively).

Patients with major bleeding were three times more likely to have polytrauma than non-bleeders (Table 5.3). Furthermore, the proportion of thoracic, abdominal, extremity and unstable pelvic injuries was 2-3 times higher in the bleeding groups compared to the non-bleeders).

Older cohort (aged ≥65)

In the older group, the proportion of females was higher in the non-bleeding group compared with the bleeding group (57.3% vs 38.5%) (Table 5.1). Penetrating injuries were infrequent in both groups (less than 2%). The leading cause of injury was RTC in the bleeding group, compared with falls <2 m in the non-bleeding groups. Patients without bleeding had lower ISS (median 9, IQR (9 to 20)) compared to the group with bleeding who had high ISS (median 35, IQR (29 to 45). The ISS for the bleeding group was equivalent to that seen in the younger bleeders.

Hypertension as a comorbidity was higher in the non-bleeding group (40.7% vs 26.2%) (Table 5.1). The mean pre-hospital pulse was similar in both bleeding and non-bleeding groups (Table 5.2). But the mean (SD) SBP was higher in the non-bleeding group (147 mmHg (32) vs 103 mmHg (44). Only 37.5% of bleeders were tachycardic (pulse ≥100 bpm) and tachycardia was present in 18.2% of non-bleeders. Hypotension, defined as SBP ≤90 mmHg, was present in 38.7% of the bleeders vs 4.1% in the non-bleeders. Polytrauma was much more frequent in bleeders (80.3% vs 10.9%). When compared with non-bleeders, bleeders on the whole had more severe injury scores across all body sites, particularly pelvic, thoracic, abdominal and extremity injuries (Table 5.3). In addition, traumatic brain injury (TBI) was almost twice as common in the bleeders vs non-bleeders (52.2% vs 29.16%) (Table 5.3).

Key differences between young and older patients with major bleeding

- There was a greater proportion of males in the younger group (368/441 (83.4%) vs 75/122 (61.5%) in older group).

- Penetrating injury was more common in the younger group (132/441 (29.9%) vs 2/122 (1.6%).
- Proportion of patients with tachycardia (HR ≥100 bpm) was 1.5 x higher in younger group compared with older group (229/441 (58.7%) vs 42 /122 (37.5%) respectively).
- Hypertension as a pre-existing comorbidity was more common in the older group. 32/122 (26.2%) of older patients had pre-existing hypertension compared with 16/441 (3.6%) in younger patients.

5.4.2 Univariate analysis

All the candidate pre-hospital factors were significantly associated with bleeding (Table 5.4). There was no multicollinearity between the variables. The results of other clinically important variables that may not necessarily be known at the scene of injury are presented in Appendix 5.2, Appendix 5.3, Appendix 5.4.

Overall cohort

On univariate analysis, all variables had P-value <0.001 (Table 5.4). Being older was significantly associated with less than half the odds of developing major bleeding compared with being younger (odds ratio (OR) = 0.387, 95% CI (0.317 to 0.474), P-value <0.001). Male gender, penetrating injury, presence of tachycardia (HR≥ 100 bpm), hypotension (SBP ≤90 mmHg), unstable pelvis were significantly associated with increased odds of major bleeding (P-value <0.001). Penetrating injury, tachycardia, systolic hypotension and unstable pelvic injury were associated with particularly high ORs of 3-10, which could be related to the small numbers of patients in the sample with bleeding.

Pre-hospital pulse and SBP were associated with bleeding, both as continuous variables and when grouped as categorical variables (P-value <0.001). With respect to mechanism of injury, the odds of developing major bleeding following shooting/stabbing injuries was 3 times greater than with RTC.

Table 5.4 Univariate logistic regression Delphi bleeding: overall

Reference MOI (mechanism of injury) group RTC (road traffic collision). Older = age 65 and above.

Variable	Odds Ratio	(95% CI)	P-value
Age	0.974	(0.970 to 0.978)	<0.001
Older	0.387	(0.317 to 0.474)	<0.001
Male	2.428	(1.983 to 2.973)	<0.001
Penetrating	7.09	(5.818 to 8.642)	<0.001
Pre-hospital SBP	0.971	(0.969 to 0.973)	<0.001
Pre-hospital pulse	1.023	(1.020 to 1.027)	<0.001
Pre-hospital pulse ≥100 bpm	3.606	(3.022 to 4.302)	<0.001
Pre-hospital SBP ≤90 mmHg	10.325	(8.474 to 12.58)	<0.001
MOI			<0.001
Fall ≥2 m	0.463	(0.362 to 0.592)	<0.001
Fall <2 m	0.018	(0.009 to 0.037)	<0.001
Shooting/stabbing	3.333	(2.703 to 4.110)	<0.001
Blow(s)	0.192	(0.099 to 0.372)	<0.001
Other	0.698	(0.438 to 1.112)	0.13
Unstable pelvis	7.526	(6.220 to 9.105)	<0.001

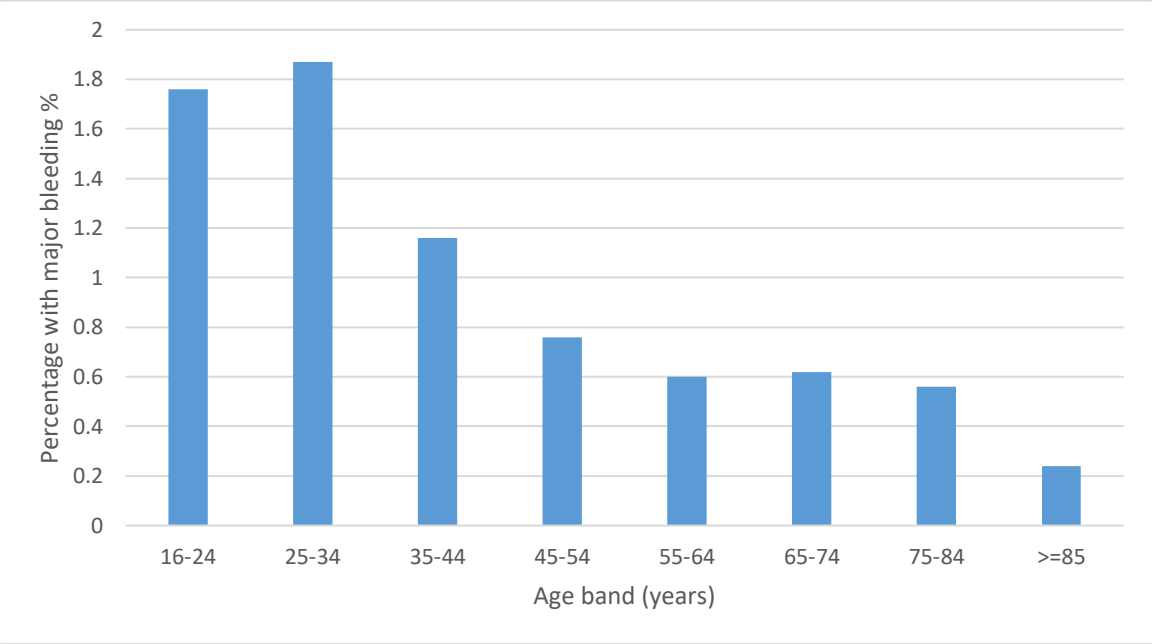
CI, confidence interval; SBP, systolic blood pressure; MOI, mechanism of injury

The relationship of age on major bleeding was examined more closely by age band. The percentage of patients with major bleeding decreased as age band increased (linear relationship) (Table 5.5, Figure 5.1).

Table 5.5. Percentage of patients with major bleeding by age band

Age band (years)	16-24 (n=7207)	25-34 (n= 6901)	35-44 (n=6299)	45-54 (n=8061)	55-64 (n=7384)	65-74 (n=7384)	75-84 (n=9573)	≥85 (n=9277)	Overall (n=63,226)
Number	127	129	73	61	51	46	54	22	563
Percentage	1.76	1.87	1.16	0.76	0.6	0.62	0.56	0.24	0.89

Figure 5.1. Graph of percentage of patients with bleeding by age band



Young and older specific cohort

Univariate analysis was also performed on the young and older groups separately to check for consistency across age groups (Appendix 5.3, Appendix 5.4). Variables were consistent in their association and trend of association with risk of major bleeding across both age groups. Variables associated with increased odds of major bleeding were male gender, presence of tachycardia (HR ≥100 bpm), hypotension (SBP ≤90 mmHg), unstable pelvis (P-value <0.001). However, the notable differences were that in the older group, there was weak evidence of an association of penetrating injury with bleeding (OR = 2.703, 95% CI (0.663 to 11.02); P-value=0.166) (Appendix 5.6). In the older group, there was no evidence of an association of shooting/stabbing injuries with bleeding compared with RTC (OR = 0.882; 95% CI (0.214 to 3.639); P-value=0.862) (Appendix 5.6).This was in contrast to the younger population where odds of bleeding were increased (OR = 3.786; 95% CI (3.037 to 4.721); P-value <0.001) (Appendix 5.5).

5.4.3 Multivariable logistic regression model and interaction with age

The final model was based on the whole cohort, as having one overall model for all adult patients may be easier to apply in the clinical setting and the factors were similar across both young and older age groups. As a blood pressure and pulse could be more readily applied to a triage criteria as categorical variables, both were included as dichotomous variables in the model. Age was included as a continuous variable in the model. The variables included in the multivariable model were age, penetrating injury, hypotension (binary), tachycardia (binary), gender, mechanism of injury (MOI) and unstable pelvic injury (Table 5.6). After adjusting for other factors, age remained significant as a factor associated with bleeding, with higher odds with increasing age (Table 5.6). When the older or younger age groups were assessed as separate groups, age as a continuous variable was no longer significantly associated with bleeding, after adjusting for other variables in the multivariable model (Appendix 5.7, Appendix 5.8, Appendix 5.9).

Table 5.6. Multivariable logistic regression model for bleeding overall cohort

	Odds Ratio	95% CI	P-value
Age	1.006	(1.001 to 1.011)	0.016
Penetrating	2.330	(0.977 to 5.556)	0.057
Pre-hospital pulse ≥100 bpm	2.355	(1.930 to 2.873)	<0.001
Pre-hospital SBP ≤90 mmHg	5.618	(4.554 to 6.932)	<0.001
Male	1.433	(1.122 to 1.831)	0.004
MOI			<0.001
Fall ≥2 m	0.567	(0.428 to 0.751)	<0.001
Fall <2 m	0.034	(0.016 to 0.074)	<0.001
Shooting/stabbing	1.491	(0.612 to 3.633)	0.380
Blow(s)	0.272	(0.120 to 0.616)	0.002
Other	0.511	(0.284 to 0.919)	0.025
Unstable pelvis	4.499	(3.544 to 5.710)	<0.001

SBP, systolic blood pressure; MOI, mechanism of injury

The next stage of the investigation was to examine the effect of interaction of factors with age in the multivariable model. These are presented in Appendix 5.10, Appendix 5.11, Appendix 5.12, Appendix 5.13, Appendix 5.14, Appendix 5.15 and a summary of the significant interactions are shown in Table 5.7. In the multivariable model, after adjusting for other variables, there was a negative interaction between penetrating injury and age, the odds of penetrating injury on bleeding were reduced with increasing age (OR = 0.979; 95% CI (0.964 to 0.995), P-value=0.009). Similar negative relationships were seen between male gender-age in the multivariable model where the odds of male gender on bleeding were lower with increasing age (OR 0.988, 95% CI (0.977 to 0.999), P-value=0.030). Additionally, there was also a negative MOI-age interaction where after adjusting for other variables, the odds of shooting/stabbing injury compared with RTC on bleeding was lower with increasing age.

Table 5.7. Exploration of interactions in a multivariable logistic regression analysis of the overall cohort

The OR (95% CI) and P-value for each interaction term in the overall model is presented. (Using the covariates age, penetrating injury, hypotension (binary), tachycardia (binary), gender, mechanism of injury (MOI), unstable pelvic injury and the interaction term).

	Odds ratio	95% CI	P-value
Penetrating #age	0.979	(0.964 to 0.995)	0.009
Male #age	0.988	(0.977 to 0.999)	0.030
MOI #age			0.023
Fall ≥2 m	0.988	(0.975 to 1.002)	0.087
Fall <2 m	1.007	(0.960 to 1.056)	0.768
Shooting/stabbing	0.976	(0.960 to 0.993)	0.005
Blow(s)	1.035	(0.990 to 1.081)	0.132
Other	1.005	(0.973 to 1.037)	0.769
Unstable pelvis #age	1.005	(0.994 to 1.016)	0.340
Pre-hospital pulse ≥100 bpm #age	0.998	(0.988 to 1.008)	0.665
Pre-hospital SBP ≤90 mmHg #age	1.000	(0.990 to 1.010)	0.963

SBP, systolic blood pressure; MOI, mechanism of injury

After stepwise elimination of combinations of interaction terms, I was left with two models. Each included one interaction term with age that was significant: one that showed a negative interaction between penetrating injury and age (Table 5.8) and the other containing the MOI and age interaction (Table 5.9).

The variables included in the final models were age, penetrating injury, hypotension (binary), tachycardia (binary), gender, mechanism of injury (MOI), unstable pelvic injury and the interaction term.

Table 5.8. Multivariable logistic regression model with penetrating-age interaction (Model 1)

(Overall cohort, N=52,903).

Variable	Odds Ratio	(95% CI)	P-value
Age	1.009	(1.004 to 1.015)	0.001
Penetrating	5.235	(1.83 to 14.977)	0.002
Pre-hospital pulse ≥100 bpm	2.372	(1.943 to 2.895)	<0.001
Pre-hospital SBP ≤90 mmHg	5.658	(4.585 to 6.982)	<0.001
Male	1.433	(1.121 to 1.832)	0.004
Unstable pelvis	4.478	(3.528 to 5.685)	<0.001
MOI			<0.001
Fall ≥2 m	0.552	(0.417 to 0.733)	<0.001
Fall <2 m	0.032	(0.015 to 0.069)	<0.001
Shooting/stabbing	1.377	(0.561 to 3.381)	0.485
Blow(s)	0.273	(0.121 to 0.619)	0.002
Other	0.511	(0.285 to 0.919)	0.025
Penetrating#age	0.979	(0.964 to 0.995)	0.009

SBP, systolic blood pressure; MOI, mechanism of injury

Table 5.9. Multivariable logistic regression model with MOI-age interaction (Model 2)

(Overall cohort, N=52,903).

	Odds Ratio	(95% CI)	P-value
Age	1.011	(1.004 to 1.017)	0.001
Penetrating	2.417	(1.009 to 5.787)	0.048
Pre-hospital pulse ≥100 bpm	2.371	(1.942 to 2.894)	<0.001
Pre-hospital SBP ≤90 mmHg	5.656	(4.583 to 6.980)	<0.001
Male	1.435	(1.123 to 1.836)	0.004
Unstable pelvis	4.383	(3.449 to 5.570)	<0.001
MOI			0.003
Fall ≥2 m	1.031	(0.491 to 2.167)	0.936
Fall <2 m	0.018	(0.0004 to 0.698)	0.031
Shooting/stabbing	3.340	(1.165 to 9.57)	0.025
Blow(s)	0.052	(0.004 to 0.652)	0.022
Other	0.394	(0.07 to 2.205)	0.289
MOI#age			0.023
Fall ≥2 m	0.988	(0.975 to 1.002)	0.087
Fall <2 m	1.007	(0.960 to 1.056)	0.768
Shooting/stabbing	0.976	(0.960 to 0.993)	0.005
Blow(s)	1.035	(0.990 to 1.081)	0.132
Other	1.005	(0.973 to 1.037)	0.769

In Model 1 (with the penetrating-age interaction) (Table 5.8), all variables were significant independent factors associated with major bleeding, apart from the subcategory of shooting/stabbing injury compared with RTC. The strongest factors were penetrating injury, hypotension and unstable pelvis. Age had a modest effect on increasing the odds of bleeding adjusting for the other factors (OR = 1.009, 95% CI (1.004 to 1.015), P-value=0.001). There was a negative interaction between penetrating injury and age on the odds of bleeding.

In Model 2 (with the MOI-age interaction), age, male gender, penetrating injury, shock, tachycardia and unstable pelvis were significantly independently associated with increased odds of bleeding (Table 5.9). Age had a modest effect on increasing the odds of bleeding adjusting for the other factors (OR = 1.011, 95% CI (1.004 to 1.017), P-value=0.001). Including the interaction term between MOI and age in the model altered the odds of bleeding related to the type of MOI. Falls ≥2 m and blows were not significantly associated with bleeding when compared with the baseline risk of RTC. The statistical significance of the interaction between MOI and age was mainly due to the negative relationship between shooting/stabbing injuries and increasing age.

5.4.4 Assessment of missing data

The pattern of missing variables and outcome is shown in Table 5.10. Nearly a quarter of cases had only outcome data missing and 13.6% of cases had outcome and both vital signs missing.

Table 5.10 Percentage and pattern of missing data

Pre-hospital pulse	Pre-hospital SBP	Delphi bleeding	Number of cases (%)
✓	✓	✓	52,903(51.7%)
X	X	✓	23,646(23.1%)
X	X	X	13,899(13.6%)
✓	✓	X	7,977(7.8%)
✓	X	✓	1,921(1.9%)
X	✓	✓	1,273(1.2%)
X	✓	X	425 (0.4%)
✓	X	X	333 (0.3%)
			102,377

Tick = data present; cross = data missing

New variables were generated to indicate missing pre-hospital pulse, missing pre-hospital systolic blood pressure and missing outcome. A logistic regression model identified factors associated with the missingness of each variable (Table 5.11, Table 5.12, Table 5.13).

Table 5.11. Univariable logistic regression for predictors of missing pre-hospital pulse

Parameter	Odds Ratio	95% CI	P-value
Incident date time substituted	3.772	3.657 to 3.890	<0.001
ISS	0.983	0.982 to 0.985	<0.001
Pre-hospital arrest	0.670	0.563 to 0.797	<0.001
Open fracture	0.632	0.592 to 0.675	<0.001
Limb injury (AIS 3+)	0.799	0.772 to 0.827	<0.001
Tranexamic acid	0.412	0.393 to 0.433	<0.001

ISS, injury severity score; AIS, abbreviated injury score

Table 5.12. Univariable logistic regression for predictors of missing pre-hospital systolic blood pressure

Parameter	Odds Ratio	95% CI	P-value
Incident date time substituted	3.423	3.324 to 3.526	<0.001
ISS	0.991	0.990 to 0.993	<0.001
Pre-hospital arrest	1.576	1.377 to 1.805	<0.001
Open fracture	0.673	0.633 to 0.715	<0.001
Limb injury (AIS 3+)	0.805	0.779 to 0.831	<0.001
Tranexamic acid	0.533	0.511 to 0.557	<0.001

ISS, injury severity score; AIS, abbreviated injury score

Table 5.13. Univariable logistic regression for predictors of missing outcome

Parameter	Odds Ratio	95% CI	P-value
Incident date time substituted	1.000		
ISS	0.997	0.996 to 0.998	<0.001
Pre-hospital arrest	0.935	0.818 to 1.067	0.317
Open fracture	0.802	0.763 to 0.844	<0.001
Limb injury (AIS 3+)	0.819	0.796 to 0.842	<0.001
Tranexamic acid	0.702	0.678 to 0.727	<0.001

ISS, injury severity score; AIS, abbreviated injury score

These variables and variables correlated with the values of the missing pre-hospital pulse and systolic blood pressure (emergency department pulse and blood pressure) informed the auxiliary variables that were included in the imputation model.

5.4.5 Imputation model and complete case analysis

The imputation approach assumed the data were MAR. The results of the main analysis using CCA and multiple imputation are shown for the penetrating-age model in Table 5.14. The results for the MOI-age model are shown in Table 5.15.

Table 5.14. Comparison of CCA and imputation model for major bleeding (including penetrating-age interaction) (Model 1)

	CCA, N=52,903			Multiple Imputation, N=102,377 *m*=20		
Parameter	**OR**	**95% CI**	**P-value**	**OR**	**95%CI**	**P-value**
Age	1.011	(1.004 to 1.015)	0.001	1.005	(0.999 to 1.010)	0.108
Penetrating	5.235	(1.83 to 14.977)	0.002	5.819	(2.627 to 12.892)	<0.001
Pre-hospital pulse ≥100 bpm	2.372	(1.943 to 2.895)	<0.001	2.351	(1.981 to 2.791)	<0.001
Pre-hospital SBP ≤90 mmHg	5.658	(4.585 to 6.982)	<0.001	6.093	(4.972 to 7.466)	<0.001
Male	1.433	(1.121 to 1.832)	0.004	1.402	(1.133 to 1.736)	0.002
Unstable pelvis	4.478	(3.528 to 5.685)	<0.001	4.622	(3.810 to 5.606)	<0.001
MOI			<0.001			<0.001
Fall ≥2 m	0.552	(0.417 to 0.733)	<0.001	0.545	(0.433 to 0.686)	<0.001
Fall <2 m	0.032	(0.015 to 0.069)	<0.001	0.056	(0.003 to 0.093)	<0.001
Shooting/ stabbing	1.377	(0.165 to 3.381)	0.485	0.983	(0.487 to 1.984)	0.962
Blow(s)	0.273	(0.121 to 0.619)	0.002	0.237	(0.130 to 0.431)	<0.001
Other	0.511	(0.285 to 0.919)	0.025	0.452	(0.283 to 0.722)	0.001
penetrating# age	0.979	(0.964 to 0.995)	0.009	0.982	(0.969 to 0.995)	0.007

CCA, complete case analysis; bpm, beats per minute; SBP, systolic blood pressure; MOI, mechanism of injury

Table 5.15. Comparison of CCA and imputation model for major bleeding (including MOI-age interaction) (Model 2)

	CCA, N=52,903			Multiple Imputation, N=102,377, *m*=20		
Parameter	**OR**	**95% CI**	**P-value**	**OR**	**95%CI**	**P-value**
Age	1.011	(1.004 to 1.017)	0.001	1.007	(1.001 to 1.013)	0.018
Penetrating	2.417	(1.009 to 5.787)	0.048	3.178	(1.591 to 6.348)	0.001
Pre-hospital pulse ≥100 bpm	2.371	(1.942 to 2.894)	<0.001	2.337	(1.959 to 2.786)	<0.001
Pre-hospital SBP ≤90 mmHg	5.656	(4.583 to 6.980)	<0.001	6.079	(5.063 to 7.300)	<0.001
Male	1.435	(1.123 to 1.836)	0.004	1.329	(1.075 to 1.644)	0.009
Unstable pelvis	4.383	(3.449 to 5.570)	<0.001	4.470	(3.610 to 5.534)	<0.001
MOI			0.003			0.016
Fall ≥2 m	1.031	(0.491 to 2.167)	0.936	0.973	(0.551 to 1.721)	0.926
Fall <2 m	0.032	(0.015 to 0.069)	<0.001	0.047	(0.003 to 0.896)	0.042
Shooting/ stabbing	3.340	(1.165 to 9.570)	0.025	1.661	(0.751 to 3.676)	0.209
Blow(s)	0.052	(0.004 to 0.652)	0.022	0.164	(0.029 to 0.927)	0.041
Other	0.394	(0.070 to 2.205)	0.289	0.400	(0.100 to 1.591)	0.191
MOI#age			<0.001			0.163
Fall ≥2 m	0.988	(0.975 to 1.002)	0.087	0.989	(0.978 to 1.000)	0.047
Fall <2 m	1.007	(0.960 to 1.056)	0.768	0.993	(0.953 to 1.034)	0.722
Shooting/ stabbing	0.976	(0.960 to 0.993)	0.005	0.985	(0.970 to 1.001)	0.060
Blow(s)	1.035	(0.990 to 1.081)	0.132	1.012	(0.976 to 1.049)	0.520
Other	1.005	(0.973 to 1.037)	0.769	1.005	(0.982 to 1.030)	0.658

CCA, complete case analysis; bpm, beats per minute; SBP, systolic blood pressure; MOI, mechanism of injury

When comparing complete case and multiple imputation models, on the whole, factors that were significant in the CCA still remained significant in the imputation model. However, for the multiple imputation penetrating-age model, age was not statistically significant (P-value=0.108). The proportion of patients with penetrating injury and bleeding was approximately 1-2% higher in the imputed datasets than in the CCA group

(range 25.3%-27.3% vs 23.8%). For the model that included the MOI-age interaction, the interaction term was not significant (P-value=0.163). There was no statistical significance in the main effect of risk of bleeding with shooting/stabbing relative to RTC injury in the imputation model (OR 1.661, 95% CI (0.751 to 3.676), P-value=0.209). This was different to the CCA model where shooting/stabbing injuries were associated with greater risk of bleeding.

5.5 Discussion

5.5.1 Key findings

The aim of this chapter was to identify factors associated with early major bleeding after trauma and to investigate the impact of age on bleeding, rather than to develop a prediction model.

The data, from which these factors were identified, were taken from the UK trauma registry database (TARN). Patients were included in this study if they were admitted directly to a major trauma centre (MTC) between January 2012 and end of December 2017. During this period, there were 102,377 patients admitted directly to an MTC and 62,226 patients had a known major bleeding outcome. There were 563 patients with the Delphi study-derived definition for major bleeding (≥4 units of any blood component within 2 hours of injury). The majority of patients were male, with a mean (SD) age 44 (22), and were severely injured (mean ISS (SD) 34 (16)). Approximately a quarter of patients had penetrating injuries.

From the multivariable analysis, I identified a set of pre-hospital factors that are associated with major bleeding in trauma requiring early blood component therapy

(defined by the Delphi definition of major bleeding). I found that age was an independent factor for major bleeding both in a multivariable model and also in its interaction with penetrating injury and MOI.

Factors associated with major bleeding were assessed by logistic regression using simple variables that would be captured at the scene of injury. The factors included in the final multivariable model were age, penetrating injury, hypotension (SBP ≤90 mmHg), tachycardia (pulse ≥100 bpm), male gender, mechanism of injury (MOI) and unstable pelvic injury and the interaction term with age. Factors associated with particularly high ORs were penetrating injury, tachycardia ≥100 bpm, systolic hypotension ≤90 mmHg and unstable pelvic injury; high ORs could be related to small sample sizes in the respective categories.

There were two models as both penetrating injury and MOI demonstrated an interaction with age. In the first model with the penetrating injury-age interaction, age was a significant factor in the model, both as an individual factor (P-value=0.001) and in the interaction (there was a negative interaction between increasing age and penetrating injury on risk of bleeding (P-value=0.009)). A similar pattern was observed in the model with the MOI-age interaction.

Results derived from multiple imputation were broadly similar to the CCA model. Although, the effect of age was diminished in the imputation model, there was still a strong evidence of interaction between penetrating injury and age, and the association between age and bleeding also remained highly significant. For the model with MOI-age interaction, the pattern was different where in the imputation model, the interaction term lost statistical significance but age remained significant.

The results showed the significance of the main risk factors for the imputation model remained the same as the CCA model for the penetrating-age model, apart from age which was not statistically significant (P-value=0.108). For the MOI-age interaction model, the main risk factors remained significant, except for shooting/stabbing mechanism of injury where the risk of bleeding (relative to baseline category RTC) did not reach statistical difference, compared with the CCA model where it was associated with increased risk.

Several reasons may explain the differences between imputation and CCA models. One of the reasons for the difference between imputation and CCA models is due to small numbers in some of the subgroups that make the model more sensitive, but the reasons are often not fully known. There was moderate evidence of a correlation between penetrating mechanism and MOI (shooting/stabbing are likely to be penetrating in mechanism), R=0.707. In the complete dataset, there was a small number of penetrating and shooting/stabbing injuries among the older group with bleeding (only 2 cases of penetrating injury in the older group). It is possible that given the small numbers of events of penetrating injury in the older group, the significance was lost once the missing data were accounted for in the imputation model. There could be many reasons for the inconsistencies between the results derived from CCA and imputation models, for example, I may not have included variables that explain the missing data mechanism fully in the CCA or data were following some form of missing not at random mechanism. Nevertheless, the risk factors that I have shown to be associated with major bleeding are consistent.

The bleeding outcome is a composite outcome calculated from blood component transfusion and timing of injury. To impute the outcome, the method I used imputed the outcome for bleeding as a whole, not separate components that made up the outcome. O'Keeffe et al compared direct multiple imputation of a composite outcome with separate imputation of the components of a composite outcome.[183] Their results suggested that both approaches were comparable but that for each, separate imputation offered some improvement on the direct imputation of a composite outcome.[183] Separate imputation was not performed in this analysis but could be undertaken for future work of composite outcomes. Furthermore, multiple imputation assumes missing data are MAR but it is not possible to test the MAR assumption because there is also missingness due to unobserved variables that are not known, so we could never know for certain if the missingness is MAR. If the data were missing not at random, this could also lead to differences between CCA and imputation models. I did not explore missing not at random sensitivity analyses, which could be undertaken in future work.

Multiple imputation was chosen in this analysis to handle missing data. An alternative method is inverse probability weighting where the complete cases are weighted by the inverse of their probability of being a complete case.[184] Inverse probability weighting can be preferable to multiple imputation, as it may be easier to specify the missingness model rather than an imputation model, especially where the main analysis contains non-linear relationships, which can be hard to correctly fit into the imputation model.[185] However, multiple imputation is in general more efficient than inverse probability

weighting as it uses all observed data from the incomplete cases, whereas inverse probability weighting omits the incomplete cases.[185]

TARN has a clearly defined process for data checking. This resulted in excellent completeness (100%) for most of the risk factors in the model except pre-hospital pulse and blood pressure. Approximately a quarter of pre-hospital pulse and blood pressure data were missing with under 10% missing in the corresponding emergency department variables. This suggests that data are lost in the transfer from pre-hospital to hospital and reasons for this need exploring. Better linkage between electronic patient records and information technology systems will reduce the amount of missing data. Missing data in the outcome was primarily due to missing data on time of the injury. A way of reducing missing data would be to use time at scene instead which is better recorded. However, this would modify the definition of major bleeding.

It is acknowledged that there are limitations to the multiple imputation approach taken to handle missing data in this study. There were small numbers of cases of some types of injury, a large percentage of missing data across covariates and outcomes, and potential data could be missing not at random. Further work could explore the impact of increasing the number of imputations. These illustrate some of the practical and statistical challenges associated with the handling of missing data in observational studies, and are areas where further research is needed.[186] It is inevitable that registry data have missing data but registry data are invaluable in research, and it is better to ensure good data collection at source to minimise the amount of missing data.

The interactions can be attributed to the frequency in which different types of injuries occur at different ages. The baseline characteristics show that shooting/stabbing injuries accounted for 28.6% of patients with bleeding in the under 65s compared with only 1.2% in the older group. A possible explanation is that younger people are more likely to suffer from these types of injuries and therefore their risk of significant bleeding is higher than older people. Shooting/stabbing injuries are often associated with penetrating injury. This was reflected in the TARN data and this may also explain the significant interaction of penetrating injury and age.

The purpose of the analysis was to identify factors associated with bleeding and the effect of age on these factors, rather than to develop a prediction model. Both pulse and SBP (categorical) were associated with bleeding on univariable analysis and in the final multivariable model. But in the overall multivariable analysis including the other main factors, neither the interaction between SBP-age nor pulse-age were statistically significant. The predictive power of using these thresholds or alternative thresholds was not explored and may be useful to explore further if a prediction tool is to be developed.

Comparison with other studies

There is little in the literature about specific age-related risk factors for major bleeding. The focus of previous work has been on the development of prediction scores for major bleeding. There is some work that demonstrates current scoring systems are less sensitive at predicting massive transfusion in the older population than in the younger population.[84,187] However, none of these scores have explored the interaction of age with other predictors. The results from this TARN analysis show that age is an important

factor to consider. In order to refine prediction models, further work is needed to investigate the impact of age on other predictors.

The factors selected for the model of bleeding in this TARN study share some similarities with other models of massive transfusion (although this current TARN model utilised pre-hospital risk factors). Tachycardia and hypotension all feature in the ABC, TASH and PWH scores (but all three use a higher threshold of HR ≥120 bpm). In the present study, a lower threshold for tachycardia (HR ≥100 bpm) was used as this is consistent with earlier stage of haemodynamic instability in shock (class II shock, Acute Trauma Life Support).[188] Penetrating injury and unstable pelvic injury are also included in at least one of the aforementioned scores. Of note, the SBP and pulse in this current model were pre-hospital values as opposed to admission parameters that were used for the massive transfusion prediction scores. The main difference in this current model is that age and MOI are included as factors and an interaction term was included.

Previous studies have demonstrated that 'normal' vital signs in blunt trauma in older populations are not always reassuring, masking traditional signs of patients in shock.[55,189] Due to physiological differences, older patients may fail to meet physiological cut-offs for shock, leading to under-triage.[187] In the general population, the incidence of hypertension rises with increasing age.[52] This trend was also observed in the TARN cohort with major bleeding. Older patients were more likely to have an underlying diagnosis of hypertension than the younger group (26.2% vs 3.6%). It is possible that because blood pressure rises with age, in older people by the time the blood pressure falls into the 'hypotensive' range for shock, this heralds a significant (and

potentially catastrophic) manifestation of shock than for younger people who do not have such a high baseline blood pressure, culminating in functional hypotension.

If separate tools were developed for different age groups, for example using different thresholds for SBP and pulse, this may improve the performance and accuracy of the prediction tool but a difficulty with this approach is ageing often represents a continuum and a threshold of age 65 and above for the elderly is based purely on age and does not account for this 'gray area.'[190]

This present TARN model focuses on pre-hospital factors and is not a prediction tool. There has been some work on pre-hospital prediction scores for massive transfusion in the civilian setting. These have examined the ABC score and shock index on activating the major haemorrhage protocol, but these have not been widely adopted into clinical practice due to issues with clinical resources and problems with over- and under-triage.[75]

More recently, others have also acknowledged a clinical need for early (pre-hospital) recognition of patients at risk of bleeding and that the traditional massive transfusion of the need for 10 or more units of RBCs is a less clinically relevant outcome.[92] Hamada et al have recently published a pre-hospital red flag alert to predict for significant haemorrhage in a French trauma population.[92] They defined significant haemorrhage as a composite of any of the following 6 measures: the need for RBC transfusion in the trauma room, transfusion ≥4 RBC in the first 6 hours, lactate ≥5 mmol/L, immediate haemostatic surgery, interventional radiology and/or death of haemorrhagic shock. Age >50 was included in the multivariable prediction model. In their final model, they chose five pre-hospital variables: shock Index (calculated by heart rate/SBP) ≥1, mean arterial

blood pressure ≤70 mmHg, point of care haemoglobin ≤13 g/dL, unstable pelvis and pre-hospital intubation.[92] The score demonstrated favourable predictive performance: sensitivity 75% (72–79%), specificity 79% (77–80%) and area under the receiver operating characteristic curve 0.83 (0.81–0.84) in the derivation cohort.[92]

The population in whom the red flag score was derived is different to patients in the TARN study. The score was developed in a French cohort of patients with blunt injury only (excluded those with penetrating injury) and patients with pre-hospital cardiac arrest were also excluded, so may not capture the most severely injured patients. The TARN model included patients with blunt and penetrating injuries and did not exclude those in cardiac arrest. The French red flag alert may not be widely generalisable to other countries where pre-hospital point of care blood testing is not performed as standard of care, for example in the UK. Nevertheless, this French registry study is the first to develop a prediction tool for a composite definition of bleeding in the pre-hospital setting.

Another difference with the study data was that their dataset had low levels of missing data (a maximum of 5% missing data was observed for the imputed variables). This is less than that which was observed in the present TARN dataset. (Missing data for the TARN dataset will be discussed in Chapter 6. Briefly, 38.2% of the outcomes were missing, and pulse and blood pressure up to 25% missing). Nevertheless, the French group used multiple imputation to handle missing data, even with the low level of missing data.

Impact of age on massive transfusion outcomes

Recently, a group from Ohio evaluated the effect of age on massive transfusion using data from the Trauma Quality Improvement Program database.[91] They defined massive transfusion as ≥4 units of RBCs within 4 hours of admission. In a subset of their registry data (n=440), admission heart rate was significantly lower in older patients than in younger patients, but systolic blood pressure was similar. In the TARN data, although I used a different definition for bleeding, similar trends were observed for vital signs where younger patients were more tachycardic than older patients and systolic blood pressure was similar, albeit in the pre-hospital setting.

The group also found that increasing age and high-volume transfusion were associated with progressively increased mortality with an incremental increase of mortality for each later decade of life.[91] The study also demonstrated overall mortality of approximately 30% in patients with massive transfusion. However, to illustrate the difference in mortality and transfusion across age, they demonstrated an octogenarian was already at 30% risk of mortality after 2-3 units of RBCs, compared to a 20-year-old, who did not reach 30% mortality until after a 10-unit transfusion. The authors suggested that age should be considered when defining massive transfusion, especially if the primary outcome of interest is mortality.

The focus of the present TARN study was not on mortality but this is an important outcome to consider when modeling major bleeding and could be a further area of work. Future work could also explore non-linear relationships of bleeding with age.

Scoring systems for major bleeding

Comparing major bleeding scoring systems is complicated by the different contexts and populations from which they were developed and the variable definitions of massive transfusion.[75] Composite definitions or definitions that focus on the rate of transfusion within a shorter timeframe of 30-60 minutes, such as critical administration threshold, are better at including patients with rapid bleeding in the modern era of trauma resuscitation.[88] However, a lot of the information on timings or specific outcomes that combine to form the composite outcome is not captured in most trauma registries and hence have not been used to create major bleeding prediction scores.[75] The Delphi definition also has its limitations. Ultimately, unless there is a prospectively designed study, the decision of which outcome definition to use may need to be a pragmatic one based on what is feasible with registry data.

In summary, this TARN study has identified factors associated with bleeding and has shown that age is an important factor and also modifies the effect of MOI and of penetrating injury. Identifying factors at the scene of injury could help inform patient risk. Patients at high risk of bleeding could be triaged to a major trauma centre with the facilities and expertise to manage severe injuries and bleeding. The model based on the TARN data could be extended to develop a prediction tool or an age-adapted major haemorrhage protocol. The Delphi definition could be applied to other populations with similar trauma systems outside of the UK to see if the risk factors and impact of age as a risk factor and effect modifier are consistent across populations.

5.5.2 Limitations

There are limitations with this study, related to the retrospective nature of this study. These include data which is not routinely captured in a database that could be relevant in the analysis and interpretation of the results. Pre-existing medical conditions and/or medication may act as confounders and medications that are taken for rate-control and attenuate the pulse such as beta-blockers were not available as part of this dataset.

For the pulse and blood pressure readings, only the initial pre-hospital reading was captured in TARN and there are no repeated measurements to be able to identify trends in the vital sign parameters (the next parameter captured for vital signs is on hospital admission). As these signs could vary within a short space of time, depending on the clinical situation of the patient, monitoring the trend is more helpful in practice rather than solely relying on a single reading. It is also possible that tachycardia and hypotension may be due to other reasons apart from bleeding such as hypovolaemia, tension pneumothorax, cardiac tamponade, stress or pain. There could also be a non-linear relationship for blood pressure and pulse, which was not explored in this study, nor was the shock index investigated, which has been reported in other studies.[75,187,191,192]

In the TARN cohort, there also appeared to be a lower heart rate in older people with bleeding compared with younger people. It is not clear how many patients were on medications for heart rate control, which may have blunted any tachycardic response (particularly for the elderly where the incidence of arrhythmias e.g. atrial fibrillation is higher). A study that explored factors predicting massive transfusion in the elderly found that heart rate did not predict massive transfusion, although other blood pressure

parameters did.[187] Another study that looked at severe injury in general and not specifically patients with bleeding proposed a different triage criteria for older people.[55] Based on the results of their study, they suggested using a SBP of 110 mmHg as a cut-off for shock instead of 90 mmHg to indicate who should be triaged to a major trauma centre in order to reduce under-triage of older patients.[55]

In the present study, unstable pelvic fracture was used as a predictor. In TARN this is captured from imaging reports. A limitation of this study is that the imaging and clinical assessment of unstable pelvic fracture at the scene of injury may not always correspond, especially if clinical signs of pelvic injury such as pain are masked due to altered consciousness,[193] as clinical assessment of pelvic fracture in the pre-hospital setting is not collected in the TARN registry.

The performance of this model has not been tested, as this study aimed to identify candidate factors. It shows that age is an important factor and that factors associated with bleeding are similar for both young and older patients. In this model assessing the effect of age, all age groups were included and age was included as a predictor as a continuous variable. This approach was taken because at the scene of injury having one overall scoring tool may be simpler than having a separate tool for older and younger people. A limitation of taking this approach is that the power of an overall prediction tool may be lower than for separate models of old and young.

As previously described in Chapter 3 (Delphi study), the outcome for major bleeding uses a proxy measure of transfusion within 2 hours of injury. This early time-point has not been investigated in other models of bleeding. An early endpoint such as this relies on swift hospital transfer and may miss patients with delay in transport who may have

had significant bleeding but did not receive blood products as quickly as intended. For this reason, only patients directly admitted to MTCs were eligible for this study, and this selected population may have different characteristics to those who were not triaged to an MTC but were admitted to a trauma unit.

Finally, the focus of this study was to investigate the impact of ageing on factors associated with bleeding. Other interactions were not looked at apart from age and these could be important to explore in future analyses. Further work would be to develop a prediction model and to externally validate it on another dataset.

5.6 Conclusion

Clinical prediction models have been developed to enable early identification of patients at risk of significant bleeding. Historically, however, the models predict for massive transfusion, are intended for use after the patient has arrived in hospital, and are based on predominantly younger patients.[78,79] The concept of the golden hour in trauma has highlighted the importance of initial resuscitation and stabilisation of the patient in the acute setting. There is scope to improve how patients with bleeding are identified in the pre-hospital setting so they can be appropriately triaged to centres best able to treat severely injured bleeding patients.

This study shows that in a multivariable model for major bleeding, occurring early within two hours of injury, hypotension, tachycardia, penetrating injury, age, MOI, unstable pelvic fracture and male gender were associated with bleeding. Age is an important factor and as demonstrated in two separate interaction models it modifies the effect of penetrating injury and MOI. This work could be extended further to develop an age-adapted prediction tool to predict early bleeding in trauma.

Despite best efforts, missing data are a problem in registry data. Multiple imputation was used to handle missing data in the TARN registry. Risk factors for major bleeding in the multiple model were broadly similar to the CCA model and support the finding that age affects the risk of bleeding in trauma. Strategies to minimise missing data and to improve the quality of data in trauma registries are needed. Improved data quality will facilitate accurate analysis across registries and enhance research studies in areas that primarily utilise observational data, e.g. in the development of prediction models or risk scores.

Chapter 6 Coagulation profile of older and younger patients with bleeding

6.1 Introduction

Acute traumatic coagulopathy (ATC) is a derangement of the haemostatic system that exacerbates bleeding in severely injured patients. ATC is a complex endogenous process, characterised by systemic anticoagulation, hypofibrinogenaemia and hyperfibrinolysis.[23] It is present in about a quarter of patients at the time of admission to the emergency department and is closely associated with higher injury severity and hypoperfusion.[7,23,194]

Compared with patients who do not have coagulopathy, patients with ATC have higher transfusion requirements, increased risk of multi-organ failure, longer hospital stays and a 3- to 4-fold increased risk of mortality.[7,17] Improved management of ATC has the potential to reduce morbidity and mortality from bleeding in trauma.[15] Up till now, studies that have informed the diagnosis and management of coagulopathy have involved predominantly younger populations in their 30s and 40s.[195,196]

Among older trauma patients, there are few data on the spectrum of coagulation changes in trauma and their relationship with injury severity and clinical outcomes such as bleeding or mortality. Changes in haemostasis that occur with normal ageing could affect the haemostatic profile in trauma (Table 6.1, Table 6.2).

Table 6.1 Haemostatic changes in normal ageing

Modified from reference.[197] Gender= (possible effect of gender)

System affected	Marker affected
Coagulation system (secondary haemostasis)	Fibrinogen ↑ Factor II, X = Factor V, VII, VIII, IX, XI, FXIII ↑
Markers of coagulation activation	PT fragments 1+2, fibrinopeptide A, activated factor VII ↑
Anticoagulant proteins	Antithrombin, gender ↑women, ↓men Protein C =, gender Protein S =, gender TFPI ↑
Fibrinolysis markers	Plasminogen =, gender (↓ women) PAI-1 ↑ PAP, D-dimers ↑ TAFI ↑
Thrombin generation	Thrombin generation ↑
Primary haemostasis and platelet function	VWF ↑ Platelet activation ↑ PFA-100 closure time ↓

TFPI; tissue factor pathway inhibitor; PAI-1, plasminogen activator inhibitor-1; PAP, plasmin-antiplasmin complex; TAFI, thrombin activatable fibrinolysis inhibitor; VWF, von Willebrand Factor; PFA, platelet function analyser

Table 6.2. Summary of coagulation and fibrinolytic changes across age and in trauma

Based on references [61,197,198]

	Younger trauma ATC	Older trauma	Normal ageing
Primary haemostasis			
VWF	↑	↑	↑
Secondary haemostasis			
Fibrinogen	↓↓	↓	↑
FV, FVIII	↓	?	↑
FVII	?	?	↑
Fibrinolysis			
PAI-1	↓	?	↑
PAP	↑	?	↑
t-PA	↑	↑↑/?	↑

VWF, Von Willebrand Factor; PAI-1, plasminogen activation inhibitor-1; PAP, plasminogen antiplasmin complex; t-PA, tissue plasminogen activator

As part of the ageing process, levels of pro-thrombotic factors such as fibrinogen, FVIII, VWF rise with age.[199] Studies have also shown increased fibrinolytic activity in normal ageing.[197] It is hypothesised that these changes could alter the profile and magnitude of coagulation factor depletion and fibrinolysis in trauma patients at different ages, particularly in older patients.

Current international management guidelines for the management of ATC are generic across age, and recommend treating patients with blood components to reach a target APTT/PT within 1.5x normal range, fibrinogen > 1.5g/L and early empiric use of TXA.[27] It is possible that differences might be found in older age, which may mean that different thresholds are needed across age.

6.1.1 Aims

The overall aim of this chapter was to evaluate the baseline characteristics and coagulation changes in patients with trauma across different ages and injury severity. Specific objectives were to describe the:

i) demographics, physiology, transfusion use and outcomes of trauma patients

ii) standard coagulation and rotational thromboelastometry (ROTEM) profile

iii) extended coagulation and fibrinolytic profile.

6.2 Methods and materials

6.2.1 ACIT Study

This study was in collaboration with the on-going Activation of Coagulation and Inflammation in Trauma (ACIT) research study, which commenced in 2008. The ACIT study is a multi-centre, prospective, cohort study of trauma patients presenting directly to one of 6 European level 1 trauma centres (Amsterdam, Cologne, Copenhagen, Oslo, Oxford, London). Clinical and laboratory data are collected for each patient alongside blood samples on admission. A summary of the ACIT study methodology is provided below. The study data were collected by other investigators and I analysed the data.

6.2.2 Inclusion and exclusion criteria

The inclusion/exclusion criteria, data collection, blood sampling, assays, and outcome measures for the ACIT study have previously been reported.[23,196]

Inclusion criteria

All adult trauma patients (age ≥16 years) who required a full trauma team activation.

Exclusion criteria

Patients who received >2 L intravenous fluids pre-hospital, who arrived >2 hours after injury in the Emergency Department (ED), who were transferred from other hospitals and patients who had burns covering more than 5% of the total body surface area. Patients were retrospectively excluded if they declined to give informed consent, were taking anticoagulant medications other than aspirin (<650 mg/day), had moderate or severe liver disease (Child-Pugh's classification B or C3) and had a known bleeding diathesis.

6.2.3 Data collection

The following data were collected prospectively to a centralised database: patient demographics, time of injury, trauma mechanism, vital signs on admission, base deficit, viscoelastic assay and standard laboratory tests, Injury Severity Score (ISS), Abbreviated Injury Scale Score (AIS, which classifies individual injuries by body regions) and 28-day mortality. Data were collected on transfusion of blood products: number of red blood cell units (RBCs), fresh frozen plasma (FFP), platelet units and cryoprecipitate. Use of TXA was also collected (but data regarding the timing of blood sampling relative to administration of the first TXA dose were not collected).

In the study, in addition to the admission blood sample, samples are also collected at serial time points, (24 hours, 72 hours and 7 days post admission), but as I was interested in the baseline changes of coagulation, these data were not extracted.

6.2.4 Blood sampling and local haemostatic assays

Blood was drawn and collected in citrated tubes immediately on arrival in the ED. Standard trauma laboratory assays (including full blood count and routine coagulation screen) and ROTEM/TEG were performed at each participating centre. Two ROTEM® assays (EXTEM and FIBTEM) were performed by trained personnel. Within each assay, the following ROTEM® parameters were analysed; the clotting time (CT), the clot amplitude after 5 minutes (CA5), the angle of tangent at 20 mm amplitude (alpha angle), the maximum clot firmness (MCF) and the lysis index of the clot after 30 minutes (LY30).

6.2.5 Extended haemostatic assays

Blood samples were processed and stored for subsequent testing. The blood sample for extended haemostatic assays was placed in a citrated tube and spun down within 2 hours of blood draw. The sample was first spun at 1,750g for 10 minutes; the supernatant was then extracted and respun at 1,750g for a further 10 minutes. The extracted platelet poor plasma was stored in aliquots at −80°C.

In 2014, a subset of patients enrolled in the ACIT study had extended haemostatic assays performed. Samples were analysed centrally at the Royal London Hospital with an automated analyser (Sysmex CA-CS2100i System; Siemens AG, Germany) to measure coagulation factor activity (normal range): II (78 to 117 iu/mL), V (66 to 114 iu/mL), VII (50 to 150 iu/mL) VIII (52 to 153 iu/mL), IX (58 to 138 iu/mL), X (50 to 150 iu/mL), XI (50 to 150 iu/mL), XIII (70 to 140 iu/mL), von Willebrand factor (vWF; 50 to 160 iu/mL), PC (75 to 134 iu/mL), and antithrombin (80 to 130 iu/mL).

Enzyme linked immunoassays were used to quantify t-PA (Asserachrom tPA; Diagnostica Stago, France; normal range, 2 to 12 ng/ml), plasminogen activator inhibitor-1 (PAI-1)

(Asserachrom PAI-1; Diagnostica Stago), prothrombin fragments 1 + 2 (Enzygnost F1 + 2 monoclonal; Siemens Healthcare Diagnostics, Germany; normal range, 69 to 229 pmol/l), plasmin–α2-antiplasmin complex (PAP) (plasmin-antiplasmin; DRG Plasmin-Antiplasmin micro, Germany; normal range, 120 to 700 µmol/l), and thrombomodulin (thrombomodulin, Abcam; normal range, 2.9 to 7.6 ng/ml).

6.2.6 Data extraction and analysis

In order to evaluate the impact of age on haemostasis in trauma, as ISS and hypoperfusion (assessed by base deficit) are known to influence coagulopathy, patients who had either ISS or base deficit data missing were excluded from this study. Data were extracted for patients recruited between January 2008 - March 2017 (patients aged under 65 (RLH only, as a single reference centre that uses ROTEM) and patients aged 65 and above (from all 6 centres)). Within the eligible cohort, two groups were examined in order to compare coagulation changes in patients at opposite ends of injury severity and bleeding:

1) Patients with minor injuries and no shock

2) Severely injured patients with shock and bleeding.

Minor injury was defined as ISS 0-4, severe injury: ISS >15, presence of shock: base deficit less than -6 mmol/L (as reported in).[195] RBC transfusion was used as a surrogate marker of bleeding and bleeding was defined as ≥4 units RBC in 12 hours.[200] For each injury category, I explored demographic, physiology, transfusion, mortality and standard coagulation data across four age groups (16-49, 50-64, 65-74, ≥75).

The variables of interest were:

- Baseline characteristics: Age, ISS, gender, penetrating injury, mechanism of injury (MOI), AIS of body region, isolated traumatic brain injury (TBI)
- Physiology: admission SBP, HR, GCS, base deficit
- Transfusion: 24-hr RBC, FFP, Platelets, Cryoprecipitate use
- Outcome (survival) at 28 days, TXA use
- Standard coagulation and ROTEM parameters: Hb, Platelets, APTT, INR, fibrinogen, ROTEM (CT, MCF, CA5, alpha angle, LY30)

The extended coagulation and fibrinolytic profile of patients was examined in the subset of patients who had extended haemostatic assays performed. As PAP is a key marker of fibrinolysis, patients without PAP data were excluded. These data were described across two age groups (young, aged 16-64 and older, 65 and above) due to the small sample size (Figure 6.1).

The parameters of interest were:

- Factors: FXIII, FV, FVIII, FII, FVII, FIX, FXI, FX, von Willebrand factor antigen (VWF Ag)
- Fibrinolysis: D dimer, TAFIa, TAFI, PAI-1, t-PA, A2AP, PAP
- Other markers: Protein C (anticoagulant), sFMC (soluble fibrin monomer complex, indicator of coagulation activation), Prothrombin fragments 1+2 (indicator of thrombin formation), thrombomodulin (marker of endothelial dysfunction/activation).

6.2.7 Statistical analysis

Data were presented descriptively as mean and standard deviation if normally distributed and as median and IQR for non-parametric data. Categorical data were presented as frequencies and percentages.

The effect of age group on key fibrinolytic and coagulation markers was also explored using linear regression, adjusting for ISS, base deficit, presence of bleeding, severe head/neck injury (defined by AIS ≥3 in this body region) and gender, using the youngest age group (16-49) as the reference group. These variables were included in the multivariable regression model as they have an effect on coagulation and fibrinolysis, and traumatic brain injury in older people is associated with increased fibrinolysis.[201] The following haemostatic markers of interest were selected, as these have been demonstrated in previous studies to be deranged in ATC and/or are markers of fibrinolysis: fibrinogen, FV, t-PA, A2AP, PAP, TAFIa and PAI-1.[196,198] Because TXA is an anti-fibrinolytic and can attenuate the haemostatic assays of fibrinolysis, the regression analysis was performed in patients who did not receive TXA, in the years preceding 2015 (as the extended fibrinolysis assays were performed in 2014). Only patients with fibrinogen measured were included in the analysis. Non-parametric fibrinolytic parameters were log transformed to normality prior to regression.

6.2.8 Ethics

For the ACIT study, written informed consent was obtained from each patient. If the patient was incapacitated, consent was obtained from a legal representative. The study was conducted according to the Statement of the Declaration of Helsinki and performed after approval by the local ethics committees.

6.3 Results

Of the patients recruited into the ACIT study between Jan 2008 – March 2017 a total of 1575 patients had ISS and base deficit data available. The flow of patients for analysis is presented in Figure 6.1.

Overall, the mean age was 44 years (SD 21), 77.8% of the cohort were male, the mean ISS was 19 (SD 14). Blunt injuries accounted for over 80% of injuries. In the youngest group (aged 16-49) there was a greater proportion of penetrating injuries (27% compared with less than 10% in the older groups). RTC and shooting/stabbing accounted for 70% of injuries in the youngest group compared with RTC and falls as the most frequent mechanisms of injury in the older groups (Table 6.3). In general, patients received a mean of 3 units of RBC at 24 hours (SD 6) (Table 6.4).

Figure 6.1. Flow of patients for analysis

There were 1575 patients with complete ISS and base deficit data. Four subsets of patients were analysed (not mutually exclusive) to evaluate the effect of age on injury severity, shock and bleeding; extended haemostatic assays and fibrinogen. Minor injury: ISS 0-4, severe injury: ISS >15, presence of shock: base deficit less than -6 mmol/L; bleeding ≥4 units RBC in 12 hours. ISS, injury severity score; PAP, plasmin-antiplasmin complex; Fg, fibrinogen.

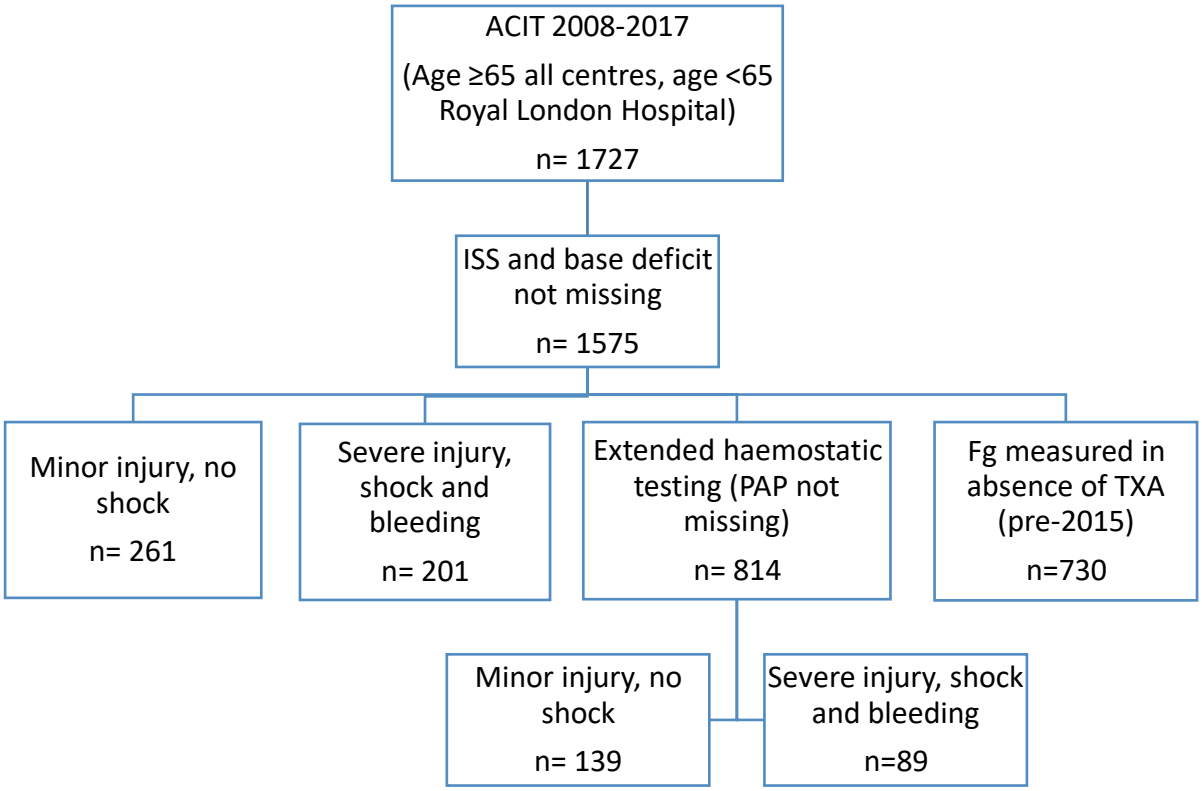


Table 6.3. Overall summary measures by age band

	16-49 (N=956)	50-64 (N=223)	65-74 (N=224)	≥75 (N=172)	Overall (N=1575)
Age, mean (SD)	30 (9)	56 (4)	69 (3)	82 (5)	45 (21)
ISS, median (IQR)	14 (8 to 27)	24 (10 to 34)	19 (9 to 29)	17 (9 to 27)	17 (9 to 29)
ISS category, n (%)					
ISS 0-4	192 (20.1%)	16 (7.2%)	33 (14.7%)	30 (17.4%)	271 (17.2%)
ISS 5-15	292 (30.5%)	52 (23.3%)	56 (25.0%)	49 (28.5%)	449 (28.5%)
ISS >15	472 (49.4%)	155 (69.5%)	135 (60.3%)	93 (54.1%)	855 (54.3%)
Male, n (%)	799 (83.6%)	181 (81.2%)	149 (66.5%)	97 (56.4%)	1226 (77.8%)
Penetrating injury, n (%)	265 (27.7%)	17 (7.6%)	10 (4.5%)	9 (5.2%)	301 (19.1%)
Mechanism of injury, n (%)					
RTC	423 (44.2%)	112 (50.2%)	110 (49.1%)	89 (51.7%)	734 (46.6%)
Fall/jump from height	164 (17.2%)	63 (28.3%)	65 (29.0%)	55 (32.0%)	347 (22.0%)
Shooting/stabbing	255 (26.7%)	16 (7.2%)	8 (3.6%)	5 (2.9%)	284 (18.0%)
Blunt assault	27 (2.8%)	7 (3.1%)	1 (0.4%)	0 (0.0%)	35 (2.2%)
Other	87 (9.1%)	25 (11.2%)	23 (10.3%)	11 (6.4%)	146 (9.3%)
Missing, n (%)	*0 (0.0%)*	*0 (0.0%)*	*17 (7.6%)*	*12 (7.0%)*	*29 (1.8%)*
Head Neck AIS ≥3, n (%)	254 (26.6%)	89 (39.9%)	94 (42.0%)	75 (43.6%)	512 (32.5%)
Missing, n (%)	*3 (0.3%)*	*2 (0.9%)*	*1 (0.4%)*	*1 (0.6%)*	*7 (0.4%)*
Thorax AIS ≥3, n (%)	369 (38.6%)	110 (49.3%)	73 (32.6%)	61 (35.5%)	613 (38.9%)
Missing, n (%)	*3 (0.3%)*	*2 (0.9%)*	*1 (0.4%)*	*4 (2.3%)*	*10 (0.6%)*
Abdomen/Pelvis AIS ≥3, n (%)	135 (14.1%)	29 (13.0%)	20 (8.9%)	7 (4.1%)	191 (12.1%)
Missing, n (%)	*3 (0.3%)*	*2 (0.9%)*	*1 (0.4%)*	*6 (3.5%)*	*12 (0.8%)*
Extremity AIS ≥3, n (%)	277 (29.0%)	81 (36.3%)	61 (27.2%)	41 (23.8%)	460 (29.2%)
Missing, n (%)	*3 (0.3%)*	*2 (0.9%)*	*1 (0.4%)*	*3 (1.7%)*	*9 (0.6%)*
Isolated TBI, n (%)	112 (11.7%)	35 (15.7%)	52 (23.2%)	39 (22.7%)	238 (15.1%)
Missing, n (%)	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*

ISS, injury severity score; AIS, abbreviated injury score

Table 6.4. Overall physiology, transfusion and outcome by age band

CRASH3 – some patients were also recruited into the CRASH-3 RCT evaluating tranexamic acid (TXA) in traumatic brain injury (TBI).

	16-49 (N=956)	50-64 (N=223)	65-74 (N=224)	≥75 (N=172)	Overall (N=1575)
SBP (mmHg), mean (SD)	126 (28)	130 (38)	132 (40)	138 (40)	129 (33)
HR (bpm), mean (SD)	96 (27)	91 (28)	86 (24)	88 (23)	93 (27)
GCS, mean (SD)	12 (4)	11 (4)	11 (5)	11 (5)	12 (4)
Base deficit (mmol/l), median (IQR)	-1.4 (-4.6 to 0.6)	-2.0 (-5.5 to 0.2)	-0.7 (-3.5 to 1.4)	-1.2 (-4.7 to 1.7)	-1.4 (-4.6 to 0.8)
Units at 24 hours					
RBC, mean(SD)	2 (6)	3 (6)	2 (6)	3 (6)	3 (6)
FFP, mean(SD)	2 (4)	2 (5)	1 (4)	1 (5)	2 (4)
Platelets, mean(SD)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)
Cryoprecipitate, mean(SD)	0 (1)	1 (2)	0 (1)	0 (1)	0 (1)
Base deficit category, n (%)					
Less than -6 mmol/l	199 (20.8%)	49 (22.0%)	39 (17.4%)	31 (18.0%)	318 (20.2%)
≥ -6 mmol/l	757 (79.2%)	174 (78.0%)	185 (82.6%)	141 (82.0%)	1257 (79.8%)
Outcome at 28 days, n (%)					
Dead	89 (9.3%)	40 (17.9%)	59 (26.3%)	50 (29.1%)	238 (17.0%)
Missing, n(%)	*8 (0.8%)*	*2 (0.9%)*	*1 (0.4%)*	*3 (1.7%)*	*14 (1.0%)*
TXA, n (%)					
No	705 (73.7%)	132 (59.2%)	159 (71.0%)	124 (72.1%)	1120 (71.1%)
Yes	213 (22.3%)	70 (31.4%)	43 (19.2%)	30 (17.4%)	356 (22.6%)
CRASH-3	38 (4.0%)	21 (9.4%)	12 (5.4%)	9 (5.2%)	80 (5.1%)
Missing, n(%)	*0 (0.0%)*	*0 (0.0%)*	*10 (4.5%)*	*9 (5.2%)*	*19 (1.2%)*

SBP, systolic blood pressure; HR, heart rate; GCS, glasgow coma scale; RBC, red blood cells; FFP, fresh frozen plasma

6.3.1 Minor injury

In the cohort of 261 patients with minor injury and no shock, the pattern of injury was similar to that of the overall cohort, with a larger proportion of males and penetrating injuries in the youngest group (Table 6.5). In this group with minor injury (median ISS was 1 across all age groups). The results of the vital signs showed the admission systolic blood pressure rose with age but heart rate did not show any significant alterations with age (Table 6.6). Across all age groups, patients with minor injury received minimal blood transfusion and survival was 100% at 28 days (Table 6.6). Standard laboratory and ROTEM data are shown in Table 6.7. These parameters were similar across age groups apart from fibrinogen, which increased with age.

Table 6.5. Minor injury (ISS 0-4) and no shock: summary measures by age band

	16-49 (N=185)	50-64 (N=16)	65-74 (N=31)	≥75 (N=29)	Overall (N=261)
Age, mean (SD)	31 (10)	56 (5)	68 (3)	82 (6)	42 (21)
	29 (22 to 39)	54 (52 to 60)	67 (66 to 71)	81 (78 to 87)	37 (25 to 58)
ISS, median (IQR)	1 (1 to 4)	1 (1 to 1)	1 (1 to 2)	1 (1 to 4)	1 (1 to 4)
Male, n (%)	160 (86.5%)	12 (75.0%)	20 (64.5%)	18 (62.1%)	210 (80.5%)
Penetrating injury, n (%)	79 (42.7%)	2 (12.5%)	7 (22.6%)	3 (10.3%)	91 (39.2%)
Mechanism of injury, n (%)					
RTC	60 (32.4%)	7 (43.8%)	12 (38.7%)	10 (32.3%)	89 (38.4%)
Fall/jump from height	24 (13.0%)	6 (37.5%)	9 (29.0%)	13 (41.9%)	52 (22.4%)
Shooting/stabbing	*77 (41.6%)*	*1 (6.3%)*	*5 (16.1%)*	*2 (6.9%)*	*85 (36.6%)*
Blunt assault	11 (5.9%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	12 (5.2%)
Other	13 (7.0%)	1 (6.3%)	3 (9.7%)	2 (6.5%)	19 (8.2%)
Missing, n (%)	0 (0.0%)	0 (0.0%)	2 (6.5%)	2 (6.5%)	4 (1.7%)
Head Neck AIS ≥3, n (%)	0 (0.0%)	0 (0.0%)	2 (6.5%)	*0 (0.0%)*	2 (0.9%)
Missing, n (%)	*1 (0.5%)*	*0 (0.0%)*	*0 (0.0%)*	*1 (3.4%)*	*2 (0.8%)*
Thorax AIS ≥3, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	*1 (3.4%)*	1 (0.4%)
Missing, n (%)	*1 (0.5%)*	*0 (0.0%)*	*0 (0.0%)*	*1 (3.4%)*	*2 (0.9%)*
Abdomen/Pelvis AIS ≥3, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	*0 (0.0%)*	0 (0.0%)
Missing, n (%)	*1 (0.5%)*	*0 (0.0%)*	*0 (0.0%)*	*1 (3.4%)*	*2 (0.9%)*
Extremity AIS ≥3, n (%)	0 (0.0%)	0 (0.0%)	1 (3.2%)	*0 (0.0%)*	1 (0.4%)
Missing, n (%)	*1 (0.5%)*	*0 (0.0%)*	*0 (0.0%)*	*1 (3.4%)*	*2 (0.9%)*
Isolated TBI, n (%)	0 (0.0%)	0 (0.0%)	1 (3.2%)	*0 (0.0%)*	1 (0.4%)
Missing, n (%)	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*

ISS, injury severity score; AIS, abbreviated injury score

Table 6.6. Minor injury (ISS 0-4) and no shock: physiology, transfusion and outcome by age band

	16-49 (N=185)	50-64 (N=16)	65-74 (N=31)	≥75 (N=29)	Overall (N=261)
SBP (mmHg), mean (SD)	135 (23)	147 (28)	145 (27)	160 (36)	140 (27)
HR (bpm), mean (SD)	88 (23)	78 (13)	79 (20)	82 (19)	86 (22)
GCS, median (IQR)	15 (14 to 15)	15 (14 to 15)	15 (15 to 15)	15 (14 to 15)	15 (14 to 15)
Base deficit ($mmolL^{-1}$), mean (SD)	0.6 (-1.2-1.9)	0.6 (-1.4-1.7)	1.0 (-1.1-2.0)	-0.6 (-2.1-1.2)	0.6 (-1.2-1.9)
Units at 24 hours					
RBC, mean (SD)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
FFP, mean (SD)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Platelets, mean (SD)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Cryoprecipitate, mean (SD)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Outcome at 28 days, n (%)					
Dead	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Missing, n(%)	*1 (0.5%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*1 (0.4%)*
TXA, n (%)					
No	176 (95.1%)	16 (100.0%)	26 (83.9%)	28 (96.6%)	246 (94.3%)
Yes	9 (4.9%)	0 (0.0%)	4 (12.9%)	1 (3.4%)	14 (5.4%)
CRASH-3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing, n(%)	*0 (0.0%)*	*0 (0.0%)*	*1 (3.2%)*	*0 (0.0%)*	*1 (0.4%)*

SBP, systolic blood pressure; HR, heart rate; GCS, glasgow coma scale; RBC, red blood cells; FFP, fresh frozen plasma; TXA, tranexamic acid

Table 6.7. Minor injury (ISS 0-4), no shock: Overall haematology and coagulation parameters by age band

	16-49 (N=185)	50-64 (N=16)	65-74 (N=31)	≥75 (N=29)	Overall (N=261)
Hb, mean (SD)	14.5 (1.4)	14.4 (1.3)	13.8 (1.7)	13.0 (1.5)	14.2 (1.5)
Platelet count, mean (SD)	238.3 (64.1)	228.0 (49.3)	247.9 (84.4)	197.7 (41.8)	234.3 (65.0)
APTT, mean (SD)	23.1 (2.2)	23.0 (4.2)	27.2 (4.8)	30.5 (7.2)	24.5 (4.5)
INR, mean (SD)	1.0 (0.1)	1.0 (0.0)	1.0 (0.1)	1.1 (0.1)	1.0 (0.1)
Missing, n (%)	*26 (14.1%)*	*0 (0.0%)*	*3 (9.7%)*	*1 (3.4%)*	*30 (11.5%)*
Fibrinogen, mean (SD)	2.5 (0.6)	2.9 (0.7)	3.1 (0.7)	3.2 (0.8)	2.7 (0.7)
Missing, n (%)	*54 (29.2%)*	*2 (12.5%)*	*5 (16.1%)*	*3 (10.3%)*	*64 (24.5%)*
Extem CA5, mean (SD)	44.9 (7.7)	46.5 (12.2)	47.5 (7.7)	49.0 (7.9)	45.6 (8.1)
Extem CFT, mean (SD)	93.7 (51.6)	75.3 (17.3)	84.5 (22.3)	78.6 (29.2)	90.3 (46.5)
Extem alpha angle, mean (SD)	71.7 (7.5)	75.1 (3.5)	73.5 (4.4)	74.5 (5.6)	72.4 (7.0)
Extem CT, mean (SD)	62.9 (26.7)	57.7 (29.7)	55.3 (14.4)	65.8 (26.2)	62.1 (25.8)
Extem MCF, mean (SD)	61.9 (6.9)	62.3 (15.4)	64.3 (6.5)	65.7 (6.0)	62.6 (7.7)
Extem LY30, mean (SD)	99.3 (1.2)	98.9 (3.6)	99.5 (0.8)	99.9 (0.3)	99.3 (1.4)

Hb, haemoglobin; APTT, activated partial thromboplastin time; INR, international normalised ratio; CFT, clot firmness time; CT, clotting time; MCF, maximum clot firmness; LY30, lysis time at 30 minutes

6.3.2 Severe injury, shock and bleeding

6.3.2.1 *Patient and injury characteristics*

The gender and type of injury in the 201 patients with severe injury, shock and bleeding were similar to the minor injury group (male preponderance and more penetrating injuries in the youngest group (Table 6.8)). The predominant MOI in the over 65s was RTC accounting for over 70% of injuries. In the younger groups the main mechanisms of injury were RTC (46.5%) and shooting/stabbing (29.5%). The pattern of injury severity was different across age groups. Older patients predominantly suffered severe head/neck and thoracic injuries with fewer severe abdominal/pelvic injuries; in the younger groups in addition to these injuries, a third of patients also presented with severe abdominal/pelvic injuries.

6.3.2.2 *Vital signs*

Patients were hypotensive across all age groups (Table 6.9). However, the degree of tachycardia was blunted with increasing age; this is seen most clearly in the over 65 and over 75 age groups who did not present with the same degree of tachycardia as the youngest group (median HR 100, IQR 70 to 120 in the over 75s vs median HR 127, IQR 105 to 140 in the under 50s. Admission GCS was different across age groups with the older groups presenting with the lowest GCS (median 3, IQR 3 to 10) compared with a median GCS of 10 (IQR 3 to 14) in the youngest group (Table 6.9)).

6.3.2.3 *Transfusion requirements and Tranexamic acid*

RBC transfusion requirements were similar across age groups but patients in the older age groups received less FFP than the younger groups (Table 6.9). At 24 hours, the ratio of RBC:FFP was 2:1 in the older groups compared with 1.5:1 in the younger groups. The

older age groups received minimal platelet and cryoprecipitate transfusion compared with the youngest group (Figure 6.2, Figure 6.3). Similarly, TXA use varied with age. Older patients were less likely to receive TXA. Only a quarter of patients in the oldest age group received TXA compared with over 70% in the under 50 group.

6.3.2.4 *Mortality*

Outcomes were poorer for patients with severe injury and bleeding compared with those with minor injury (Table 6.9); this was most marked in the older groups. At 28 days, 60% of the youngest group were alive; this dropped to 33% in the over 65 and over 75 age groups.

Table 6.8. Severe injury (ISS >15), shock and bleeding: summary measures by age band

	16-49 (N=129)	50-64 (N=39)	65-74 (N=21)	≥75 (N=12)	Overall (N=201)
Age, mean (SD)	29 (9)	56 (5)	69 (3)	85 (5)	42 (20)
ISS, median (IQR)	33.6 (12.5)	34.4 (10.5)	36.4 (14.9)	30.3 (8.5)	33.9 (12.2)
	30 (25 to 43)	34 (25 to 41)	33 (29 to 41)	28 (25 to 37)	33 (25 to 43)
Male, n (%)	100 (77.5%)	30 (76.9%)	13 (61.9%)	7 (58.3%)	150 (74.6%)
Penetrating injury, n (%)	40 (31.0%)	5 (12.8%)	0 (0.0%)	2 (16.7%)	47 (23.4%)
Mechanism of injury, n (%)					
RTC	60 (46.5%)	20 (51.3%)	15 (71.4%)	10 (83.3%)	105 (52.2%)
Fall/jump from height	13 (10.1%)	10 (25.6%)	4 (19.0%)	0 (0.0%)	27 (13.4%)
Shooting/stabbing	38 (29.5%)	5 (12.8%)	0 (0.0%)	1 (8.3%)	44 (21.9%)
Blunt assault	2 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)
Other	16 (12.4%)	4 (10.3%)	2 (9.5%)	1 (8.3%)	23 (11.4%)
Head Neck AIS ≥3, n (%)	50 (38.8%)	16 (41.0%)	9 (42.9%)	7 (58.3%)	82 (40.8%)
Missing, n (%)	*1 (0.8%)*	*1 (2.6%)*	*1 (4.8%)*	*0 (0.0%)*	*3 (1.5%)*
Thorax AIS ≥3, n (%)	92 (71.3%)	30 (76.9%)	10 (47.6%)	11 (91.7%)	143 (71.1%)
Missing, n (%)	*1 (0.8%)*	*1 (2.6%)*	*1 (4.8%)*	*0 (0.0%)*	*3 (1.5%)*
Abdomen/Pelvis AIS ≥3, n (%)	39 (30.2%)	13 (33.3%)	6 (28.6%)	2 (16.7%)	60 (29.9%)
Missing, n (%)	*1 (0.8%)*	*1 (2.6%)*	*1 (4.8%)*	*1 (8.3%)*	*4 (2.0%)*
Extremity AIS ≥3, n (%)	66 (51.2%)	20 (51.3%)	8 (38.1%)	8 (66.7%)	102 (50.7%)
Missing, n (%)	*1 (0.8%)*	*1 (2.6%)*	*1 (4.8%)*	*0 (0.0%)*	*3 (1.5%)*
Isolated TBI, n (%)	7 (5.4%)	1 (2.6%)	3 (14.3%)	1 (8.3%)	12 (6.0%)
Missing, n (%)	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*

ISS, injury severity score; AIS, abbreviated injury score; TBI, traumatic brain injury

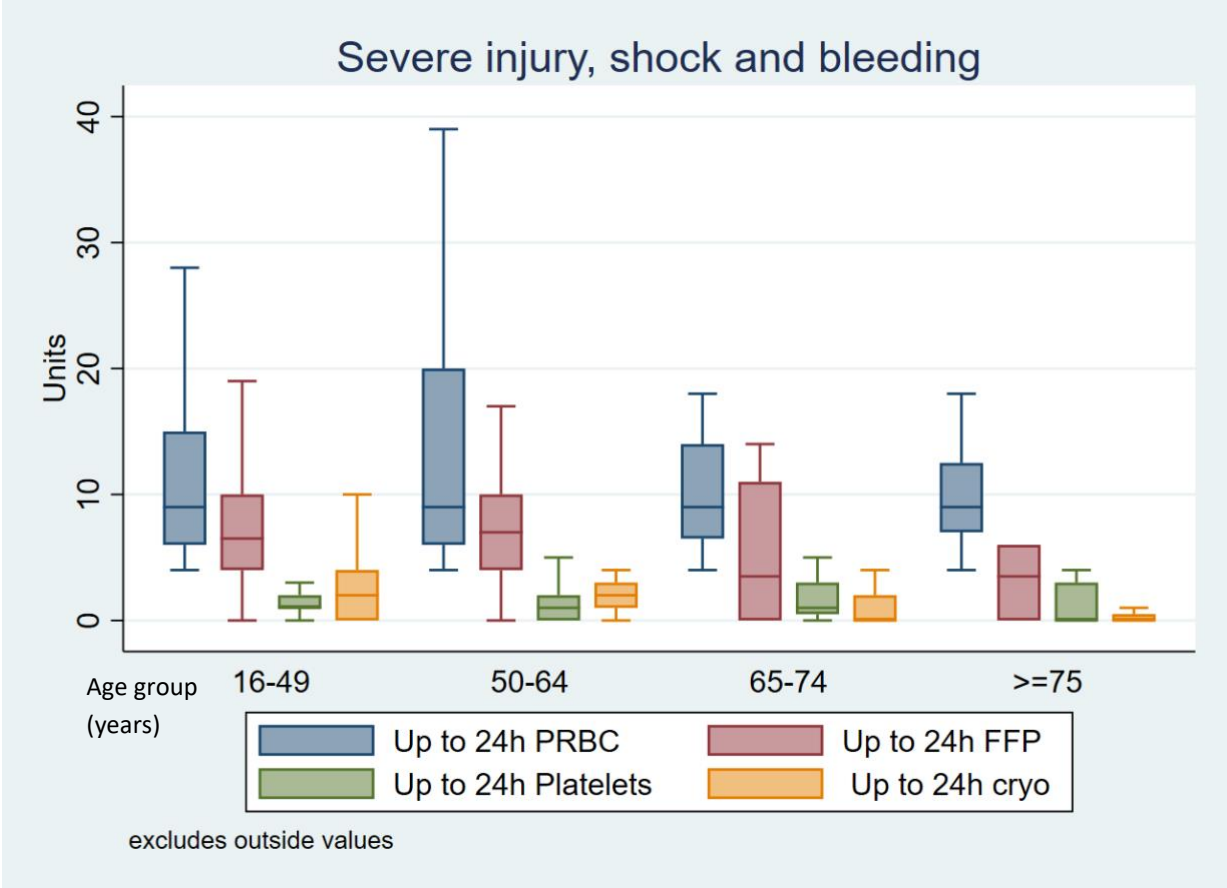
Table 6.9. Severe injury (ISS >15) and shock: overall physiology, transfusion and outcome by age band

	16-49 (N=129)	50-64 (N=39)	65-74 (N=21)	≥75 (N=12)	Overall (N=201)
SBP (mmHg), median (IQR)	90 (71-115)	82 (59-118)	87 (69-100)	79 (69-117)	90 (70-114)
HR (bpm), median (IQR)	127 (105-140)	118 (85-127)	103 (74-119)	100 (70-120)	120 (94-136)
GCS, median (IQR)	9 (3-14)	13 (6-14)	4 (3-13)	3 (3-10)	9 (3-14)
Base deficit (mmol/L), median (IQR)	-13.1 (-20.0- -8.4)	-10.8 (-17.0- -8.8)	-13.4 (-18.7- -9.2)	-9.3 (-11.7- -7.7)	-12.0 (-18.7- -8.7)
Units at 24 hours					
RBC, mean (SD)	9.0 (6.0-15.0)	9.0 (6.0-20.0)	9.0 (6.5-14.0)	9.0 (7.0-12.5)	9.0 (6.0-15.0)
FFP, mean (SD)	6.5 (4.0-10.0)	7.0 (4.0-10.0)	3.5 (0.0-11.0)	3.5 (0.0-6.0)	6.0 (4.0-10.0)
Platelets, mean (SD)	1.0 (1.0-2.0)	1.0 (0.0-2.0)	1.0 (0.5-3.0)	0.0 (0.0-3.0)	1.0 (0.0-2.0)
Cryoprecipitate, mean (SD)	2.0 (0.0-4.0)	2.0 (1.0-3.0)	0.0 (0.0-2.0)	0.0 (0.0-0.5)	2.0 (0.0-4.0)
RBC:FFP ratio	1.4	1.3	2.6	2.6	1.5
Outcome at 28 days, n (%)					
Dead	47 (36.4%)	19 (48.7%)	14 (66.7%)	8 (66.7%)	88 (46.6%)
Missing, n (%)	*4 (3.1%)*	*1 (2.6%)*	*0 (0.0%)*	*0 (0.0%)*	*5 (2.6%)*
TXA, n (%)					
No	35 (27.1%)	11 (28.2%)	11 (52.4%)	7 (58.3%)	64 (31.8%)
Yes	93 (72.1%)	27 (69.2%)	8 (38.1%)	3 (25.0%)	131 (65.2%)
CRASH-3	1 (0.8%)	1 (2.6%)	1 (4.8%)	0 (0.0%)	3 (1.5%)
Missing, n (%)	*0 (0.0%)*	*0 (0.0%)*	*1 (4.8%)*	*2 (16.7%)*	*3 (1.5%)*

SBP, systolic blood pressure; HR, heart rate; GCS, glasgow coma scale; RBC, red blood cells; FFP, fresh frozen plasma; TXA, tranexamic acid

Figure 6.2. Box plot of transfusion requirements within 24 hours: patients with severe injury, shock and bleeding

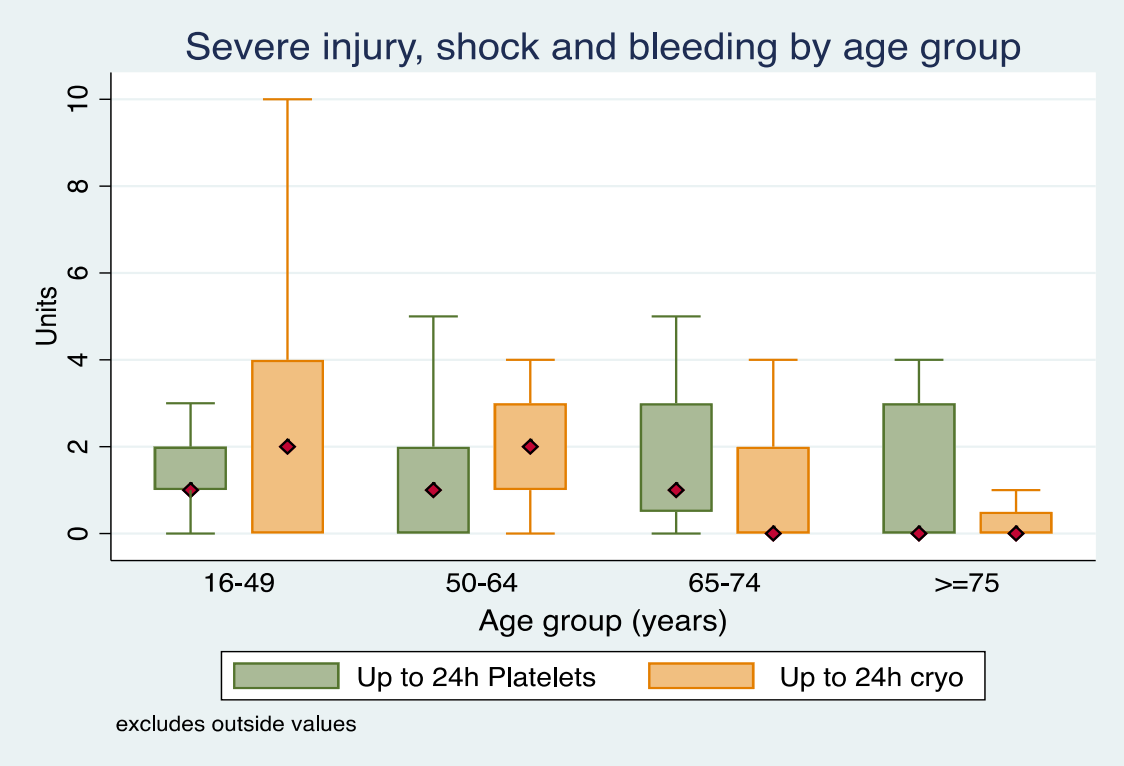
Median and IQR units presented.



PRBC, packed red blood cells; FFP, fresh frozen plasma; cryo, cryoprecipitate

Figure 6.3. Box plot of platelet and cryoprecipitate requirements within 24 hours: patients with severe injury, shock and bleeding

Median and IQR units presented



Cryo, cryoprecipitate

6.3.2.5 *Standard haematology and coagulation profile*

Haematology and coagulation data are presented in Table 6.10. Admission fibrinogen levels were lowest in the youngest group (median 1.3, IQR 0.9 to 1.6) and rose with age (median 2.0, IQR 1.8 to 2.3 in the over 75s). Median INR was similar (1.2-1.3) across all age groups. ROTEM CA5 was less than 40 mm in all age groups except the oldest group (age ≥75 median CA5 43.5, IQR 41.0 to 46.0).

Table 6.10. Severe injury (ISS >15), shock and bleeding: Haematology and coagulation parameters by age band

	16-49 (N=129)	50-64 (N=39)	65-74 (N=21)	≥75 (N=12)	Overall (N=201)
Hb, mean (SD)	12.8 (2.5)	12.0 (2.6)	12.1 (2.5)	10.2 (2.4)	12.4 (2.6)
Platelet count, mean (SD)	191.0 (70.7)	182.6 (76.0)	161.9 (45.5)	181.7 (84.6)	185.7 (70.5)
APTT, mean (SD)	47.0 (35.8)	49.4 (45.7)	50.8 (33.3)	44.6 (34.4)	47.7 (37.4)
INR, median (IQR)	1.3 (1.2-1.5)	1.2 (1.1-1.3)	1.2 (1.1-1.2)	1.2 (1.1-1.3)	1.3 (1.1-1.4)
Missing, n (%)	*23 (17.8%)*	*6 (15.4%)*	*6 (28.6%)*	*1 (8.3%)*	*36 (17.9%)*
Fibrinogen, mean (SD)	1.3 (0.5)	1.7 (0.7)	1.5 (0.5)	2.1 (0.4)	1.4 (0.6)
Missing, n (%)	*31 (24.0%)*	*6 (15.4%)*	*9 (42.9%)*	*2 (16.7%)*	*48 (23.9%)*
Extem CA5, mean (SD)	34.1 (10.0)	34.7 (13.5)	28.6 (14.6)	43.7 (3.9)	34.3 (11.4)
Extem CFT, mean (SD)	176.9 (168.1)	215.4 (474.3)	230.8 (259.5)	94.5 (11.7)	184.7 (263.7)
Extem alpha angle, mean (SD)	62.2 (12.9)	67.0 (9.6)	62.3 (16.5)	71.9 (2.8)	63.7 (12.5)
Extem CT, mean (SD)	129.8 (330.2)	94.7 (99.2)	104.9 (71.9)	107.9 (110.2)	119.1 (270.6)
Extem MCF, mean (SD)	53.0 (11.8)	54.9 (12.0)	45.8 (20.0)	61.7 (2.2)	53.1 (12.8)
Extem LY30, mean(SD)	94.8 (21.5)	97.0 (16.9)	88.2 (33.2)	99.5 (1.3)	94.9 (21.5)

Hb, haemoglobin; APTT, activated partial thromboplastin time; INR, international normalised ratio; CFT, clot firmness time; CT, clotting time; MCF, maximum clot firmness; LY30, lysis time at 30 minutes

6.3.3 Extended haemostatic assays in minor and severe injury

Of the patients who had PAP assays performed as part of their extended haemostatic panel, there were 139 patients with minor injury and no shock and 89 with severe injury shock and bleeding. Data are presented in Appendix 6. Patient characteristics were broadly similar to the overall cohort.

6.3.3.1 *Patient characteristics*

In the minor injury group, younger patients (aged under 65) presented with more penetrating injuries, injuries due to shooting/stabbing and over 85% were male compared with 50% in the over 65s. Systolic blood pressure was higher in the older group (median 165), similar to that of the cohort described in Table 6.6. Likewise, transfusion use was low and mortality was 0% across both young and older age groups.

In the severely injured group, older patients presented with a blunted tachycardic response and lower GCS compared with the younger group (GCS 4 vs 11). The ratio of RBC:FFP was higher in the older group 3:1 compared with the younger group who received transfusion approaching a 1:1 ratio. Again, older patients received less TXA (20% vs 56% in the younger group).

6.3.3.2 *Extended haemostatic assays*

In the group with minor injuries, the main differences across age in the extended haemostatic assays were in FV and fibrinolytic parameters (t-PA, PAP, A2AP) (Table 6.11) Factor V was lower in the older group compared with the younger group and fibrinolytic parameters were higher in the older group.

In the severely injured group with bleeding, the decrease in FV was more marked and for both old and young, activity levels were below 50%. For PAP, the magnitude of PAP elevation was twice as high in older patients, with a 10-fold increase in severely injured patients compared to those with minor injuries. As these results could be influenced by other co-variates, a separate multivariable analysis was performed using linear regression analysis (see section 6.3.4).

Table 6.11. Extended haemostatic profile for patients who had plasmin-antiplasmin assays performed

	Minor injury, no shock N=139		Severe injury, shock and bleeding N=89	
	Younger Age <65 N=111	**Older Age ≥65 N=28**	**Younger Age <65 N=72**	**Older Age ≥65 N=17**
FXIII	101.5 (86.2 to 124.0)	117.1 (98.4 to 135.3)	87.1 (63.7 to 108.1)	87.3 (69.9 to 99.7)
Missing	1	2	1	1
FV	95.0 (77.0 to 118.0)	84.6 (67.0 to 92.9)	46.5 (26.5 to 68.7)	37.0 (26.0 to 55.8)
Missing	1	3	0	0
FVIII	228.6 (169.9 to 295.2)	157.5 (133.1 to 233.2)	271.1 (153.7 to 400.1)	191.2 (114.7 to 229.5)
Missing	1	3	0	0
FII	97.0 (83.0 to 107.6)	86.4 (76.7 to 104.6)	67.8 (56.8 to 83.0)	63.8 (58.2 to 70.4)
Missing	1	2	0	0
FVII	89.0 (69.6 to 111.0)	95.6 (80.8 to 106.9)	77.3 (64.3 to 97.8)	88.9 (79.0 to 96.7)
Missing	1	2	0	0
FIX	116.0 (99.8 to 132.8)	102.6 (79.6 to 115.5)	88.0 (66.8 to 112.5)	83.4 (69.8 to 92.4)
Missing	1	3	0	0
FXI	106.5 (85.0 to 123.9)	94.1 (74.6 to 107.3)	71.6 (47.5 to 95.0)	65.2 (54.4 to 79.0)
Missing	1	3	0	0
Von Willebrand factor antigen (iu/dL)	170.4 (134.8 to 209.2)	190.8 (140.1 to 255.0)	298.9 (233.9 to 375.1)	291.4 (189.8 to 376.9)
Missing	1	4	0	1
Protein C (%)	93.0 (80.0 to 104.0)	102.0 (91.0 to 121.0)	69.0 (55.0 to 82.0)	79.5 (64.5 to 94.0)
Missing	1	3	1	1
Soluble fibrin monomer complex (µg/ml)	18.0 (2.4 to 62.5)	7.3 (0.0 to 44.1)	225.3 (145.4 to 275.0)	206.7 (170.5 to 279.0)
Missing	1	3	1	0
Thrombomodulin (ng/mL)	8.4 (5.0 to 17.0)	3.1 (2.5 to 5.0)	6.8 (5.2 to 9.7)	6.1 (4.0 to 8.3)
Missing	7	2	14	1
Prothrombin fragments 1+2 (pmol/L)	376.6 (240.9 to 634.9)	621.4 (294.0 to 1038.3)	2463.2 (796.4 to 4432.1)	3830.6 (595.3 to 7457.8)
Missing	1	1	7	1

	Minor injury, no shock N=139		Severe injury, shock and bleeding N=89	
	Younger Age <65 N=111	**Older Age ≥65 N=28**	**Younger Age <65 N=72**	**Older Age ≥65 N=17**
Fibrinolysis				
PAI-1 (ng/mL)	18.1 (9.5 to 27.7)	18.5 (12.8 to 39.8)	30.5 (18.7 to 47.9)	28.3 (17.2 to 37.9)
Missing	1	0	3	0
t-PA (ng/mL)	8.1 (5.3 to 12.1)	14.7 (10.2 to 19.6)	25.7 (16.7 to 38.2)	25.5 (17.9 to 43.0)
Missing	0	0	1	0
A2AP (iu/dL)	123.5 (107.7 to 140.0)	94.3 (83.5 to 104.7)	57.5 (44.0 to 88.8)	46.6 (22.2 to 51.5)
Missing	5	4	4	1
PAP (ng/mL)	1169.2 (839.8 to 1707.9)	1910.7 (1352.2 to 2694.0)	11527.7 (4572.9 to 20820.3)	22851.1 (11141.4 to 29255.9)
Standard coagulation				
Hb (g/dL)	14.8 (13.7 to 15.4)	13.3 (12.5 to 14.6)	12.6 (10.5 to 14.0)	11.7 (10.2 to 13.7)
Missing	4	2	3	2
Platelet count ($x10^9$/L)	235 (207 to 284)	210 (177 to 244)	209 (166 to 257)	184 (147 to 211)
Missing	4	2	3	2
APTT (seconds)	23.0 (22.0 to 25.0)	27.5 (24.0 to 33.0)	29.5 (24.0 to 45.0)	32.0 (27.0 to 82.0)
Missing	14	2	10	6
INR	1.0 (1.0 to 1.1)	1.0 (1.0 to 1.1)	1.2 (1.1 to 1.3)	1.2 (1.1 to 1.2)
Missing	14	1	10	5
INR >1.2	5 (5.2%)	2 (7.4%)	37 (59.7%)	7 (58.3%)
Missing	14	1	10	5
Fibrinogen (g/L)	2.5 (2.1 to 2.9)	3.1 (2.5 to 3.5)	1.4 (1.2 to 1.8)	1.8 (1.6 to 2.0)
Missing	27	3	17	7
Extem CA5 (mm)	45.0 (39.0 to 49.0)	47.0 (41.5 to 54.0)	37.0 (32.0 to 45.0)	38.5 (23.0 to 43.0)
Missing	4	4	8	3
Extem CFT (mm)	89.0 (71.0 to 108.0)	87.5 (65.5 to 97.0)	112.0 (84.0 to 139.0)	103.0 (95.5 to 174.5)
Missing	5	4	11	5
Extem Alpha angle (°)	72.0 (68.0 to 76.0)	72.0 (71.0 to 76.5)	69.0 (65.0 to 74.0)	70.0 (63.0 to 73.0)
Missing	4	4	11	4
Extem CT (sec)	60.5 (51.0 to 72.0)	55.0 (47.0 to 60.0)	65.5 (53.0 to 84.0)	78.0 (70.0 to 194.0)
Missing	3	4	8	3

	Minor injury, no shock N=139		Severe injury, shock and bleeding N=89	
	Younger Age <65 N=111	**Older Age ≥65 N=28**	**Younger Age <65 N=72**	**Older Age ≥65 N=17**
Extem MCF (mm)	62.0 (57.5 to 65.0)	64.5 (61.5 to 70.0)	58.0 (52.0 to 63.0)	58.0 (46.0 to 61.0)
Missing	3	4	9	3
Extem LY30 (%)	100.0 (99.0 to 100.0)	100.0 (99.0 to 100.0)	100.0 (100.0 to 100.0)	100.0 (100.0 to 100.0)
Missing	6	6	10	3

A2AP, α-2-antiplasmin; PAP, plasmin-antiplasmin complex; t-PA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor -1; Hb, haemoglobin; APTT, activated partial thromboplastin time; INR, international normalised ratio; CFT, clot firmness time; CT, clotting time; MCF, maximum clot firmness; LY30, lysis time at 30 minutes

6.3.4 Regression analysis of key coagulation and fibrinolytic parameters

The descriptive characteristics for patients who did not receive TXA pre-2015 (and who had fibrinogen measured) are shown in Table 6.12. Compared with the baseline group (age 16-49), there was a statistically significant increase in fibrinogen with increasing age (adjusting for ISS, base excess, gender, severe head injury and bleeding status) (Table 6.13). The largest mean increase in fibrinogen was 0.6 g/L (0.4 to 0.8) in the over 75s compared with the youngest group. The adjusted FV levels were lower in the over 65s and over 75s compared with under 50s (mean difference -9.5 (-16.0 to -3.0); P-value=0.004 and -11.4 (-20.2 to -2.6); P-value=0.001). There was a statistically significant decrease in A2AP in the two oldest age groups compared with the reference group.

The results of the adjusted analyses for PAP, t-PA, PAI-1 and TAFIa were presented as ratios (initial data log transformed). There was a statistically significant increase in PAP and t-PA in older age groups compared with the youngest group. For PAP, the greatest change was in the over 75s where PAP was 2-fold higher compared with the youngest

(reference) group. Similar changes were seen with t-PA, which was 1.7x higher in the older age groups (ratio 1.7 (1.4 to 2.0); P-value <0.0001). TAFIa (an inhibitor of fibrinolysis) was elevated in the two oldest age groups. There was no significant difference in PAI-1 across age.

Table 6.12. Overall summary measures by age band for patients pre-2015 who had fibrinogen measured (and did not receive TXA)

	16-49 (N=435)	50-64 (N=91)	65-74 (N=119)	≥75 (N=85)	Overall (N=730)
Age, mean (SD)	30 (9)	55 (4)	69 (3)	81 (5)	45 (21)
ISS, median (IQR)	10 (4 to 24)	20 (9 to 29)	16 (8 to 29)	13 (4 to 25)	13 (5 to 25)
Male, n (%)	409 (82.5%)	87 (84.5%)	96 (71.1%)	55 (56.1%)	647 (77.8%)
Type of injury, n (%) Blunt	333 (76.6%)	87 (95.6%)	113 (95.0%)	80 (94.1%)	613 (84.0%)
Mechanism of injury, n (%)					
RTC	203 (46.7%)	44 (48.4%)	52 (43.7%)	44 (51.8%)	343 (47.0%)
Fall/jump from height	82 (18.9%)	27 (29.7%)	35 (29.4%)	25 (29.4%)	169 (23.2%)
Shooting/stabbing	100 (23.0%)	3 (3.3%)	4 (3.4%)	2 (2.4%)	109 (14.9%)
Blunt assault	13 (3.0%)	3 (3.3%)	1 (0.8%)	0 (0.0%)	17 (2.3%)
Other	37 (8.5%)	14 (15.4%)	10 (8.4%)	5 (5.9%)	66 (9.0%)
ISS category, n (%)					
ISS 0-4	117 (26.9%)	11 (12.1%)	21 (17.6%)	24 (28.2%)	173 (23.7%)
ISS 5-15	154 (35.4%)	23 (25.3%)	36 (30.3%)	23 (27.1%)	236 (32.3%)
ISS >15	164 (37.7%)	57 (62.6%)	62 (52.1%)	38 (44.7%)	321 (44.0%)
Base deficit, median (IQR)	-0.8 (-3.0 to 1.0)	-1.2 (-4.4 to 0.8)	-0.3 (-3.7 to 1.7)	-0.8 (-3.9 to 1.9)	-0.8 (-3.2 to 1.2)
Head Neck AIS ≥3, n (%)	102 (23.4%)	29 (31.9%)	49 (41.2%)	25 (29.4%)	205 (28.1%)
Thorax AIS ≥3, n (%)	145 (33.3%)	43 (47.3%)	28 (23.5%)	26 (30.6%)	242 (33.2%)
Abdomen/Pelvis AIS ≥3, n (%)	41 (9.4%)	7 (7.7%)	7 (5.9%)	1 (1.2%)	56 (7.7%)
Extremity AIS ≥3, n (%)	122 (28.0%)	30 (33.0%)	31 (26.1%)	20 (23.5%)	203 (27.8%)
Isolated TBI, n (%)	47 (10.8%)	13 (14.3%)	31 (26.1%)	13 (15.3%)	104 (14.2%)
Bleeding, n (%)	42 (8.5%)	17 (16.5%)	23 (17.0%)	19 (19.4%)	127 (15.3%)
RBC transfusion in 12 hours					
0 units	361 (83.0%)	68 (74.7%)	85 (71.4%)	53 (62.4%)	567 (77.7%)
≥1 unit	74 (17.0%)	23 (25.3%)	34 (28.6%)	32 (37.7%)	163 (22.3%)

Bleeding (≥4 RBC in 12 hours); ISS, injury severity score; RTC, road traffic collision; AIS, abbreviated injury score; TBI, traumatic brain injury; RBC, red blood cell

Table 6.13. Linear regression model of the effect of age group on fibrinolytic parameters in patients who did not receive TXA and who had fibrinogen measured

Adjusted for ISS, base deficit, gender, type of injury (blunt/penetrating), severe head injury (head/neck AIS ≥3) and bleeding (≥ 4 units RBC in 12 hours). (Pre-2015).

Parameter	Age 16-49 (ref)	Age 50-64			Age 65-74			Age ≥75		
	n	n	Mean difference (95% CI)	P value	n	Mean difference (95% CI)	P value	n	Mean difference (95% CI)	P value
Fibrinogen (g/l)	435	91	0.3 (0.1 to 0.4)	0.002	119	0.4 (0.3 to 0.5)	<0.001	85	0.5 (0.4 to 0.7)	<0.001
FV, % activity	350	70	6.6 (-0.2 to 13.4)	0.057	82	-9.5 (-16.0 to -3.0)	0.004	40	-11.4 (-20.2 to -2.6)	0.001
A2AP (iu/dl)	340	68	-2.1 (-6.4 to 5.7)	0.544	78	-24.4 (-31.0 to -17.9)	<0.001	38	-34.3 (-43.2 to -25.4)	<0.001
		n	Geometric mean ratio (95% CI)	P value	n	Geometric mean ratio (95% CI)	P value	n	Geometric mean ratio (95% CI)	P value
PAP	317	61	1.2 (1.0 to 1.5)	0.073	81	1.8 (1.5 to 2.3)	<0.001	41	1.9 (1.5 to 2.4)	<0.001
t-PA	315	61	1.3 (1.1 to 1.6)	0.002	79	1.4 (1.2 to 1.7)	<0.001	40	1.7 (1.4 to 2.1)	<0.001
TAFIa	166	32	1.0 (0.9 to 1.2)	0.359	18	1.3 (1.0 to 1.7)	0.052	8	1.2 (0.9 to 1.7)	0.170
PAI-1	315	62	1.1 (0.9 to 1.4)	0.229	80	1.0 (0.8 to 1.2)	0.949	40	1.0 (0.7 to 1.3)	0.855

Reference age group 16-49. TXA (tranexamic acid); A2AP, α-2-antiplasmin; PAP, plasmin-antiplasmin complex; t-PA, tissue plasminogen activator; TAFIa, Activated thrombin activatable fibrinolysis inhibitor; PAI-1, plasminogen activator inhibitor -1

6.4 Discussion

6.4.1 Key findings

Patient characteristics and outcomes

The first aim of this chapter was to describe the clinical characteristics of patients with trauma. The main findings were that vital signs for HR and SBP varied across age. A rise in SBP (to levels in the hypertensive range, SBP ≥130 mmHg) with increasing age was observed in patients with minor injury and no major bleeding. In severely injured patients with bleeding, the median SBP in all age groups was less than 100 mmHg. Although older patients presented with tachycardia (HR ≥100 bpm), the degree of tachycardia was less marked in older people compared to younger people. This blunted response may be due to decreased compensatory mechanisms in older people and/or the concurrent use of medication to control cardiac arrhythmias such as atrial fibrillation, which have a higher prevalence in older people (but not captured in the study data).

For patients with major bleeding and severe injury, there was a difference in the 24-hour FFP:RBC transfusion ratio; older people received a ratio of 2.6 compared with 1.4 in younger people. Cryoprecipitate and platelet transfusion was infrequent in older people. Likewise, TXA use was lower in older people.

In trauma haemorrhage, current guidelines recommend maintaining the Fibrinogen level above a threshold of 1.5g/L and to aim for a FFP:RBC transfusion ratio of at least 1:2.[27] A possible reason that may explain the infrequent transfusion of cryoprecipitate in the older age groups is that the fibrinogen level did not drop below this threshold in older

people (Table 6.10). However, the results also suggest that optimal haemostatic resuscitation ratios are not being achieved for older patients. Furthermore, only a quarter of patients in the over 65s received TXA at any time point, this improved to 38% in the 54-74 age group but was still considerably lower than for the youngest group (73%).

Several reasons may contribute to these differences in transfusion and TXA. It is possible that for older people there may be concerns regarding the volume aspect of FFP transfusion and risk of fluid overload (each unit of FFP = ~250ml). In general, older people are more likely to have cardiovascular comorbidities, such as heart failure that may increase the risk of transfusion associated circulatory compromise. Consequently, in these patients RBC transfusion may be prioritised over FFP. Another possibility is that bleeding in older people is less well recognised in older people, due to a blunted tachycardic response or low impact mechanism of injury (MOI), which could impact on optimal transfusion and TXA administration.

Haemostasis

The second part of this study showed that age has an impact on haemostasis in trauma. The key findings were that the level of fibrinogen increased with age. However, for each age group, patients with severe injuries and bleeding had lower fibrinogen levels compared to patients with minor injuries. Apart from fibrinogen, standard coagulation and ROTEM parameters were broadly similar across age.

There appeared to be attenuated fibrinolysis across age. In a group of patients who did not receive TXA, after adjusting for bleeding, gender, ISS, severe head injury and base

deficit, there was a statistically significant increase in PAP and t-PA in older patients compared to the under 50s. In patients aged 65 and above, A2AP was lower than the under 50s. Taken together, the pattern of these findings are consistent with higher levels of fibrinolytic activation in older people with trauma. However, the results of the multivariable regression model should be interpreted with caution as these patients are a historical cohort who did not receive TXA, which is now standard care and TXA acts as an anti-fibrinolytic. Nevertheless, the data show a signal towards higher fibrinolytic activation in older people, who would potentially have the most to gain from early anti-fibrinolytic therapy.

However, within the ACIT data, patients with shock and bleeding (who may have benefited most from TXA), there was an age discrepancy in TXA use. Only a quarter of older patients were given TXA compared with over 70% in the under 50 age group. The reasons for this are not fully understood. Given the results here that suggest higher fibrinolytic activity in older people, this is an area that should be explored further to understand the patterns of TXA use across age, reasons for any difference in prescribing and to determine the effectiveness of TXA and doses across age.

In the regression analysis, factor V activity was lower in patients aged 65-74 and patients aged 75 and above compared to the under 50s. The reasons for this are not clear, however as factor V can be derived from platelets, further work could also investigate to see if this difference is remains after adjusting for the platelet count.

The ACIT data is one of the largest multicentre datasets where the impact of age on haemostasis has been evaluated. As previously alluded to, there have been few studies exploring coagulation in trauma across age. Those that have been published have

tended to be single centre studies. Mador et al study explored transfusion and coagulation in elderly trauma in a Level 1 trauma centre in Canada.[43] Propensity matched analysis of 61 older (aged 55 and above) and 61 younger patients, who received at least one RBC transfusion, showed a significant difference in the proportion of patients with fibrinogen <2.0g/L (44% in the younger group vs 33% in the older group, P-value=0.05). Although the study population dated back to 2007 and transfusion practice may be different today, they support the ACIT study results and show an age difference in fibrinogen levels in patients requiring blood transfusion in trauma.

Ohmori et al conducted a single centre analysis in Japan from 2011-2014 (n=251) and showed older patients with severe injury (ISS >15) had a statistically significantly higher Fibrinogen level compared to those aged under 65.[61] However, in the subset of patients who received massive transfusion (≥10 units RBC) (n=46), there was no difference in the fibrinogen level between old and younger patients. This contrasts with the ACIT data where there was a difference in fibrinogen across age for patients with major bleeding. This discrepancy could be due to differences in analysis. The ACIT cohort was larger (Table 6.10) and I adjusted for other factors and used a different definition of bleeding.

Clinical implications and further work

In major bleeding, fibrinogen is the first coagulation factor to reach critically low thresholds than other coagulation proteins.[202] There is a rise in fibrinogen with normal ageing. This could mean that in older people, as baseline levels are higher than in younger people (normal ageing), the same fibrinogen target may not be adequate for both young and older people. The group from Canada[43] showed that fibrinogen levels are different across age; fewer older patients had a fibrinogen level < 2g/L compared

with younger patients. The ACIT study results add to this and suggest that age should be considered in the interpretation of fibrinogen levels in trauma. Another area in which the importance of fibrinogen levels has been demonstrated is in obstetric haemorrhage. We know that fibrinogen levels at the end of pregnancy rise above 4.0g/L and below 2.0g/L is associated with progression of postpartum bleeding.[203] These discoveries have transformed the management of obstetric haemorrhage and led to better understanding of the coagulopathy related to obstetric bleeding and what is considered a 'normal range' in pregnancy.

In the trauma setting, fibrinogen levels may need to be interpreted in the context of age. For an older person, even if the admission level is within the 'normal range', it may not be 'normal' for the age of the patient and could be falsely reassuring. Hence, it would be important to continue to monitor trends to check for a drop in fibrinogen.[61] Whether there should be a higher target for older people requires further research and a better mechanistic understanding of the role of fibrinogen in clot strength and stability. Likewise, a blunted tachycardic response in older people could affect the recognition or major bleeding and appropriate transfusion and TXA management.

Hyperfibrinolysis plays a key role in the coagulopathy of trauma. Higher levels of fibrinolytic activation have been observed in trauma in older people. Older people with trauma have higher D-dimer levels.[61] t-PA has been shown to be higher in older people with trauma[198] compared to younger people. The ACIT study is one of the first to explore other markers of fibrinolysis in haemorrhage; PAP and t-PA were almost 2-fold higher in older people compared with younger people and markedly above levels seen in the group with minor injuries. It is possible in severely injured patients, shock and high

injury severity are particularly detrimental in older people. Older people may be more susceptible to endothelial damage (that releases t-PA and hence increases fibrinolysis), similar to the proposed mechanism of fibrinolysis in older people with traumatic brain injury.[201] This is not fully understood. Further work to understand the mechanisms of fibrinolytic activation in older people is needed and to test the effectiveness of anti-fibrinolytic therapy and dosing across age.

6.4.2 Strengths and limitations

One of the strengths of this study is the availability of matched clinical and laboratory data for each patient. This enabled analysis of standard and extended coagulation parameters in the context of important clinical parameters such as injury severity, shock, bleeding. The sampling of blood samples early after hospital admission permitted analysis during the acute phase during which ATC is thought to occur.

There are limitations to the study. Due to the observational nature of the study, there is the potential for selection bias and it is possible that participants recruited may differ to real-world patients. This may limit the generalisability of the results to wider populations. Despite being one of the largest analyses of the impact of age in coagulation in trauma, there were relatively small numbers of older patients within this cohort. It is acknowledged that there may be potential variations in laboratory assays between sites (only one centre (Royal London Hospital) for the aged under 65 group, however the other centres were included for those aged ≥65). Potentially, the coagulation differences detected across age may in part be related to inter-laboratory differences between the Royal London and other centres. However, PAP and t-PA were twice as high in the older groups compared with the young and this magnitude of

change is less likely to be due to centre differences. Furthermore, the trends in higher fibrinogen levels with higher age have been observed in other studies on massive haemorrhage.[43,61]

Although the data were analysed according to low and high injury severity and give an indication of coagulation parameters in trauma across injury severity, how these compare to a non-trauma population is uncertain. It is recognised that patients with the lowest injury severity are not equivalent to those without injury and baseline 'normal' ranges may be different in the non-trauma population. The magnitude of any of the age-related changes in coagulation and fibrinolytic parameters in trauma compared to a non-normal trauma population needs to be established.

The regression results are in the absence of TXA. Data were not available on the timing of TXA, so the impact of TXA on coagulation and fibrinolytic parameters across age could not be assessed. Moving forwards, it would be beneficial to collect data on the timing of TXA (and timing relative to blood sampling), especially as recent data have demonstrated the greatest benefit and reduction in mortality if TXA is given within one hour of injury.[98] This is changing clinical practice and will mean many more patients receive TXA in the pre-hospital setting before the first admission blood sample is taken. This would be important to consider in the design and interpretation of future studies as assays of fibrinolytic parameters are likely to be affected by the presence of TXA.

Coagulation is an evolving process. The haemostatic assays were performed at a single time-point. It is not always feasible in a study context to perform serial assays, which would be useful in showing a spectrum of changes that evolve over time. In addition, the assays reported here do not assess platelet dysfunction or the activated protein C

pathway, which have been more recently shown to be other important aspects in the coagulopathy of trauma.

Current laboratory assays are limited in their ability to accurately assess global haemostasis under flow conditions and for further study, assays such as microfluidic assays assessing the effect of blood flow on haemostasis and platelet function studies could be developed. The analysis of haemostasis could be extended to investigate the pattern of coagulation and fibrinolytic parameters, for example using a principal components analysis.

In this current study, any differences in clinical characteristics and laboratory data should be considered bearing in mind the incomplete dataset and presence of missing data. Methods to handle missing data such as multiple imputation were not used here but could be employed in future work.

6.5 Conclusion

The results of this exploratory study show there is an effect of age on coagulation and fibrinolytic parameters in trauma with differences seen between older and younger patients. The most clinically relevant differences were in fibrinogen and fibrinolytic activity that increased with age, particularly in severely injured patients with bleeding and shock. Further study is needed to refine understanding of the mechanisms involved. Differences may mean that we need to adjust treatments for older groups and develop age-appropriate strategies in the recognition and management of traumatic haemorrhage.

Chapter 7 Thesis summary and future work derived from this thesis

The aim of this thesis was to explore the impact of the changing trauma demographic on the presentation and management of bleeding and coagulopathy. This was achieved through several different study designs. This work has provided new data showing that age has a significant effect on the clinical presentation and risk factors for bleeding, and that older age is associated with heightened fibrinolytic activity and fibrinogen levels in trauma-related bleeding. These data are hypothesis-generating and inform future research questions on the management of bleeding in an ageing population. The main findings and implications of this thesis are summarised below.

1. What is the evidence base for the use of blood for the acute management of trauma-related bleeding across age in trauma?

Chapter 2 examined the RCT evidence for the use of blood components in trauma haemorrhage. I found a lack of high-quality evidence for a beneficial effect of one blood component strategy over another in trauma-related major bleeding. There were no randomised trials in older people or trials that evaluated specific interventions for different age groups. The average age of patients in the 10 included studies was between 30 and 50. There was marked inter-trial clinical heterogeneity, as the trials were conducted in a variety of pre-hospital and in-hospital clinical settings with different local practice and standard of care. Outcomes reported in the studies varied as there was no core outcome set for trauma haemorrhage trials.

2. Is there a consensus definition of major bleeding in trauma, and if not can a definition be developed?

In chapter 3, the Delphi study among trauma experts reached consensus on transfusion-based research definition for major bleeding in trauma: 4 or more units of RBC, FFP, platelets or cryoprecipitate. This is a new definition in the literature and is novel in that it is not just limited to RBC transfusion but also includes other blood components in the early time period after injury including in the pre-hospital setting. The historical transfusion definition of massive transfusion was voted out and shows that the trauma community is now thinking differently about what constitutes major bleeding.

3. What are the clinical characteristics of patients with major bleeding and do they vary with age?

In the TARN cohort (n=63,226), the incidence of major bleeding was low; 441 (0.7%) of young patients and 122 (0.2%) of older patients suffered from major bleeding (Chapter 4). Differences were observed in the baseline characteristics of older (aged 65 and over) and young (aged <65) patients with major bleeding in the TARN registry. Younger patients were more likely to be male and a quarter of injuries were due to penetrating injuries. Older patients had fewer penetrating injuries and there was a greater proportion of females than in the younger group. Significant differences were observed in the mechanism of injury (MOI) across age. There was no evidence of association between the pre-hospital systolic blood pressure and age of patients (P-value=0.455), but the pre-hospital heart rate was significantly associated: mean (SD) heart rate was 102 (41) in the younger group vs 89 (31) in the older group (P-value=0.001). Tachycardia may be a less reliable sign of hypovolaemic shock or bleeding in the older population.

This could have clinical implications on how patients with bleeding are triaged and managed. In the younger group, the ratio of blood products appeared to be sub-optimal according to trauma resuscitation guidelines, patients received mainly RBCs only and half of patients did not receive FFP. The ratio of FFP: RBC transfusion in the older group was better and in keeping with recommended practice at 1:2. However, mortality was twice as high in older patients, by 30 days nearly two-thirds of older patients had died.

4. Which factors are associated with major bleeding and what is the impact of age on these factors?

In multivariable logistic regression, age, penetrating injury, male gender, unstable pelvic injury, hypotension, tachycardia and MOI were found to be significantly associated with bleeding. I explored interactions between age and risk factors for bleeding. In the multivariable model including penetrating-age interaction, there was a negative interaction between increasing age and the risk of penetrating injury on the odds of bleeding. Likewise, for the MOI-age model, there was a negative interaction between increasing age and MOI (mainly attributed to shooting and stabbing injuries) on the odds of bleeding. Age was found to be an independent risk factor in both models, with increasing age associated with an increased risk of bleeding (OR 1.011 (95% CI 1.004 to 1.017), P-value = 0.001) in the MOI-age model, and in the penetrating-age model (OR 1.009 (95% CI 1.004 to 1.015, P-value = 0.001).

The original TARN dataset (n=102,377) contained missing data in the outcome and variables of interest in the model for bleeding. Pre-hospital pulse was missing in 22.1% of cases, pre-hospital systolic blood pressure in 24.5% and the outcome (38.2%).

Multiple imputation was used to handle missing data. The significance of the risk factors in the imputation model was broadly similar to the CCA model.

5. What is the haematological and coagulation profile of patients with major bleeding in trauma and does the profile differ across age groups?

This study of ACIT data provides detailed description of patient characteristics and coagulation problems across age, in patients with and without shock and bleeding (chapter 6). In patients with significant bleeding, the fibrinogen level was higher in older patients compared with younger patients. This raises the question of whether a higher baseline fibrinogen level that occurs with ageing may be 'protective' in older people or if critical thresholds might vary with age (similar to obstetrics where research has demonstrated higher fibrinogen targets in post-partum haemorrhage). The rate of fibrinolytic activation was higher in older age groups and this requires more investigation, as this patient cohort did not receive TXA (which is now standard practice). Further work is needed to evaluate whether the same finding is replicated in patients who receive TXA and to assess the effectiveness of TXA across age.

The definition of major bleeding in the ACIT study was the need for 4 or more units of RBCs in 12 hours. Although this definition is different to the one used for the TARN analysis, the trends in vital signs suggested that the presenting heart rate varied across age. For severely injured patients with bleeding, the median systolic blood pressure in all age groups was less than 100mmHg. Although older patients presented with tachycardia (heart rate ≥100bpm), the degree of tachycardia appeared to be less marked in older people (median heart rate 100, (IQR 70 to 120) in the over 75s, compared with younger patients aged 16-49 who had median heart rate 127, (IQR 105

to 140). This highlights apparent differences in presenting vital signs that could affect triage and potential under-triage of older people, similar to findings from the TARN study in chapter 4.

7.1 Strengths and limitations

There were large numbers of patients across both the TARN and ACIT datasets. TARN is the largest trauma registry in Europe and there were over 100,000 patients with demographic and clinical data in the dataset and 60,000 for the complete case analysis. There was an excellent level of completeness of injury-related characteristics of patients in the TARN registry, which provides data on a national level involving all major trauma centres. The collaboration with the International Trauma Research Network (INTRN) group in the ACIT study provided a unique repository of clinical and laboratory data that enabled me to undertake analysis of coagulation across age in trauma and bleeding. The ACIT study is one of the largest dedicated prospective studies in trauma coagulopathy that collects paired clinical, haematological and coagulation data. Both datasets complement each other and enabled me to study the closely related processes of coagulation and bleeding in trauma where observational data are foundational to help guide prospective studies or interventional studies.

Routinely collected data is becoming popular in many areas of research as the data reflect real world populations and practice and provide valuable information on all groups of patients, who may otherwise not be well represented in RCTs. However, there are downsides as the quality of the data is often less optimal and may suffer from missing data. Despite these limitations, observational data can be valuable in exploration of associations between risk factors and disease.

However, missing data can cause bias and affect inferences, despite the use of sensitivity analyses such as multiple imputation. For the TARN study, I only looked at the missing at random mechanism and it is possible that some of the inconsistency between the results derived from complete case analysis and multiple imputations could be due to data missing not at random.

A transfusion-based definition using transfusion as a proxy for bleeding has limitations. It will not necessarily capture all patients who have severe bleeding, such as those who bleed but died early from bleeding or if other indicators such as the need for surgery or radiology to control bleeding are required. For future studies, a composite inclusive definition may be the way forwards. It would overcome some of these weaknesses but is challenging to use pragmatically as these fields are not routinely well captured in registry data. Consequently, retrospective analysis is usually dependent on which data fields are available. In addition, transfusion intensity is not usually captured in registry data. Further studies would need to collect prospective data specifically for these fields. Further development of a definition for major bleeding could consider whether the same definition of major bleeding applies to all all-groups, especially if mortality from major bleeding is a key outcome for prediction models, as data from this thesis and others have shown higher mortality in older age groups.

A limitation with the time-based nature of the delphi definition meant that if the time of injury was not known it was difficult to accurately determine the number of units transfused and which patients met the criteria for major bleeding. Using time at scene, which is better recorded, instead of time of injury is an area that could be explored.

Finally, this thesis evaluated ageing but relevant syndromes such as frailty were not available in the registry data at the time of data interrogation. Clinical frailty assessment is now part of the best practice tariff for major trauma in England and will incentivise data capture in this field.

7.2 Further work arising from this thesis

This work has demonstrated there are gaps in our understanding relating to age and ageing in trauma. Despite many RCTs in adult trauma, there is no RCT that has evaluated transfusion strategies in older people. Future work could develop and test the effectiveness of an age-adapted major haemorrhage protocol with targeted therapy to avoid the risk associated with unnecessary over- or under-transfusion and development of vital sign parameters to guide triage that take age into consideration.

This work is hypothesis generating. Risk factors identified in the TARN study could be used to develop a prediction model for major bleeding and to evaluate its effectiveness across age. The laboratory work showed interesting results - fibrinogen levels appeared to rise with age and older people appeared to have increased fibrinolytic activation. Leading on from this, further work is needed to:

1) define fibrinogen ranges in the normal population

2) improve understanding, on an *in vitro* and functional level, of the relationship between fibrinogen level and blood clot integrity across age groups

3) test the hypothesis that the minimum fibrinogen thresholds to reduce bleeding is different across age groups

4) understand the fibrinolytic profile of older people in normal health and in trauma, to determine whether the same tranexamic acid dose is effective across age at reducing fibrinolysis or if higher doses are required in older people.

Another area for further work relates to methodology. There is scope to develop this consensus on reporting of RCTs and data fields captured by trauma registry data, which will have benefits in improving the quality of data and assimilation of research findings. Potential areas for development that have arisen from this thesis are:

1. **Development of core outcome set and reporting transfer time and time to intervention for RCTs in trauma haemorrhage.**

Conducting trauma RCTS is particularly challenging and large numbers of patients are needed for appropriately powered trials. Large multicentre trials have much more power than single centre studies. For the systematic review on trauma haemorrhage, there was no consensus core outcome and core reporting set (transfer time and time to intervention are particularly useful parameters to consider when comparing trials and are not universally reported). Working on consensus would greatly improve the quality of trial reporting, identification of clinically relevant endpoints and facilitate meta-analysis of trial data where appropriate.

2. **Standardised data fields for trauma registry data.**

Trauma registries are powerful tools and have been used to improve patient care and conduct research over the past few decades. Within this time period, trauma care has also evolved, and there are opportunities to develop registries in light of changing practice and epidemiological change. For example, consensus core variables for registry

data collection and transfusion data on timings of transfusion and linkage to outcomes could be developed. This is particularly relevant if composite definitions for major bleeding are to be used in the future, and to allow cross-validation across different trauma registries.

3. **Improving data quality or completeness in trauma registries.**
   - Improved data collection through use of electronic records to improve data quality and minimise data error.
   - Improved linkage of data from pre-hospital, hospital, GP and outcome data.
   - Establishing standards for data quality or completeness.

The field of trauma haemorrhage is an exciting but challenging one. Much progress has been made over the past two decades in understanding and managing coagulopathy and bleeding. Going forwards, it would be encouraging to see more international collaboration and joint priorities for research to streamline resources, avoid duplication so further advances can be made in the field.

7.3 Final conclusions

The incidence of major trauma and numbers of patients at risk of major bleeding is likely to increase in coming years, driven by an ageing and more active population. The work in this thesis shows that age impacts on risk factors for bleeding and is associated with changes in the coagulation profile. This has potential clinical implications on how bleeding is identified and managed. One size does not fit all and this thesis provides data on the impact of age in trauma-related bleeding and coagulopathy that requires further study. Older people with major bleeding are a vulnerable group who have particularly high mortality after injury. Trauma haemorrhage research has led to transformations in

trauma care and improved outcomes in recent years. With the changing trauma age demographic, it is essential to build on the work that has been done and to develop facets of trauma care for the ageing population so that outcomes can be improved across all age groups.

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Appendix 1: Search strategy for systematic review

NEW SEARCH STRATEGIES

CENTRAL

#1 MeSH descriptor: [Multiple Trauma] this term only

#2 MeSH descriptor: [Shock, Hemorrhagic] this term only

#3 MeSH descriptor: [Shock, Traumatic] explode all trees

#4 MeSH descriptor: [Trauma Severity Indices] explode all trees

#5 MeSH descriptor: [Trauma Centers] explode all trees

#6 MeSH descriptor: [Accidents] explode all trees

#7 MeSH descriptor: [Traumatology] this term only

#8 (stabb* or shooting or gunshot* or blast* or bomb* or explosi* or disaster* or casualt* or catastroph* or combat* or battlefield*):ti

#9 ((uncontroll* or ongoing or massive* or major or shock* or critical* or serious* or severe* or life-threatening* or trauma* or pelvic or pelvis or abdominal* or arterial* or catastrophic* or control* or manag*) near/3 (haemorrhag* or hemorrhag* or bleed* or bloodloss* or "blood loss"))

#10 ((trauma* or injur*) near/3 (penetrating or blunt or multip*))

#11 (trauma* or combat* or gunshot* or blast* or battle*) near/2 surg*

#12 (trauma* or injur* or accident* or wound*) near/3 (critical* or massive* or major or serious* or severe* or life-threatening* or coagulopath* or coagulat*)

#13 (injur* or wound*) near/3 (lacerat* or crush* or stab* or penetrating or blunt)

#14 (polytrauma* or "hypotensive resuscitation" or "hypovolemic shock" or "hypovolaemic shock")

#15 (trauma* or exsanguin* or hypovolemi* or hypovolaemi* or coagulopath* or (abnormal* near/2 coagulation) or hyperfibrinolysis):ti

#16 MeSH descriptor: [Military Medicine] explode all trees

#17 MeSH descriptor: [Amputation, Traumatic] this term only

#18 MeSH descriptor: [Blast Injuries] this term only

#19 MeSH descriptor: [Rupture] explode all trees

#20 MeSH descriptor: [Wounds, Penetrating] explode all trees

#21 MeSH descriptor: [Lacerations] explode all trees

#22 MeSH descriptor: [Resuscitation] this term only

#23 MeSH descriptor: [Femoral Fractures] explode all trees

#24 ((hip* or pelvi* or femoral or femur) near/2 fracture*):ti

#25 MeSH descriptor: [Craniocerebral Trauma] explode all trees

#26 ((head or brain or cerebrocranial* or cranial* or craniocerebral* or cerebral or intracranial* or intra-cranial* or intracortical* or intra-cortical* or subcortical* or sub-cortical* or intraventricul* or intra-ventricular* or periventricular* or peri-ventricular* or cerebell* or cerebrum or corpus callosum or posterior fossa or hemispher*) near/5 (trauma* or injur* or wound*)):ti

#27 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 in Other Reviews and Trials

#28 MeSH descriptor: [Blood Transfusion] this term only

#29 MeSH descriptor: [Blood Component Transfusion] explode all trees

#30 (RBC* or "red cell" or "red cells" or "red blood cell" or "red blood cells" or platelet* or FFP or cryoprecipitate or transfus* or pretransfus* or posttransfus* or retransfus* or hypertransfus*):ti

#31 ((RBC* or "red cell" or "red cells" or "red blood cell" or "red blood cells" or platelet* or plasma or FFP or "whole blood" or cryoprecipitate) near/6 (transfus* or pretransfus* or posttransfus* or retransfus* or hypertransfus*)):ab

#32 ("liquid plasma" or "fresh plasma" or "frozen plasma" or "cryopreserved plasma" or octaplas or "thawed plasma" or "platelet concentrate*" or "cold-storage platelets" or "rehydrated platelets" or "fresh whole blood")

#33 ((lyophili?ed or freeze-dried) near/3 (plasma or platelet*))

#34 ("blood product*" or "blood component*" or "blood management" or "blood therapy" or "blood replacement therapy")

#35 (blood near/2 (storage or age or new* or old* or fresh* or stored)):ti

#36 ((massive* or major) near/3 transfus*):ab

#37 #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36

#38 #27 and #37

#39 MeSH descriptor: [Thrombelastography] explode all trees

#40 (thrombo-elastogra* or thrombelastogra* or thrombelasto-gra* or thromboelastogra* or TEG or ROTEM or ROTEG or haemoscope* or hemoscope* or haemonetics or hemonectics or EXTEM or INTEM or FIBTEM or HEPTEM or APTEM or thrombo-elastomet* or thrombelastomet* or thromboelastomet* or Sonoclot or sono-clot)

#41 ((thromb* near/2 (elastogra* or elasto-gra* or elastom*)) or (rotational near/2 (thrombelast* or thromboelast*)))

#42 (viscoelastic or visco-elastic) and (detect* or coagulation or haemostatic or hemostatic)

#43 whole blood hemosta* system* or whole blood haemosta* system*

#44 #39 or #40 or #41 or #42 or #43

#45 #27 and #44

#46 #38 or #45

MEDLINE (OvidSP)

1. BLOOD TRANSFUSION/

2. exp BLOOD COMPONENT TRANSFUSION/

3. (transfus* or pretransfus* or posttransfus* or retransfus* or hypertransfus* or RBC* or red cell* or red blood cell* or platelet* or FFP or cryoprecipitate).ti.

4. (blood product* or blood component* or blood management or blood therapy or blood replacement therapy).tw,kf.

5. (blood adj2 (storage or age or new* or old* or fresh* or stored)).ti,kf.

6. ((RBC* or red cell* or red blood cell* or platelet* or plasma or FFP or whole blood or cryoprecipitate) adj6 (transfus* or pretransfus* or posttransfus* or retransfus* or hypertransfus*)).ab,kf.

7. (liquid plasma or fresh plasma or frozen plasma or cryopreserved plasma or thawed plasma or octaplas or platelet concentrate* or cold-storage platelets or rehydrated platelets or fresh whole blood).tw,kf.

8. ((lyophili?ed or freeze-dried) adj3 (plasma or platelet*)).tw,kf.

9. ((massive* or major) adj3 transfus*).ab,kf.

10. or/1-9

11. exp Multiple Trauma/

12. Shock, Hemorrhagic/

13. exp Shock, Traumatic/

14. exp Trauma Severity Indices/

15. Traumatology/

16. Trauma Centers/

17. Military Medicine/

18. Amputation, Traumatic/

19. Blast Injuries/

20. exp Crush Syndrome/

21. exp *Rupture/

22. exp *Wounds, Penetrating/

23. *Lacerations/

24. *Resuscitation/

25. (trauma* or exsanguin* or hypovolemi* or hypovolaemi* or coagulopath* or (abnormal* adj2 coagulation) or hyperfibrinolysis).ti.
26. (polytrauma* or hypotensive resuscitation or hypovolemic shock or hypovolaemic shock).tw,kf.
27. ((uncontroll* or ongoing or massive* or major or shock* or critical* or serious* or severe* or life-threatening* or trauma* or pelvic or pelvis or abdominal* or arterial* or catastrophic* or control* or management) adj3 (haemorrhag* or hemorrhag* or bleed* or bloodloss* or blood loss*)).tw,kf.
28. ((trauma* or injur* or accident* or wound*) adj3 (critical* or massive* or serious* or severe* or life-threatening* or coagulopath* or coagulat*)).tw,kf.

29. ((trauma* or injur*) adj3 (penetrating or blunt or multip*)).tw,kf.
30. ((injur* or wound*) adj3 (lacerat* or stab* or crush* or penetrating or blunt)).tw,kf.

31. (stabb* or shooting or gunshot* or blast* or bomb* or explosi* or disaster* or casualt* or catastroph* or combat* or battlefield*).ti,kf.

32. ((trauma* or combat* or gunshot* or blast* or battle*) adj2 surger*).tw,kf.

33. exp *Femoral Fractures/ or ((pelvi* or femoral* or femur* or hip*) adj2 fracture*).ti,kf.

34. exp Craniocerebral Trauma/

35. ((head or brain or cerebrocranial* or cranial* or craniocerebral* or cerebral or intracranial* or intra-cranial* or intracortical* or intra-cortical* or subcortical* or sub-cortical* or intraventricul* or intra-ventricular* or periventricular* or peri-ventricular* or cerebell* or cerebrum or corpus callosum or posterior fossa or hemispher*) adj5 (trauma* or injur* or wound*)).ti,kf.

36. or/11-35

37. Thrombelastography/

38. (thrombo-elastogra* or thrombelastogra* or thrombelasto-gra* or thromboelastogra*).tw,kf.

39. (TEG or ROTEM or ROTEG).tw,kf.
40. (thromb* adj2 (elastogra* or elasto-gra*)).tw,kf.

41. (haemoscope* or hemoscope* or haemonetics or hemonectics).tw,kf.

42. whole blood h?emosta* system*.tw,kf.

43. (EXTEM or INTEM or FIBTEM or HEPTEM or APTEM).tw,kf.

44. (thrombo-elastomet* or thrombelastomet* or thromboelastomet*).tw,kf.

45. ((thromb* adj2 elasto?m*) or (rotational adj2 thromb?elast*)).tw,kf.

46. (Sonoclot or sono-clot).tw,kf.

47. ((viscoelastic or visco-elastic) adj5 (detect* or coagulation or haemostatic or hemostatic) adj5 (system* or process or test or tests or analyz* or analys* or assay* or device* or measurement*)).tw,kf.

48. or/37-47

49. (10 or 48) and 36

50. Meta-Analysis.pt.

51. ((meta analy* or metaanaly*) and (trials or studies)).ab.

52 (meta analy* or metaanaly* or evidence-based).ti.

53. ((systematic* or evidence-based) adj2 (review* or overview*)).tw,kf.

54. (cochrane or embase or cinahl or cinhal or lilacs or citation index or psyclit or psychlit or psycinfo or psychinfo or "web of science" or scopus).ab.

55. Cochrane Database of systematic reviews.jn.

56. ((literature or systematic* or comprehensive* or electronic*) adj2 search*).ab.

57. (additional adj (papers or articles or sources)).ab.

58. (bibliograph* or handsearch* or hand search* or manual* search* or searched or reference list*).ab.

59. (relevant adj (journals or articles)).ab.

60. or/50-59

61. Review.pt.

62. RANDOMIZED CONTROLLED TRIALS AS TOPIC/

63. selection criteria.ab. or critical appraisal.tw,kf.

64. (data adj (extraction or analys*)).ab.

65. RANDOMIZED CONTROLLED TRIALS/

66. or/62-65

67. 61 and 66

68. 60 or 67

69. randomized controlled trial.pt.

70. controlled clinical trial.pt.

71. randomi*.tw,kf.

72. placebo.ab.

73. clinical trials as topic.sh.

74. randomly.ab.

75. groups.ab.

76. trial.tw.

77. or/69-76

78. 68 or 77

79. (ANIMALS/ or exp ANIMAL EXPERIMENTATION/ or exp MODELS, ANIMAL/) not HUMANS/

80. (Comment or Editorial).pt.

81. 79 or 80

82. (78 not 81) and 49

Embase (OvidSP)

1. exp Blood Component Therapy/

2. Blood Transfusion/

3. ((RBC* or red cell* or red blood cell* or platelet* or plasma or FFP or whole blood or cryoprecipitate) adj6 (transfus* or pretransfus* or posttransfus* or retransfus* or hypertransfus*)).ab.

4. (liquid plasma or fresh plasma or frozen plasma or platelet concentrate* or cold-storage platelets or rehydrated platelets or fresh whole blood).tw.

5. ((lyophili?ed or freeze-dried) adj3 (plasma or platelet*)).tw.

6. (transfus* or pretransfus* or posttransfus* or retransfus* or hypertransfus* or RBC* or red cell* or red blood cell* or platelet* or plasma or FFP or cryoprecipitate).ti.

7. (blood product* or blood component* or blood management or blood therapy or blood replacement therapy).tw.

8. (blood adj2 (storage or age or new* or old* or fresh* or stored)).ti.

9. ((massive* or major) adj3 transfus*).ab.

10. or/1-9

11. Multiple Trauma/

12. Exsanguination/ or Hemorrhagic Hypotension/ or Hemorrhagic Shock/

13. exp Injury Scale/

14. exp Traumatology/

15. Battle Injury/ or Blast Injury/ or Blunt Trauma/ or Crush Trauma/ or Traumatic Amputation/

16. Military Medicine/ or Gunshot Injury/ or Missile Wound/ or Stab Wound/ or Wound Hemorrhage/

17. ((uncontroll* or ongoing or massive* or major or critical* or serious* or severe* or life-threatening* or trauma* or pelvic or pelvis or abdominal* or arterial* or catastrophic* or control* or management) adj3 (haemorrhag* or hemorrhag* or bleed* or bloodloss* or blood loss*)).ti.

18. (polytrauma* or haemorrhag* shock* or hemorrhag* shock* or hypotensive resuscitation or hypovolemic shock or hypovolaemic shock or (massive* adj1 transfus*) or ((trauma* or injur*) adj3 (penetrating or blunt or multip*))).tw.

19. (trauma* or exsanguin* or hypovolemi* or hypovolaemi* or coagulopath* or (abnormal* adj2 coagulation) or hyperfibrinolysis).ti.

20. ((trauma* or injur* or accident* or wound*) adj3 (critical* or massive* or serious* or severe* or life-threatening* or coagulopath* or coagulat*)).tw.

21. ((injur* or wound*) adj3 (lacerat* or crush* or penetrating or blunt)).ti.

22. (stabb* or shooting or gunshot* or blast* or bomb* or explosi* or disaster* or casualt* or catastroph* or combat* or battlefield*).ti.

23. (trauma surger* or combat surger* or ((gunshot* or blast* or battle*) adj2 surger*)).tw.

24. exp *Hip Fracture/ or ((femoral* or femur* or hip* or pelvi*) adj2 fracture*).ti.
25. exp *"head and neck injury"/

26. ((head or brain or cerebrocranial* or cranial* or craniocerebral* or cerebral or intracranial* or intra-cranial* or intracortical* or intra-cortical* or subcortical* or sub-cortical* or intraventricul* or intra-ventricular* or periventricular* or peri-ventricular* or cerebell* or cerebrum or corpus callosum or posterior fossa or hemispher*) adj5 (trauma* or injur* or wound*)).ti.

27. blood clotting disorder/ and trauma*.mp.

28. or/11-27

29. 10 and 28

30. Thrombelastography/

31. (thrombo-elastogra* or thrombelastogra* or thrombelasto-gra* or thromboelastogra* or TEG).tw,kf,ot.

32. (thromb* adj2 (elastogra* or elasto-gra*)).tw,ot,kf.

33. (haemoscope* or hemoscope* or haemonetics or hemonectics).tw,ot,kf.

34. whole blood h?emosta* system*.tw,ot,kf.

35. (ROTEM* or ROTEG).tw,ot,kf.

36. (thrombo-elastomet* or thrombelastomet* or thromboelastomet*).tw,ot,kf.

37. ((thromb* adj2 elasto?m*) or (rotational adj2 thrombelast*) or "TEM international").tw,ot,kf.

38. (Sonoclot or sono-clot).tw,ot,kf.

39. ((viscoelastic or visco-elastic) and (detect* or coagulation) and (system* or process or test or tests or analyz* or analys* or assay* or device* or measurement*)).tw,ot,kf.

40. or/30-39

41. 28 and 40

42. 29 or 41

43. Meta Analysis/

44. Systematic Review/

45. (meta analy* or metaanalys*).tw.

46. (systematic adj2 (review* or overview* or search*)).tw.

47. (literature adj2 (review* or overview* or search*)).ti,ab.

48. (cochrane or embase or cinahl or cinhal or lilacs or BIDS or science citation index or psyclit or psychlit or psycinfo or psychinfo or cancerlit).ti,ab.

49. (electronic* adj (sources or resources or databases)).ab.

50. reference lists.ab.

51. (bibliograph* or handsearch* or hand search* or manual* search*).ab.

52. (hand-search* or handsearch*).ab.

53. (additional adj (papers or articles or sources)).ab.

54. (relevant adj (journals or articles)).ab.

55. (search term* or published articles or search strateg*).ab.

56. 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55

57. (data extraction or selection criteria).ab.

58. review.pt.

59. 57 and 58

60. editorial.pt.

61. 59 not 60

62. crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/

63. (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or doubl* blind* or singl* blind* or assign* or allocat* or volunteer*).mp.

64. or/61-63

65. exp animal experiment/ not (exp human experiment/ or human/)

66. 64 not 65

67. 42 and 66
68. limit 67 to (conference abstracts or embase)

PubMed

#1 trauma[TI] OR traumatic*[TI] OR exsanguin*[TI] OR hypovolemi*[TI] OR hypovolaemi*[TI] OR stab[TI] OR stabb*[TI] OR shooting[TI] OR gunshot*[TI] OR blast[TI] OR bomb*[TI] OR explosi*[TI] OR disaster*[TI] OR casualt*[TI] OR catastroph*[TI] OR combat*[TI] OR battlefield*[TI] OR coagulopathy*[TI]

#2 ((uncontroll*[TI] OR ongoing[TI] OR massive*[TI] OR major[TI] OR shock*[TI] OR critical*[TI] OR serious*[TI] OR severe*[TI] OR life-threatening*[TI] OR pelvic[TI] OR pelvis[TI] OR abdominal*[TI] OR arterial*[TI] OR catastrophic*[TI] OR control*[TI] OR manag*[TI]) AND (haemorrhag*[TI] OR hemorrhag*[TI] OR bleed*[TI] OR bloodloss*[TI] OR blood loss*[TI]))

#3 "critical injury"[TIAB] OR "critical injuries"[TIAB] OR "critically injured"[TIAB] OR "serious injury"[TIAB] OR "serious injuries"[TIAB] OR "seriously injured"[TIAB] OR

"severe injury"[TIAB] OR "severe injuries"[TIAB] OR "severely injured"[TIAB] OR "life-threatening injuries"[TIAB] OR "life-threateningly injured" OR "penetrating injury"[TIAB] OR "penetrating injuries"[TIAB] OR "blunt injury"[TIAB] OR "multiple injuries"[TIAB] OR "multiply injured"[TIAB]

#4 ((trauma[TIAB] OR traumatic*[TIAB] OR combat*[TIAB] OR gunshot*[TIAB] OR blast[TIAB] OR battle*[TIAB]) AND (surgery[TIAB] OR surgical*[TIAB] OR coagulopath* OR coagulat*[TIAB]))

#5 polytrauma*[TIAB] OR "hypotensive resuscitation"[TIAB] OR "hypovolemic shock"[TIAB] OR "hypovolaemic shock"[TIAB]

#6 (hip*[TI] OR pelvi*[TI] OR femoral[TI] OR femur[TI]) AND fracture*[TI]

#7 ((head[TI] OR brain[TI] OR cerebrocranial*[TI] OR cranial*[TI] OR craniocerebral*[TI] OR cerebral[TI] OR intracranial*[TI] OR intra-cranial*[TI] OR intracortical*[TI] OR intra-cortical*[TI] OR subcortical*[TI] OR sub-cortical*[TI] OR intraventricul*[TI] OR intra-ventricular*[TI] OR periventricular*[TI] OR peri-ventricular*[TI] OR cerebell*[TI] OR cerebrum[TI] OR corpus callosum[TI] OR posterior fossa[TI] OR hemispher*[TI]) AND (trauma*[TI] OR injur*[TI] OR wound*[TI]))

#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

#9 (thrombo-elastogra* OR thrombelastogra* OR thrombelasto-gra* OR thromboelastogra* OR TEG OR ROTEM OR ROTEG OR haemoscope* OR hemoscope* OR haemonetics OR hemonetics OR EXTEM OR INTEM OR FIBTEM OR HEPTEM OR APTEM OR thrombo-elastomet* OR thrombelastomet* OR thromboelastomet* OR Sonoclot OR sono-clot)
#10 (thromb-elastom* OR thrombo-elastom*) OR (rotational AND (thromboelast* OR thrombelast*))
#11 ((viscoelastic OR visco-elastic) AND (detect* OR coagulation OR haemostatic OR hemostatic) AND (system OR systems OR process OR test OR tests OR analyz* OR analys* OR assay* OR device* OR measurement*))
#12 whole blood hemosta* system* OR whole blood haemostat* system*
#13 RBC*[TI] OR "red cell"[TI] OR "red cells"[TI] OR "red blood cell"[TI] OR "red blood cells"[TI] OR platelet*[TI] OR FFP[TI] OR cryoprecipitate[TI] OR transfus*[TI] OR pretransfus*[TI] OR posttransfus*[TI] OR retransfus*[TI] OR hypertransfus*[TI]

#14 ((RBC*[TIAB] OR "red cell"[TIAB] OR "red cells"[TIAB] OR "red blood cell"[TIAB] OR "red blood cells"[TIAB] OR platelet*[TIAB] OR plasma[TIAB] OR FFP[TIAB] OR "whole blood"[TIAB] OR cryoprecipitate[TIAB]) AND (transfus*[TIAB] OR pretransfus*[TIAB] OR posttransfus*[TIAB] OR retransfus*[TIAB] OR hypertransfus*[TIAB]))

#15 ("liquid plasma" OR "fresh plasma" OR "frozen plasma" OR "cryopreserved plasma" OR octaplas OR "thawed plasma" OR "platelet concentrate*" OR "cold-storage platelets" OR "rehydrated platelets" OR "fresh whole blood")

#16 ((lyophilized OR lyphilised OR freeze-dried) AND (plasma OR platelet*))

#17 ("blood product" OR "blood products" OR "blood component" OR "blood components" OR "blood management" OR "blood therapy" OR "blood replacement therapy")

#18 (blood[TI] AND (storage[TI] OR age[TI] OR new*[TI] OR old*[TI] OR fresh*[TI] OR stored[TI]))

#19 "massively transfused"[TIAB] OR "massive transfusion"[TIAB] OR "major transfusion"[TIAB]

#20 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19

#21 #8 AND #20

#22 (random* OR blind* OR "control group" OR placebo* OR controlled OR groups OR trial* OR "systematic review" OR "meta-analysis" OR metaanalysis OR "literature search" OR medline OR pubmed OR cochrane OR embase) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])

#23 #21 AND #22

TRANSFUSION EVIDENCE LIBRARY

Clinical Specialty: Trauma

WEB OF SCIENCE

#1 TI=(RBC* OR "red cell" OR "red cells" OR "red blood cell" OR "red blood cells" OR platelet* OR FFP OR cryoprecipitate OR transfus* OR pretransfus* OR posttransfus* OR retransfus* OR hypertransfus*)

#2 TS=(transfus* OR pretransfus* OR posttransfus* OR retransfus* OR hypertransfus* OR "liquid plasma" OR "fresh plasma" OR "frozen plasma" OR "cryopreserved plasma" OR octaplas OR "thawed plasma" OR "platelet concentrate" OR "platelet concentrates" OR "cold-storage platelets" OR "rehydrated platelets" OR "whole blood" OR "massive transfusion" OR "massively transfused" OR "major transfusion" OR "lyophilized plasma" OR

"lyophilised plasma" OR "freeze-dried plasma" OR "lyophilized platelets" OR "lyophilised platelets" OR "freeze-dried platelets" OR "blood product*" OR "blood component*" OR "blood management" OR "blood therapy" OR "blood replacement therapy")

#3 #1 OR #2

#4 TS=(thrombo-elastogra* OR thrombelastogra* OR thrombelasto-gra* OR thromboelastogra* OR TEG OR ROTEM OR ROTEG OR haemoscope* OR hemoscope* OR haemonetics OR hemonetics OR EXTEM OR INTEM OR FIBTEM OR HEPTEM OR APTEM OR thrombo-elastomet* OR thrombelastomet* OR thromboelastomet* OR Sonoclot OR sono-clot)

#5 TS=((thromb-elastom* OR thrombo-elastom*) OR (rotational AND (thromboelast* OR thrombelast*)))

#6 TS=((viscoelastic OR visco-elastic) AND (detect* OR coagulation OR haemostatic OR hemostatic) AND (system OR systems OR process OR test OR tests OR analyz* OR analys* OR assay* OR device* OR measurement*))

#7 TS=(whole blood hemosta* system* OR whole blood haemostat* system*)

#8 #3 OR #4 OR #5 OR #6 OR #7

#9 TS=(trauma* OR "haemorrhagic shock" OR "hemorrhagic shock" OR "hip fracture" OR "pelvic fracture" OR "critical injury" OR "critical injuries" OR "critically injured" OR "serious injury" OR "serious injuries" OR "seriously injured" OR "severe injury" OR "severe injuries" OR "severely injured" OR "life-threatening injuries" OR "life-threateningly injured" OR "penetrating injury" OR "penetrating injuries" OR "blunt injury" OR "multiple injuries" OR "multiply injured" OR polytrauma* OR "hypotensive resuscitation" OR "hypovolemic shock" OR "hypovolaemic shock" OR coagulopath*)

#10 TI=(stabb* OR stab OR shooting OR gunshot* OR blast* OR bomb* OR explosi* OR disaster* OR casualt* OR catastroph* OR combat* OR battlefield* OR trauma* OR "haemorrhagic shock" OR "hemorrhagic shock" OR "hip fracture" OR "pelvic fracture")

#11 TS=((head OR brain OR cerebrocranial* OR cranial* OR craniocerebral* OR cerebral OR intracranial* OR intra-cranial* OR intracortical* OR intra-cortical* OR subcortical* OR sub-cortical* OR intraventricul* OR intra-ventricular* OR periventricular* OR peri-ventricular* OR cerebell* OR cerebrum OR corpus callosum OR posterior fossa OR hemispher*) AND (injur* OR wound*))

#12 #9 OR #10 OR #11

#13 TS=(random* OR "controlled trial" OR "control group" OR "controlled study" OR "systematic review" OR blind*) OR TI=(randomi* OR trial OR systematic)

#14 #3 AND #12 AND #13

CLINICALTRIALS.GOV

Terms: randomized OR randomised OR randomly

Study Type: Interventional Studies

Conditions: trauma OR polytrauma OR hip fracture OR hemorrhagic shock OR coagulopathy OR head injury OR brain injury

Interventions: transfusion OR "blood products" OR "blood components" OR FFP OR platelets OR cryoprecipitate OR "red cells" OR "red blood cells" OR "whole blood" OR plasma OR thromboelastography OR thromboelastometry OR TEG OR ROTEM

WHO ICTRP

Title OR Condition: trauma OR polytrauma OR hip fracture OR hemorrhagic shock OR coagulopathy OR head injury OR brain injury

AND

Intervention: transfusion OR massive transfusion OR FFP OR platelets OR cryoprecipitate OR red OR fresh frozen plasma OR thromboelastography OR thrombelastometry OR TEG OR ROTEM OR ROTEG

AND

Recruitment Status: All

Appendix 2: Detailed characteristics of included studies

Appendix 2.1 Trial-defined intervention vs standard of care (pre-hospital)

NR, not reported

Moore 2018[124]

Methods	**Study design:** Single-centre, 2-arm, parallel-group RCT **Setting:** Level 1 civilian trauma centre in North America **Country:** USA **Dates study conducted:** April 1 2014 to March 31 2017 **Length of follow up:** 28 days **Aim of study:** To test the hypothesis that mortality would be lower among patients who received plasma before arrival at a level 1 trauma facility than among those who received standard care with normal saline **Definition of major haemorrhage:** More than 10 units RBC transfused **Definition of coagulopathy:** INR >1.3
Participants	**Inclusion criteria:** Eligible patients were injured adults (age >18 years), with systolic blood pressure 70 mm Hg or lower or 71–90 mm Hg and heart rate 108 beats per min thought to be due to acute blood loss. **Exclusion criteria:** Prisoner status, known pregnancy, isolated gunshot to the head, asystole or cardiopulmonary resuscitation before randomisation, known objection to blood products, opt-out bracelets or necklaces, or family objection to the patient's enrolment. **Baseline Characteristics** Intervention 1: FFP (N=65) • Age median (IQR): 33 (25-51) • Male n (%): 52 (80%) • Blunt injury n (%): 30 (46) • Injury severity score median (IQR): 27 (10.0-41.0) • Isolated TBI: NR • Pre-injury anticoagulant/antiplatelet therapy: NR • Received tranexamic acid (%): 6 (9%) • Baseline INR median (IQR): 1.1 (1.0-1.2) • Baseline PT: (NR) • Pre-randomisation red blood cells (units) median (IQR): NR • Pre-randomisation FFP (units) median (IQR): 0 (0-0)

	• Time from injury to hospital (mins) median (IQR): 28 (22-34) • Transport time (mins) median (IQR): 19 (16-23) • Time from injury to randomisation: NR Intervention 2: Normal saline (standard of care) (N=60) • Age median (IQR): 32.5 (25.5-42.0) • Male n (%): 51 (85) • Blunt injury n (%): 32 (53) • Injury severity score median (IQR): 27 (11.5-36.0) • Isolated TBI: NR • Pre-injury anticoagulant/antiplatelet therapy: NR • Received tranexamic acid (%): 8 (13%) • Baseline INR median (IQR): 1.1 (1.0-1.1) • Baseline PT: (NR) • Pre-randomisation red blood cells (units) median (IQR): NR • Pre-randomisation FFP (units) median (IQR): 0 (0-0) • Time from injury to hospital (mins) median (IQR): 24 (19-31) • Transport time (mins) median (IQR): 16 (14-22) • Time from injury to randomisation: NR **Number randomised:** Plasma group 75, Control group 69 **Number analysed:** Plasma group 75, control group 69 ITT analysis. Plasma group 65, control group 60 per protocol. **Number lost to FU/drop out:** 0 for intention to treat (ITT) analysis, 19 for per protocol analysis
Interventions	**Intervention Characteristics** Intervention 1: FFP • Description and dose: 2 units of AB fresh frozen plasma frozen within 24 hours of collection. Plasma was stored and defrosted with a field plasma system for quick thawing of plasma. • Timing: Prehospital • Route: intravenous (IV) Intervention 2: Normal saline (standard of care) • Description and dose: Normal saline (0·9%) per the standard of care • Timing: Prehospital • Route: IV
Outcomes	**Primary outcome** • 28-day mortality

	Secondary outcomes • Time from injury to need for first red blood cell transfusion • Thromboelastography indices, number of ventilation-free days, number of intensive-care-free days, and development of multiorgan failure. • Acute lung injury within 28 days • Transfusion-related acute lung injury
Identification	**Registration:** prospectively registered (NCT01838863) **Sponsorship source:** US Department of Defense **Conflict of interest:** none declared **Comments:** Study terminated early due to futility. **Authors name:** Hunter B Moore **Institution:** University of Colorado Denver, School of Medicine **Email:** michael.chapman@ucdenver.edu **Address:** Department of Radiology, University of Colorado Denver, School of Medicine, Aurora, CO 80045, US
Notes	NISS reported, not ISS Short transport time from injury to hospital arrival (median 28 min plasma group and 24 min control group) 28-day mortality, not 30-day mortality. INR on hospital arrival - medians presented so not able to calculate mean difference. In plasma group median INR 1.27 (1.11-1.4) vs 1.15 (1.08-1.29) in control group. All outcomes presented per protocol. ITT safety analysis: mortality plasma 12/75 (16%) vs 6/69 (9%) p=0.19, total thrombotic events in plasma group 4 vs 2. Mortality at 28 days (not 30 days). Median red cells in control group 1.5. Fresh frozen plasma excluded units given in the field (2 units in all cases).

Risk of bias table, Moore 2018[124]

Bias	Judgement	Support for judgement
Random sequence generation (selection bias)	Unclear	Randomly assigned 1:1 in blocks of 20 according to a schedule generated by the research coordinators. The nature of this schedule is not specified.
Allocation concealment (selection bias)	Low	These were delivered to the DHMC Paramedic Division in sealed aluminium cassettes by study staff not involved in enrolment or data analysis, to mask allocation.
Blinding of participants and personnel (performance bias) Transfusion requirements	High	Not blinded
Blinding of participants and personnel (performance bias) Outcomes except transfusion requirements	High	Not blinded
Blinding of outcome assessment (detection bias) Outcomes except cause of death	High	Not specified in the paper. In the protocol it states that this trial is open label.
Blinding of outcome assessment (detection bias) Death due to haemorrhage	High	Not specified in the paper. In the protocol it states that this trial is open label.
Incomplete outcome data (attrition bias)	Low	All patients accounted for in the final analysis. Both per protocol and intention to treat analyses were performed.
Selective reporting (reporting bias)	Low	The trial was prospectively registered. Some pre-specified subgroup analyses were not performed but this does not put the paper at risk of bias.
Other bias	Low	No other clear sources of bias

Sperry 2018[118]

Methods	**Study design:** Multi-centre parallel-group cluster RCT **Setting:** Level 1 trauma centres with active air medical helicopter transport programs **Country:** USA **Dates study conducted:** May 2014 - October 2017 **Number of centres:** 9 trauma centres and 27 air medical bases (clusters) **Length of follow up:** 30 days **Aim of study:** To determine the efficacy and safety of prehospital plasma resuscitation as compared with standard-care resuscitation (not including plasma administration) in severely injured patients at risk for haemorrhagic shock. **Definition of major haemorrhage:** Patients at risk of haemorrhagic shock **Definition of coagulopathy:** Coagulopathy based on measurements of prothrombin time and thromboelastography (not specified)
Participants	**Inclusion criteria:** Patients transported from the scene of their injury to a participating trauma centre or who were transferred from an outside referral emergency department to a participating trauma centre were eligible for enrolment in the PAMPer trial if they had at least one episode of hypotension (systolic blood pressure 90 mm Hg) and tachycardia (defined in this trial as a heart rate>108 beats per minute) or if they had any severe hypotension (systolic blood pressure 70 mm Hg), either before the arrival of air medical transport or any time before arrival at the trauma centre. **Exclusion criteria:** Exclusion criteria include age18 or>90 years old, inability to obtain intravenous or interosseous access, isolated fall from standing mechanisms, radiographically documented cervical spinal cord injury with motor deficit, prisoner, pregnancy, cardiac arrest>5 minutes without return of vital signs, penetrating cranial injury, traumatic brain injury with brain matter ex-posed, isolated drowning or hanging victims, isolated burn injury with>20% estimated total body surface area, referral from facility for an in-patient, or wearing an opt-out bracelet **Number lost to FU/drop out:** 23 lost to follow up standard group, 19 in plasma group. **Definition of major haemorrhage:** Patients at risk of haemorrhagic shock **Number randomised:** standard group 284, plasma group 239 **Number analysed:** standard group 271, plasma group 230 for primary

	outcome (used multiple imputation for missing outcome data- 10 in each arm) **Baseline Characteristics** Intervention 1: Thawed plasma (N=230) • Age median (IQR) : 44 (31-59) • Male n (%): 164 (71.3) • Blunt injury n (%): 187 (81.3) • Penetrating injury n (%): 46 (20.0) • Injury severity score median (IQR): 22 (14-33) • Isolated traumatic brain injury n (%): NR • Pre-injury anticoagulant/antiplatelet therapy n (%): 6 (2.6) anticoagulant, 20 (8.7) antiplatelet • Received tranexamic acid (%): NR • Baseline PT median (IQR): NR • Baseline INR median (IQR): NR • Pre-randomisation red blood cells (units) median (IQR): NR • Pre-randomisation FFP (units) median (IQR): NR • Time from injury to hospital (mins) median (IQR): NR • Transport time (mins) median (IQR): 42 (34-53) • Time from injury to randomisation: NR Intervention 2: Standard air medical care (N=271) • Age median (IQR) : 46 (28-60) • Male n (%): 200 (73.8) • Blunt injury n (%): 226 (83.4) • Penetrating injury n (%): 49 (18.1) • Injury severity score median (IQR): 21 (12-29) • Isolated traumatic brain injury n (%): NR • Pre-injury anticoagulant/antiplatelet therapy n (%): 8 (3.0) anticoagulant, 18 (6.6) antiplatelet • Received tranexamic acid (%): NR • Baseline PT median (IQR): NR • Baseline INR median (IQR): NR • Pre-randomisation red blood cells (units) median (IQR): NR • Pre-randomisation FFP (units) median (IQR): NR • Time from injury to hospital (mins) median (IQR): NR • Transport time (mins) median (IQR): 40 (33-51) • Time from injury to randomisation: NR
Interventions	Intervention 1: Thawed plasma • Description and dose: 2 units of either group AB or group A with a low anti-B antibody titer (1:100) thawed plasma. This was followed by standard care resuscitation.

	• Timing: Prehospital before other resuscitative fluids • Route: IV or intraosseous (IO) Intervention 2: Standard air medical care • Description and dose: standard-care resuscitation, which included infusion of a crystalloid solution as the primary resuscitative fluid, during the flight. As part of their standard resuscitation practice, air transport teams at 13 of the 27 air medical bases that participated in the trial also carried 2 units of universal donor red cells on all their flights. • Timing: Prehospital • Route: IV or IO
Outcomes	**Primary outcome** • 30-day mortality **Secondary outcomes** • 24-hour mortality • In-hospital mortality • Volumes of blood components and resuscitation fluid administered within 24 hours after enrolment • Incidence of multi-organ failure, acute lung injury–acute respiratory distress syndrome, transfusion-related acute lung injury, and nosocomial infection • Indices of coagulopathy on the basis of measurements of prothrombin time and thromboelastography
Identification	**Registration:** NCT01818427 **Sponsorship source:** Funded by the U.S. Army Medical Research and Materiel Command **Conflict of interest:** Dr. Neal reports receiving grant support and consulting fees from Janssen Pharmaceuticals, advisory board fees from CSL Behring, grant support and equipment provision from Haemonetics, and grant support from Accriva Diagnostics and being named on a patent (9,072,760) on TLR4 inhibitors for the treatment of human inflammatory and infectious disorders. No other potential conflict of interest relevant to this article was reported. **Authors name:** Dr. J Sperry **Institution:** University of Pittsburgh **Email:** sperryjl@upmc.edu

	Address: University of Pittsburgh, Department of Surgery and Critical Care Medicine, 200 Lothrop St., Pittsburgh, PA, 15213
Notes	Group differences Demographics similar but plasma group received less crystalloid. Standard care group received more RBC pre hospital. These were adjusted for in primary analyses. Prehospital crystalloid was lower in plasma group median 500mls (0-1250) vs 900mls (0-1500) Prehospital RBC transfusion was lower in plasma group 26.1% vs 42.1% **Pre-treatment:** Demographics similar but plasma group received less crystalloid. Standard care group received more RBC pre hospital. These were adjusted for in primary analyses. Prehospital crystalloid was lower in plasma group median 500mls (0-1250) vs 900mls (0-1500). Prehospital RBC transfusion was lower in plasma group 26.1% vs 42.1% **Outcomes** median plasma transfusion over 24 hours in plasma group did not include plasma given as part of the intervention. All-cause mortality at 30 days - 10 imputed patients **Population** Only 26% received pre hospital RBC in plasma group. 42% in standard care group.

Risk of bias table, Sperry 2018[118]

Bias	Judgement	Support for judgement
Random sequence generation (selection bias)	Low	Computer-generated block randomization, air medical bases at each participating institution were assigned to the plasma group or the standard-care group for 1-month time intervals. Because of the cluster design of the trial, the treatment group to which eligible patients were assigned was based on the random assignment of the transporting base, irrespective of whether a patient received plasma or standard care resuscitation at an outside hospital. The block scheme varied randomly among 2-month, 4-month, and 6-month block sizes during the period of enrolment.
Allocation concealment (selection bias)	Unclear	Insufficient information
Blinding of participants and personnel (performance bias) Transfusion requirements	High	open label
Blinding of participants and personnel (performance bias) Outcomes except transfusion requirements	High	open label
Blinding of outcome assessment (detection bias) Outcomes except cause of death	Low	outcome assessors were blinded to treatment allocation
Blinding of outcome assessment (detection bias) Death due to haemorrhage	Low	outcome assessors were blinded to treatment allocation
Incomplete outcome data (attrition bias)	Low	Primary outcome data available for 95.7% participants. Intention to treat analysis. Multiple imputation used for missing data
Selective reporting (reporting bias)	Low	Trial was prospectively registered. All pre-specified outcomes were reported.
Other bias	Low	Statistical significance for the primary analysis (P<0.038) was adjusted for two interim analyses by the external data safety monitoring board

Appendix 2.2 Trial-defined intervention vs standard of care (in-hospital)

Curry 2015[99]

Methods	**Study design:** 2-centre, 2-arm, parallel-group RCT **Setting:** 2 civilian major trauma centres **Country:** UK **Dates study conducted:** July 2012 to October 2013 **Length of follow up:** 28 days **Aim of study:** To evaluate whether it was possible to deliver cryoprecipitate early (i.e. within 90 min of admission), to trauma patients with major haemorrhage. **Definition of major haemorrhage:** Actively bleeding and required activation of the MHP. **Definition of coagulopathy:** NR
Participants	**Inclusion criteria:** adult trauma patients (age ≥16 yrs), who were actively bleeding and required activation of the major haemorrhage protocol (MHP). MHP was activated when a patient had both on-going bleeding and signs of clinical shock. **Exclusion criteria:** arrived >3 h after injury; were transferred from another hospital; or if the trauma team leader deemed the patient unsuitable (i.e. injuries incompatible with life). **Number randomised:** 44 **Number analysed:** 41 **Number lost to FU/drop out:** 5 lost to follow-up but included in ITT analysis.1 no major haemorrhage therefore not treated despite randomised.1 withdrew consent for follow-up. 1 patient excluded because unclear if cryoprecipitate given within 90 minutes.

	Baseline Characteristics Intervention 1: Early cryoprecipitate (N=20) • Age median (IQR): 31 (25-57) (unpublished data provided by authors) • Male n (%): 17 (85) • Blunt injury n (%): 18 (90) • Injury severity score median (IQR): 28 (22–42) • Isolated TBI: NR • Pre-injury anticoagulant/antiplatelet therapy: NR • Received tranexamic acid (%): 20 (100) • Baseline INR: NR • Baseline PT median (IQR): 12.6 (11.1–13.4) • Pre-randomisation red blood cells (units) median (IQR): 3 (2–4) • Pre-randomisation FFP (units) median (IQR): 0 (0-0) • Time from injury to hospital (mins) median (IQR): 95 (76–119) • Transport time (mins) median (IQR): NR • Time from injury to randomisation: NR Intervention 2: Standard MHP (N=21) • Age median (IQR) : 50 (29-59) (unpublished data provided by authors) • Male n (%): 15 (71.4) • Blunt injury n (%): 15 (71) • Injury severity score median (IQR): 41 (29–45) • Isolated TBI: NR • Pre-injury anticoagulant/antiplatelet therapy: NR • Received tranexamic acid (%): 19 (95) • Baseline INR: NR • Baseline PT median (IQR): 13.2 (11.8–15.8) • Pre-randomisation red blood cells (units) median (IQR): 2 (1–3) • Pre-randomisation FFP (units) median (IQR): 0 (0-0) • Time from injury to hospital (mins) median (IQR): 96 (75–106) • Transport time (mins) median (IQR): NR • Time from injury to randomisation: NR
Interventions	Intervention 1: Early cryoprecipitate • Description and dose: 2 pools of early cryoprecipitate and standard major haemorrhage therapy. • Timing: Started within 90 min of admission • Route: IV

	Intervention 2: Standard MHP • Description and dose: Standard major haemorrhage therapy. MHP based on delivery of an empiric 'MHP pack (6 units RBC) and 4 units fresh frozen plasma (FFP)). Tranexamic acid (TXA) (1 g i.v. bolus, 1 g 8-h infusion) was part of the MHP protocol. If haemorrhage continued after completion of MHP pack 1, MHP pack 2 was transfused (6 units RBC, 4 units FFP, 2 pools cryoprecipitate and 1 adult pool of platelets (4 pooled buffy coat platelets or 1 single apheresis unit)). During active bleeding the targets for MHP therapy (using standard laboratory tests) were: PTr≤1.5; Clauss Fg≥1.5 g litre−1; platelet count>100×10−9 litre; haemoglobin 8–10 g dl−1 • Timing: Started within 90 min of admission, for duration of active bleeding. • Route: IV
Outcomes	**Primary outcomes** Feasibility: • Proportion of patients in the intervention arm who receive cryoprecipitate within 90 minutes of admission • Recruitment rate (the proportion of eligible patients enrolled) **Secondary outcomes** Clinical endpoints: • All-cause mortality up to day 28 from randomisation • Bleeding outcomes, as assessed by numbers of all blood components transfused (RBC, FFP, platelets, cryoprecipitate) at 6 hr, 24 hr and 28 days from randomisation • Thrombotic events; venous thromboembolism (pulmonary embolus, deep vein thrombosis), arterial events (myocardial infarction, stroke) to 3 months from randomisation • Organ failure as defined by single or multi-organ failure, to day 28 from randomisation • Length of hospital stay (including ITU or HDU stay) • Non-acute and acute transfusion reactions deemed to be related to cryoprecipitate up to day 28 from randomisation

	Laboratory endpoints: • Longitudinal changes in Clauss fibrinogen, and ROTEM FIBTEM/EXTEM measurements (CA and MCF) at three pre-specified transfusion time points (after 4, 8 and 12 units of red cells), at 24 hours and 72 hours from randomisation • Longitudinal changes in Clauss fibrinogen at days 7, 14, 21 and 28 from randomisation
Identification	**Registration:** www.controlled-trials.com ISRCTN55509212 **Sponsorship source:** This study was supported by the NHS Blood and Transplant Trust Fund, UK (TF020) CRYOSTAT team acknowledges the support of the National Institute for Health Research Clinical Research Network. **Conflict of interest:** None declared. **Authors name:** Nicola Curry **Institution:** Oxford University Hospitals NHS Foundation Trust **Email:** nicola.curry@ouh.nhs.uk **Address:** Department of Haematology, Oxford University Hospitals NHS Trust, John Radcliffe Hospital, Oxford, UK
Notes	**Pre-treatment:** In the STANDARD arm, subjects were older, more severely injured and had a greater number of head injuries (lower GCS). Additional data regarding 24-hour mortality and death from bleeding within 24 hours obtained on request from author.

Risk of bias table, Curry 2015[99]

Bias	Judgement	Support for judgement
Random sequence generation (selection bias)	Low	Quote: "Subjects were block-randomised by centre. The randomisation lists were prepared centrally using a computerised random number generator."
Allocation concealment (selection bias)	Low	Quote: "Allocation was concealed using a sealed opaque envelope system and occurred within one h of hospital arrival."
Blinding of participants and personnel (performance bias) Transfusion requirements	High	Open label study. Transfusion requirements in either group could be influenced by lack of blinding.
Blinding of participants and personnel (performance bias) Outcomes except transfusion requirements	Low	Open label study. For participants, low risk of bias as no patient reported outcomes and patient knowledge of their intervention arm is unlikely to have an effect on outcomes. For personnel, knowledge of intervention unlikely to significantly affect management (except transfusion).
Blinding of outcome assessment (detection bias) Outcomes except cause of death	Low	No blinding of outcome assessment. The outcome measurements are unlikely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Death due to haemorrhage	High	No blinding of outcome assessment. Assigning cause of death due to bleeding could be influenced by lack of blinding. (This outcome was requested from the study authors and not one of the pre-specified outcome measures).
Incomplete outcome data (attrition bias)	Low	Participants followed up and included in intention to treat analysis.
Selective reporting (reporting bias)	Low	Retrospectively registered after trial underway for two months. All pre-specified outcomes reported.
Other bias	Low	No other clear sources of bias

Nascimento 2013[119]

Methods	**Study design:** Single-centre, 2-arm, parallel-group RCT **Setting:** Level 1 urban Trauma centre in Toronto **Country:** Canada **Dates study conducted:** July 2009 to October 2011 **Length of follow up:** 28 days **Aim of study:** To assess the feasibility and safety of the fixed- ratio protocol in patients with severe trauma. **Definition of major haemorrhage:** Either anticipated need for 4 units of RBC within the next 2hours ≥10 units of RBC in 24h, or required un-crossmatched RBC. **Definition of coagulopathy:** Abnormal tests of coagulation
Participants	**Inclusion criteria:** 16–90 years old; had bleeding and were expected to require massive transfusion (either anticipated need for 4 units of RBC within the next 2 h or >= 10 units of RBC in 24 h, or required un-crossmatched RBC); and had an episode of systolic blood pressure 90 mm Hg. **Exclusion criteria:** arrived more than 6 hours after injury; received more than 2 units of RBC before arrival; had a severe brain injury (defined as any of a score of 3 on the Glasgow Coma Scale owing to brain injury; need of immediate neurosurgery; focal signs such as anisocoria; or computed tomography [CT] evidence of intracranial bleeding with mass effect); had a catastrophic brain injury (defined as transcranial gunshot wound, open skull fracture with exposure or loss of brain tissue, or expert medical opinion based on initial clinical or CT findings); had shock unrelated to haemorrhage (i.e. cardiogenic, septic, neurogenic or obstructive [cardiac tamponade, tension pneumothorax or massive pulmonary emboli]); had an underlying hereditary or acquired coagulopathy; or were moribund and unlikely to survive more than a few hours. **Number randomised:** 78 **Number analysed:** 75 in ITT for mortality **Number lost to FU/drop out:** 3 not analysed in control arm **Baseline Characteristics** Intervention 1: Formula-Driven Arm (fixed ratio) 1:1:1 strategy (N=37) • Age median (IQR): 41 (23–58) • Male n (%): 24 (65) • Penetrating injury n (%): 13 (35)

	• Isolated traumatic brain injury n (%): NR • Pre-injury anticoagulant/antiplatelet therapy: antiplatelet use NR (patients taking anticoagulation were excluded) • Injury severity score mean (SD): 35 (13) • Received tranexamic acid (%): 5 (13.5) • Baseline INR median (IQR): 1.2 (1.1–1.5) • Baseline PT: NR • Pre-randomisation red blood cells (units) median (IQR): NR • Pre-randomisation FFP (units) median (IQR): 0 (0-0) • Time from injury to hospital (mins) median (IQR): 46 (30–59) • Transport time (mins) median (IQR): NR • Time from injury to randomisation: NR Intervention 2: Standard MHP (N=32) • Age median (IQR): 34 (25–40) • Male n (%): 23 (72) • Penetrating injury n (%): 12 (38) • Isolated traumatic brain injury n (%): NR • Injury severity score mean (SD): 35 (13) • Isolated traumatic brain injury n (%): NR • Pre-injury anticoagulant/antiplatelet therapy: antiplatelet use NR (patients taking anticoagulation were excluded) • Received tranexamic acid (%): 6 (18.7) • Baseline INR median (IQR): 1.4 (1.2–1.7) • Baseline PT: NR • Pre-randomisation red blood cells (units) median (IQR): NR • Pre-randomisation FFP (units) median (IQR): 0 (0-0) • Time from injury to hospital (mins) median (IQR): 45 (30–67) • Transport time (mins) median (IQR): NR • Time from injury to randomisation: NR
Interventions	**Intervention Characteristics** Intervention 1: Formula-Driven Arm (fixed ratio) 1:1:1 strategy • Description and dose: Patients randomized to this arm were transfused RBCs, FFP, and platelets at a 1:1:1 ratio. This formula-driven protocol was used for up to 12 hours but was terminated earlier if the attending surgeon felt that haemostasis was achieved. Once randomized to the formula-driven arm, the blood bank released blood products in predefined ratios. However, we did not have thawed plasma available for this study. Therefore, 1:1:1 could only begin with the availability of FFP and platelets. As such, RBCs were transfused as clinically indicated until the arrival of the blood products in the 1:1:1 ratio. Blood products arrived in a transport box containing 4 units of FFP, 1 pool of Buffy coat platelets (4 units of platelets), and 4 units of RBCs. FFP was thawed in the standard warm water bath fashion. • Timing: Up to 12 hours from enrolment

	• Route: IV Intervention 2: Standard MHP • Description and dose: Institution's massive transfusion protocol. In this protocol, red cell transfusions were administered to maintain euvolemia and to maintain haemoglobin levels above 70 g/L. FFP was transfused in 3 units to 4 units aliquots for international normalized ratio (INR) >1.8. Platelets were transfused one pool at a time (4 units Buffy coat platelets or one single donor apheresis) to maintain the platelet count above 50 x 10^9/L. Cryoprecipitate was transfused 10 units at a time to keep fibrinogen above 1.0 g/L. Blood work, including complete blood count, INR, APTT, fibrinogen, and arterial blood gases were performed at least every 2 hours while the massive transfusion protocol was in effect. • Timing: Up to 12 hours from enrolment • Route: IV
Outcomes	**Primary outcome** • Feasibility, as measured by the proportion of patients in the fixed-ratio group who received appropriate blood products in the predefined (1:1:1) ratio. **Secondary outcomes** • 28-day mortality (all-cause mortality and rate of death by exsanguination • Incidence of any degree of acute respiratory distress syndrome (based on the Berlin consensus definition for acute respiratory distress syndrome), measured as days free of acute respiratory distress syndrome • Transfusion-related complications
Identification	**Registration:** NCT00945542 **Sponsorship source:** Grants from the Canadian Forces Health Services; Defense Research and Development Canada; and the National Blood Foundation, American Association of Blood Banks. **Conflict of interest:** : Bartolomeu Nascimento received the 2010 National Blood Foundation Grant of the American Association of Blood Banks for the conduct of research related to coagulopathy in trauma. Yulia Lin is a site investigator for a registry on the off-label use of recombinant factor VIIa that is funded by an unrestricted educational grant from NovoNordisk. Sandro Rizoli received a Canadian Institutes of Health Research investigator award in partnership with NovoNordisk, the manufacturer of recombinant factor VIIa;

	he was also a consultant for NovoNordisk in the past and is a member of the advisory board for CSL Behring, manufacturer of fbrinogen concentrate. No competing interests declared by the other authors. **Authors name:** Bartolomeu Nascimento **Institution:** Departments of Surgery, Critical Care, and Clinical Pathology, Tory Regional Trauma Centre, Sunnybrook Health Sciences Centre, **Email:** rizolis@smh.ca **Address:** Departments of Surgery, Critical Care, and Clinical Pathology, Tory Regional Trauma Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada; and Canadian Forces Health Services.
Notes	INR post-treatment reported as median (IQR): intervention: 1.19 (1.1-1.3), control 1.34 (1.2-1.5) INR post treatment in fixed group median and IQR 1.19 (1.1-1.3), control 1.34 (1.2-1.5) mortality from exsanguination assessed at 12 hours after admission Thawed plasma not available in this study

Risk of bias table, Nascimento 2013[119]

Bias	Judgement	Support for judgement
Random sequence generation (selection bias)	Low	A computerised random-number generator was used to generate sequences of random numbers. The randomization was stratified by type of trauma (blunt versus penetrating), and with an allocation sequence derived from blocks of four for the control and fixed-ratio groups.
Allocation concealment (selection bias)	Low	Allocation was concealed within sealed opaque envelopes in the blood bank. Allocation sequence was derived from blocks of 4 for the control and intervention groups, and randomization was stratified by type of trauma (blunt or penetrating) to assure balanced groups.
Blinding of participants and personnel (performance bias) Transfusion requirements	High	Open label study. Transfusion requirements in either group could be influenced by lack of blinding.
Blinding of participants and personnel (performance bias) Outcomes except transfusion requirements	Low	Open label study. For participants, low risk of bias as no patient reported outcomes and patient knowledge of their intervention arm is unlikely to have an effect on outcomes. For personnel, knowledge of intervention unlikely to significantly affect management (except transfusion).
Blinding of outcome assessment (detection bias) Outcomes except cause of death	Low	Open label study. The outcome measurements are unlikely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Death due to haemorrhage	Low	Cause of death was adjudicated by an independent physician and one of the principal investigators, blinded to the treatment allocation.
Incomplete outcome data (attrition bias)	Low	High levels of data completeness.
Selective reporting (reporting bias)	Low	Prospectively registered and all pre-specified outcomes reported.
Other bias	Low	No other clear sources of bias

Nathens 2006[123]

Methods	**Study design:** Single-centre, 2-arm, parallel-group RCT **Setting:** Level 1 Trauma centre in Seattle **Country:** USA **Dates study conducted:** February 2003 and August 2004 **Length of follow up:** 28 days **Aim of study:** To evaluate the effects of leukoreduced blood transfusions as compared with standard transfusions on rates of infections in trauma patients transfused within 24 hours of injury. **Definition of major haemorrhage:** Not given. Eligible patients received crossmatched or uncrossmatched red blood cells for expected transfusion **Definition of coagulopathy:** not defined
Participants	**Inclusion criteria:** All injured patients were considered eligible for randomization if their physician requested either crossmatched or uncrossmatched red blood cells for expected transfusion. Inclusion criteria were age of above 17 years and red cell transfusion within 24 hours of injury. **Exclusion criteria:** An anticipated survival of less than 48 hours (gunshot wounds to the head, cardiopulmonary resuscitation in the field or in the emergency department), active infection at presentation, or receipt of blood products for the current injury before randomization. Also blood group AB Rh negative or group B Rh negative and patients with clinically significant red cell alloantibodies requiring an antiglobulin crossmatch were ineligible. Recipients with prior requirements for irradiation, leukoreduction, or cytomegalovirus (CMV) protection, according to blood bank computer records, were ineligible, as were subjects enrolled in a concurrent study of prehospital hypertonic saline resuscitation. Incarcerated subjects were not eligible for randomization. **Number randomised:** 1864 **Number analysed:** 268 **Number lost to FU/drop out:** 0

	Baseline Characteristics Intervention 1: Standard red cells (N=136) • Age mean (SD) 42.1 (18) • Male n (%): 93 (69) • Penetrating injury n (%): 24 (18) • Injury severity score mean (SD) 25.5 (11) • Isolated traumatic brain injury n (%): NR • Pre-injury anticoagulant/antiplatelet therapy: NR • Baseline INR: NR • Baseline PT: NR • Pre-randomisation red blood cells (units) median (IQR): NR • Pre-randomisation FFP (units) median (IQR): NR Intervention 2: Leukoreduced red cells (N=132) • Age mean (SD) 42.3 (19) • Male n (%): 87 (66) • Penetrating injury n (%): 25 (19) • Injury severity score mean (SD) 23.9 (11) • Isolated traumatic brain injury n (%): NR • Pre-injury anticoagulant/antiplatelet therapy: NR • Baseline INR: NR • Baseline PT: NR • Pre-randomisation red blood cells (units) median (IQR): NR • Pre-randomisation FFP (units) median (IQR): NR
Interventions	**Intervention Characteristics** Intervention 1: Standard red cells. • Description and dose: Other blood components given as directed. • Timing: In first 24 hours up to 28 days • Route: IV Intervention 2: Leukoreduced red cells. • Description and dose: Red cells were leukoreduced within 24 hours of collection using the Leukotrap SCRC Leukocyte Reduction Filtration System with a high efficiency Pall BPF4 filter (Pall, East Hills, NY). Other blood components given as directed. • Timing: In first 24 hours up to 28 days • Route: IV

Outcomes	**Primary outcome** • Infection within 28 days of randomization **Secondary outcomes** • Ventilator days • Length of hospital stay • Length of intensive care unit stay • Mortality (hospital and 28-day) • Degree of multiple organ dysfunction
Identification	**Registration:** www.clinicaltrials.gov NCT00135291 **Sponsorship source:** National Institutes of Health (NIH NIGMS R01 GM66117-01 and NIH NHLBI 1 P50 HL073996-01). **Conflict of interest:** no statement reported in paper **Authors name:** Avery Nathens **Institution:** Harborview Medical Center, University of Washington **Email:** anathens@u.washington.edu **Address:** 325 9th Avenue, Box 359796, Seattle, WA
Notes	Group 1 (standard), group 2 (leukoreduced) Mean age (SD) 42.1 (18) 42.3 (19)Male sex 93 (69) 87 (66)Penetrating 24 (18) 25 (19)ISS (SD) 25.5 (11) 23.9 (11) Non-trauma patients were also included in this study. **Funding:** National Institutes of Health (NIH NIGMS R01 GM66117-01 and NIH NHLBI 1 P50 HL073996-01)

Risk of bias table, Nathens 2006[123]

Bias	Judgement	Support for judgement
Random sequence generation (selection bias)	Low	Quote: "The hospital-based transfusion support service performed the randomization in a 1:1 ratio, using a permuted block scheme (block size of six), with stratification based on age (<55 or >55 years) and mechanism of injury (blunt or penetrating)."
Allocation concealment (selection bias)	Low	Quote: "pre-printed sealed opaque envelopes containing the study identification number and randomization arm (listed as arm 1 or arm 2) to conceal allocation, transfusion support personnel provided the appropriate (leukoreduced or standard) uncrossmatched red cells or requested the leukoreduced or standard crossmatched red cells from the centralized transfusion service."
Blinding of participants and personnel (performance bias) Transfusion requirements	Unclear	Outcome NR.
Blinding of participants and personnel (performance bias) Outcomes except transfusion requirements	Low	Open label study. For participants, low risk of bias as no patient reported outcomes and patient knowledge of their intervention arm is unlikely to have an effect on outcomes. For personnel, knowledge of intervention unlikely to significantly affect management (except transfusion).
Blinding of outcome assessment (detection bias) Outcomes except cause of death	Low	A nurse abstractor blinded to the study arm was responsible for the daily assessment of infectious complications and the degree of organ dysfunction.
Blinding of outcome assessment (detection bias) Death due to haemorrhage	Unclear	Outcome NR.
Incomplete outcome data (attrition bias)	Low	Intention to treat analysis. Reasons for exclusion after randomisation described.
Selective reporting (reporting bias)	Low	Study was prospectively registered and all pre-specified clinical outcomes were reported. Pre-specified laboratory outcomes NR but this is unlikely to lead to bias.
Other bias	Low	No other clear sources of bias

Appendix 2.3 Trial-defined intervention vs trial-defined intervention (in-hospital)

Cotton 2013[121]

Methods	**Study design:** Single-centre, 2-arm, parallel-group RCT **Setting:** Texas Trauma Institute at Memorial Hermann Hospital, Level 1 trauma centre **Country:** USA **Dates study conducted:** May 2011 to December 2012 **Length of follow up:** 30 days **Aim of study:** To assess the use of whole blood (WB) for early resuscitation of civilian patients with trauma. **Definition of major haemorrhage:** Evidence of haemorrhagic shock and predicted to receive a large volume transfusion **Definition of coagulopathy:** Not reported
Participants	**Inclusion criteria:** patient appeared to be 18 years of age or older, met highest-level trauma activation criteria, and had evidence of active bleeding requiring emergent un-crossmatched blood while in the emergency department. **Exclusion criteria:** If patient received more than 4 units of RBC pre-randomisation, were moribund (cardiopulmonary resuscitation or ED thoracotomy pre-randomisation), had noted religious objection to transfusion, had do not resuscitate order documented, were "obviously pregnant," were incarcerated/prisoners, or had an "opt-out" bracelet. Three other critical exclusions were added to the study protocol after initial protocol development and approval on the basis of a pragmatic design. First, in those clinical situations in which the physician stated that the patient could not wait the additional time for blood typing (an additional 5–10 minutes to the first cooler's arrival), the patient was excluded and standard of care massive transfusion protocol delivered. Second, blood groups (B and AB) were excluded from the study after typing and standard of care massive transfusion coolers were released. Third, patients with severe TBI. **Number randomised:** 107

	Number analysed: 107 **Number lost to FU/drop out:** 0 **Baseline Characteristics** Intervention 1: Modified WB (N=55) • Age median (IQR) : 40 (29-56) • Male n (%): 43 (78) • Blunt injury n (%): 38 (69) • Injury severity score median (IQR): 22 (13-34) • Isolated TBI: NR • Pre-injury anticoagulant/antiplatelet therapy: NR • Baseline INR median (IQR): 1.3 (1.1-1.4) • Baseline PT: NR • Pre-randomisation red blood cells (units) median (IQR): 3 (no IQR) + unclear if RBC only or also FFP • Received tranexamic acid: NR Intervention 2: Component therapy 6 units red cells, 6 units FFP, 1 dose of apheresis platelets (N=52) • Age median (IQR): 38 (25-56) • Male n (%): 43 (83) • Blunt injury n (%): 35 (67) • Injury severity score median (IQR): 22 (14-32) • Isolated TBI: NR • Pre-injury anticoagulant/antiplatelet therapy: NR • Baseline INR median (IQR): 1.1 (1.1-1.3) • Baseline PT: NR • Pre-randomisation red blood cells (units) median (IQR): 3 (no IQR) + unclear if RBC only or also FFP • Received tranexamic acid: NR
Interventions	**Intervention Characteristics** Intervention 1: Modified whole blood (WB) • Description and dose: Modified WB. A study cooler contained 6 units of WB. Whole blood was leukoreduced. WB units were kept at 1 to 6°C for up to 5 days. As platelets were rendered non-functional, every 6 units of WB (as with every 6 units of RBC and plasma) were supplemented with 1 dose of apheresis platelets • Timing: From admission until haemostasis achieved or death,

	up to 24 hours post enrolment • Route: IV Intervention 2: Component therapy 6 units red cells, 6 units FFP, 1 dose of apheresis platelets • Description and dose: 6 units red cells, 6 units FFP, 1 dose of apheresis platelets • Timing: From admission until haemostasis achieved or death up to 24 hours post enrolment • Route: IV
Outcomes	**Primary outcome** • 24-hour blood product use. (Total RBC, plasma, and platelets transfused in the first 24 hours). **Secondary outcomes** • 24-hour and 30-day mortality • Length of stay • Transfusion associated complications, and infections.
Identification	**Registration:** ClinicalTrials.gov NCT01227005 **Sponsorship source:** Supported by a grant from the Department of Defense via W81XWH-08-C-0712 **Conflict of interest:** Dr Rizoli reported receiving grant funding from TEM International and CSL Behring. Dr Stein reported serving as an advisor for Decisio Health for which she receives travel reimbursement. No other disclosures were reported. **Authors name:** Bryan A. Cotton **Institution:** University of Texas Health Science Center **Email:** bryan.a.cotton@uth.tmc.edu **Address:** Center for Translational Injury Research, 6410 Fannin, 1100UPB, Houston, TX77030
Notes	**Comments:** No cryoprecipitate in either arm. death due to exsanguination - overall % not in first 24 hours

	median plasma and RBC pre randomisation 3 in each group **Pre-treatment:** GCS on arrival lower in whole blood group: median 5 (IQR 3, 15) vs 14 (3, 15), although the authors report this was not a statistically significant difference. Modified WB group had higher head AIS score.

Risk of bias table, Cotton 2013[121]

Bias	Judgement	Support for judgement
Random sequence generation (selection bias)	Unclear	No detail on sequence generation procedure. Insufficient detail for judgement
Allocation concealment (selection bias)	Low	Quote: "Blood bank personnel randomized the patient by opening a sealed envelope with the assigned study group (WB or component). The products were released to the ED tech who returned the products to the patient's bedside (intention-to-treat group). The products remained sealed (and all personnel outside the blood bank blinded) until trauma faculty ordered subsequent transfusion."
Blinding of participants and personnel (performance bias) Transfusion requirements	High	Open label study. Transfusion requirements in either group could be influenced by lack of blinding.
Blinding of participants and personnel (performance bias) Outcomes except transfusion requirements	Low	Open label study. For participants, low risk of bias as no patient reported outcomes and patient knowledge of their intervention arm is unlikely to have an effect on outcomes. For personnel, knowledge of intervention unlikely to significantly affect management (except transfusion).
Blinding of outcome assessment (detection bias) Outcomes except cause of death	Low	No blinding of outcome assessment. The outcome measurements are unlikely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Death due to haemorrhage	High	No blinding of outcome assessment. Assigning cause of death due to bleeding could be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low	All patients followed up with intention to treat analysis.
Selective reporting	Low	Prospectively registered and all prespecified

(reporting bias)		outcomes reported.
Other bias	High	Potential bias in study conduct. Amendment to study exclusion criteria after trial started. e.g. Patients with TBI was added as an exclusion criterion. Quote: "There was no objective scoring system in this study to randomize patients and, therefore, did not always include patients who would have received an MT. 4 years elapsed from design of protocol to first randomisation. In this time, the MT protocol changed and massive transfusion cooler delivery was reduced to less than 10 minutes, and blood and plasma were immediately available in the ED. Therefore, when faced with an additional delay for WB randomization (an additional 5–10 minutes for blood typing), trauma faculty often excluded the sickest patients from the study, opting for delivery of the first MT cooler in a more timely fashion (within 10 minutes vs 15–20 minutes)." A high proportion of patients were not treated per protocol: WB arm 16/55 (29%); component therapy arm 10/52 (19%).

Garrigue 2018[120]

Methods	**Study design:** Single-centre, 2-arm, parallel-group RCT **Setting:** Civilian major trauma centre **Country:** France **Dates study conducted:** July 2013- March 2016 **Length of follow up:** 30 days **Aim of study:** To evaluate whether French lyophilised plasma (FLyP) more effective than FFP for the initial management of trauma-induced coaguolathy **Definition of major haemorrhage:** Not defined **Definition of coagulopathy:** Not defined
Participants	**Inclusion criteria:** Severely injured adult trauma patients admitted directly to the trauma centre from the injury scene were eligible for the trial if the attending doctor decided on an immediate transfusion of an 'emergency pack' of 4 RBC associated with 4 plasma units in a 1:1 ratio within 6 h of injury. **Exclusion criteria:** Transfusion of any blood product or coagulation factor concentrate prior to randomization, admission from another healthcare facility, devastating injuries and expected imminent death, recent history of anticoagulant therapy, known pregnancy, age under 18 years, or lack of mental capacity per national legal standards prior to trauma. **Number randomised:** 48 **Number analysed:** 47 (23 FLyP, 24 FFP ITT. 21 FLyP, 21 FFP per protocol analysis) **Number lost to FU/drop out:** 1 for primary endpoint, 6 for secondary endpoints

	Baseline Characteristics Intervention 1: Lyophilised plasma (FLyP) (N=23) • Age mean (SD) : 48 (16.5) • Male n (%): 19 (82.6) • Blunt injury n (%): 48 (16.5) • Injury severity score mean (SD): 23.5 (9.7) • Isolated TBI: NR • Pre-injury anticoagulant/antiplatelet therapy: antiplatelet therapy NR (anticoagulant use in exclusion criteria) • Received tranexamic acid (%): 19 (82.6) • Baseline INR: NR • Baseline PT mean (SD): 1.54 (0.6) • Pre-randomisation red blood cells (units) median (IQR): 0 (0-0) • Pre-randomisation FFP (units) median (IQR): 0 (0-0) • Time from injury to hospital (mins) median (IQR): NR • Transport time (mins) median (IQR): NR • Time from injury to randomisation: 122 (88-205) Intervention 2: FFP (N=24) • Age mean (SD) : 38 (15.6) • Male n (%): 16 (66.7) • Blunt injury n (%): 22 (91.7) • Injury severity score median (IQR): 27.5 (11.4) • Isolated TBI: NR • Pre-injury anticoagulant/antiplatelet therapy: antiplatelet therapy NR (anticoagulant use exclusion criteria) • Received tranexamic acid (%): 22 (91.7) • Baseline INR: NR • Baseline PT mean (SD): 1.53 (0.3) • Pre-randomisation red blood cells (units) median (IQR): 0 (0-0) • Pre-randomisation FFP (units) median (IQR): 0 (0-0) • Time from injury to hospital (mins) median (IQR): NR • Transport time (mins) median (IQR): NR • Time from injury to randomisation: 117 (80-147)
Interventions	Intervention 1: FLyP Description and dose: 4 units lyophilised plasma (in addition to 4 RBC), immediately reconstituted in trauma centre by patient bedside

	Timing: within 6 hours of injury Route: IV Intervention 2: FFP Description and dose: 4 units FFP (in addition to 4 RBC) issued by blood bank after thawing Timing: within 6 hours of injury Route: IV
Outcomes	**Primary outcomes** • Fibrinogen concentration at 45 minutes after randomisation. **Secondary outcomes** Clinical endpoints: • Time to transfusion, including interval between randomization and transfusion of the first plasma unit and interval between randomisation to end of transfusion of the fourth plasma unit • Fibrinogen concentrate and blood product requirements over the first 24 h after randomization • All-cause hospital death within 30 days of injury. Laboratory endpoints: • Rate of patients with a fibrinogen concentration above the recommended 1.5 g /L threshold at 45 min, (ii) changes from randomization in haemostatic parameters measured at different time-points(45 min, 6, 12 and 24 h after randomization), including fibrinogen concentration, PT, APTT, factors II and V, fibrin monomer, base excess, lactate.
Identification	**Registration:** ClinicalTrials.gov NCT02750150 **Sponsorship source:** Funded by The French Society of Anaesthesia and Intensive Care Medicine (Societe Francaised'Anesthesie Reanimation), The French Military Blood Institute (Centre de Transfusion Sanguine des Armees), and The French Blood Institute (Etablissement Francais du Sang), Universite de Lille Nord de France. **Conflict of interest:** E. Kipnis reports non-financial support from Laboratoire Francais du Biomedicament (LFB), outside the submitted work. S. Susen reports research grants from Laboratoire Franc¸ais du Biome´dicament (LFB) and from Stago, outside the submitted work.

	The other authors state that they have no conflict of interest. **Authors name:** D Garrigue **Institution:** CHU de Lille **Email:** sophiesusen@aol.com **Address:** Centre de Biologie Pathologie, CHU de Lille, 59037, Lille Cedex, France
Notes	**Pre-treatment:** Patients were older in the lyophilised plasma group. More severely injured patients in the FFP group. (More patients received TXA in the FFP group -unclear at what time-point TXA was given).

Risk of bias table, Garrigue 2018[120]

Bias	Judgement	Support for judgement
Random sequence generation (selection bias)	Low	Participants were randomly assigned in a 1: 1 ratio to receive either FLyP or FFP. The allocation sequence was provided by a statistician, who did not take part in assessing the patients at any point of the study. The sequence was based on a computer-generated list of random numbers that was used to assign the patients to either the FLyP or FFP group, in blocks of four participants (2:2 per block).
Allocation concealment (selection bias)	Low	Allocation was concealed using a sealed opaque envelope and occurred as soon as inclusion was determined. The patient was declared randomized when the envelope seal was broken.
Blinding of participants and personnel (performance bias) Transfusion requirements	High	Open label trial
Blinding of participants and personnel (performance bias) Outcomes except transfusion requirements	High	Open label trial
Blinding of outcome assessment (detection bias) Outcomes except cause of	High	Open label trial. Laboratory outcome assessors blinded to treatment allocation

death		
Blinding of outcome assessment (detection bias) Death due to haemorrhage	High	Open label trial. Laboratory outcome assessors blinded to treatment allocation
Incomplete outcome data (attrition bias)	Low	High rates of follow-up for primary outcome and clear reasons for exclusion for secondary outcomes.
Selective reporting (reporting bias)	Low	Trial was prospectively registered and pre-specified outcomes were reported
Other bias	Low	No other clear source of bias

Holcomb 2015[71]

Methods	**Study design:** Multicentre, 2-arm, parallel-group RCT **Setting:** 12 Level 1 civilian trauma centres in North America **Country:** USA, Canada **Dates study conducted:** August 2012 to December 2013 **Length of follow up:** Follow up to hospital discharge or up to the 30th day of hospitalization (whichever came first) and had a 30-day follow-up mortality assessment **Aim of study:** To address the effectiveness and safety of a 1:1:1 transfusion ratio compared with a 1:1:2 transfusion ratio in patients with trauma who were predicted to receive a massive transfusion (MT) **Definition of major haemorrhage:** massive transfusion defined as receiving 10 units or more RBCs within the first 24 hours **Definition of coagulopathy:** not defined by a laboratory measure
Participants	**Inclusion criteria:** Highest trauma level activation; estimated age of 15 years or older or weight of 50 kg or greater if age unknown; received directly from the injury scene; initiated transfusion of at least 1U of blood component within the first hour of arrival or during prehospital transport; predicted to receive a massive transfusion by exceeding the threshold score of either the Assessment of Blood Consumption score of 2 or greater or based on the attending trauma physician's judgment.

	Exclusion criteria: At least 1 of the following: Received a lifesaving intervention from an outside hospital or healthcare facility; had devastating injuries and expected to die within 1 hour of admission; directly admitted from a correctional facility; required a thoracotomy prior to receiving randomized blood products in the emergency department; younger than 15 years or weighed less than 50 kg if age unknown; known pregnancy in the emergency department; burns covering greater than 20% total body surface area; suspected inhalation injury; received greater than 5 consecutive minutes of cardiopulmonary resuscitation prior to arriving at the hospital or within the emergency department; known do-not-resuscitate order prior to randomization; enrolled in a concurrent, ongoing, interventional, randomized clinical trial; activated the opt-out process for the PROPPR trial; more than 3 U of red blood cells given before randomization. **Number randomised:** 680 **Number analysed:** 680 **Number lost to FU/drop out:** 24 hours- 0 lost to FU 30-days 3 vs 1 **Baseline characteristics** Intervention 1: 1:1:1 plasma, platelets, RBC (N=348) • Age median (IQR) : 34.5 (25-51) • Male n (%): 263 (77.8) • Blunt injury n (%): 185 (54) • Penetrating injury n (%): 157 (46.4) • Injury severity score median (IQR): 26.5 (17-41) • Isolated TBI: NR • Pre-injury anticoagulant/antiplatelet therapy: NR • Received tranexamic acid (%): 64 (18.9) • Baseline PT median (IQR): missing • Baseline INR median (IQR): 1.3 (1.2-1.5) • Pre-randomisation red blood cells (units) median (IQR): 2 (missing) • Pre-randomisation FFP (units) median (IQR): NR Intervention 2: 1:1:2 plasma, platelets, RBC (N=342) • Age median (IQR) : 34 (24-50)

	• Male n (%): 283 (82.7) • Blunt injury n (%): 173 (50.6) • Penetrating injury n (%): 173 (50.6) • Isolated TBI: NR • Pre-injury anticoagulant/antiplatelet therapy: NR • Injury severity score median (IQR): 26 (17-38) • Received tranexamic acid (%): 68 (19.9) • Baseline PT median (IQR): missing • Baseline INR median (IQR): 1.3 (1.2-1.5) • Pre-randomisation red blood cells (units) median (IQR): 2 (missing) • Pre-randomisation FFP (units) median (IQR): NR
Interventions	**Intervention characteristics** Intervention 1 arm: 1:1:1 plasma, platelets, RBC • Description and dose: 6U of plasma, 1 dose of platelets (a pool of 6U on average), and 6U of RBCs, transfused in the following order: platelets first, then alternating RBC and plasma units. • Timing: From hospital admission until bleeding stopped. Administered 10 minutes from blood bank • Route: IV Intervention 2 arm: 1:1:2 plasma, platelets, RBC • Description and dose: The initial and all subsequent odd-numbered containers for the 1:1:2 group included 3 U of plasma, 0 doses of platelets, and 6U of RBCs, which were transfused in the following order: alternating 2 U of RBCs and1 U of plasma. The second and all subsequent even-numbered containers included 3U of plasma,1dose of platelets (a pool of 6U on average), and 6U of RBCs, which were transfused in the following order: platelets first, then alternating 2 U of RBCs and 1 unit of plasma • Timing: From hospital admission until bleeding stopped. Administered 10 minutes from blood bank • Route: IV
Outcomes	**Primary outcome** • 24-hour and 30-day mortality

	Secondary outcomes • Time to haemostasis • The number and type of blood products used from randomization until haemostasis was achieved • The number and type of blood products used after haemostasis was achieved up to 24 hours post admission • 23 complications • Hospital-,ventilator-,and ICU-free days (within the first 30 days or hospital discharge, whichever occurred first) • Incidence of major surgical procedures • Functional status at hospital discharge or 30 days, whichever occurred first, as measured by discharge destination and Glasgow Outcome Scale-Extended.
Identification	**Registration:** clinicaltrials.gov NCT01545232 **Sponsorship source:** Supported by grant U01HL077863 from the US National Heart, Lung, and Blood Institute and funding from the US Department of Defense, the Defence Research and Development Canada in partnership with the Canadian Institutes of Health Research-Institute of Circulatory and Respiratory Health (grant CRR-120612) **Conflict of interest:** Dr Rizoli reported receiving grant funding from TEM International and CSL Behring. Dr Stein reported serving as an advisor for Decisio Health for which she receives travel reimbursement. No other disclosures were reported. **Authors name:** John Holcomb **Institution:** University of Texas Health Science Center **Email:** john.holcomb@uth.tmc.edu **Address:** Centre for Translational Injury Research, University of Texas Health Science Center, 6410 Fannin St, Houston, TX 77030, USA
Notes	24hr mortality HR 0.72 (95% CI, 0.49-1.07). 30d mortality HR 0.83 (95% CI, 0.61-1.12) Thrombotic events calculated by number of patients. Some patients may have had more than one event.

	Time to haemostasis reported as median (IQR). 1:1:1 group 105 (64 to 179); 1:1:2 group 100 (56 to 181) Transfusion over first 24 hours reported as median (IQR)Plasma 1:1:1 group 7 (3,13), 1:1:2 group 5 (2,10)Platelets 1:1:1 group (US units) 12 (6,18), 1:1:2 group 6 (0,12)Red cells 1:1:1 group 9 (5,15), 1:1:2 group 9 (6,16) Cryo 1:1:1 group 0 (0,0), 1:1:2 group 0 (0,9) INR at baseline reported as median (IQR)1:1:1 group 1.3 (1.2 to 1.5), 1:1:2 group 1.3 (1.2 to 1.5) ICU free days reported as median (IQR)1:1:1 group 5 (0 to 11) (n-337), 1:1:2 group 4 (0 to 10) (n=340) **Outcomes** Median and IQR time to haemostasis Venous events (PE +DVT)Arterial events (stroke + MI) ICU - reported ICU free days not ICU length of stay Transfusion units median + IQR For platelets - record number of units (will convert to NHSBT/UK standards later) For cryoprecipitate - record number of units (will convert to NHSBT/UK standards later) Individuals who died within the first 24 hours from admission were assigned zero ICU-, ventilator-, and hospital-free days Time to anatomic haemostasis, median (IQR), 105 (64 to 179) in group 1 vs 100 (56 to 181) in group 2 To clarify - Surgical/radiological procedures to stop bleeding = after haemostasis achieved. Not clear whether it is within 24 hours or not. Problems reconciling total number of units transfused in supplement and in main body of text

Risk of bias table, Holcomb 2015[71]

Bias	Judgement	Support for judgement
Random sequence generation (selection bias)	Low	A stratified, permuted blocked randomization scheme was used.
Allocation concealment (selection bias)	Low	Randomization of blood products was completed in the blood bank.
Blinding of participants and personnel (performance bias) Transfusion requirements	High	Open label study. Transfusion requirements in either group could be influenced by lack of blinding.
Blinding of participants and personnel (performance bias) Outcomes except transfusion requirements	Low	Open label study. For participants, low risk of bias as no patient reported outcomes and patient knowledge of their intervention arm is unlikely to have an effect on outcomes. For personnel, knowledge of intervention unlikely to significantly affect management (except transfusion).
Blinding of outcome assessment (detection bias) Outcomes except cause of death	Low	Unclear whether outcome assessors were blinded to group assignment. The outcome measurements are unlikely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Death due to haemorrhage	Low	Each death was adjudicated by a clinician blinded to group assignment and external to the trial site and 1 or more causes of death were assigned.
Incomplete outcome data (attrition bias)	Low	High levels of follow-up and ITT analysis.
Selective reporting (reporting bias)	High	
Selective reporting (reporting bias)	High	Laboratory outcomes have not been reported yet. Death due to exsanguination presented in detail, not pre-specified in protocol.
Selective reporting (reporting bias)	High	
Other bias	Low	No other clear sources of other bias.

Reed 1986[117]

Methods	**Study design:** Single-centre, 2-arm, parallel-group RCT **Setting:** Civilian trauma centre, Harborview Medical Centre **Country:** USA **Dates study conducted:** September 1982 to November 1983 **Length of follow up:** NR **Aim of study:** To examine the hypothesis that prophylactic platelet transfusions are more efficacious than prophylactic FFP transfusions in the prevention of the microvascular bleeding and thrombocytopenia associated with the massive transfusion of stored blood. **Definition of major haemorrhage:** Likely to require massive transfusion (defined as 12 or more units of blood within a 12 hour period) **Definition of coagulopathy:** not defined
Participants	**Inclusion criteria:** Aged 18 and above, likely to require massive transfusion (defined as 12 or more units of blood) within 12 hours. **Exclusion criteria:** Severe pre-existing liver disease or portal hypertension, platelet count <100 or pre-existing coagulopathy, penetrating wounds to the head with concurrent brain injury, GI haemorrhage, burns over >10% body surface or use of low molecular weight dextran. **Number randomised:** 41 **Number analysed:** 33 **Number lost to FU/drop out:** 8 (protocol violations) **Baseline Characteristics** Intervention 1: Platelets (N=17 (included 4 patients with ruptured aneurysm)) • Age mean (SD) 58 (19) • Gender - NR for trauma subgroup (overall 64.7) • Blunt injury n (%): 11 (65) • Penetrating injury n (%): 2 (12) • Injury severity score: NR

	• Isolated traumatic brain injury n (%): NR • Pre-injury anticoagulant/antiplatelet therapy: patients with pre-existing coagulopathy excluded • Baseline INR: NR • Baseline PT: NR • Pre-randomisation red blood cells (units) median (IQR): NR • Pre-randomisation FFP (units) median (IQR): 0 (0-0) Intervention 2: FFP (N=16 (included 3 patients with ruptured aneurysm)) • Age mean (SD) 43 (22) • Gender - NR for trauma subgroup (overall 81.3) • Blunt injury n (%): 12 (75) • Penetrating injury n (%): 1 (6) • Injury severity score: NR • Isolated traumatic brain injury n (%): NR • Pre-injury anticoagulant/antiplatelet therapy: patients with pre-existing coagulopathy excluded • Baseline INR: NR • Baseline PT: NR • Pre-randomisation red blood cells (units) median (IQR): NR • Pre-randomisation FFP (units) median (IQR): 0 (0-0)
Interventions	**Intervention Characteristics** Intervention 1: Platelets • Description and dose: 6 units of platelets (containing ~ 420 ml plasma) • Timing: After 12 units of blood, then repeated every 12 units thereafter • Route: IV Intervention 2: FFP • Description and dose: 2 units FFP (containing 440 ml plasma) • Timing: After 12 units of blood, then repeated every 12 units thereafter • Route: IV
Outcomes	**Primary outcome** • Unclear

	Secondary outcomes • Unclear
Identification	**Registration:** not prospectively registered **Sponsorship source:** NIGMS grant 5-RO1-GM31150-03 and NIH grant 5-T32-GM07037 **Conflict of interest:** No statement reported in paper **Authors name:** R. Lawrence Reed **Institution:** Harborview Medical Center **Email:** N/A **Address:** Department of Surgery, University of Texas Health Sciences Center at Houston, 6431 Fannin, Texas Medical Center, Houston, TX 77030 **Dates study conducted:** September 1982 to November 1983
Notes	Trial did not report any outcomes that were specified in this review. Trial includes less than 80% trauma patients and there is no trauma subgroup reported separately. Timing of mortality outcome not clear. 10/17 (19%) in platelet arm; 8/16 (50%) FFP arm Patients not restricted to trauma and no trauma subgroup was reported. **Pre-treatment:** FFP group were older

Risk of bias table, Reed 1986[117]

Bias	Judgement	Support for judgement
Random sequence generation (selection bias)	Unclear	Insufficient information for judgement
Allocation concealment (selection bias)	Unclear	Insufficient information for judgement
Blinding of participants and personnel (performance bias) Transfusion requirements	Unclear	Participants and personnel blinded. Either blood component was packaged in a single transfusion pack of identical appearance. Transfusion requirement outcome was NR.
Blinding of participants and personnel (performance bias) Outcomes except transfusion requirements	Unclear	Participants and personnel blinded. Either blood component was packaged in a single transfusion pack of identical appearance. Transfusion requirement outcome was NR.
Blinding of outcome assessment (detection bias) Outcomes except cause of death	Unclear	No outcomes relevant to this systematic review reported.
Blinding of outcome assessment (detection bias) Death due to haemorrhage	Unclear	No outcomes relevant to this systematic review reported.
Incomplete outcome data (attrition bias)	Unclear	Not an intention to treat analysis, no outcomes relevant to this systematic review reported.
Selective reporting (reporting bias)	Unclear	No pre-registration. Insufficient information for judgement
Other bias	Unclear	Insufficient information for judgement

Appendix 2.4 Viscoelastic haemostatic assay (VHA) vs conventional laboratory testing (in-hospital)

Gonzalez 2015[122]

Methods	Study design: Single centre, 2-arm, parallel-group RCT Setting: Denver Health Medical Center, Level 1 trauma centre Country: USA Dates study conducted: September 2010 - July 2014 Length of follow up: 28 days Aim of study: To compare the effect of an massive transfusion protocol goal directed by TEG to a standard massive transfusion protocol guided by CCA on the primary outcome of survival after injury Definition of major haemorrhage: Needed massive transfusion protocol activation. SBP =70 or SBP 71-90 and HR >=108 Definition of coagulopathy: not defined
Participants	Inclusion criteria: injured patients at least 18 years of age that met criteria for massive transfusion protocol activation upon ED arrival; massive transfusion protocol activation activation was based on the Resuscitation Outcome Consortium criteria [systolic blood pressure (SBP) 70 mm Hg or SBP 70–90 mm Hg with heart rate (HR) 108 beats/min], in addition to any of the following injury patterns: penetrating torso wound, unstable pelvic fracture, or abdominal ultrasound suspicious of bleeding in more than one region. Exclusion criteria: prisoners or pregnant; patients were removed from the study if these criteria became known after activation of the massive transfusion protocol. Number randomised: 122 Number analysed: 111 Number lost to FU/drop out: 11 Baseline Characteristics Intervention 1: Goal directed by conventional coagulation assays (CCA) (N=55) Age median (IQR): 38 (25–53) Male n (%): 41 (74.5) Blunt injury n (%): 36 (65.4) Injury severity score median (IQR): 33 (25–43) Isolated TBI: NR Pre-injury anticoagulant/antiplatelet therapy: NR Received tranexamic acid (%): 9 (16.4) Baseline INR median (IQR): 1.46 (1.2–2.3) Baseline PT: NR Pre-randomisation red blood cells (units) median (IQR): 0 (0-0) Pre-randomisation FFP (units) median (IQR): 0 (0-0) Time from injury to hospital (mins) median (IQR): 29 (21–72)

	Transport time (mins) median (IQR): NR Time from injury to randomisation: NR Intervention 2: Goal directed by TEG (N=56) Age median (IQR): 41 (28–54) Male n (%): 37 (66) Blunt injury n (%): 39 (69) Injury severity score median (IQR): 29.5 (23–41) Isolated TBI: NR Pre-injury anticoagulant/antiplatelet therapy: NR Received tranexamic acid (%): 4 (7.1) Baseline INR median (IQR): 1.45 (1.2–1.7) Baseline PT: NR Time from injury to hospital (mins) median (IQR): 35.5 (23–94 Transport time (mins) median (IQR): NR Time from injury to randomisation: NR
Interventions	Intervention Characteristics Intervention 1: Goal directed by conventional coagulation assays Description and dose: massive transfusion protocol goal directed by conventional coagulation assays. Upon activation of the massive transfusion protocol the blood bank delivered 4 units of type-O, Rh-negative, RBC units and 2 of type-A plasma units to the patient's bedside. This occurred regardless of randomization group, and these first units were administered according to the treating clinicians' criteria while awaiting results of coagulation tests (conventional coagulation assays or TEG). In the conventional coagulation assays group, the following parameters triggered the following transfusions: INR equal or greater than 1.5 =2 units of plasma; fibrinogen less than 150 mg/dL =10-pack of cryoprecipitate; platelet count less than 100,000/mL =1 unit of apheresis platelets. Antifibrinolytic medication (tranexamic acid, 1 g, IV) was administered in the setting of suspicion of fibrinolysis with an elevated D-dimer (>0.5mg/mL). Timing: Acute admission. Results generally available within 30-45 minutes. Route: IV Intervention 2: Goal directed by TEG Description and dose: massive transfusion protocol directed by TEG. Those patients with a first measurement of activated clotting time equal or greater than 140 seconds received 2 plasma units, 10-pack of cryoprecipitate, and 1 unit of apheresis platelets while awaiting results of angle and MA. If the activated clotting time was 111 to 139, only 2 units of plasma were given. For subsequent TEGs, an activated clotting time greater than 110 seconds triggered transfusion of 2 plasma units, angle less than 63 degrees a 10-pack of cryoprecipitate, MA less than 55 mm 1 apheresis platelet unit, and LY30 equal or greater than 7.5% administration of tranexamic acid (1 g, IV). Timing: Acute admission. First TEG results generally available within 5 mins)

	Route: IV
Outcomes	Primary outcome 28-day survival Secondary outcomes Blood product requirements in the first 2, 4, 6, 12, and 24 hours from time of injury Mechanical ventilation time and intensive care unit (ICU) stay (ventilator-free days and ICU-free days). Death due to coagulopathic bleeding (pre-specified on clinical trials site) Change in INR, fibrinogen, platelet, r-TEG ACT/angle/MA/LY30, d-dimer (pre-specified on clinical trials site)
Identification	Registration: NCT01536496 Sponsorship source: Support was provided in the way of laboratory reagents by Haemonetics Inc, which had no role in the study design, data collection, data analysis, data interpretation of the study, or preparation of this manuscript. The investigators requested this support after the study was initially conceived. Haemonetics Inc provided no salary or financial compensation to any of the authors or managing physicians. Funding by National Institute of General Medical Sciences and National Heart, Lung, and Blood Institute. Conflict of interest: The authors EG, EEM, HBM, and MPC received support from Haemonetics Inc in the way of laboratory reagents. The author reports no conflicts of interest. Authors name: Eduardo Gonzalez Institution: Denver Health Medical Center Email: ernest.moore@dhha.org Address: 655 Broadway, Suite 365, Denver, CO 80203
Notes	INR post treatment reported as median (IQR): TEG 1.4 (1.3-2.0), standard 1.5 (1.4-1.7) ICU free days in conventional coagulation assays group 8.5 Median INR at 12.1-24 hours 1.5 (1.4–1.7) in conventional coagulation assays group, 1.4 (1.3–2.0) TEG group Male 41 (74.5%) in conventional coagulation assays group, 37 (66% in TEG group) Mortality difference and difference in transfusion at 6 hours noted in favour of TEG group.

Risk of bias table, Gonzalez 2015[122]

Bias	Judgement	Support for judgement
Random sequence generation (selection bias)	High	Weekly alternation of the two treatment modalities.
Allocation concealment (selection bias)	High	Allocation not concealed
Blinding of participants and personnel (performance bias) Transfusion requirements	High	Open label study. Transfusion requirements in either group could be influenced by lack of blinding.
Blinding of participants and personnel (performance bias) Outcomes except transfusion requirements	Low	Open label study. For participants, low risk of bias as no patient reported outcomes and patient knowledge of their intervention arm is unlikely to have an effect on outcomes. For personnel, knowledge of intervention unlikely to significantly affect management (except transfusion).
Blinding of outcome assessment (detection bias) Outcomes except cause of death	Low	No blinding of outcome assessment. The outcome measurements are unlikely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Death due to haemorrhage	High	Quote: "Cause of death was ascribed by the attending physician based on clinical findings, and, when available, autopsy results." No blinding of outcome assessment. Assigning cause of death due to bleeding could be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low	Intention to treat analysis. Eight patients crossed over from standard treatment to TEG arm.
Selective reporting (reporting bias)	Low	Study was prospectively registered. All pre-specified outcomes were reported.
Other bias	Low	No other clear sources of bias.

Appendix 3: On-going trials (Chapter 2)

Trial name and identifier	Intervention	Comparator
Trial-defined intervention vs standard of care/trial-defined intervention: pre-hospital		
Pre-hospital Administration of Lyophilized Plasma for Post-traumatic Coagulopathy Treatment (PREHO-PLYO) NCT02736812	French lyophilised plasma	Normal saline
A multi-centre randomised controlled trial of pre-hospital administration of packed red blood cells and freeze-dried plasma to patients with low blood pressure after major injuries (REPHILL) ISRCTN62326938	Up to 2 RBC, 2 Lyoplas	Up to 4x Crystalloid
Pre-Hospital Use of Plasma for Traumatic Hemorrhage (PUPTH) NCT02303964	Up to 2 units plasma	Saline
Trial-defined intervention vs standard of care: in-hospital		
CRYOSTAT-2 ISRCTN14998314	Early cryoprecipitate	Standard MHP
Pragmatic Prehospital Group O Whole Blood Early Resuscitation Trial (PPOWER) NCT03477006	Low titer, group O, leukocyte reduced, platelet replete, cold stored whole blood	Standard prehospital air medical care and standard of care component (1:1:1) trauma resuscitation through the early in-hospital phase of care
Trial-defined intervention v trial defined intervention: in-hospital		
Cluster randomized crossover non-inferiority trial by limiting blood transfusion for severe trauma patients UMIN000035992	Volume of transfusion	Target haemoglobin index

Trial name and identifier	Intervention	Comparator
Restrictive transfusion strategy for critically injured patients trial (RESTRIC) UMIN000034405	Target haemoglobin level of red cell concentrate transfusion is defined as 7-9 g/dL.	Target haemoglobin level of red cell concentrate transfusion is defined as 10-12 g/dL.
VHA vs conventional laboratory test guided transfusion		
i-TACTIC trial NCT02593877	VHA-guided (TEG or ROTEM)	Massive transfusion protocol resuscitation aiming at ratio 1:1:1 of blood components (RBC 1: plasma 1: platelets 1) and conventional coagulation tests
Comparison of Rapid Thrombelastography and Conventional Coagulation Testing for Haemostatic in Trauma NCT01536496	r-TEG	Conventional
Use of Viscoelastic Tests in the Treatment of Traumatic Induced Coagulopathy: a Pragmatic Randomized Clinical Trial. (VISCOTRAUMA) NCT03380767	TEG or ROTEM assay guided	Conventional laboratory assay guided (platelet count, fibrinogen level, PT or INR and d dimer for fibrinolysis)
Rotational Thromboelastometry Activated Transfusion In Trauma Trial NCT03765866	ROTEM guided MTP	Standard massive transfusion protocol (MTP)
Rapid Thrombelastography Guided goal-directed Transfusion Therapy in the Severe Trauma Patient ChiCTR-ICR-15006073	r-TEG	Conventional
Strategy of transfusion in trauma trials (STATA) NCT02416817	Red blood cells, Human Fibrinogen and Prothrombin complex concentrates (PCC) based on thromboelastometry.	1:1:1 Red blood cells: Fresh Frozen Plasma: Platelets upon a major trauma trigger.

Appendix 4: Cases of major bleeding by year (TARN)

Year	Young (N = 441)	Older (N = 122)	Total (N = 563)
2012	40 (9.1%)	17 (13.9%)	57 (10.1%)
2013	67 (15.2%)	15 (12.3%)	82 (14.6%)
2014	61 (13.8%)	25 (20.5%)	86 (15.3%)
2015	71 (16.1%)	28 (23.0%)	99 (17.6%)
2016	88 (20.0%)	23 (18.9%)	111 (19.7%)
2017	114 (25.9%)	14 (11.5%)	128 (22.7%)
Total	441	122	563

Appendix 5: Logistic regression analyses (Chapter 5)

Appendix 5.1 Stata code for imputation

Variables

PH_pulse3	pre-hospital pulse
ED_pulse3	emergency department pulse
PreHospital_sbp2	pre-hospital systolic blood pressure
ED_SBP2	emergency department systolic blood pressure
delphi_bleed7	major bleeding (Delphi definition)
age_int	age
penetrating	penetrating injury
male	male gender
MoI	mechanism of injury (baseline category road traffic collision)
PelvisUnstable	unstable pelvis
incDTSub	incident date time substituted with 999 call
iss	injury severity score
ph_arrest	pre-hospital arrest
FractureOpen	open fracture
limbs	limb injury abbreviated injury score 3+
txa	tranexamic acid use
pen_age2	penetrating*age variable
MoI_age	mechanism of injury*age for each of the 6 categories of mechanism of injury

Imputation model 1 (penetrating-age interaction)

```
mi set flong
mi register imputed PH_pulse3 ED_pulse3 PreHospital_sbp2 ED_SBP2 delphi_bleed7
mi register regular age_int penetrating male MoI PelvisUnstable incDTSub iss ///
ph_arrest FractureOpen limbs txa pen_age2

mi impute chained (regress) PH_pulse3 ED_pulse3 PreHospital_sbp2 ED_SBP2 ///
(logit) delphi_bleed7 ///
= age_int penetrating male MoI PelvisUnstable incDTSub iss ///
ph_arrest FractureOpen limbs txa pen_age2, add(20) ///
replace rseed(39) dots dryrun

mi impute chained (regress) PH_pulse3 ED_pulse3 PreHospital_sbp2 ED_SBP2 ///
(logit) delphi_bleed7 ///
= age_int penetrating male MoI PelvisUnstable incDTSub iss ///
ph_arrest FractureOpen limbs txa pen_age2, add(20) ///
replace rseed(39) dots

*Generate categories for pre-hospital pulse and systolic blood pressure for imputed
data

gen PHpulse100 =.
replace PHpulse100 = 1 if PH_pulse3 >=100 & PH_pulse3 !=.
replace PHpulse100 = 0 if PH_pulse3 <100
bysort _mi_m: tab PHpulse100 delphi_bleed7, col
```

```
gen PH_SBP90 =.

replace PH_SBP90 = 1 if PreHospital_sbp2 <=90

replace PH_SBP90 = 0 if PreHospital_sbp2 >90 & PreHospital_sbp2 !=.

bysort _mi_m: tab PH_SBP90 delphi_bleed7, col


label var PHpulse100 "PH pulse_imp >=100bpm"

label define PHpulse100 1 "PH pulse >=100bpm" 0 "PH pulse <100bpm"

label var PH_SBP90 "PH SBP_imp <=90"

label define PH_SBP90 1 "PH SBP <=90" 0 "PH SBP >90"
```

***Analysis model**

```
 mi estimate, or: logit delphi_bleed7 age_int i.penetrating i.PHpulse100 ///
        i.PH_SBP90 i.male i.PelvisUnstable i.MoI i.penetrating#c.age_int if direct==1
```

***Complete case analysis model**

```
logistic delphi_bleed7 age_int i.penetrating i.PHpulse100 ///
        i.PH_SBP90 i.male i.PelvisUnstable i.MoI i.penetrating#c.age_int if direct==1 &
_mi_m==0
```

Imputation Model 2: mechanism of injury-age model

```
*Generate MOI/interaction for 5 MOI categories (the MOI_1 is baseline RTC)

gen MoI_1_age = MoI_1*age_int

gen MoI_2_age = MoI_2*age_int

gen MoI_3_age = MoI_3*age_int

gen MoI_4_age = MoI_4*age_int

gen MoI_5_age = MoI_5*age_int

gen MoI_6_age = MoI_6*age_int

tab MoI_6_age, m
```

*** Imputation**

```
mi set flong

mi register imputed PH_pulse3 ED_pulse3 PreHospital_sbp2 ED_SBP2 delphi_bleed7

mi register regular age_int penetrating male MoI PelvisUnstable incDTSub iss ///

ph_arrest FractureOpen limbs txa MoI_1_age MoI_2_age MoI_3_age MoI_4_age
MoI_5_age MoI_6_age

mi impute chained (regress) PH_pulse3 ED_pulse3 PreHospital_sbp2 ED_SBP2 ///

(logit) delphi_bleed7 ///
```

= age_int penetrating male MoI PelvisUnstable incDTSub iss ///

ph_arrest FractureOpen limbs txa MoI_1_age MoI_2_age MoI_3_age MoI_4_age MoI_5_age MoI_6_age, add(20) ///

replace rseed(39) dots dryrun

mi impute chained (regress) PH_pulse3 ED_pulse3 PreHospital_sbp2 ED_SBP2 ///

(logit) delphi_bleed7 ///

= age_int penetrating male MoI PelvisUnstable incDTSub iss ///

ph_arrest FractureOpen limbs txa MoI_2_age MoI_3_age MoI_4_age MoI_5_age MoI_6_age, add(20) ///

replace rseed(39) dots

***Generate pre-hospital pulse and systolic blood pressure categories for imputed data**

gen PHpulse100 =.

replace PHpulse100 = 1 if PH_pulse3 >=100 & PH_pulse3 !=.

replace PHpulse100 = 0 if PH_pulse3 <100

bysort _mi_m: tab PHpulse100 delphi_bleed7, col

gen PH_SBP90 =.

replace PH_SBP90 = 1 if PreHospital_sbp2 <=90

replace PH_SBP90 = 0 if PreHospital_sbp2 >90 & PreHospital_sbp2 !=.

bysort _mi_m: tab PH_SBP90 delphi_bleed7, col

label var PHpulse100 "PH pulse_imp >=100bpm"

label define PHpulse100 1 "PH pulse >=100bpm" 0 "PH pulse <100bpm"

label var PH_SBP90 "PH SBP_imp <=90"

label define PH_SBP90 1 "PH SBP <=90" 0 "PH SBP >90"

***Analysis model**

```
mi estimate, or: logit delphi_bleed7 age_int i.penetrating i.PHpulse100 ///
        i.PH_SBP90 i.male i.PelvisUnstable i.MoI i.MoI##c.age_int if direct==1
```

Appendix 5.2 Univariate logistic regression: factors associated with bleeding, overall cohort

(N=63,226)

Variable	Odds Ratio	95% CI	P-value
Male	2.428	(1.983 to 2.973)	<0.001
Penetrating	7.090	(5.818 to 8.642)	<0.001
MOI			<0.001
Fall ≥2 m	0.463	(0.362 to 0.592)	<0.001
Fall <2 m	0.018	(0.009 to 0.037)	<0.001
Shooting/stabbing	3.333	(2.703 to 4.110)	<0.001
Blow(s)	0.192	(0.099 to 0.372)	<0.001
Other	0.698	(0.438 to 1.112)	0.130
Pre-hospital pulse ≥100 bpm	3.606	(3.022 to 4.302)	<0.001
Pre-hospital SBP ≤90 mmHg	10.325	(8.474 to 12.580)	<0.001
Age	0.974	(0.970 to 0.978)	<0.001
ISS	1.086	(1.081 to 1.091)	<0.001
Pre-hospital SBP	0.971	(0.969 to 0.973)	<0.001
Pre-hospital pulse	1.023	(1.020 to 1.027)	<0.001
Head	1.861	(1.574 to 2.200)	<0.001
Thorax	8.650	(7.126 to 10.500)	<0.001
Abdomen	9.624	(8.046 to 11.512)	<0.001
Spine	1.503	(1.173 to 1.925)	0.001
Pelvis	7.517	(6.213 to 9.095)	<0.001
Limbs	1.361	(1.145 to 1.619)	<0.001
Other	4.204	(2.982 to 5.926)	<0.001
Antiplatelet	0.197	(0.028 to 1.401)	0.104
Warfarin	0.858	(0.275 to 2.679)	0.792
TBI	1.783	(1.506 to 2.112)	<0.001
Facial	1.950	(1.311 to 2.900)	0.001
Thoracic	3.779	(3.197 to 4.466)	<0.001
Abdominal	7.959	(6.645 to 9.532)	<0.001
Extremity	4.099	(3.462 to 4.853)	<0.001
Stable pelvis	1.464	(1.144 to 1.872)	0.002
Unstable pelvis	7.526	(6.220 to 9.105)	<0.001
Femur Open	4.362	(2.963 to 6.421)	<0.001
Fracture Open	2.150	(1.702 to 2.717)	<0.001
CCI Band			<0.001
Mild	0.599	(0.487 to 0.738)	<0.001
Moderate	0.381	(0.244 to 0.593)	<0.001
Severe	0.571	(0.282 to 1.154)	0.119
Anticoagulation	0.849	(0.272 to 2.651)	0.778

MOI, mechanism of injury; ISS, injury severity score; TBI, traumatic brain injury; CCI, charlston comorbidity index

Appendix 5.3 Univariate logistic regression: factors associated with bleeding in young patients

N=36,992. MOI reference RTC.

Variable	Odds Ratio	95% CI	P-value
Male	1.875	(1.457 to 2.412)	<0.001
Penetrating	5.859	(4.759 to 7.212)	<0.001
MOI			<0.001
Fall ≥2 m	0.571	(0.426 to 0.766)	<0.001
Fall <2 m	0.008	(0.001 to 0.058)	<0.001
Shooting/stabbing	3.786	(3.037 to 4.721)	<0.001
Blow(s)	0.180	(0.085 to 0.382)	<0.001
Other	0.670	(0.389 to 1.151)	0.147
Pre-hospital pulse ≥100 bpm	3.479	(2.840 to 4.262)	<0.001
PH SBP ≤90 mmHg	8.541	(6.798 to 10.729)	<0.001
Age	0.970	(0.963 to 0.976)	<0.001
ISS	1.075	(1.069 to 1.081)	<0.001
Head	1.760	(1.453 to 2.131)	<0.001
Thorax	6.570	(5.289 to 8.161)	<0.001
Abdomen	6.890	(5.646 to 8.408)	<0.001
Spine	1.542	(1.167 to 2.037)	0.002
Pelvis	5.287	(4.240 to 6.593)	<0.001
Limbs	1.320	(1.086 to 1.605)	0.005
Other	3.134	(2.162 to 4.543)	<0.001
Antiplatelet	1.091	(0.151 to 7.861)	0.931
Warfarin	1.000		
TBI	1.629	(1.342 to 1.978)	<0.001
Facial	1.924	(1.259 to 2.942)	0.002
Thoracic	2.930	(2.428 to 3.537)	<0.001
Abdominal	5.855	(4.793 to 7.153)	<0.001
Extremity	3.419	(2.814 to 4.154)	<0.001
Stable pelvis	1.435	(1.058 to 1.947)	0.020
Unstable pelvis	5.290	(4.242 to 6.596)	<0.001
Femur Open	2.779	(1.781 to 4.337)	<0.001
Fracture Open	1.475	(1.125 to 1.934)	0.005
CCI Band			0.229
Mild	0.799	(0.627 to 1.019)	0.070
Moderate	0.659	(0.325 to 1.336)	0.248
Severe	1.012	(0.449 to 2.284)	0.977

Appendix 5.4 Univariate logistic regression: factors associated with bleeding in older patients

N=26,234. MOI reference RTC.

Variable	Odds Ratio	95% CI	P-value
Male	2.139	(1.484 to 3.083)	<0.001
Penetrating	2.703	(0.663 to 11.029)	0.166
MOI			<0.001
Fall ≥2 m	0.258	(0.163 to 0.408)	<0.001
Fall <2 m	0.016	(0.007 to 0.034)	<0.001
Shooting/stabbing	0.882	(0.214 to 3.639)	0.862
Blow(s)	0.357	(0.087 to 1.462)	0.152
Other	0.849	(0.341 to 2.114)	0.725
Pre-hospital pulse ≥100 bpm	2.693	(1.834 to 3.954)	<0.001
Pre-hospital SBP ≤90 mmHg	14.830	(9.975 to 22.047)	<0.001
Age	0.952	(0.932 to 0.973)	<0.001
ISS	1.114	(1.102 to 1.126)	<0.001
Head	2.526	(1.769 to 3.607)	<0.001
Thorax	14.827	(9.603 to 22.894)	<0.001
Abdomen	22.526	(14.805 to 34.274)	<0.001
Spine	1.396	(0.812 to 2.400)	0.228
Pelvis	17.093	(11.659 to 25.060)	<0.001
Limbs	1.322	(0.905 to 1.930)	0.149
Other	7.871	(3.168 to 19.560)	<0.001
Antiplatelet	1.000		
Warfarin	1.940	(0.614 to 6.131)	0.259
TBI	2.682	(1.878 to 3.830)	<0.001
Facial	1.286	(0.408 to 4.058)	0.668
Thoracic	9.762	(6.459 to 14.755)	<0.001
Abdominal	15.685	(10.244 to 24.016)	<0.001
Extremity	7.674	(5.352 to 11.004)	<0.001
Stable pelvis	2.136	(1.390 to 3.280)	0.001
Unstable pelvis	17.140	(11.691 to 25.130)	<0.001
Femur Open	16.325	(7.419 to 35.921)	<0.001
Fracture Open	5.119	(3.214 to 8.154)	<0.001
CCI Band			0.092
Mild	0.630	(0.406 to 0.978)	0.039
Moderate	0.550	(0.294 to 1.027)	0.061
Severe	0.425	(0.103 to 1.758)	0.237
Anticoagulation	1.922	(0.608 to 6.076)	0.266

Appendix 5.5 Univariate logistic regression for major bleeding (variables known at scene): young (age <65)

Reference MOI group RTC.

Variable	Odds Ratio	95% CI	P-value
Age	0.970	(0.963 to 0.976)	<0.001
Male	1.875	(1.457 to 2.412)	<0.001
Penetrating	5.859	(4.759 to 7.212)	<0.001
Pre-hospital SBP (mmHg)	0.973	(0.971 to 0.976)	<0.001
Pre-hospital pulse (bpm)	1.023	(1.019 to 1.027)	<0.001
Pre-hospital SBP ≤90 mmHg	8.541	(6.798 to 10.729)	<0.001
Pre-hospital pulse ≥100 bpm	3.479	(2.840 to 4.262)	<0.001
MOI			<0.001
Fall ≥2 m	0.571	(0.426 to 0.766)	<0.001
Fall <2 m	0.008	(0.001 to 0.058)	<0.001
Shooting/stabbing	3.786	(3.037 to 4.721)	<0.001
Blow(s)	0.180	(0.085 to 0.382)	<0.001
Other	0.670	(0.389 to 1.151)	0.147
Unstable pelvis	5.290	(4.242 to 6.596)	<0.001

PH, pre-hospital; SBP, systolic blood pressure; MOI, mechanism of injury

Appendix 5.6 Univariate logistic regression for major bleeding (variables known at scene): older (age ≥65)

Reference MOI group RTC.

Variable	Odds Ratio	95% CI	P-value
Age	0.952	(0.932 to 0.973)	<0.001
Male	2.139	(1.484 to 3.083)	<0.001
Penetrating	2.703	(0.663 to 11.029)	0.166
Pre-hospital SBP (mmHg)	0.967	(0.963 to 0.972)	<0.001
Pre-hospital pulse (bpm)	1.013	(1.004 to 1.021)	0.004
Pre-hospital pulse ≥100 bpm	2.693	(1.834 to 3.954)	<0.001
Pre-hospital SBP ≤90 mmHg	14.830	(9.975 to 22.047)	<0.001
MOI			<0.001
Fall ≥2 m	0.258	(0.163 to 0.408)	<0.001
Fall <2 m	0.016	(0.007 to 0.034)	<0.001
Shooting/stabbing	0.882	(0.214 to 3.639)	0.862
Blow(s)	0.357	(0.087 to 1.462)	0.152
Other	0.849	(0.341 to 2.114)	0.725
Unstable pelvis	17.140	(11.691 to 25.130)	<0.001

PH, pre-hospital; SBP, systolic blood pressure; MOI, mechanism of injury

Appendix 5.7 Multivariable logistic regression for major bleeding including age in the model: young (aged <65)

	Odds Ratio	95% CI	P-value
Age	0.994	(0.986 to 1.003)	0.184
Penetrating	2.731	(1.119 to 6.669)	0.027
Pre-hospital pulse ≥100 bpm	2.447	(1.946 to 3.077)	<0.001
Pre-hospital SBP ≤90 mmHg	5.417	(4.257 to 6.892)	<0.001
Male	1.753	(1.275 to 2.412)	0.001
MOI			<0.001
Fall ≥2m	0.700	(0.499 to 0.984)	0.040
Fall <2m	0.022	(0.003 to 0.160)	<0.001
Shooting/stabbing	1.334	(0.535 to 3.328)	0.537
Blow(s)	0.218	(0.080 to 0.591)	0.003
Other	0.479	(0.236 to 0.969)	0.041
Unstable pelvis	4.288	(3.232 to 5.688)	<0.001

Appendix 5.8 Multivariable logistic regression for major bleeding excluding age in the model: young (aged <65)

	Odds Ratio	95% CI	P-value
Penetrating	2.777	(1.136 to 6.789)	0.025
Pre-hospital pulse ≥100 bpm	2.493	(1.986 to 3.130)	<0.001
Pre-hospital SBP ≤90 mmHg	5.388	(4.235 to 6.854)	<0.001
Male	1.760	(1.280 to 2.421)	0.001
MOI			<0.001
Fall ≥2 m	0.680	(0.486 to 0.953)	0.025
Fall <2 m	0.021	(0.003 to 0.148)	<0.001
Shooting/stabbing	1.343	(0.538 to 3.355)	0.528
Blow(s)	0.215	(0.079 to 0.584)	0.003
Other	0.463	(0.229 to 0.936)	0.032
Unstable pelvis	4.288	(3.233 to 5.688)	<0.001

Appendix 5.9 Multivariable logistic regression for major bleeding including age in the model: older (aged ≥65)

	Odds Ratio	95% CI	P-value
Age	1.007	(0.982 to 1.033)	0.589
Pre-hospital pulse ≥100 bpm	2.044	(1.344 to 3.107)	0.001
Pre-hospital SBP ≤90 mmHg	6.625	(4.285 to 10.241)	<0.001
Male	1.100	(0.727 to 1.665)	0.651
MOI			<0.001
Fall ≥2 m	0.390	(0.236 to 0.643)	<0.001
Fall <2 m	0.029	(0.012 to 0.070)	<0.001
Shooting/stabbing	0.997	(0.229 to 4.339)	0.997
Blow(s)	0.715	(0.170 to 3.003)	0.647
Other	0.783	(0.271 to 2.263)	0.652
Unstable pelvis	4.972	(3.142 to 7.868)	<0.001

Appendix 5.10 Multivariable logistic regression for major bleeding including mechanism of injury-age interaction: young

	Odds Ratio	95% CI	P-value
Age	0.996	(0.985 to 1.007)	0.490
Penetrating	2.754	(1.122 to 6.758)	0.027
Pre-hospital pulse ≥100 bpm	2.452	(1.949 to 3.085)	<0.001
Pre-hospital SBP ≤90 mmHg	5.424	(4.263 to 6.901)	<0.001
Male	1.744	(1.267 to 2.400)	0.001
MOI			0.223
Fall ≥2 m	0.780	(0.279 to 2.179)	0.636
Fall <2 m	0.004	(<0.001 to 98.487)	0.287
Shooting/stabbing	1.770	(0.569 to 5.511)	0.324
Blow(s)	0.019	(<0.001 to 0.984)	0.049
Other	0.584	(0.066 to 5.155)	0.629
MOI#age			0.707
Fall ≥2 m	0.997	(0.973 to 1.022)	0.818
Fall <2 m	1.032	(0.857 to 1.243)	0.738
Shooting/stabbing	0.991	(0.970 to 1.012)	0.393
Blow(s)	1.059	(0.976 to 1.148)	0.169
Other	0.995	(0.945 to 1.047)	0.842
Unstable pelvis	4.262	(3.211 to 5.658)	<0.001

Appendix 5.11 Multivariable logistic regression for major bleeding including penetrating-age interaction: young

	Odds Ratio	95% CI	P-value
Age	0.996	(0.986 to 1.006)	0.396
Penetrating	3.415	(1.105 to 10.553)	0.033
Pre-hospital pulse ≥100 bpm	2.454	(1.951 to 3.087)	<0.001
Pre-hospital SBP ≤90 mmHg	5.429	(4.267 to 6.908)	<0.001
Male	1.744	(1.267 to 2.400)	0.001
MOI			<0.001
Fall ≥2 m	0.695	(0.494 to 0.977)	0.036
Fall <2 m	0.022	(0.003 to 0.157)	<0.001
Shooting/stabbing	1.309	(0.523 to 3.275)	0.565
Blow(s)	0.217	(0.080 to 0.589)	0.003
Other	0.475	(0.235 to 0.963)	0.039
Unstable pelvis	4.278	(3.225 to 5.676)	<0.001
penetrating#age	0.994	(0.974 to 1.014)	0.528

Appendix 5.12 Multivariable logistic regression for major bleeding including unstable pelvis-age interaction: overall cohort

	Odds Ratio	95% CI	P-value
Age	1.005	(0.999 to 1.011)	0.120
Penetrating	2.341	(0.981 to 5.585)	0.055
Pre-hospital pulse ≥100 bpm	2.361	(1.935 to 2.882)	<0.001
Pre-hospital SBP ≤90 mmHg	5.607	(4.544 to 6.919)	<0.001
Male	1.421	(1.112 to 1.817)	0.005
MOI			
Fall ≥2 m	0.574	(0.433 to 0.762)	<0.001
Fall >2 m	0.035	(0.016 to 0.076)	<0.001
Shooting/stabbing	1.464	(0.600 to 3.572)	0.402
Blow(s)	0.270	(0.119 to 0.612)	0.002
Other	0.511	(0.284 to 0.919)	0.025
Unstable pelvis	3.495	(1.966 to 6.212)	<0.001
Unstable pelvis#age	1.005	(0.994 to 1.016)	0.340

Appendix 5.13 Multivariable logistic regression for major bleeding including pulse-age interaction: overall cohort

	Odds Ratio	95% CI	P-value
Age	1.007	(1.000 to 1.014)	0.039
Penetrating	2.322	(0.974 to 5.540)	0.057
Pre-hospital SBP ≤90 mmHg	5.618	(4.554 to 6.932)	<0.001
Male	1.434	(1.122 to 1.832)	0.004
MOI			
Fall ≥2 m	0.566	(0.427 to 0.750)	<0.001
Fall <2 m	0.034	(0.016 to 0.073)	<0.001
Shooting/stabbing	1.494	(0.613 to 3.641)	0.377
Blow(s)	0.272	(0.120 to 0.617)	0.002
Other	0.512	(0.285 to 0.922)	0.026
Unstable pelvis	4.495	(3.541 to 5.706)	<0.001
Pre-hospital pulse ≥100 bpm	2.591	(1.608 to 4.177)	<0.001
Pre-hospital pulse ≥100 bpm #age	0.998	(0.988 to 1.008)	0.665

Appendix 5.14 Multivariable logistic regression for major bleeding including systolic blood pressure-age interaction: overall cohort

	Odds Ratio	95% CI	P-value
Age	1.006	(1.000 to 1.012)	0.047
Penetrating	2.330	(0.977 to 5.557)	0.056
Pre-hospital pulse ≥100 bpm	2.355	(1.930 to 2.873)	<0.001
Male	1.433	(1.121 to 1.831)	0.004
MOI			
Fall ≥2 m	0.567	(0.428 to 0.752)	<0.001
Fall <2 m	0.034	(0.016 to 0.074)	<0.001
Shooting/stabbing	1.491	(0.612 to 3.633)	0.380
Blow(s)	0.272	(0.120 to 0.616)	0.002
Other	0.511	(0.284 to 0.919)	0.025
Unstable pelvis	4.498	(3.542 to 5.710)	<0.001
Pre-hospital SBP ≤90 mmHg	5.559	(3.386 to 9.128)	<0.001
Pre-hospital SBP ≤ 90 mmHg #age	1.000	(0.990 to 1.010)	0.963

Appendix 5.15 Multivariate logistic regression for major bleeding including male-age interaction: overall cohort

	Odds Ratio	95% CI	P-value
Age	1.015	(1.006 to 1.025)	0.002
Penetrating	2.306	(0.968 to 5.493)	0.059
Pre-hospital pulse ≥100 bpm	2.353	(1.928 to 2.871)	<0.001
Pre-hospital SBP ≤90 mmHg	5.660	(4.587 to 6.985)	<0.001
MOI			
Fall ≥2 m	0.568	(0.429 to 0.754)	<0.001
Fall <2 m	0.032	(0.015 to 0.069)	<0.001
Shooting/stabbing	1.477	(0.607 to 3.594)	0.390
Blow(s)	0.271	(0.120 to 0.613)	0.002
Other	0.520	(0.289 to 0.935)	0.029
Unstable pelvis	4.590	(3.614 to 5.829)	<0.001
Male	2.681	(1.425 to 5.046)	0.002
male#age	0.988	(0.977 to 0.999)	0.030

Appendix 6: Characteristics of patients by age group with extended coagulation and plasmin-alpha2-antiplasmin assays (ACIT study)

	Minor injury, no shock N=139			Severe injury, shock and bleeding N=89		
Age group	**16-64**	**≥65**	**Total**	**16-64**	**≥65**	**Total**
	(N = 111)	**(N = 28)**	**(N = 139)**	**(N = 72)**	**(N = 17)**	**(N = 89)**
Age, median (IQR)	29 (21 to 39)	72 (66 to 80)	35 (22 to 52)	35 (24 to 51)	70 (69 to 83)	42 (27 to 59)
ISS, median (IQR)	1 (1 to 3)	1 (1 to 4)	1 (1 to 4)	30 (25 to 40)	36 (29 to 41)	30 (25 to 41)
Male	95 (85.6%)	14 (50.0%)	109 (78.4%)	56 (77.8%)	11 (64.7%)	67 (75.3%)
Penetrating injury	50 (45.0%)	5 (17.9%)	55 (39.6%)	18 (25.0%)	1 (5.9%)	19 (21.3%)
Mechanism of injury						
RTC	35 (31.5%)	8 (33.3%)	43 (31.9%)	37 (51.4%)	14 (82.4%)	51 (57.3%)
Fall/jump from height	15 (13.5%)	11 (45.8%)	26 (19.3%)	10 (13.9%)	1 (5.9%)	11 (12.4%)
Shooting/ stabbing	48 (43.2%)	2 (8.3%)	50 (37.0%)	17 (23.6%)	0 (0.0%)	17 (19.1%)
Blunt assault	7 (6.3%)	0 (0.0%)	7 (5.2%)	1 (1.4%)	0 (0.0%)	1 (1.1%)
Other	6 (5.4%)	3 (12.5%)	9 (6.7%)	7 (9.7%)	2 (11.8%)	9 (10.1%)
Missing	0 (0.0%)	4 (16.7%)	4 (3.0%)			
AIS Head Neck ≥3	0 (0.0%)	2 (7.1%)	2 (1.4%)	29 (40.3%)	8 (47.1%)	37 (41.6%)
AIS Thorax ≥3	0 (0.0%)	0 (0.0%)	0 (0.0%)	52 (72.2%)	14 (82.4%)	66 (74.2%)
AIS Abdomen/pelvis ≥3	0 (0.0%)	0 (0.0%)	0 (0.0%)	20 (27.8%)	4 (23.5%)	24 (27.0%)
AIS ≥3 Extremity	0 (0.0%)	1 (3.6%)	1 (0.7%)	39 (54.2%)	6 (35.3%)	45 (50.6%)
TBI	0 (0.0%)	1 (3.6%)	1 (0.7%)	5 (6.9%)	1 (5.9%)	6 (6.7%)