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STATE OF THE ART REVIEW

Transfusion in trauma: empiric or guided therapy?

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Abstract

A state of the art lecture titled "Transfusion therapy in trauma—what to give? Empiric vs guided" was presented at the International Society on Thrombosis and Haemostasis Congress in 2024. Uncontrolled bleeding is the commonest preventable cause of death after traumatic injury. Hemostatic resuscitation is the foundation of contemporary transfusion practice for traumatic bleeding and has 2 main aims: to immediately support the circulating blood volume and to treat/prevent the associated trauma-induced coagulopathy. There are 2 broad types of hemostatic resuscitation strategy: empiric ratio-based therapy, often using red blood cells and fresh frozen plasma in a 1:1 ratio, and targeted therapy where the use of platelets, plasma, or fibrinogen is guided by laboratory or viscoelastic hemostatic tests. There are benefits, and limitations, to each strategy and neither approach has yet been shown to improve outcomes across all patient groups. Questions remain, and future directions for improving transfusion therapy are likely to require novel approaches that have greater flexibility to evaluate and treat heterogeneous trauma cohorts. Such approaches may include the integration of machine learning technologies in clinical systems, with real-time linkage of clinical and laboratory data, to aid early recognition of patients at the greatest risk of bleeding and to direct and individualize transfusion therapies. Greater mechanistic understanding of the underlying pathobiology of trauma-induced coagulopathy and the direct effects of common treatments on this process will be of equal importance to the development of new treatments. Finally, we summarize relevant new data on this topic presented at the 2024 ISTH Congress.

KEYWORDS
major hemorrhage, randomized controlled trials, transfusion protocols, trauma, trauma-induced coagulopathy

1 | INTRODUCTION

Traumatic injury accounts for as many as 6 million deaths every year worldwide and is the leading reason for the death of individuals between the ages of 5 and 29 years [1]. Uncontrolled hemorrhage is responsible for up to 40% of all trauma-related deaths, a statistic that has sustained the 2-decade long drive by the trauma research community to optimize hemorrhage therapy and improve patient outcomes [2–5]. Traumatic bleeding is associated with the severity of the sustained injury and the presence of hypotensive shock, but over and above these factors, bleeding is most severe in those patients who develop a rapid disturbance of their coagulation system, known as "trauma-induced coagulopathy" (TIC) [2–5]. TIC is a complex, heterogeneous, and incompletely understood process that can be broadly

described as having 2 phases: an early (eg, within minutes) hypocoagulable phase, often dominated by hyperfibrinolysis and which promotes bleeding, and a later (eg, 12-24 hours) procoagulant and proinflammatory state, which can increase the risk of thrombosis and organ failure [4–8].

From a clinical perspective, effective trauma hemorrhage management must not only maintain (or restore) sufficient blood volume to immediately support a patient's life while definitive control of bleeding is secured but also must treat and/or mitigate TIC to prevent worsening of bleeding [2–5]. These 2 tenets form the basis of contemporary transfusion practices for treating trauma hemorrhage, broadly described as "hemostatic resuscitation" [2–5,9] and which involves the early administration of tranexamic acid (TXA), red blood cells (RBCs), and blood products, such as fresh frozen plasma (FFP), platelets, and fibrinogen supplementation [9]. There are 2 commonly used strategies: an empiric approach, where prespecified volumes of RBC and blood products are administered (eg, RBC:FFP in a 1:1 ratio), and a guided therapeutic approach, which relies on results from either conventional coagulation tests (eg, prothrombin time/prothrombin time ratio [PT/PTr], Clauss fibrinogen) or viscoelastic tests (eg, thromboelastography [TEG] and rotational thromboelastometry [ROTEM]), to guide transfusion administration [10]. These 2 transfusion strategies confer distinct therapeutic benefits, as well as limitations, for trauma hemorrhage [10].

The aim of this narrative review is to provide an overview of the results from selected large transfusion–focused randomized controlled trials (RCTs) in trauma hemorrhage, focusing on 2 main outcomes: mortality and coagulopathy. In addition, we will ask how well the RCT data help us to understand how each strategy addresses more practical issues relating to acute major bleeding management, such as the speed of transfusion delivery and general applicability to real-world clinical situations. Our included RCTs evaluate the use of RBCs and blood products only—hemostatic factor concentrates, such as prothrombin complex or fibrinogen concentrates, are outside the scope of this review [11]. Finally, we will touch on suggestions for future directions for research within the trauma hemorrhage setting (Figure).

2 | PRACTICAL CHALLENGES TO CONSIDER WHEN MANAGING TRAUMA HEMORRHAGE

Trauma care is inherently challenging, not only because of the heterogeneity of both the patient population and the types of injuries sustained but also due to the unpredictable nature of the event and the time-critical need to treat complex injuries and associated bleeding [12]. Deaths from trauma hemorrhage occur quickly, with up to 60% taking place within the first 3 hours after injury [2]. Of note, transport times for patients from the scene of an accident to a treating hospital are often in the order of an hour or more, even in urban areas [13], which can add further challenges around accessibility to diagnostic tools and treatments in the very early postinjury phase. Military settings have additional, very specific situational challenges [14].

Identifying patients who are either at risk of, or who are, actively bleeding is also extremely challenging, even for experienced clinicians [15]. Occult bleeding from penetrating trauma and abdominal injuries is especially prone to being missed during initial assessments, with studies showing that major bleeding is accurately identified in only 70% of cases [15]. In younger individuals, compensatory physiological mechanisms that maintain a stable blood pressure and heart rate can mask early signs of shock and contribute to delays in the recognition of hemorrhage. In contrast, in older patients, the use of beta blockers, for example, can blunt the tachycardic response typically seen with bleeding [16–18]. When hemorrhage is not recognized and rapidly treated, mortality rates can increase by 3-fold [12].

The practice of evidence-based trauma care, like many other fields of medicine, can be further influenced by clinician, and/or treatment strategy, biases. For example, TXA therapy has been definitively shown to reduce mortality in trauma patients, across all ages, with the same efficacy for both sexes [19]. Despite this, a UK study evaluating real-world treatment of 200,000 adult trauma patients showed that half the number of eligible females received TXA compared with that of men, and often at a later timepoint, with the sex difference being most pronounced in older patients [20]. Recognition of such biases in trauma care—including in RCTs (see Table 1 [13,21–24] and Table 2 [25–27] for reporting participant numbers in receipt of TXA) when developing local practices will help optimize equitable treatment [20].

3 | CONSIDERATIONS WHEN APPLYING EVIDENCE FROM TRAUMA TRANSFUSION TRIALS IN REAL WORLD

RCT data offer one of the highest levels of evidence to support (or refute) the benefit of treatments. However, heterogeneous clinical situations, like trauma hemorrhage, can mean that trial results have varying degrees of applicability to day-to-day clinical work. What seems to be clear is that adoption of "major hemorrhage protocols" for trauma, when used at single centers (eg, when individualized to patient populations and the trauma facility), leads to improved clinical outcomes, including mortality [28].

4 | EMPIRIC TRANSFUSION APPROACHES

The rationale behind using an empiric approach is straightforward: immediate intervention is critical to prevent exsanguination, and a predefined "package" of transfusion therapy will (theoretically) minimize delays in administration and immediately address TIC using blood products. Numerous studies, including several RCTs (Table 1) [13,21,22,24], have shaped contemporary empiric transfusion strategies.

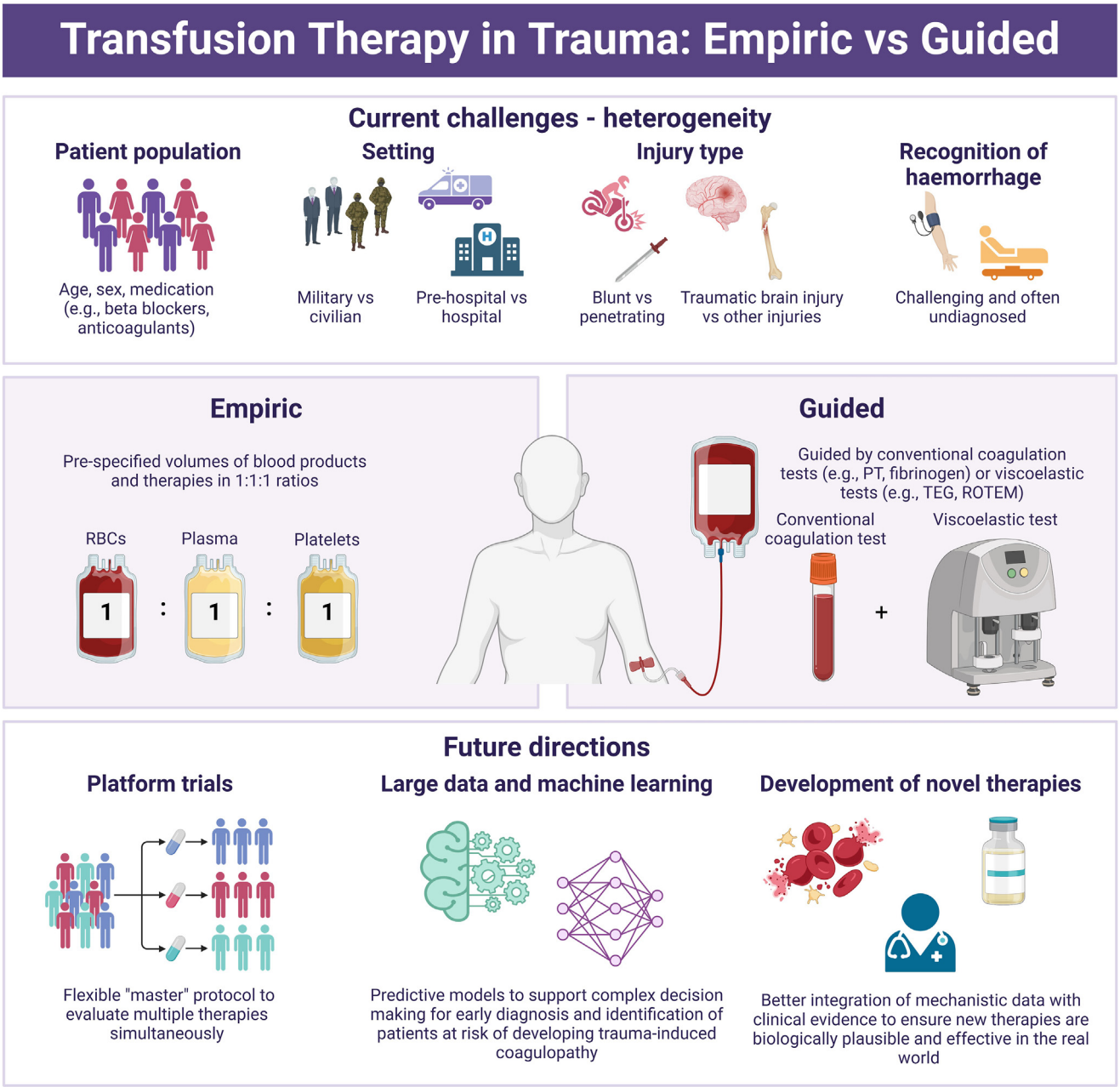

FIGURE Transfusion protocols for patients with significant bleeding after traumatic injury require rapid delivery of blood components, aiming to treat life-threatening bleeding and the associated coagulopathy. There are important challenges that clinicians face when treating these patients, not least due to the unexpected nature of the injury, which nearly always occurs outside a controlled clinical setting (eg, on the roadside or in a hostile military environment), but also due to the variability of injuries sustained and the challenges in detecting hemorrhage in a time-critical situation. Two broad strategies are adopted to help clinicians rapidly treat patients: (a) empiric, ratio-based therapy or guided therapy using laboratory or viscoelastic hemostatic test results. There are benefits, and limitations, to each of these strategies and neither approach has yet been shown to improve outcomes across all patients. Future directions for improving transfusion therapy are likely to require novel approaches that have the flexibility to evaluate heterogeneous trauma cohorts. Such approaches may include platform trials, which can also maximize real-time linkage of clinical and laboratory data, to both predict patients at the greatest risk of bleeding and direct and individualize transfusion therapies. PT, prothrombin time; ROTEM, rotational thromboelastometry; TEG, thromboelastography.

A plethora of observational studies provided weak evidence of improved survival with higher blood product:RBC ratios than was with usual care at that time [29], though no specific ratio (eg, 1:1 or 1:2 of FFP:RBC or platelet:RBC, respectively) was unequivocally superior. A detailed observational study (the Prospective, Observational, Multicenter, Major Trauma Transfusion study) aimed to better define optimal ratios and reported a 3- to 4-fold higher mortality at 6 hours from study entry for participants receiving "lower" FFP:platelet:RBC ratios (eg, <1:1:2) [30]. This study directly informed the choice of transfusion ratios (eg, 1:1:1 vs 1:1:2) subsequently compared in the

TABLE 1 Included transfusion trauma randomized controlled trials using an empiric approach.

Trial characteristics	PROPPR 2015 [21]	PAMPer 2018 [22]	COMBAT 2018 [23]	RePHILL 2022 [24]	CRYOSTAT2 2023 [13]
Trial setting	In-hospital, multicenter	Prehospital, multicenter	Prehospital, single center	Prehospital, multicenter	In-hospital, multicenter
Intervention	1:1:1 FFP:Plts:RBC (n = 338)	2 units of plasma (AB or low-titer A) (n = 205)	2 units of thawed plasma (n = 65)	RBC + Lyoplas (n = 216)	3 pools of cryoprecipitate + standard care (n = 799)
Comparator	1:1:2 FFP:Plts:RBC (n = 342)	Standard care (n = 271)	0.9% saline (n = 60)	0.9% saline (n = 216)	Standard care (n = 805)
Primary endpoint	24-h and 30-d all-cause mortality	30-d all-cause mortality	28-d all-cause mortality	All-cause mortality from injury to discharge, failure to reduce lactate by <20% per h in the first 2 h, or both.	28-d all-cause mortality
Time to study intervention	8 min	84% within 40 min	32% within 19 min	26 min	68 min
Primary outcome	No difference in 24-h or 30-d all-cause mortality (12.7% vs 17.0% at 24 h, P = .12; 22.4% vs 26.1% at 30 d, P = .26)	Reduction in 30-d all-cause mortality with plasma (23.2% vs 33.0%, P = .03)	No difference in 28-d all-cause mortality (23.9% vs 26.2%, P = .81)	No difference in composite outcome (64.7% vs 65.7%, P = .87)	No difference in 28-d all-cause mortality (36.4% vs 36.2%, P = .95)
Trial data relating to coagulopathy and TBI					
% recruits with coagulation samples taken at the study entry	INR sample drawn in 64%	INR sample drawn in 90%	INR sample drawn in 52%	INR sample drawn in 36.5%	NR
Coagulation results at study entry	I: median INR, 1.3 (IQR: 1.2-1.5); 17% INR > 1.5 C: median INR, 1.3 (IQR: 1.2-1.5); 17% INR > 1.5	I: median INR, 1.3 (IQR: 1.1-1.6) C: median INR, 1.2 (IQR: 1.1-1.4)	I: median INR, 1.1 (IQR: 1.0-1.2); 6% INR > 1.3 C: median INR, 1.1 (IQR: 1-1.1), 7% INR > 1.3	I: 14% INR > 1.5 C: 16% INR > 1.5	NR
Effect of study intervention on coagulopathy	NR	Median INR reduced from 1.3 to 1.2 with plasma	Median INR increased to 1.27 from 1.1 with plasma	NR	NR
% of total participants in receipt of tranexamic acid	NR	NR	13/125 10%	388/432 89.8%	1254/1579 80%
% of total participants reported to have TBI	NR	175/501 36%	28/125 22.4%	61/128[a] 47.6%	348/1604 21.6%

C, comparator; COMBAT, Control of Major Bleeding After Trauma; CRYOSTAT-2, Cryoprecipitate in Trauma Study; FFP, fresh frozen plasma; Hb, hemoglobin; I, intervention; INR, international normalized ratio; Lyoplas, lyophilized plasma; N, number; NR, not reported; PAMPer, Prehospital Air Medical Plasma; Plts, platelets; PROPPR, Pragmatic Randomised Optimal Platelet and Plasma Ratios; RBC, red blood cells; RePHILL, Resuscitation with Prehospital Blood Products; TBI, traumatic brain injury; TEG, thromboelastography; TXA, tranexamic acid; VHA, viscoelastic hemostatic assay.

[a]Where data were recorded; 48% of those recruited to RePHILL were designated to have an accompanying traumatic brain injury.

TABLE 2 Included transfusion trauma randomized controlled trials using a guided approach.

Trial characteristics	TrFL 2013 [25]	iTACTIC 2021 [26]	Rapid TEG study 2016 [27]
Trial setting	In-hospital, single center	In-hospital, multicenter	In-hospital, single center
Intervention	Fixed ratio (1:1:1) transfusion protocol (n = 37)	Empiric MHP augmented by VHA (n = 201)	MHP goal directed by TEG (n = 55)
Comparator	Laboratory result–guided transfusion protocol (n = 32)	Empiric MHP augmented by CCT (n = 195)	MHP goal directed by CCT (n = 56)
Primary endpoint	Feasibility of delivering a fixed ratio transfusion protocol	Alive and free of massive transfusion at 24 h	28-d survival
Time to study intervention	RBC receipt median: 25.5 mins FFP receipt median: 89 mins	VHA-guided transfusion median: 61 mins	NR
Primary outcome	Fixed ratio transfusion achieved in 57% (21/37)	No difference (VHA: 67%; CCT: 64%; OR: 1.15; 95% CI: 0.76-1.73)	Improved survival (TEG mortality 19.6% vs 36.4% CCT, P = .049)
Thresholds for therapy			
FFP supplementation	I: 1:1:1 fixed ratio C: CCT: if INR > 1.8	I: TEG: if rTEG MA > 65 mm and rTEG ACT > 120 s ROTEM: if EXTEM CA5 > 40 mm and EXTEM CT > 80 s C: CCT: if INR > 1.2 and Fg > 2 g/L	I: TEG: ACT > 140 s C: CCT: INR >1.5
Plt supplementation	I: 1:1:1 fixed-ratio C: CCT: if Plt < 50 × 10^9/L	I: TEG: if (rTEG MA − ffTEG MA) < 45 mm ROTEM: if (EXTEM CA5 − FIBTEM CA5) < 30 mm C: CCT: if Plt < 100 × 10^9/L	I: TEG: if MA < 55mm C: CCT: Plt < 100 × 10^9/L
Fibrinogen supplementation	NR	I: TEG: if ffTEG MA < 20 mm ROTEM: if FIBTEM CA5 < 10 mm C: CCT: if Fg < 2 g/L	I: TEG: if ACT > 140 s C: CCT: if Fg < 1.5 g/L
Trial data relating to coagulopathy and TBI			
% recruits with coagulation samples taken at study entry	INR and Clauss Fg taken in 100%	Samples drawn in 100%	Samples drawn in 100%
Coagulation results at study entry	I: median INR, 1.2 (1.1-1.5); mean Clauss Fg, 1.5 ± 0.8 g/L C: median INR, 1.4 (1.2-1.7); mean Clauss Fg, 1.2 ± 0.6 g/L	I: 25% PTr > 1.2; median Clauss Fg, 1.9 (1.5-2.4) C: 32% PTr > 1.2; median Clauss Fg, 2.0 (1.4-2.4)	I: median INR, 1.45 (1.2-1.7); median Clauss Fg, 1.32 (0.94-2.20) g/L C: median INR, 1.46 (1.2-2.3); median Clauss Fg, 1.13 (0.68-1.39) g/L
Effect of study intervention on coagulopathy	NR	NR	No differences between groups for TEG parameters
% of total participants in receipt of TXA	NR	377/393 96%	13/111 12%
% of total participants reported to have TBI	25/69 36%	74/392 19%	21/111 19%

a, angle (rate of fibrin polymerization); ACT, activated clotting time; C, comparator; CCT, conventional coagulation test; EXTEM, external TEM (test for clot formation in whole blood); ffMA, functional fibrinogen maximum amplitude; Fg, Clauss fibrinogen; FIBTEM, fibrin-based rotational thromboelastometry; INR, international normalized ratio; iTACTIC, Implementing Treatment Algorithms for the Correction of Trauma-Induced Coagulopathy; MHP, major hemorrhage protocol; NR, not reported; Plt, platelet; ROTEM, rotational thromboelastometry; rTEG, rapid thromboelastography; TBI, traumatic brain injury; TEG, thromboelastography; TrFL, trauma resuscitation and fixed-ratio levels; TXA, tranexamic acid; VHA, viscoelastic hemostatic assay.

first, landmark trauma transfusion RCT: the Pragmatic, Randomized Optimal Platelets and Plasma Ratios (PROPPR) trial (Table 1) [21]. Although this trial revealed no differences between arms for the primary endpoint of all-cause mortality at 24 hours and 30 days, an early, sustained separation in survival favoring the 1:1:1 group and the post hoc findings of reduced numbers of deaths from bleeding and shorter times to hemostasis in this same group led many trauma systems in higher income countries to adopt the 1:1:1 ratio of plasma, platelets, and RBCs as their recommended standard of care [3,31]. No data were reported within PROPPR on the effects of either transfusion ratio strategy on coagulopathy measures.

Subsequent RCTs built on the findings of PROPPR by exploring whether even earlier transfusion, in the prehospital setting, improved survival [22–24]. Two US-based RCTs [22,23] both investigated whether 2 units of early plasma therapy improved 28- to 30-day survival. Despite similar trial design, their headline results differed (Table 1). The Prehospital Air Medical Plasma (PAMPer) trial reported a 30% relative reduction in death rate with an accompanying improvement in TIC (as measured by INR) [22], whereas the Control of Major Bleeding After Trauma (COMBAT) trial found no survival benefit from plasma and a worsening of INR at hospital admission [23]. The third RCT, the Resuscitation with Pre-Hospital Blood Products (RePHILL) trial, which compared prehospital RBC and lyophilized plasma (up to 2 units of each) to 0.9% normal saline, found no survival benefit (the primary endpoint was a composite of in-hospital mortality and/or lactate clearance) and did not report treatment effects on coagulopathy [24].

There are noteworthy differences between the 2 US-based plasma trials, which offer insights into some of the important considerations for clinicians when developing local transfusion protocols. A combined analysis of PAMPer and COMBAT showed that the greatest survival benefit from prehospital plasma was seen for patients with blunt injury and/or those who required a "moderate-range" RBC transfusion (eg, between 4 and 7 units) [32]. Blunt injury was less common (50% vs 80%) in the COMBAT population, and fewer than 20 participants required "moderate" transfusion. Transfer times also likely played a role (40 minutes vs 19 minutes for PAMPer vs COMBAT, respectively), and a post hoc analysis suggested that prehospital plasma conferred survival benefit only for transfers longer than 20 minutes [33], suggesting that prehospital plasma may have a greater life-saving potential in rural/more austere settings.

The final large efficacy RCT we have chosen in this group of trials is the CRYOSTAT2 study [13]. This trial focused on optimizing fibrinogen levels to mitigate TIC and improve 28-day mortality. Notably, due to the pragmatic nature of this study, no pre-enrolment (or indeed posttreatment) coagulation screens were taken. The main result confirmed no difference in all-cause mortality between study arms [13]. However, as with many RCTs, subgroup analysis highlighted interesting results. The effect of early, empiric cryoprecipitate on 28-day mortality was conflicting, which was dependent on a participant's mechanism of injury: for example, blunt injury has a 34.8% vs 30.4% death rate; an odds ratio (OR) of 0.82 (95% CI: 0.62-1.09), and standard care and early cryoprecipitate, respectively, when compared with penetrating injury (10.0% vs 16.2%; OR: 1.73 [95% CI: 1.20-2.51]). This salutary suggestion for harm in the penetrating injury group indicates that a "one-size" fits all empiric therapy approach, particularly for fibrinogen replacement, is not a safe approach.

The strengths of using empiric transfusion therapy, such as rapid delivery (confirmed by PROPPR, where the average time to RBC receipt was 8 minutes; Tables 1 and 2) [21], must be tempered with the recognition that empiric transfusion may lead to overtreatment, with unnecessary interventions increasing risks of complications, or even death.

5 | COAGULATION-GUIDED TRANSFUSION STRATEGIES

Guided therapy in trauma care most commonly uses an approach that augments/adjusts empiric transfusion. Coagulation results, either conventional plasma-based or viscoelastic whole blood assays, are used (with predefined thresholds) to guide the administration of plasma, platelets, and fibrinogen (Table 2). The overarching principle behind this approach is to tailor treatment to the individual, which in such a heterogenous population has been proposed as a better means of improving patient outcomes. Three RCTs are included here [25–27].

The Trauma Fluid and Blood Resuscitation study is the only reported RCT that has directly compared an empiric strategy (1:1:1 of FFP:platelets:RBC, respectively) with conventional coagulation result–guided transfusion (using an INR of 1.8 and a platelet count of 50×10^{-9}/L as thresholds) [25]. It was a small pilot study (n = 69 in total), and the 30-day mortality endpoint was a secondary analysis. With these limitations in mind, the study reported a suggestion of improved survival with lab-guided transfusion (risk ratio of death with 1:1:1 treatment: 2.25 [95% CI: 0.90-5.62]). However, no large efficacy RCT has gone on to directly compare these 2 strategies.

Two RCTs have investigated whether viscoelastic assays (VHAs; eg, TEG and/or ROTEM) improve mortality [26,27]. The Implementing Treatment Algorithms for the Correction of Trauma-Induced Coagulopathy (iTACTIC) trial was a multicenter, large European RCT that compared VHA-guided to conventional coagulation test (CCT)–guided transfusion protocols. Notably, all patients were given immediate empiric transfusion (commonly FFP:RBC at 1:1 ratio) while awaiting coagulation results. No difference in the primary outcome—patients alive and free from massive transfusion at 24 hours—was seen in the VHA (67%) and CCT groups (64%; OR: 1.15; 95% CI: 0.76-1.73), suggesting that perhaps CCT- and VHA-directed methods are of equal benefit to trauma, although more transfusions were directed by VHA tests due to the speed of result availability. It is noteworthy that the premise of iTACTIC, which was to primarily recognize and treat TIC to thereby improve clinical outcomes, was hampered by the fact that only 28% of all participants had TIC at study enrolment [26]. The second, smaller, and single-center RCT we have included reported a significant reduction in mortality with TEG guidance (Table 2), and meta-analysis of the 2 RCTs tends to favor VHA-guided approaches: relative risk of death: 0.75 (95% CI: 0.48-1.17).

Once again, secondary endpoint data from these RCTs can help direct future research questions and, in the shorter term, the choice of local transfusion practices. A prespecified subgroup analysis in the iTACTIC trial suggested that VHA guidance was of greater longer-term benefit for participants with traumatic brain injury (TBI), reporting an adjusted OR of death at day 28: 0.16 (95% CI: 0.03-0.90) [26]. It is not clear, yet, why there is a distinction in the outcome for patients with TBI, but it does raise the question of whether in this injury type CCTs may fail to capture the hemostatic dysfunction of TBI as effectively as VHA.

6 | WHAT CAN WE LEARN FROM THESE RCTS FOR CLINICAL PRACTICE

Taking these data in totality and asking how well does the RCT evidence support whether empiric or coagulation-guided transfusion strategies improve survival and/or treat TIC, it is fairly evident that none of the large, multicenter RCTs definitively show overall survival benefit from their approach for all included participants. Equally, the results rarely show (the notable exception being PAMPer) [22] an improvement in TIC following an intervention that simultaneously improves survival. So, why is this?

There are too many interrelated variables to answer this complex question in full, but 2 important reasons stem from the challenges of conducting time-critical RCTs in a heterogeneous clinical arena. First, participant recruitment into all included RCTs was based on a methodology that supported pragmatism, by using clinical gestalt (eg, is this patient suffering from shock due to bleeding combined with simple blood pressure/pulse measures), to enroll patients rather than specific coagulation/coagulopathy parameters. This meant that many randomized patients did not have the clinical condition of interest (eg, TIC—see Tables 1 and 2 for coagulopathy rates, where reported, ranging between 6% and 28% at enrolment), or, as we have highlighted already, the heterogeneity of the patient population, particularly for important parameters such as the mechanism of injury (blunt vs penetrating) or the presence of TBI (see Tables 1 and 2 for variability across studies), which will have "diluted" overall results as these differences appear to strongly influence treatment response. Finally, most included RCTs have reported either 28- to 30-day or 24-hour mortality figures as their primary endpoint. The underlying premise for all transfusion trials is to improve outcomes by reducing early bleeding. Death from bleeding occurs in 3 quarters of trauma patients by 6 hours, with most by 3 hours [34]. Interrogation of timed mortality data for some of the included RCTs has demonstrated early separation of mortality rates by 3 hours [21,24], and so moving forward, many argue that future RCTs should use earlier timepoints.

As clinicians, therefore, these RCTs should be used as a guide while developing major hemorrhage protocols, and weight should be placed on knowledge of our local trauma populations, geography (rural vs urban), mechanisms of injury, etc. Also, with this knowledge, we will need to weigh up whether early prehospital plasma is of benefit to our patients, or whether the cost–benefit ratio of VHA-based assay regimens favors our hospital and patient demographics.

7 | INTERNATIONAL SOCIETY ON THROMBOSIS AND HEMOSTASIS 2024 CONGRESS REPORT

Several abstracts were presented at the International Society on Thrombosis and Haemostasis 2024 Congress that are relevant to trauma hemorrhage. TXA is used routinely in many, but not all countries, as immediate treatment for bleeding trauma patients [19]. Doses of TXA are often predefined for adults; for example, 1 g bolus and 1 g infusion for all trauma patients irrespective of weight, renal function, severity of bleed, etc. Quantifying TXA concentrations in plasma is likely to support a more individualized therapeutic approach, and a novel FRET-based assay using a fluorescently labeled plasminogen variant (S741C) that binds to fibrin degradation products was presented [11]. The premise of the assay was that the presence of TXA in plasma causes the dissociation of S741C from fibrin degradation products in a dose-dependent manner. The assay was shown to reliably measure TXA plasma concentrations across clinically relevant ranges (eg, 1-100 μM TXA). Future development of this assay into a point-of-care measurement will offer an exciting means for clinicians to refine optimal TXA treatment.

Two abstracts presented data using microfluidic models and investigated the effects of platelet transfusions on hemostatic function. These abstracts reported data using platelet pools that were variably stored either using standard room temperature (RT; 22 °C) or cold storage (4 °C) and for variable duration, between 0 and 14 days. The first paper focused on TBI patients who were taking antiplatelet medication at the time of injury [11]. The authors sought to answer (a) whether there was a functionally important and detectable platelet dysfunction in TBI patients prior to treatment, (b) whether transfused platelets improved the overall hemostatic function (as measured by the rate and size of platelet thrombus formation in a collagen-coated microfluidic system under a high shear of 3500 s^{-1}), and (c) whether the storage method of individual platelet pools impacted the hemostatic function. Samples pre- and posttransfusion were taken from treated TBI patients. The authors found evidence of significant platelet dysfunction in TBI patients at admission but were unable to show a differential impact of temperature on thrombus formation after platelet transfusion. There was a suggestion that platelets stored for shorter periods had greater capacity to form thrombi in the microfluidic system.

The second abstract focused on the effects of transfused platelets on blood loss in a microfluidic model that aimed to recapitulate arterial transection under high shear. The platelets were tested in a simulated "coagulopathic" (eg, via dilution of healthy volunteer whole blood with saline, 2:3 v/v) or thrombocytopenic system. Cold-stored platelets led to more rapid hemostasis when compared to RT platelets, and interestingly, most platelets recruited to the forming thrombi

came from transfused sources, rather than of recipient platelet origin. Day-2 (the shortest stored) platelet pools consistently led to lowest blood loss measures in all experiments. Both papers investigate the role of allogeneic transfusion on TIC—showing differential effects according to patient medications, platelet pool age, and storage—an area that has not been considered in any of the included RCTs in this review. The use (and differential effects) of allogeneic sex-specific blood products is gaining interest particularly in the US [35].

The final abstract we have picked comes from a broader field, looking at the crosstalk between coagulation, inflammation, and the endothelium. Blood transfusion for acquired bleeding is given to save lives and improve coagulopathy, with the (perhaps simplistic) view that all treatments will have the same effect on stopping bleeding at all endothelial/vessel surfaces. The paper presented by Humphreys et al. [11] examines the hemostatic responses of various endothelial cell (EC) types (venous and arterial origin), specifically looking at fibrinolytic measures on the EC surface. Their results confirm that the hemostatic response is highly variable and dependent on the cell type and whether it is stimulated, for example, by inflammation or not. The heterogeneity of response to insults, such as inflammation, or indeed trauma-induced shock, is likely to play some role in the variability of responses to transfusion in patients with blunt (venous injury) or penetrating (arterial injury) and is one that is of translational importance.

8 | LIMITATIONS OF RCT DESIGNS

The last 20 years of trauma research has seen the completion and publication of many transfusion trials, which have shaped clinical practice. However, these RCTs have notable limitations. Each trial is designed to answer 1 specific question (a problem in such a heterogeneous, complex setting). Completion times are protracted, with the average duration between initial funding approval and study publication estimated at 5 to 8 years, the time during which contemporary clinical practice has often developed beyond the RCT question. Finally, each trial is often very costly to run (eg, CRYOSTAT2—£1.8 million, PROPPR—$9.2 million).

9 | POSSIBLE POTENTIAL SOLUTIONS AND FUTURE DIRECTIONS

9.1 | Platform trials

While platform trials are not a new concept, their use has come to the fore since the COVID-19 pandemic, notably following the success of the RECOVERY (A randomised trial of treatments to prevent death in patients hospitalised with pneumonia) trial [36]. Platform trials are designed using a flexible "master" protocol, which allows multiple therapies to be evaluated simultaneously, with the option of introducing new treatments or discontinuing ineffective ones as results emerge [37]. Such flexibility may suit the multifaceted and complex nature of trauma care, enabling the varied needs (and research questions) of trauma patients to be addressed simultaneously, speeding up high quality evidence synthesis, and potentially costing less overall. This is not to say that platform trials offer all the answers, and challenges will remain—such as choices of intervention, agreement for primary endpoints, and an absolute commitment across countries to work together to recruit patients. It must not be forgotten that the RECOVERY trial was so successful due to the very singular global importance of the COVID-19 pandemic, which united stakeholders, including governments and research funders, and drove the rapid recruitment and completion of the study.

9.2 | Large data and machine learning

Machine learning and artificial intelligence technology methods have the potential to support complex decision-making in clinical medicine by using and adapting decision/predictive models based on iterative mining of large datasets [38]. These types of methods are already beginning to be used in clinical practice to support TIC diagnosis [39], and it is likely that many more publications will follow. Such a methodology could support future RCT recruitment by aiding the accurate prediction of patients with TIC and thus facilitating greater enrolment of relevant patient populations. At a broader level, real-world data using continuous monitoring could also be used at the hospital level to alert clinicians of "at-risk" patients—who may have occult hemorrhage and require urgent clinical review [40].

9.3 | Development of novel therapies

The future direction of trauma hemorrhage research should strive for greater integration of clinical and scientific approaches. Deepening our mechanistic understanding of underlying changes that take place during hemorrhage and how treatments (TXA, blood products, and novel therapies) influence these changes will help us to develop more targeted approaches. It is noteworthy that although TXA became a cornerstone treatment for trauma hemorrhage since CRASH-2 was published in 2010 [19], we still have only a partial understanding of the underlying mechanisms by which TXA improves survival. Perhaps if we understood this more, we could develop synergistic treatments, or more efficacious antifibrinolytics. Future research must continue to integrate mechanistic data with clinical evidence, ensuring that new therapies are not only biologically plausible but also effective in real-world settings.

10 | Conclusion

The management of trauma hemorrhage is complex, and no single transfusion approach works for all patient settings. Best practice for trauma facilities at present will need to be adjusted according to local trauma populations, including ease of access to coagulation tests and transfusion products. Future advances in transfusion therapy will depend on our ability to translate mechanistic insights into the clinical

arena, with the help of advanced data analytics, to optimize the individualization of our future practices.

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Both L.B. and N.C. wrote the manuscript.

RELATIONSHIP DISCLOSURE

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