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The Role of Antifibrinolytics and Haemostatic Agents in Pillar II: Are We Making the Most of the Evidence?

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Abstract

Patient blood management is a multimodal, multidisciplinary approach designed to optimise the management of the patient's blood. Within this framework, Pillar II specifically focuses on minimising blood loss and optimising coagulation. Although surgical techniques are fundamental to this pillar, the pharmacological management of haemostasis using antifibrinolytics and haemostatic agents has emerged as a critical component of modern care. This article critically evaluates the current evidence supporting the use of tranexamic acid, fibrinogen concentrates, and prothrombin complex concentrates in major surgery and trauma. The robust evidence from landmark trials such as CRASH-2 and WOMAN showing reduced death due to bleeding with early tranexamic acid, and FIBRES demonstrating non-inferior clinical efficacy of fibrinogen concentrate versus cryoprecipitate, clinical adoption remains inconsistent. We explore the "implementation gap" and the disparity between high-level evidence and bedside practice, particularly regarding the timing of administration and the reliance on empiric fixed-ratio massive transfusion protocols over goal-directed bleeding management. The article argues that although we have powerful pharmacological tools to stabilise the "lethal triad" of coagulopathy, acidosis, and hypothermia, we are not yet maximising their potential. By integrating point-of-care viscoelastic haemostatic assays and adhering to evidence-based dosing and timing, clinicians can significantly improve patient outcomes and resource utilisation within PBM Pillar II.

Key words: patient blood management (PBM), tranexamic acid (TXA), fibrinogen concentrate (FC), prothrombin complex concentrate (PCC), viscoelastic hemostatic assay (VHA), goal-directed therapy, perioperative hemorrhage

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INTRODUCTION

Bleeding and coagulopathy remain major contributors to morbidity, mortality, and healthcare costs in surgery and trauma. The paradigm of patient blood management (PBM) has shifted the clinical focus from the blood products to the patient. Defined by the World Health Organization (WHO) as a patient-focused, evidence-based, and systematic approach, PBM aims to optimise the management of patients and the transfusion of blood products to ensure high-quality and effective patient care.[1] The strategy is built upon three pillars: optimisation of red cell mass (Pillar I), minimisation of blood loss and bleeding (Pillar II), and optimisation of tolerance to anaemia (Pillar III). Pillar II is perhaps the most dynamic of the three, operating primarily during the intraoperative and immediate postinjury phases where physiological insults are most acute. This pillar addresses a broad spectrum of contributors to haemorrhage and coagulopathy, including surgical bleeding, trauma-induced and dilutional coagulopathy, hyperfibrinolysis, hypothermia, acidosis, and the effects of anticoagulant or antiplatelet therapies. Although meticulous surgical haemostasis remains the cornerstone of minimising blood loss, the management of coagulopathy, often termed "medical haemostasis," is equally vital. Uncontrolled haemorrhage remains a leading cause of preventable death in trauma[2] and a significant source of morbidity in major surgery.[3] The physiological derangement known as the "lethal triad," consisting of coagulopathy, hypothermia, and acidosis, can rapidly render surgical control ineffective if not managed early and aggressively.

In recent decades, the pharmacological armamentarium for Pillar II has expanded significantly. Pharmacological modulation of haemostasis offers an opportunity to interrupt this cycle early, stabilise clot formation, and reduce reliance on allogeneic blood products.

Antifibrinolytics, specifically tranexamic acid (TXA), and specific clotting factor concentrates such as fibrinogen concentrate (FC) and prothrombin complex concentrates (PCCs), have moved from niche applications to central roles in haemorrhage management protocols. However, a critical question remains: Are we making the most of the evidence?

This article argues that "making the most of the evidence" requires a paradigm shift: moving beyond treating coagulopathy after it occurs to a preemptive, precision-based approach. By bridging the gap between clinical trials and bedside implementation, healthcare systems can significantly reduce allogeneic transfusion requirements and improve patient outcomes.

THE ANTIFIBRINOLYTIC IMPERATIVE: TRANEXAMIC ACID

Mechanism of Action

To understand the utility of TXA, one must understand the pathophysiology of coagulopathy. Surgical trauma and tissue injury release tissue plasminogen activator (t-PA). t-PA converts plasminogen into plasmin, an enzyme that aggressively degrades fibrin clots. Hyperfibrinolysis is a maladaptive response to severe tissue injury and shock, leading to the premature breakdown of clots thus exacerbating haemorrhage. TXA is a synthetic antifibrinolytic agent that exerts its effect primarily by competitively and reversibly inhibiting the activation of plasminogen, an action achieved by binding to the lysine-binding sites on plasminogen molecules. This blockade prevents plasminogen from binding to the fibrin matrix and subsequently being converted into plasmin by t-PA, thereby inhibiting fibrinolysis and stabilising blood clots to reduce haemorrhage (Figure).

At higher concentrations, TXA may also noncompetitively inhibit plasmin and, by reducing plasmin formation, can attenuate the plasmin-mediated activation of inflammatory pathways involving complement, monocytes, and neutrophils. It is critical to understand what TXA does not do. It is not a procoagulant. It does not promote new clot formation, activate platelets, or increase thrombin generation. It simply stabilises existing, appropriate clots by preventing their premature destruction. TXA is generally safe and effective when used appropriately. Large randomised trials show no clear increase in thrombotic events in trauma and postpartum haemorrhage when TXA is administered early. However, safety and net clinical benefit depend on indication, dose, and timing.

Clinical Applications

The evidence base for TXA in acute haemorrhage is consistent. The CRASH-2 trial (Clinical Randomisation of an Antifibrinolytic in Significant Trauma Haemorrhage), a landmark study involving 20211 trauma patients, fundamentally changed trauma resuscitation. It demonstrated that early administration of TXA (loading dose 1 g over 10 min followed by an infusion of 1 g over 8 h) reduced all-cause mortality and death due to bleeding within 4 weeks of injury without increasing the risk of vascular occlusive events.[4] Critically, the CRASH-2 trial and subsequent analyses highlighted the paramount importance of timing. The survival benefit was greatest when TXA was administered as early as possible, and within 3 h, administration after 3 hours was associated with an increased risk of death due to bleeding.[5] This time dependency suggests that the pathophysiology of coagulopathy evolves rapidly; early hyperfibrinolysis may transition to a fibrinolytic shutdown state, where antifibrinolytics could theoretically be harmful, although this mechanism is still debated. The CRASH-3 trial subsequently investigated TXA in 12737 patients with isolated traumatic brain injury (TBI).[6] It found that TXA reduced head injury–related death in patients with mild to

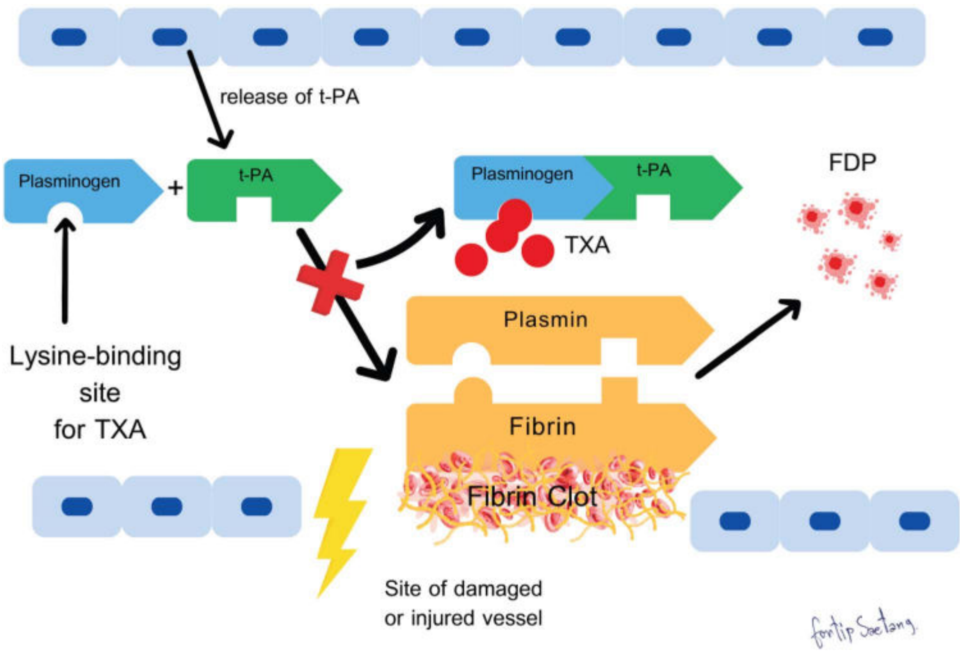

Figure – TXA binds reversibly to the lysine-binding sites on the plasminogen molecule. By occupying these sites, TXA prevents plasminogen from binding to the surface of fibrin. Consequently, the clot remains stable. FDP, fibrin degradation product; t-PA, tissue plasminogen activator; TXA, tranexamic acid moderate TBI (Glasgow Coma Scale score 9–15) and did not increase the risk of seizures or venous thromboembolism (VTE).

In obstetrics, the WOMAN trial (World Maternal Antifibrinolytic Trial) replicated these findings in the context of postpartum haemorrhage (PPH).[7] In 20 060 women, TXA significantly reduced death due to bleeding. The trial reinforced the safety profile of TXA, finding no increase in thromboembolic events even in this prothrombotic population. Consequently, WHO guidelines now recommend early TXA (a fixed dose of 1 g [100 mg/mL] intravenously at 1 mL/min, i.e., administered over 10 min, with a second dose of 1 g intravenously if bleeding continues after 30 min, or if bleeding restarts within 24 h of completing the first dose) for all cases of PPH, regardless of the cause.[8]

On the other hand, there is evidence suggesting that the administration of TXA may confer an unfavourable profile in certain specific conditions during the acute management of bleeding. The HALT-IT trial, which enrolled 12 009 patients, demonstrated that a TXA regimen of 1 g intravenously followed by 3 g over 24 h provided no mortality benefit in gastrointestinal haemorrhage.[9] Furthermore, this dosage was linked to a significant increase in adverse outcomes, including thromboembolic events and seizures. The increased risk of thromboembolic disease and seizures in this population likely stems from advanced age (mean 58 years), comorbidities such as cancer, and a high prevalence of liver disease (40%). In particular, the reduced fibrinolysis associated with cirrhosis may have predisposed this specific cohort to thrombotic complications compared with younger populations in previous trauma studies.

In the POISE-3 trial, a prophylactic regimen of 1 g intravenous TXA administered at both the start and the end of noncardiac surgery was evaluated in approximately 9500 patients.[10] This strategy successfully reduced the risk of major bleeding by an absolute 2.6%, demonstrating its efficacy in a broad surgical population. These findings suggest that TXA is a viable tool for improving perioperative outcomes in patients undergoing general surgery.

A previous systematic review and meta-analysis of over 129 trials showed that TXA reduces the probability of blood transfusion by approximately 34% in surgical patients.[11] In orthopaedic surgery, such as total hip and knee arthroplasty, both intravenous and topical TXA have been shown to reduce blood loss and transfusion rates significantly, with high-level evidence supporting its routine use.[12] Klingemann et al. published a pivotal systematic review and meta-analysis showing that TXA significantly reduces the need for blood transfusions in elderly patients (>65 years) undergoing hip fracture surgery.[13] The data indicate a 39% relative risk reduction in transfusion rates, whereas no increase in thromboembolic events was observed. The authors suggest that a higher dose of TXA (around 2 g total or 30 mg/kg) might be more effective than lower doses.

The ATACAS trial provided clarity in 4631 high-risk cardiac surgery patients.[14] TXA was superior to placebo in reducing blood loss and allogeneic transfusion (46% fewer units of blood product) and reduced the need for reoperation due to bleeding. Although higher doses of TXA (50–100 mg/kg) are effective, they carry a risk of seizures due to gamma-aminobutyric acid inhibition. The current evidence favours modest dosing regimens (e.g., 1 g bolus + 1 g infusion, or weight-based equivalents) that maximise haemostasis while mitigating neurotoxicity and theoretical thrombotic risks (Table 1).[15]

At least with regard to the use of TXA in cardiac surgery, following the publication of the ATACAS trial, several smaller studies and meta-analyses have corroborated the utility of lysine analogues, to the extent that their use is currently supported as a highest-level recommendation in clinical practice guidelines for PBM in cardiac surgery[16] Importantly, higher doses than those described in ATACAS have demonstrated a modest additional benefit in preventing major bleeding after cardiopulmonary bypass.[17] There have also been reports of an increased incidence of seizure events, albeit inconsistently across the literature.[18] Moreover, the advent of viscoelastic technologies for the assessment of haemostatic profiles in cardiac and noncardiac surgical patients has enabled not only the appropriate indication of TXA during episodes of perioperative bleeding but also dose titration and the differential diagnosis of other coagulopathies beyond hyperfibrinolysis. The accurate diagnosis and targeted management aimed at controlling specific pathophysiological processes, as well as the hierarchical and justified replacement of haemostatic components, are beyond the scope of this publication. Nevertheless, it is worth noting that the use of viscoelastic coagulation assessment technologies has made it possible to integrate both prophylactic and therapeutic indications of TXA within a multifactorial framework for haemostatic control.[19]

Systemic Haemostatic Agents

When antifibrinolytics alone are insufficient, or when specific coagulation defects arise, systemic haemostatic agents come into play. Pillar II advocates for goal-directed bleeding management using viscoelastic haemostatic assays (VHAs) such as rotational thromboelastometry (ROTEM) and thromboelastography (TEG) rather than empiric transfusion in fixed ratios of fresh frozen plasma (FFP), platelets, and red blood cells (RBCs).

From Cryoprecipitate to Fibrinogen Concentrate

Fibrinogen (factor I) is the final substrate of the coagulation cascade. It acts as the “bricks” of the clot. Thrombin converts soluble fibrinogen into insoluble fibrin monomers, which then polymerise to form the stable fibrin clot. Fibrinogen is the first coagulation factor to reach critically low levels during severe haemorrhage, due to consumption, dilution, and fibrinogenolysis. Hypofibrinogenemia is an independent predictor of mortality in trauma and major surgery.[20] Restoring fibrinogen levels is therefore a priority in Pillar II.

Historically, cryoprecipitate has been the standard source of fibrinogen replacement. As an allogeneic plasma-derived product, it carries inherent transfusion-related risks. However, operational delays and variability in fibrinogen content represent its principal disadvantages.

FC offers a purified, virus-inactivated alternative with precise dosing capabilities and rapid reconstitution. Its ability to be administered rapidly without cross-matching allows for earlier intervention.[21] In

Table 1 – Practical Guide: Tranexamic Acid

Indication	Prophylactic	All major surgery with expected blood loss >500 mL (e.g., cardiac, ortho, spine, neurosurgery)
	Therapeutic	Active Major bleeding in trauma, major surgery, or PPH
Timing	Elective	Give 15–30 min before surgical incision The goal is to have the drug at target concentration when bleeding starts.
	Trauma/PPH	As soon as possible, and always within 3 h of injury/bleeding onset (golden hour)
Dosing	Elective (e.g., ortho/spine)	1g IV fixed dose or 15–20 mg/kg A second dose (or infusion) sometimes used for long procedures
	Cardiac	10–mg/kg IV loading dose followed by an infusion 1 mg/kg/h
	Trauma/PPH	1 g IV over 10 min, followed by 1-g infusion over 8 h (per CRASH-2/WOMAN trial)
Safety & Risk	Thrombosis	Large RCTs (CRASH-2, WOMAN, ATACAS trial) confirm no increased risk of VTE, MI, or stroke. The HALT-IT trial demonstrated no mortality benefit in gastrointestinal haemorrhage and was associated with a significant increase in thromboembolic events and seizures.
	Seizures	This is a dose-dependent risk, especially at very high doses (>50–100 mg/kg), rapid injection, and in patients with renal failure.
Contraindications	Absolute	Known allergy
	Relative	Active thromboembolic disease (weigh risk/benefit) History of seizures Severe renal dysfunction (require dose adjustment)

Abbreviations: MI, myocardial infarction; PPH, postpartum haemorrhage; RCT, randomised controlled trial; TXA, tranexamic acid; VTE, venous thromboembolism.

fact, a recent study comparing FC with blood bank products (cryoprecipitate and FFP) for the management of hypofibrinogenemia in general surgery showed that failure to use FC delays intervention and increases the risk of inadequate correction.[22]

The pivotal FIBRES trial (Fibrinogen Replenishment in Surgery) compared FC with cryoprecipitate in patients undergoing cardiac surgery with cardiopulmonary bypass. The noninferiority trial demonstrated that FC was as effective as cryoprecipitate in reducing transfusion requirements and maintaining haemostasis, with a comparable safety profile.[23] The volume-sparing effect is crucial in preventing transfusion-associated circulatory overload (TACO), a major complication of massive transfusion. Studies in aortic surgery suggest that early fibrinogen replacement, guided by VHA (targeting improved maximum clot firmness in the thromboelastometric fibrin-based clot quality test [FIBTEM] on ROTEM), reduces the need for RBC and platelet transfusion.[24]

Another iconic study comparing FC with cryoprecipitate in the management of severe trauma was the FEISTY trial.[21] This multicentre randomised pilot study demonstrated that early fibrinogen replacement with FC significantly reduced the time to fibrinogen repletion with more predictable correction of hypofibrinogenemia compared with cryoprecipitate. The challenge remains in defining the "trigger" level. Current guidelines recommend maintaining the plasma fibrinogen level above 1.5 g/L in active bleeding[25] and calculating the dose of fibrinogen for a targeted increase in FIBTEM A10 (A5) amplitude.[26] However, special populations such as patients with PPH may need a higher level (>2 g/L).

Prothrombin Complex Concentrate

Four-factor PCCs (4F-PCCs) contain high concentrations of vitamin K–dependent clotting factors (II, VII, IX, X) involved in the coagulation cascade and are the gold standard for urgent warfarin reversal. However, their role in PBM Pillar II is expanding into the management of coagulopathy in trauma and complex surgery, challenging the dogma of FFP. FFP has been the mainstay of coagulopathy management for decades. However, it is an inefficient source of coagulation factors. To increase factor levels by just 10%, large volumes (10–15 mL/kg) are required, which carries significant risks of TACO, TRALI, and allergic reactions. Furthermore, the length of time required to thaw and issue FFP often delays resuscitation.

Prothrombin Complex Concentrate in Acquired Coagulopathy

PCCs offers a low-volume, rapidly administered source of coagulation factors that can immediately correct the international normalised ratio (INR) and restore thrombin generation. In the context of cardiac surgery, Nemeth et al. have shown that PCC-guided algorithms can reduce allogeneic blood transfusion, stage 3 acute kidney injury, and 30-day mortality rates compared with FFP-based strategies.[27] In trauma, the RETIC (Reversal of Trauma-Induced Coagulopathy) study suggested that first-line therapy with factor concentrates (fibrinogen and PCCs) was superior to FFP in reversing coagulopathy and reducing massive transfusion needs.[28]

However, the use of PCC for nonwarfarin coagulopathy is fraught with safety concerns, primarily thrombotic complications. In the PROCOAG multicentre randomised controlled trial involving 324 severe trauma patients at risk of massive transfusion, the early administration of 4F-PCCs combined with a ratio-based transfusion protocol did not reduce 24-hour blood product consumption compared to placebo (median 12 vs 11 units; p=0.72). However, patients receiving 4F-PCCs experienced a significantly higher rate of thromboembolic events (35% vs 24%; relative risk 1.48; p=0.03), indicating that systematic use of 4F-PCCs in this population is not supported and may be harmful.[29] Unlike TXA, where safety is well-established, PCCs are potent prothrombotic agents. The "blanket" use of PCC in trauma without evidence of factor deficiency is controversial. PCCs in trauma should not be used empirically; if used at all, it should be highly selected and embedded in a goal-directed algorithm with a clear rationale and awareness of the thrombotic risk (Table 2). With respect to the use of PCCs, specifically in the context of cardiac surgery, approximately 10% to 20% of patients require replacement of enzymatic coagulation factors according to goal-directed haemostatic therapy protocols.[30] The FARES-II trial helps to clarify several previously unresolved questions.[31] This multicentre, randomised, phase 3 noninferiority study demonstrated that 4F-PCCs provide superior haemostatic effectiveness compared with FFP for the treatment of coagulopathic bleeding after cardiopulmonary bypass while reducing allogeneic blood product transfusion requirements. In addition, PCCs use was associated with fewer serious adverse events and a lower incidence of acute kidney injury, without an increase in mortality or thromboembolic complications. Collectively, these findings support PCCs as a more effective and potentially safer alternative to plasma for coagulation factor replacement in bleeding cardiac surgery patients, reinforcing its role within contemporary PBM and goal-directed haemostatic therapy algorithms. The evidence presented here does not mean universal adoption, but rather highly selected, goal-directed use.

The Role of Viscoelastic Haemostatic Assay

For decades, transfusion decisions in active bleeding were guided by traditional coagulation tests (prothrombin time, activated partial thromboplastin time, INR, platelet count). This approach is fundamentally flawed because the results are slow, correlate poorly with clinical bleeding, and provide an incomplete picture by measuring only the initiation of clot formation in plasma. To truly "make the most of the evidence" regarding these potent agents, blind administration must be replaced by precision medicine.

VHAs, such as ROTEM and TEG, provide a point-of-care, real-time, global assessment of clot formation, strength, and lysis.[32] VHAs are the "brain" of Pillar II pharmacological interventions. They allow clinicians to differentiate the following:

1. Delayed clotting time due to factor deficiency (indicating a need for coagulation factor replacement)
2. Low clot firmness due to fibrinogen deficiency (indicating a need for fibrinogen replacement)
3. Platelet dysfunction (indicating the need for platelet function correction)
4. Hyperfibrinolysis (indicating a need for antifibrinolytics)

The evidence supports VHA-guided transfusion algorithms over fixed-ratio (e.g., 1:1:1) massive transfusion protocols in reducing blood product utilisation and improving outcomes in cardiac surgery and trauma.[33,34] PBM guidelines increasingly recommend VHAs as the standard for monitoring coagulation in major haemorrhage.[2,3] However, VHAs demonstrable outcome benefits depend on clinical context, implementation strategy, and protocol adherence.

Bridging the Gap: Evidence versus Practice

Several barriers persist that prevent the full realisation of Pillar II's pharmacological potential.

- **The Implementation Gap in Trauma:** Despite CRASH-2, prehospital TXA administration is inconsistent. Logistics, a lack of protocol integration between ambulance services and trauma centres, and a lack of awareness in nontrauma surgical specialties contribute to missed "golden hour" opportunities. Availability of TXA during early evaluation and transportation of these populations may help overcome this gap.
- **The "Plasma First" Dogma:** Many institutions cling to FFP-heavy massive transfusion protocols despite evidence that FFP is poor at correcting coagulopathy and carries higher risks than factor concentrates. The slow adoption of FC in place of cryoprecipitate is driven more by unit cost (pharmacy budget versus blood bank budget) than by clinical efficacy or total cost of care.
- **Lack of Goal-Directed Bleeding Management:** The majority of hospitals still lack availability of VHAs in the operating

Table 2 – Practical Guide Factor(s) Concentrate

Agents	Indications	Dosing
Fibrinogen Concentrate	Hypofibrinogenemia in active major bleeding	2–4-g IV bolus, or weight-based (25–50 mg/kg)
	– ROTEM-FIBTEM A10 <10–12 mm – Lab fibrinogen ≤1.5 g/L	Check VHA/labs after dose
4-Factor PCCs	On-label: Urgent reversal of vitamin K antagonists	INR-based dosing (e.g., 25–50 IU/kg)
	Off-label: GDBM-proven thrombin generation deficit: prolonged EXTEM-CT after fibrinogen/platelets are corrected	GDBM: 20–30 IU/kg

Abbreviations: EXTEM-CT, extrinsic pathway coagulation time measured by the rotational thromboelastometry; GDBM, goal-directed bleeding management; IV, intravenous; ROTEM-FIBTEM, rotational thromboelastometry/thromboelastometric fibrin-based clot quality test; VHA, viscoelastic haemostatic assay.

theatre or emergency department (due to experience and cost). Without VHAs, clinicians are forced to treat empirically, leading to either undertreatment (ongoing bleeding) or overtreatment (thrombosis risk).

- **Silos of Care:** PBM requires multidisciplinary buy-in. Anaesthesiologists may drive the use of TXA and factor concentrates in a goal-directed strategy for preventing bleeding and maintaining haemostasis perioperatively, but if surgeons are not aligned or if haematologists rigidly control access to factor concentrates as replacement therapies in acquired coagulopathies (on-label use), therapy is delayed. Here, education and collaboration is key for quality improvement.

SUMMARY

Pillar II of PBM has evolved from a reliance on surgical ligation and allogeneic transfusion to a sophisticated pharmacological strategy targeting the specific pathophysiology of coagulopathy as indicated by the results from VHAs. The evidence for TXA is incontrovertible; it should be ubiquitously available, used early, and routinely in major haemorrhage. The evidence for FC and, to a lesser extent, PCCs, suggests they are superior alternatives to cryoprecipitate and FFP in specific goal-directed contexts, offering safety and efficiency benefits (Table 2). To optimise Pillar II, healthcare systems must move toward goal directed and personalised haemostatic resuscitation. We must ensure TXA is given within minutes, not hours, of injury. We must transition from "plasma for everyone" to "factors for the specific deficiency." Only by closing the gap between the published trials and the bedside protocol can we truly fulfil the PBM promise of improving patient outcomes while preserving the precious resource of donor blood.

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