

Early Goal-Directed Hemostatic Therapy for Severe Acute Bleeding Management in the Intensive Care Unit: A Narrative Review

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This is a narrative review of the published evidence for bleeding management in critically ill patients in different clinical settings in the intensive care unit (ICU). We aimed to describe “The Ten Steps” approach to early goal-directed hemostatic therapy (EGDHT) using point-of-care testing (POCT), coagulation factor concentrates, and hemostatic drugs, according to the individual needs of each patient. We searched National Library of Medicine, MEDLINE for publications relevant to management of critical ill bleeding patients in different settings in the ICU. Bibliographies of included articles were also searched to identify additional relevant studies. English-language systematic reviews, meta-analyses, randomized trials, observational studies, and case reports were reviewed. Data related to study methodology, patient population, bleeding management strategy, and clinical outcomes were qualitatively evaluated. According to systematic reviews and meta-analyses, EGDHT guided by viscoelastic testing (VET) has been associated with a reduction in transfusion utilization, improved morbidity and outcome in patients with active bleeding. Furthermore, literature data showed an increased risk of severe adverse events and poor clinical outcomes with inappropriate prophylactic uses of blood components to correct altered conventional coagulation tests (CCTs). Finally, prospective, randomized, controlled trials point to the role of goal-directed fibrinogen substitution to reduce bleeding and the amount of red blood cell (RBC) transfusion with the potential to decrease mortality. In conclusion, severe acute bleeding management in the ICU is still a major challenge for intensive care physicians. The organized and sequential approach to the bleeding patient, guided by POCT allows for rapid and effective bleeding control, through the rational use of blood components and hemostatic drugs, since VET can identify specific coagulation disorders in real time, guiding hemostatic therapy with coagulation factor concentrates and hemostatic drugs with individual goals. (Anesth Analg 2023;XXX:00–00)

GLOSSARY

4F-PCC = Four-Factor Prothrombin Complex Concentrate; **A5 and A10** = amplitude 5 or 10 minutes after CT; **ABC** = Ensure patient's Airway, Breathing, and Circulation; **ADPTEM** = adenosine diphosphate; **APA** = antiplatelet agents; **aPCC** = activated prothrombin complex concentrate; **APTEM** = aprotinin; **AP-test** = aprotinin-test; **aPTT** = activated partial thromboplastin time; **ARATEM** = arachidonic acid; **ARU** = aspirin reaction units; **AT** = antithrombin; **ATLS** = advanced trauma life support; **CBC** = complete blood count; **CCTs** = coagulation conventional tests; **CT** = clotting time; **DDAVP** = desmopressin; **DIC** = disseminated intravascular coagulation; **DOACs** = direct oral anticoagulants; **DTIs** = direct thrombin inhibitors; **dTT** = diluted thrombin time; **ECA-test** = and the ecarin test; **ECT** = ecarin clotting time; **EGDHT** = early goal-directed hemostatic therapy; **EXTEM** = extrinsic pathway, **EX-test** = extrinsic test; **FDA** = Food and Drug Administration; **FDP** = fibrin degradation products; **FFP** = fresh frozen plasma; **FIBTEM** = fibrinogen test, **FIB-test** = fibrinogen test; **FVII** = factor VII; **FXIII** = factor XIII; **Hb** = hemoglobin; **HEPTEM** = heparinase; **HEP-test** = heparinase test; **ICU** = intensive care unit; **INR** = international normalized ratio; **INTEM** = intrinsic pathway, **IN-test** = intrinsic test; **IV** = intravenous; **LI30,45 and 60** = lysis index at 30, 45 and 60 min after CT; **LMWH** = low molecular weight heparin; **LOT** = lysis onset time; **MAP** = mean arterial pressure; **MCF** = maximum clot

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firmness; **ML** = maximum lysis; **MODS** = multiple organ dysfunction syndrome; **NSAID** = nonsteroidal anti-inflammatory drugs; **NA-test** = native test; **PAI-1** = plasminogen activator inhibitor type 1; **PBM** = patient blood management; **PCC** = prothrombin complex concentrate; **PFT** = platelet function test; **POCT** = point-of-care testing; **POB** = perioperative bleeding; **PPH** = postpartum hemorrhage; **PRU** = P2Y12 reaction units; **PT** = prothrombin time; **RBC** = red blood cell; **RCTs** = randomized controlled trials; **ROTEM** = rotational thromboelastometry; **RR** = relative risk; **RVV-test** = Russell's viper venom test; **t-PA** = tissue plasminogen activator; **TACO** = transfusion-associated circulatory overload; **TAFI** = thrombin activatable fibrinolysis inhibitor; **TBI** = traumatic brain injury; **TEG** = thromboelastography; **TEM** = thromboelastometry; **TF** = tissue factor; **TFPI** = tissue factor pathway inhibitor; **TIC** = trauma-induced coagulopathy; **TRALI** = transfusion-related acute lung injury; **TRAPTEM** = thrombin-activating peptide test; **TRIM** = transfusion-related immunomodulation; **TXA** = tranexamic acid; **VET** = viscoelastic testing; **VKA** = vitamin K- antagonists; **vWD** = von Willebrand disease; **vWF** = von Willebrand factor; **xabans** = direct factor Xa inhibitors

Hemorrhage and thrombosis are frequent complications in the intensive care unit (ICU), compromising the clinical outcome of patients.¹ Among them, the main cause of death in the world is thrombosis. However, there is concern about the risk of bleeding in patients who have pathological results from conventional coagulation tests (CCTs).² For this reason, prophylactic transfusion of allogeneic blood components is still very frequent, even in the absence of bleeding. However, transfusion is associated with life-threatening adverse events.³ In this literature review, we aimed to describe critical aspects of the approach to patients with severe acute bleeding in the ICU, focusing on the importance of point-of-care testing (POCT) for early identification of coagulopathy to guide early goal-directed hemostatic therapy (EGDHT) using coagulation factor concentrates and hemostatic drugs.

HEMOSTASIS

Hemostasis considers the interrelation of physical, cellular, and biochemical processes and involves an activation of coagulation proteins, inhibitors, platelets, and components of the vascular wall to form a clot at the site of vessel injury, preventing or stopping bleeding.⁴ Hemostasis is an interplay between the endothelium, primary hemostasis, procoagulant system, natural inhibitors as well as fibrinolytic and antifibrinolytic systems (Figure 1).⁵ In the current understanding, the cell-based model of coagulation replaces the traditional "cascade" or "waterfall model" and proposes that coagulation takes place on cell surfaces in 4 subsequent steps (initiation, amplification, propagation, and stabilization).⁶ The recognition of the role of cell surface in clot formation allows an integrated understanding of the dynamic mechanisms of hemostasis in the vascular system.⁷ The biochemical environment determined by pH, temperature, and Ca^{2+} , is critical for thrombin generation and clot formation. The coagulation cascade is also downregulated by physiological inactivation of coagulation factors.⁸ The natural inhibitors composed of antithrombin (AT), protein C and its cofactor protein S, as well as tissue factor pathway inhibitor (TFPI)

play a regulatory role in the procoagulant activity, thus limiting the formation of the thrombus (Supplemental Digital Content, Supplemental Figures 1 and 2, <http://links.lww.com/AA/E583>).⁸⁻¹¹ Fibrinolysis is an enzymatic process that dissolves the fibrin clot into fibrin degradation products (FDP and D-dimers) by plasmin during the activation of the coagulation cascade limiting the size and extent of clots (Supplemental Digital Content, Supplemental Figure 3, <http://links.lww.com/AA/E583>).⁵

A severe deficiency of only 1 procoagulant factor (<10%), for example, factor VII (FVII), can be associated with bleeding.⁹ Hence, bleeding in critically ill patients has most often a multifactorial etiology.^{10,11} In fact, the presence of bleeding will occur as a result of the imbalance of different pathways that comprise hemostasis, including coagulation factors, natural inhibitors, fibrinolysis, and endothelium. For a proper approach to patients with coagulopathy, it is essential to use a diagnostic tool that allows assessing in real time, the cellular component, biochemical phenomenon, and the whole process of clot formation, as well as platelet function.¹²

LABORATORY TESTS

Conventional Coagulation Tests

Prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT) are important tests for the monitoring of anti-coagulant drugs such as warfarin and heparin.¹³ In contrast, CCTs are poor predictors of bleeding in the setting of critically ill patients.¹⁴ CCTs are performed in plasma at a standardized temperature of 37°C. Due to removal of the cellular fraction, these tests do not consider the role of blood cells and the platelet component.¹⁵ Further, do they only access the first 5% of the process of thrombin generation,¹⁶ and fibrinolysis cannot be determined.

Viscoelastic Testing

Viscoelastic testing (VET) provides a quick and comprehensive graphical representation of the dynamics of the entire clot formation and lysis process that can

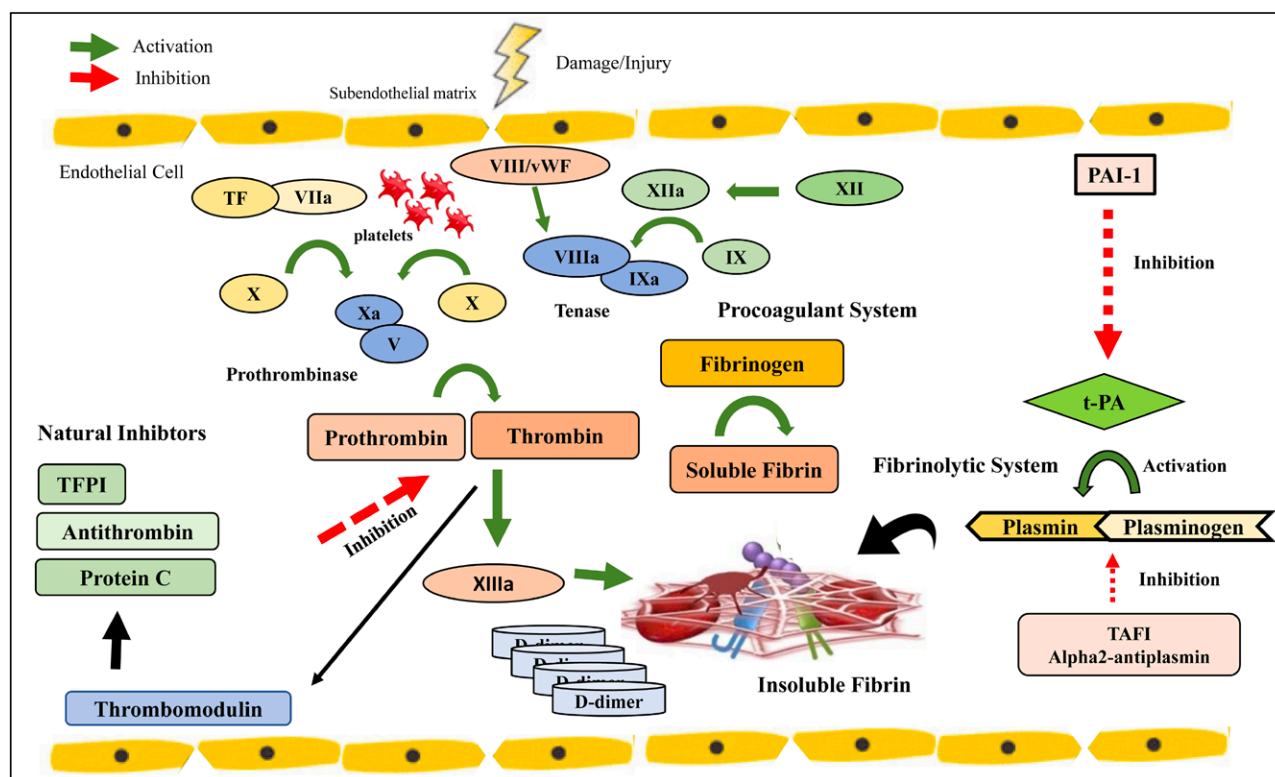


Figure 1. Hemostasis. PAI-1 indicates plasminogen activator inhibitor type 1; TAFI, thrombin activatable fibrinolysis inhibitor; TF, tissue factor; TFPI, tissue factor pathway inhibitor; t-PA, tissue plasminogen activator; vWF, von Willebrand factor.

be evaluated and reviewed at the point of care. This technology is over 70 years old; however, in recent years there has been a significant increase in research examining the use of VET in acute critical bleeding settings. Currently, best practice guidelines for implementing the use of VET-guided algorithms are an essential part of the patient blood management (PBM) concept, and recommend the use of VET in the diagnosis of trauma-induced coagulopathy (TIC), as well as to guide hemostatic interventions in perioperative bleeding (POB). The main technologies studied include rotational thromboelastometry (TEM, Tem Innovation GmbH), and thromboelastography (TEG, Haemonetics Corporation). However, more recently, the Quantra analyzer (HemoSonics LLC) is based on sonorheometry, and the ClotPro system (enicor GmbH; Haemonetics Corporation) based on thromboelastometry has been introduced into the market, too.^{20,21}

Thromboelastography and Thromboelastometry

The TEG method was first described by Helmut Hartert in 1948, a VET to evaluate the function of the coagulation system.¹⁷ The first commercial generation of modern VET-devices, the TEG5000, was very sensitive to agitation and therefore required a specific environment in the laboratory to avoid artifacts.¹⁸ Furthermore, assays with tissue factor (TF) as an activator and additional additives (such as platelet

inhibitors or aprotinin) for more specific diagnostic tests were developed later.¹⁹

Rotational thromboelastometry including rotational thromboelastometry (ROTEM) 05, *gamma*, and *delta*, came up in the mid-1990s to assess the viscoelastic changes of blood during the whole period of clot formation. ROTEM 05, *gamma*, and *delta* are semiautomated devices using modern software, composed of 4 integrated channels, an electronic pipette, and color-coded reagents and graphics (temograms).²⁰ Currently, ROTEM *sigma* is a fully automated device with 2 different cartridges allowing closed-tube sampling, without pipetting or manual reagent handling. The automatization of testing reduces technical and avoids pipetting errors. Five reagents are used in clinical practice to allow rapid identification of specific coagulation disorders: EXTEM (activation of the extrinsic pathway by TF and heparin neutralization by polybrene), INTEM (activation of the intrinsic pathway by ellagic acid), FIBTEM (elimination of platelet contribution to clot firmness by cytochalasin D), HEPTTEM (elimination of heparin effects by heparinase), and APTEM (elimination of hyperfibrinolysis by aprotinin). Coagulation factor deficiencies, hypofibrinogenemia, decreased platelet contribution to clot firmness, hyperfibrinolysis, fibrinolysis shutdown, heparin-like effects, protamine overdose, and oral anticoagulants may be quickly identified at the bedside.^{12,21–24}

Like other VET devices, ROTEM does not provide a comprehensive or sensitive reflection of von Willebrand disease (vWD) or impaired platelet aggregation.^{25,26} Limitations of VETs include the absence of endothelium and blood flow, as the tests are performed on whole blood with low shear stress.²⁰ VET is a cornerstone of the EGDHT concept, since it globally accesses the entire clot formation process in real time, from clot initiation, clot formation to its lysis. ROTEM not only allows for a shorter turnaround time compared to CCTs, hence earlier identification of coagulopathy within 5 minutes, but ROTEM assays, such as FIBTEM, have also been shown to be superior to CCTs, such as plasma fibrinogen concentration, for predicting bleeding and transfusion in multiple clinical settings.³¹ Several institutions moved during the last years to fully-automated VET devices such as ROTEM sigma, TEG6s, or Quantra, particularly if used at the point-of-care.³²

Notably, TEG and -metry algorithms follow different concepts of result interpretation and clinical strategies in bleeding management, besides technical differences and different assay compositions. In this review paper, we focus on the concept of EGDHT for severe acute bleeding management based on thromboelastometry algorithms.^{15,24,33,34}

VET has been shown to be effective in reducing bleeding, transfusion requirements, complication rates, and health care costs in perioperative settings.¹² Systematic reviews and meta-analyses demonstrated growing evidence, particularly in cardiac surgery, liver transplantation, trauma, and more recently in postpartum hemorrhage (PPH), as a useful tool for the management of severe acute bleeding, allowing the rationalization in the use of blood components.^{27,28} Therapeutic alternatives to transfusion, such as hemostatic drugs, antifibrinolytics, and coagulation factor concentrates, reduced the incidence of adverse effects related to allogeneic blood components, such as transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), and transfusion-related immunomodulation (TRIM) with nosocomial infections.^{38,39} A retrospective cohort study observed reduced blood product use, and less infections in severely burned patients with treatment guided by a goal-directed coagulation algorithm.²⁹ A systematic review with meta-analysis published in 2017 by Wikkelsø et al showed a significant reduction in mortality using TEG or ROTEM-guided algorithms versus any comparison in longer follow-up mortality (3.9% vs 7.4%).³⁰ This corresponds to a relative risk reduction of 48% favoring a TEG- or ROTEM-guided transfusion. These results were confirmed by the last meta-analysis published by Santos et al³⁶ based on 21 randomized controlled trials (RCTs) including 8900 participants: relative risk (RR) for mortality in ROTEM studies 0.48 ($P = .09$), in TEG studies 0.71 ($P = .15$) and for ROTEM and TEG together 0.64 ($P = .03$).³¹

Other VET Devices

The Quantra platform is a cartridge-based VET device that uses ultrasound to characterize dynamic changes in the viscoelastic properties of blood during clot formation.²⁰ There are currently limited studies addressing the interchangeability of VET parameters.³²

ClotPro is a recent device that uses a modified viscoelastic clotting test based on the established cup-and-pin technology principle of ROTEM.²¹ This technology features a dual-bearing guidance system, 6 multitest channels, and 8 different assays. Some assays are comparable to commonly used ROTEM assays (eg, extrinsic test [EX-test], fibrinogen test [FIB-test], aprotinin-test [AP-test], intrinsic test [IN-test], heparinase test [HEP-test], and native test [NA-test]). Additional assays have been developed specifically for the detection and differentiation of direct oral anticoagulants (DOACs): the Russell's viper venom test (RVV-test) and the ecarin test (ECA-test). The tissue plasminogen activator assay contains a recombinant tissue plasminogen activator and may be used to identify impaired fibrinolysis and fibrinolytic resistance.^{43,44} As ROTEM *delta*, ClotPro is a semiautomatic VET analyzer that requires pipetting. Its clinical application has been based on studies using well-established ROTEM cutoff values which may have to be adapted to ClotPro.³³⁻³⁵

FUNCTIONAL CLASSIFICATION OF THE COAGULATION SYSTEM

For a better interpretation of hemostasis at the bedside and to support decision-making for optimum hemostatic therapy, we propose a functional classification of coagulation based on the physiology in 3 phases: thrombin generation, clot firmness, and clot stabilization (Figure 2). Thrombin generation is determined by enzymatic coagulation factors and can be modified by the biochemical environment, anticoagulants, inhibitors, and coagulation factor deficiencies. This phase is represented by CT (clotting time) in ROTEM.¹² Clot firmness is determined by fibrin polymerization, platelet aggregation, and platelet-fibrin-interaction. This can be modified by factor XIII (FXIII) and colloids.^{12,36-40} This phase can be altered by deficiency of any of these components and corresponds to early (amplitude 5 or 10 minutes after CT: A5 and A10) and late clot firmness parameters (maximum clot firmness: MCF) in ROTEM.¹² Clot stabilization is determined by fibrinolysis, FXIII, and platelet-mediated clot retraction, and is represented by maximum lysis (ML), lysis onset time (LOT), and lysis index at 30, 45, and 60 minutes after CT (LI30, LI45, and LI60).^{12,41-44} FIBTEM is the most sensitive and specific assay for the detection of hyperfibrinolysis.⁴⁵⁻⁴⁷ The combination of EXTEM (sensitive to fibrinolysis and platelet-mediated clot retraction), FIBTEM (not sensitive to platelet-mediated

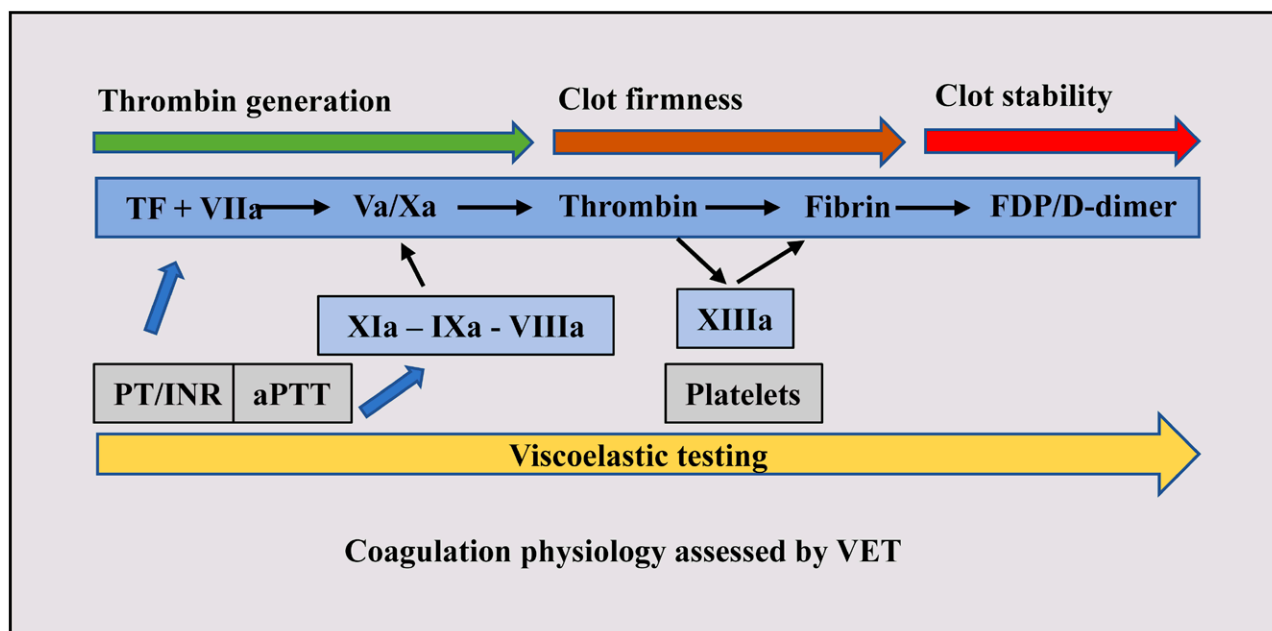


Figure 2. Functional classification of the coagulation. aPTT indicates activated partial thromboplastin time; FDP, fibrin degradation products; INR, international normalized ratio; PT, prothrombin time; TF, tissue factor; VET, viscoelastic testing.

clot retraction but very sensitive to fibrinolysis), and APTEM (not sensitive to fibrinolysis but to platelet-mediated clot retraction) can be used to differentiate between hyperfibrinolysis and platelet-mediated clot retraction.^{25,26,55,56} Fortunately, the latter is not associated with bleeding and does not require therapy with antifibrinolytics.^{57,58}

BLEEDING MANAGEMENT IN THE ICU

Based on physiology of hemostasis, pathophysiology of different diseases, as well as the use of VET to monitor hemostasis and guide hemostatic therapy in face of a severe acute bleeding, we suggest the concept of “The Ten Steps” for severe acute bleeding management in the ICU, including an EGDHT algorithm to support clinicians in decision-making (Figure 3).

The Ten Steps

We propose the following “ten steps” approach (Figure 4):

1. ABC: Ensure patient’s Airway, Breathing, and Circulation (oxygen supply, vascular access, and restrictive volume resuscitation).
2. Tissue perfusion and oxygenation: Optimize perfusion parameters and intravascular volume resuscitation with crystalloids and RBC. Target mean arterial pressure (MAP) > 65 mm Hg, lactate <2 to 4 mmol/L, diuresis >0.5 mL/kg/h. Blood lactate is considered as a sensitive test to estimate the extent of tissue hypoperfusion: If

lactate results are not available, base deficit can be used in this context. Permissive hypotension may be necessary in some cases such as variceal bleeding or active arterial bleeding until surgical or interventional hemostasis. Administration of large volumes of crystalloids and colloids should be avoided since this is associated with dilutional coagulopathy, which may lead to transfusion- and tissue edema-related adverse outcomes.⁵⁹ Ideally, balanced crystalloid solutions are recommended by the European guideline for volume therapy in hypotensive patients due to trauma-induced bleeding.

3. Anemia management: A restrictive transfusion strategy (RBC transfusion trigger of hemoglobin [Hb] < 7 g/dL) for most stable patients is recommended. RBC transfusion should be performed based on the estimated volume of blood loss during active bleeding.^{48,49} In hemorrhagic shock with hemodynamic instability, one should consider that RBC are fundamental for the hemostasis mechanism of platelet marginalization to the vessel wall.^{50–52} Two units of RBC (4 units in case of massive bleeding) and blood typing should be requested.
4. A recent Cochrane review published in 2021 on transfusion thresholds to guide RBC transfusion suggests that allogeneic RBC transfusion can be avoided in most patients with Hb thresholds between 7.0 and 8.0 g/dL, even if the evidence for a reduction in mortality by a restrictive compared to a liberal transfusion

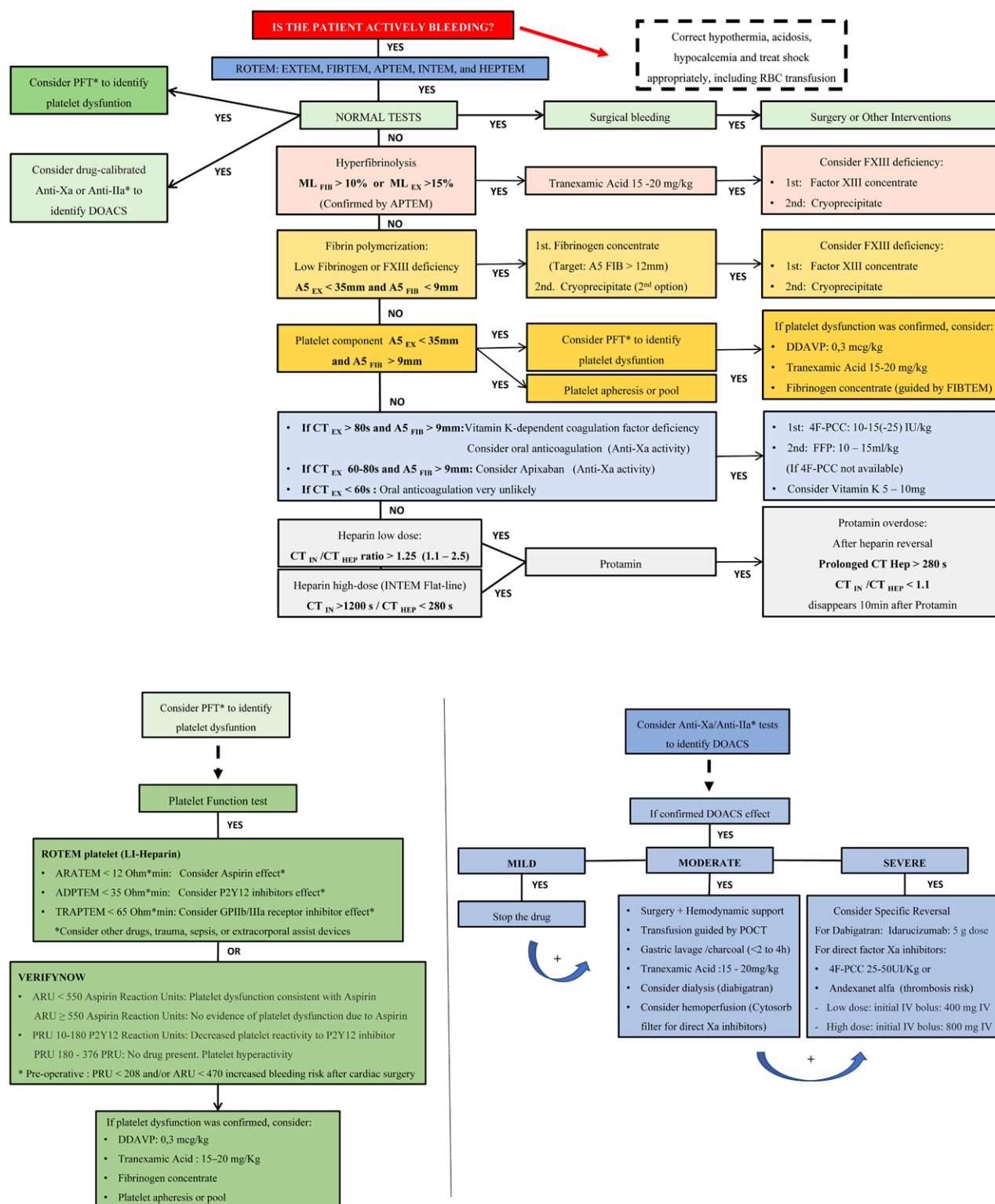


Figure 3. EGDHT algorithm. 4F-PCC indicates four-factor prothrombin complex concentrate; ADPTEM, adenosine diphosphate; APTEM, aprotinin; ARATEM, arachidonic acid; ARU, aspirin reaction units; CT, clotting time; DDAVP, desmopressin; DOACS, direct oral anticoagulants; EGDHT, early goal-directed hemostatic therapy; EXTEM, extrinsic pathway; FIBTEM, fibrinogen test; HEPTM, heparinase; INTEM, intrinsic pathway; IV, intravenous; ML, maximum lysis; PCC, prothrombin complex concentrate; PFT, platelet function test; POCT, point-of-care testing; PRU, P2Y12 reaction units; RBC, red blood cell; ROTEM, rotational thromboelastometry; TRAPTEM, thrombin-activating peptide.

strategy is limited.⁶⁴ Notably, a meta-analysis published in 2017 comparing restrictive versus liberal blood transfusion in gastrointestinal

bleeding demonstrated that restrictive transfusion was associated with a lower risk of all-cause mortality.⁶⁵

5. Biochemical environment. Once clinically relevant bleeding has been identified, a “clot friendly” environment is mandatory for proper thrombin generation and clot formation. Hypothermia causes coagulopathy due to impaired platelet aggregation and reduced activity of enzymes in the coagulation cascade. Anemia, acidemia, hypocalcemia should also be promptly corrected.⁶⁶ Hypocalcemia can be corrected by the administration of Ca^{2+} gluconate or Ca^{2+} chloride with a ionized Ca^{2+} concentration of 4.7 to 5.2 mg/dL (1.17–1.30 mmol/L) as a target. Cornerstone of acidemia management is shock therapy by correcting hypovolemia with crystalloids and RBC, and the correct acidosis before hemostatic interventions with 8.4% sodium bicarbonate (target pH > 7.35). To avoid or correct hypothermia, (re)warm the patient by using warm infusions and transfusions, thermal blankets, convective warming therapy, and increased room temperature.
6. Bleeding source: VET allows to differentiate between coagulopathy or surgical reasons for the bleeding.⁶⁷ If there is an “open vessel,” surgical hemostasis is mandatory, including manual compression, clips, sutures, or interventional radiology.^{53,68} In case of microvascular bleeding, VET may help to identify specific coagulation disorders and may be complemented by platelet function testing (PFT).⁶⁹
7. EGDHT: consider the use of coagulation factor concentrates and/or hemostatic drugs instead of allogeneic blood components since liberal transfusion has been associated with severe adverse events.^{70–73}
8. Early administration of tranexamic acid (TXA) within the first 3 hours after injury or delivery in TIC and PPH.^{74,75} Fibrinogen concentration should be monitored early, and in the presence of hypofibrinogenemia, supplementation should be performed with fibrinogen concentrate or cryoprecipitate.^{67,69}
9. CCTs: Complete blood count (CBC) should be performed to assess platelet count, PT/INR, and aPTT to monitor the anticoagulant effects, anti-Xa activity for low-molecular-weight heparin (LMWH). D-dimer is helpful for differentiating disseminated intravascular coagulation (DIC) from other conditions potentially associated with a low platelet count, low fibrinogen, and prolonged clotting times, such as in liver disease. The role of CCTs in the assessment of DOAC effects is described below.
10. PFT: PFT can be helpful to detect the effects of antiplatelet agents (APAs), antiplatelet effects of other drugs used in critically ill patients (eg, beta-blockers, Ca^{2+} antagonists, antibiotics, antidepressants, and analgetic drugs), and the effects of trauma, sepsis, and extracorporeal assist devices on platelet function.^{76–81} Some studies suggest that VET and PFT better predict bleeding than platelet count.^{82–85}
11. DOACs: Specific assays can assess the effects of DOACs and IV direct thrombin inhibitors (DTIs), such as anti-Xa activity (calibrated for rivaroxaban, apixaban, and edoxaban), and diluted thrombin time (dTT; DTI assay), or ecarin clotting time (ECT; chromogenic anti-IIa assay) for dabigatran, argatroban, and bivalirudin.^{23,24,54–57} Standard and modified thromboelastometric assays can be helpful, too.^{23,56–59,86–91}

1. ABC: ensure patient's Airway, Breathing, and Circulation
2. Tissue perfusion and oxygenation optimization
3. Anemia Management: target Hb < 7 g/dl – RBC 2 units (4 units in case of massive bleeding) and blood typing
4. Biochemical environment improvement: acidemia, hypothermia and hypocalcemia
5. Bleeding Source: identifying bleeding cause (coagulopathy x surgical bleeding) using VET
6. EGDHT: VET-guided coagulation factor concentrates and hemostatic drugs instead of allogeneic blood components
7. Early administration of TXA in trauma and PPH. In the presence of hypofibrinogenemia, supplementation should preferably be performed with fibrinogen concentrate or cryoprecipitate
8. Lab tests: CCTs, platelet count, Anti-Xa activity for LMWH. D-dimer for DIC
9. Platelet function: to access possible effect of antiplatelet drugs and platelet dysfunction due to trauma, sepsis, extracorporeal support devices, and other drugs
10. DOACs: Anti-Xa activity (calibrated for rivaroxaban, apixaban and edoxaban), Anti-IIa (dabigatran, argatroban, and bivalirudin)

Figure 4. The Ten Steps. ABC indicates Ensure patient's Airway, Breathing, and Circulation; CCTs, coagulation conventional tests; DIC, disseminated intravascular coagulation; DOACs, direct oral anticoagulants; EGDHT, early goal-directed hemostatic therapy; Hb, hemoglobin; LMWH, low-molecular-weight heparin; PPH, postpartum hemorrhage; RBC, red blood cell; TXA, tranexamic acid; VET, viscoelastic testing.

“REVERSE TREATMENT”

Once the coagulopathy is identified, an individualized treatment should be considered in a retrograde way following the advanced trauma life support (ATLS) concept of “treat first what kills first” (Figure 5).⁹² Accordingly, we should firstly stabilize the clot by blocking hyperfibrinolysis, secondly improve clot firmness, and third improve thrombin generation. In this case, the order of factor replacement may compromise the result of bleeding control.

First Step: Clot Stabilization

(Supplemental Digital Content, Supplemental Figure 4.1, <http://links.lww.com/AA/E583>): The early use of antifibrinolytic drugs should be first line with an empirical approach within 3 hours after injury.^{74,75,93,94} For bleeding trauma patients, TXA should be administered as soon as possible within 3 hours of injury without the need to wait for VET results, preferably on the route to the hospital. Recommended loading dose is 1 g infused over 10 minutes, followed by an IV infusion of 1 g over 8 hours.^{67,74}

In massive bleeding, the replacement of FXIII, using factor XIII concentrate or cryoprecipitate may improve clot stabilization after antifibrinolytics.^{95,96}

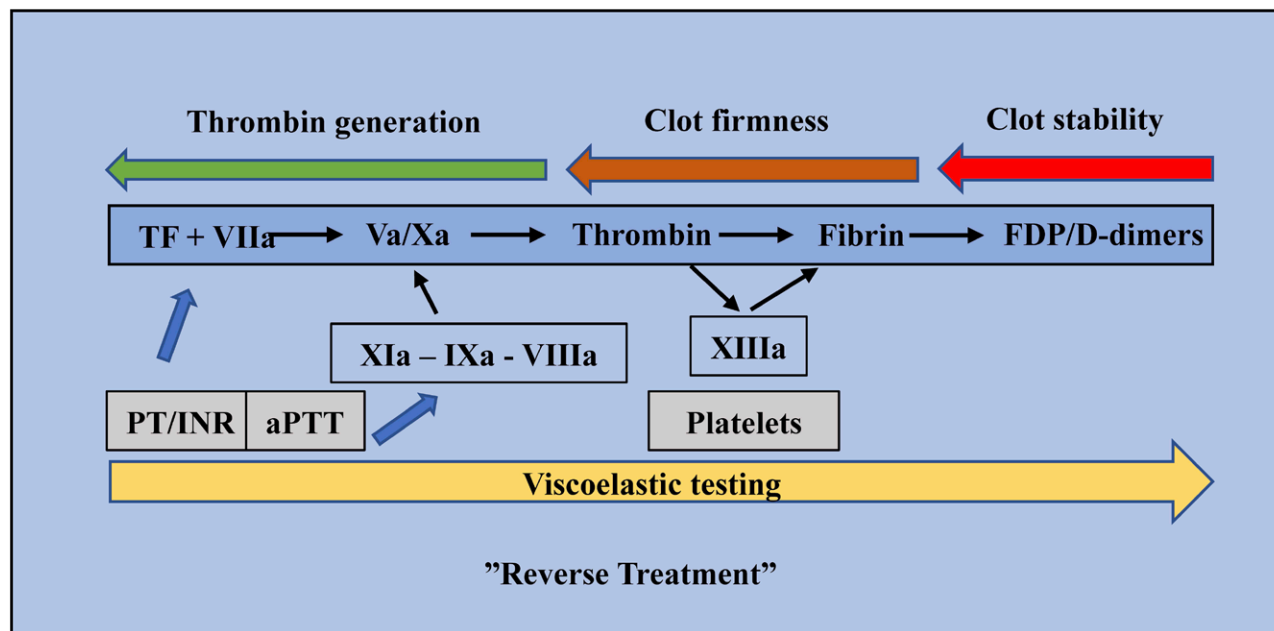
Second Step: Clot Firmness

(Supplemental Digital Content, Supplemental Figure 4.2, <http://links.lww.com/AA/E583>): Fibrinogen and

platelets have been considered as the main determinants of clot firmness, as well as FXIII. Fibrinogen plays several key roles in the maintenance of hemostasis. It is the substrate for coagulation. Its transformation to fibrin monomers by thrombin and the subsequent polymerization to a crosslinked fibrin network by FXIII is essential to form a stable clot. Fibrinogen is the first coagulation factor to decline to a critical level of 1.5 to 2 g/L in massive hemorrhage.^{97,98} In trauma, low fibrinogen levels are associated with increased transfusion requirements and mortality.⁶⁰ Therefore, fibrinogen supplementation should be performed early to improve clot firmness and to reduce transfusion requirements.^{99–101}

The trigger for fibrinogen supplementation according to thromboelastometry may vary according to the underlying pathology. While in the cardiac surgery scenario FIBTEM A5 is considered <9 mm, some studies suggest FIBTEM A5 < 7mm in trauma and peripartum hemorrhage, and FIBTEM A5 < 8 mm in liver transplantation.^{12,61,62}

Fresh frozen plasma (FFP) contains coagulation factors and inhibitors in a physiologic composition but unpredictable, low concentration.¹⁰² Therefore, even high volumes of FFP (10–15 mL/kg body weight) are insufficient to reverse coagulopathy in bleeding patients.^{103–105} This approach is associated with several complications such as TACO, TRALI, and TRIM, multiple-organ dysfunction syndrome (MODS), and nosocomial infection.^{106–110} Current



“Reverse treatment”: The sequential approach in the opposite direction to clot formation.

Figure 5. Reverse treatment. aPTT indicates activated partial thromboplastin time; FDP, fibrin degradation products; INR, international normalized ratio; PT, prothrombin time; TF, tissue factor.

guidelines recommend using lyophilized fibrinogen concentrate or cryoprecipitate to restore the fibrinogen concentration.^{67,69}

Although cryoprecipitate contains a higher concentration of fibrinogen than FFP, it has some common disadvantages with FFP. The fibrinogen concentration is not standardized; transfusion should be compatible with type A, type B, type O, or type AB blood; and cryoprecipitate preparation requires more time for thawing and pooling.¹¹¹ In addition, it carries a risk of viral transmission similar to FFP.¹¹²

In contrast, fibrinogen concentrate is derived from human plasma, pasteurized, lyophilized, and stored at room temperature, and can be reconstituted quickly in low volume and high concentration. Since it does not require blood typing or thawing, it is immediately available for use, with lower risk of allergic reactions since antibodies are removed.¹¹³ Literature data have demonstrated the role of fibrinogen concentrates in acquired hypofibrinogenemia in different settings of severe acute bleeding.^{114,115}

Clot firmness can also be impaired by thrombocytopenia and/or severe platelet dysfunction (Supplemental Digital Content, Supplemental Figure 4.3, <http://links.lww.com/AA/E583>). To identify the latter, PFT may be performed to complement VET. Platelet concentrates should be considered (dose: 0.7×10^{11} per 10 kg body weight in adults) in bleeding situations associated with inherited or acquired dysfunction (eg Glanzmann's thrombasthenia or drug effects) or to thrombocytopenia of less than $50 \times 10^9 \text{ L}^{-1}$.⁶³ As an attempt to improve platelet/vWF interaction, desmopressin (DDAVP; dose: $0.3\text{--}0.4 \mu\text{g kg}^{-1}$) is an option to improve platelet function, for example, in uremic patients. DDAVP induces vWF release, improving platelet adhesion/aggregation, and has been shown to be effective for the treatment of POB.¹¹⁶

Platelet activity may be compromised by APAs such as aspirin, P2Y₁₂ inhibitors, and glycoprotein IIb/IIIa inhibitors, other widely used drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, cardiovascular and lipid-lowering drugs, and selective serotonin reuptake inhibitors, as well as trauma, sepsis, and extracorporeal assist devices.^{76–80} For further evaluation of platelet function, methods such as multiplate, ROTEM *platelet* or VerifyNow can be used. Considering low platelet counts, PFT should be interpreted with caution to identify a dysfunction correctly in the patient with active bleeding, and to assist in planning for the need for further intervention. Notably, platelet transfusions may cause more harm than benefits in patients with traumatic brain injury (TBI) or intracerebral hemorrhage on APA.^{72,117} A meta-analysis published in 2017 evaluated the use of DDAVP for the treatment of platelet dysfunction and reversal of APA in patients undergoing cardiac surgery. Administration of

DDAVP ($0.3 \mu\text{g/kg}$) resulted in a 25% reduction in RBC transfusion, a 23% reduction in blood loss compared to control, and a lower incidence of reoperation due to bleeding.¹¹⁸ Furthermore, TXA results in improved platelet function in patients treated with APA.¹¹⁹

Factor XIII deficiency cannot be measured directly by VETs, but indirectly. In patients who present persistent low clot firmness in FIBTEM after the replacement of fibrinogen, FXIII deficiency could be considered.^{48,49,120} Reduced levels of EXTEM and FIBTEM MCF but not high levels of EXTEM ML and APTTEM ML are associated with factor XIII deficiency in patients with liver disease.³⁸

FXIII is a plasma transglutaminase essential for normal hemostasis in the final stage of the coagulation cascade. It is responsible for crosslinking fibrin fibers and subsequent improvement of the mechanical stability of the fibrin clot as well as its protection against fibrinolysis.¹²¹ In the presence of activatable platelets, FXIII protects the clot from premature degradation by crosslinking α_2 -antiplasmin to fibrin.^{50,122,123} FXIII can be supplemented using cryoprecipitate or factor XIII concentrate. Schlimp et al¹²⁴ showed that the combination of fibrinogen concentrate and factor XIII concentrate to be highly effective in raising FIBTEM clot firmness after hemodilution.

Third Step: Thrombin Generation Phase

After taking care of the clot stabilization and firmness, efforts will be aiming at improving thrombin generation – in case of ongoing bleeding.^{15,125–127} The impairment in the thrombin generation can be the result of a coagulation factor deficiency, or the effect of anticoagulants, and can be accessed by ROTEM CT (Supplemental Digital Content, Supplemental Figure 4.4, <http://links.lww.com/AA/E583>).²⁸ Notably, ROTEM CT results can be prolonged by severe hypofibrinogenemia, too, and can be normalized by fibrinogen administration, only, in most cases.^{15,128} Therefore, prolonged CT results should only be considered to trigger FFP or Four-Factor Prothrombin Complex Concentrate (4F-PCC) administration in bleeding patients with normal FIBTEM clot firmness. The supplementation of coagulation factors may improve thrombin generation and can be done by the administration of FFP or 4F-PCC.^{69,126,129} 4F-PCC is a human plasma-derived coagulation factor concentrate, produced by ion-exchange chromatography with viral inactivation, and contains vitamin K-dependent coagulation factors and inhibitors: factor II, VII, IX, X as well as AT, protein C, S, Z, and heparin. Its Food and Drug Administration (FDA)-cleared indication is the reversal of the effect of vitamin K- antagonists (VKA), whereas in Europe it is approved for the prophylaxis and therapy of bleeding due to vitamin K-dependent factor deficiencies.^{130,131} 4F-PCC has several advantages

over FFP in reversing VKA. It is a virus-inactivated, pasteurized, nanofiltrated, lyophilized powder, standardized to the factor IX activity, with factor activities 25 times higher compared to plasma. It can be reconstituted in small volumes. The reversal occurs within minutes after 4F-PCC administration.^{132–134} While FFP must be thawed, even transfusion of large volumes is often inadequate to correct INR.^{134,135}

Once heparin (exogenous unfractionated heparin or endogenous heparin-like effects) has been detected by an INTEM/HEPTEM CT-ratio above 1.25 in the presence of acute bleeding, protamine administration may be considered to reverse this effect (Supplemental Digital Content, Supplemental Figure 4.5, <http://links.lww.com/AA/E583>).^{28,136}

Limitations of VET include a low sensitivity to platelet dysfunction.²⁵ Accordingly, PFT devices such as Multiplate, ROTEM *platelet* or VerifyNow can be used, complementarily. These tests make it possible to differentiate between the effects of different APA. Changes found in these tests may indicate the need for platelet concentrate transfusion, DDAVP, or TXA administration to improve platelet function.^{67,69,118,119}

MANAGEMENT OF BLEEDING DUE TO DOACs

In the presence of ongoing bleeding, with normal ROTEM results (Supplemental Digital Content, Supplemental Figure 4.6, <http://links.lww.com/AA/E583>), normal PFT results, and exclusion of mechanical reasons for bleeding, a residual effect of DOACs should be considered measuring the activities of calibrated Anti-Xa (for Rivaroxaban, Apixaban and Edoxaban), anti-IIa or dTT (for Dabigatran).^{27,28,137} Normal PT and aPTT exclude supratherapeutic concentrations of rivaroxaban and edoxaban but might not fully exclude clinically relevant drug concentrations.

On the other hand, in the presence of CT prolongation in EXTEM, this alteration is less pronounced for Apixaban than for rivaroxaban and edoxaban. Therefore, it is critical to measure calibrated anti-Xa activity in addition to ROTEM to detect an elevated apixaban plasma level.

Furthermore, coagulation screening using CCTs might be normal in patients taking apixaban. A normal TT excludes clinically relevant dabigatran concentrations; if the dTT assay is prolonged, a dabigatran effect might be present. ECT can be performed to detect dabigatran. Anti-Xa activity (calibrated for rivaroxaban, apixaban or edoxaban) should be performed to quantify direct factor Xa inhibitors (xabans).^{138,139} Once clinically relevant bleeding has been detected, some points should be considered: last ingestion of the drug, chronic disorders like kidney or liver disease. As life-saving measures stopping the anticoagulant effect, hemodynamic support with fluid resuscitation and blood products, mechanical

compression, or surgical or radiological intervention to identify and treat the cause of bleeding should be considered. Laboratory screening (CCTs, CBC, liver, and renal function) may help to estimate potential accumulation and the remaining duration of drug effects. If ingestion was within the past 2 hours, oral activated charcoal can be administered. Furthermore, intravenous TXA and specific reversal agents for different DOACs can be administered in life-threatening bleeding.

NONSPECIFIC REVERSAL THERAPIES

Two systematic reviews and meta-analyses demonstrated the efficacy and safety of the off-label use of 4F-PCC in major bleeding associated with xabans. 4F-PCC is considered an option for managing direct FXa-related major bleeding.^{140,141} Dager et al¹⁴² reported on the use of activated prothrombin complex concentrate (aPCC) to reverse the anticoagulation effects of DOACs, which appears to be safe and has the potential to restore hemostasis in critical bleeding situations. Both low dose with repeat option and moderate dose, depending on the urgency of the situation, can be an effective management strategy with a positive clinical benefit for major bleeding events of DOACs. aPCC doses of 25 units/kg or less could be a potential strategy for ICH or life-threatening massive bleeding events. Furthermore, dabigatran plasma concentrations can be decreased by hemodialysis and plasma concentrations of xabans by hemoperfusion with Cytosorb filters during cardiopulmonary bypass.^{143–147}

SPECIFIC DRUGS FOR REVERSAL OF ANTICOAGULANTS

For dabigatran reversal, a specific antidote is available. Idarucizumab, a humanized antibody fragment that specifically binds dabigatran with high affinity and reverses its effects within minutes. The recommended dose is 5 g, given intravenously when rapid reversal is required in uncontrolled bleeding.¹⁴⁸ For reversal of xabans, Andexanet alfa is available, a recombinant modified human activated factor X protein, recently approved by the FDA, that specifically binds xabans. Andexanet alfa is indicated for reversal of either rivaroxaban or apixaban due to life-threatening bleeding.¹⁴⁹ However, thromboembolic events have been identified and considered to be of high frequency with Andexanet alfa.¹⁵⁰ Another potential disadvantage might be the need for a continuous infusion of the drug and very high costs.

CONCLUSIONS

Understanding the concept of the cell-based model of hemostasis, as well as the pathophysiology of specific

coagulopathies, allows for a better approach to bleeding management in critically ill patients. The dynamic and structured performance of the step-by-step approach for EGDHT using VET to guide hemostatic drugs and coagulation factor concentrates administration are key for the successful control of severe acute bleeding in the ICU. Patients' outcome will be determined by the diagnostic performance of POCT to differentiate between surgical and coagulopathic bleeding, the precision in differentiation between different coagulopathies guiding hemostatic therapy, the avoidance of inappropriate blood transfusion, and subsequent transfusion-related complications and costs. ■

DISCLOSURES

Name: Tomaz Crochemore, MD.

Contribution: This author helped perform this study through the literature review, the creation of the concept of "early goal-directed hemostatic therapy" and the proposal of "The 10 steps" for the bleeding management; creating figures and tables; writing and revising the article; and approving the final version.

Conflicts of Interest: T. Crochemore has worked as a medical manager of Werfen Latin America since 2022.

Name: Klaus Görlinger, MD.

Contribution: This author helped thoroughly review the article, including figures and tables, reviewed the references, and approved the final version.

Conflicts of Interest: K. Görlinger has worked as the medical director of TEM Innovations since 2012.

Name: Marcus Daniel Lance, MD, PhD.

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REFERENCES

- Levi M. Thrombosis and hemostasis issues in critically ill patients. *Semin Thromb Hemost.* 2015;41:7–8.
- Wendelboe AM, Raskob GE. Global burden of thrombosis: epidemiologic aspects. *Circ Res.* 2016;118:1340–1347.
- Görlinger K, Saner FH. Prophylactic plasma and platelet transfusion in the critically ill patient: just useless and expensive or even harmful? *BMC Anesthesiol.* 2015;15:86.
- Tomaiuolo M, Brass LF, Stalker TJ. Regulation of platelet activation and coagulation and its role in vascular injury and arterial thrombosis. *Interv Cardiol Clin.* 2017;6:1–12.
- Palta S, Saroa R, Palta A. Overview of the coagulation system. *Indian J Anaesth.* 2014;58:515–523.
- Hoffman M, MONROE DM. A cell-based model of hemostasis. *Thromb Haemost.* 2001;85:958–965.
- Smith SA. The cell-based model of coagulation. *J Vet Emerg Crit Care (San Antonio).* 2009;19:3–10.
- Sanrattana W, Maas C, de Maat S. SERPINs-from trap to treatment. *Front Med (Lausanne).* 2019;6:25.
- Quinsey NS, Greedy AL, Bottomley SP, Whisstock JC, Pike RN. Antithrombin: in control of coagulation. *Int J Biochem Cell Biol.* 2004;36:386–389.
- Bernard GR, Vincent JL, Laterre PF, et al; Recombinant Human Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) Study Group. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med.* 2001;344:699–709.
- Lindahl AK. Tissue factor pathway inhibitor: from unknown coagulation inhibitor to major antithrombotic principle. *Cardiovasc Res.* 1997;33:286–291.
- Napolitano M, Siragusa S, Mariani G. Factor VII deficiency: clinical phenotype, genotype and therapy. *J Clin Med.* 2017;6:38.
- Bolliger D, Görlinger K, Tanaka KA. Pathophysiology and treatment of coagulopathy in massive hemorrhage and hemodilution. *Anesthesiology.* 2010;113:1205–1219.
- Bulut Y, Sapru A, Roach GD. Hemostatic balance in pediatric acute liver failure: epidemiology of bleeding and thrombosis, physiology, and current strategies. *Front Pediatr.* 2020;8:618119.
- Görlinger K, Pérez-Ferrer A, Dirkmann D, et al. The role of evidence-based algorithms for rotational thromboelastometry-guided bleeding management. *Korean J Anesthesiol.* 2019;72:297–322.
- Boroumand M, Goodarzynejad H. Monitoring of anticoagulant therapy in heart disease: considerations for the current assays. *J Tehran Heart Cent.* 2010;5:57–68.
- Crochemore T, Corrêa TD, Lance MD, et al. Thromboelastometry profile in critically ill patients: a single-center, retrospective, observational study. *PLoS One.* 2018;13:e0192965.
- Kozek-Langenecker SA. Perioperative coagulation monitoring. *Best Pract Res Clin Anaesthesiol.* 2010;24:27–40.
- Haas T, Fries D, Tanaka KA, Asmis L, Curry NS, Schöchl H. Usefulness of standard plasma coagulation tests in the management of perioperative coagulopathic bleeding: is there any evidence? *Br J Anaesth.* 2015;114:217–224.
- Volod O, Viola F. The quantra system: system description and protocols for measurements. *Methods Mol Biol.* 2023;2663:743–761.
- Núñez-Jurado D, Santotoribio JD, Noval-Padillo JA. ClotPro viscoelastometry evaluation in cardiac surgery with cardiopulmonary bypass. *J Cardiothorac Vasc Anesth.* 2023;37:392–398.
- Hartert H. Blutgerinnungsstudien mit der Thrombelastographie, einem neuen Untersuchungsverfahren. *Klin Wochenschr.* 1948;26:577–583.
- Espinosa A, Seghatchian J. What is happening? The evolving role of the blood bank in the management of the bleeding patient: the impact of TEG as an early diagnostic predictor for bleeding. *Transfus Apher Sci.* 2014;51:105–110.
- Larsen OH, Fenger-Eriksen C, Christiansen K, Ingerslev J, Sørensen B. Diagnostic performance and therapeutic consequence of thromboelastometry activated by kaolin versus a panel of specific reagents. *Anesthesiology.* 2011;115:294–302.
- Shander A, Görlinger K. Blindspots and limitations in viscoelastic testing in pregnancy. *Int J Obstet Anesth.* 2019;38:4–9.
- Crochemore T, Piza FMT, Rodrigues RDR, Guerra JCC, Ferraz LJR, Corrêa TD. A new era of thromboelastometry. *Einstein (Sao Paulo).* 2017;15:380–385.
- Schäfer ST, Otto AC, Acevedo AC, et al. Point-of-care detection and differentiation of anticoagulant therapy: development of thromboelastometry-guided decision-making support algorithms. *Thromb J.* 2021;19:63.
- Pavoni V, Ganesello L, Conti D, et al. "In Less than No Time": feasibility of rotational thromboelastometry to detect anticoagulant drugs activity and to guide reversal therapy. *J Clin Med.* 2022;11:1407.
- Schmidt DE, Majeed A, Bruzelius M, Odeberg J, Holmström M, Ågren A. A prospective diagnostic accuracy study evaluating rotational thromboelastometry and thromboelastography in 100 patients with von Willebrand disease. *Haemophilia.* 2017;23:309–318.

30. Wikkelsø A, Wetterslev J, Møller AM, Afshari A. Thromboelastography (TEG) or rotational thromboelastometry (ROTEM) to monitor haemostatic treatment in bleeding patients: a systematic review with meta-analysis and trial sequential analysis. *Anaesthesia*. 2017;72:519–531.
31. Song JG, Jeong SM, Jun IG, Lee HM, Hwang GS. Five-minute parameter of thromboelastometry is sufficient to detect thrombocytopenia and hypofibrinogenemia in patients undergoing liver transplantation. *Br J Anaesth*. 2014;112:290–297.
32. Volod O, Bunch CM, Zackariya N, et al. Viscoelastic hemostatic assays: a primer on legacy and new generation devices. *J Clin Med*. 2022;11:860.
33. Holcomb JB, Minei KM, Scerbo ML, et al. Admission rapid thromboelastography can replace conventional coagulation tests in the emergency department: experience with 1974 consecutive trauma patients. *Ann Surg*. 2012;256:476–486.
34. Solomon C, Schöchl H, Ranucci M, Schlomp CJ. Can the viscoelastic parameter α -angle distinguish fibrinogen from platelet deficiency and guide fibrinogen supplementation? *Anesth Analg*. 2015;121:289–301.
35. Wikkelsø A, Wetterslev J, Møller AM, Afshari A. Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemostatic treatment versus usual care in adults or children with bleeding. *Cochrane Database Syst Rev*. 2016;2016:CD007871.
36. Santos AS, Oliveira AJF, Barbosa MCL, Nogueira JLD. Viscoelastic haemostatic assays in the perioperative period of surgical procedures: systematic review and meta-analysis. *J Clin Anesth*. 2020;64:109809.
37. Bugaev N, Como JJ, Golani G, et al. Thromboelastography and rotational thromboelastometry in bleeding patients with coagulopathy: Practice management guideline from the Eastern Association for the Surgery of Trauma. *J Trauma Acute Care Surg*. 2020;89:999–1017.
38. Khanna P, Sinha C, Singh AK, Kumar A, Sarkar S. The role of point of care thromboelastography (TEG) and thromboelastometry (ROTEM) in management of primary postpartum haemorrhage: a meta-analysis and systematic review. *Saudi J Anaesth*. 2023;17:23–32.
39. Görlinger K, Dirkmann D, Hanke AA, et al. First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: a retrospective, single-center cohort study. *Anesthesiology*. 2011;115:1179–1191.
40. Sahli SD, Pedrazzi N, Braun J, Spahn DR, Kaserer A, Plock JA. Effect of a factor-based coagulation management on blood product use after major burn injury: a retrospective cohort study. *Burns*. 2021;47:1486–1494.
41. Wikkelsø A, Wetterslev J, Møller AM, Afshari A. Thromboelastography (TEG) or rotational thromboelastometry (ROTEM) to monitor haemostatic treatment in bleeding patients: a systematic review with meta-analysis and trial sequential analysis. *Anaesthesia*. 2017;72:519–531.
42. DeAnda A, Levy G, Kinsky M, et al. Comparison of the quantra qplus system with thromboelastography in cardiac surgery. *J Cardiothorac Vasc Anesth*. 2021;35:1030–1036.
43. Oberladstätter D, Voelckel W, Schlomp C, et al. A prospective observational study of the rapid detection of clinically-relevant plasma direct oral anticoagulant levels following acute traumatic injury. *Anaesthesia*. 2021;76:373–380.
44. Groene P, Wagner D, Kammerer T, et al. Viscoelastometry for detecting oral anticoagulants. *Thromb J*. 2021;19:18.
45. Yoshii R, Sawa T, Kawajiri H, Amaya F, Tanaka KA, Ogawa S. A comparison of the ClotPro system with rotational thromboelastometry in cardiac surgery: a prospective observational study. *Sci Rep*. 2022;12:17269.
46. Weber CF, Görlinger K, Meininger D, et al. Point-of-care testing: a prospective, randomized clinical trial of efficacy in coagulopathic cardiac surgery patients. *Anesthesiology*. 2012;117:531–547.
47. Fenger-Eriksen C, Moore GW, Rangarajan S, Ingerslev J, Sørensen B. Fibrinogen estimates are influenced by methods of measurement and hemodilution with colloid plasma expanders. *Transfusion*. 2010;50:2571–2576.
48. Bedreli S, Sowa JP, Malek S, et al. Rotational thromboelastometry can detect factor XIII deficiency and bleeding diathesis in patients with cirrhosis. *Liver Int*. 2017;37:562–568.
49. Raspé C, Besch M, Charitos EI, et al. Rotational thromboelastometry for assessing bleeding complications and factor XIII deficiency in cardiac surgery patients. *Clin Appl Thromb Hemost*. 2018;24:136S–144S.
50. Dirkmann D, Görlinger K, Gisbertz C, Dusse F, Peters J. Factor XIII and tranexamic acid but not recombinant factor VIIa attenuate tissue plasminogen activator-induced hyperfibrinolysis in human whole blood. *Anesth Analg*. 2012;114:1182–1188.
51. Kuiper GJ, Kleinegris MC, van Oerle R, et al. Validation of a modified thromboelastometry approach to detect changes in fibrinolytic activity. *Thromb J*. 2016;14:1.
52. Harr JN, Moore EE, Chin TL, et al. Viscoelastic hemostatic fibrinogen assays detect fibrinolysis early. *Eur J Trauma Emerg Surg*. 2015;41:49–56.
53. Abuelkasem E, Lu S, Tanaka K, Planinsic R, Sakai T. Comparison between thromboelastography and thromboelastometry in hyperfibrinolysis detection during adult liver transplantation. *Br J Anaesth*. 2016;116:507–512.
54. Wang IJ, Park SW, Bae BK, et al. FIBTEM improves the sensitivity of hyperfibrinolysis detection in severe trauma patients: a retrospective study using thromboelastometry. *Sci Rep*. 2020;10:6980.
55. Lang T, Toller W, Gütl M, et al. Different effects of abcximab and cytochalasin D on clot strength in thromboelastography. *J Thromb Haemost*. 2004;2:147–153.
56. Hartmann M, Lorenz B, Brenner T, Saner FH. Elevated pre- and postoperative ROTEM™ clot lysis indices indicate reduced clot retraction and increased mortality in patients undergoing liver transplantation. *Biomedicines*. 2022;10:1975.
57. Katori N, Tanaka KA, Szlam F, Levy JH. The effects of platelet count on clot retraction and tissue plasminogen activator-induced fibrinolysis on thromboelastography. *Anesth Analg*. 2005;100:1781–1785.
58. Tutwiler V, Litvinov RI, Lozhkin AP, et al. Kinetics and mechanics of clot contraction are governed by the molecular and cellular composition of the blood. *Blood*. 2016;127:149–159.
59. Miller TE, Myles PS. Perioperative fluid therapy for major surgery. *Anesthesiology*. 2019;130:825–832.
60. Hayes MM, Uhl L. To transfuse or not transfuse: an intensive appraisal of red blood cell transfusions in the ICU. *Curr Opin Hematol*. 2018;25:468–472.
61. Cable CA, Razavi SA, Roback JD, Murphy DJ. RBC transfusion strategies in the ICU: A Concise Review. *Crit Care Med*. 2019;47:1637–1644.
62. Weisel JW, Litvinov RI. Red blood cells: the forgotten player in hemostasis and thrombosis. *J Thromb Haemost*. 2019;17:271–282.
63. Tamura N, Shimizu K, Shiozaki S, et al. Important regulatory roles of erythrocytes in platelet adhesion to the von Willebrand factor on the wall under blood flow conditions. *Thromb Haemost*. 2022;122:974–983.

64. Carson JL, Stanworth SJ, Dennis JA, et al. Transfusion thresholds for guiding red blood cell transfusion. *Cochrane Database Syst Rev*. 2021;12:CD002042.
65. Odutayo A, Desborough MJ, Trivella M, et al. Restrictive versus liberal blood transfusion for gastrointestinal bleeding: a systematic review and meta-analysis of randomised controlled trials. *Lancet Gastroenterol Hepatol*. 2017;2:354–360.
66. Lier H, Krep H, Schroeder S, Stuber F. Preconditions of hemostasis in trauma: a review. The influence of acidosis, hypocalcemia, anemia, and hypothermia on functional hemostasis in trauma. *J Trauma*. 2008;65:951–960.
67. Rossaint R, Afshari A, Bouillon B, et al. The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition. *Crit Care*. 2023;27:80.
68. Pereira BM, Bortoto JB, Fraga GP. Topical hemostatic agents in surgery: review and prospects. *Rev Col Bras Cir*. 2018;45:e1900.
69. Kietai I, Ahmed A, Afshari A, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: second update 2022. *Eur J Anaesthesiol*. 2023;40:226–304.
70. Inaba K, Branco BC, Rhee P, et al. Impact of plasma transfusion in trauma patients who do not require massive transfusion. *J Am Coll Surg*. 2010;210:957–965.
71. Zheng W, Zhao KM, Luo LH, Yu Y, Zhu SM. Perioperative single-donor platelet apheresis and red blood cell transfusion impact on 90-day and overall survival in living donor liver transplantation. *Chin Med J (Engl)*. 2018;131:426–434.
72. Thorn S, Güting H, Mathes T, Schäfer N, Maegele M. The effect of platelet transfusion in patients with traumatic brain injury and concomitant antiplatelet use: a systematic review and meta-analysis. *Transfusion*. 2019;59:3536–3544.
73. Mohanty A, Kapuria D, Canakis A, et al. Fresh frozen plasma transfusion in acute variceal haemorrhage: results from a multicentre cohort study. *Liver Int*. 2021;41:1901–1908.
74. CRASH-2 Collaborators, Intracranial Bleeding Study. Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). *BMJ*. 2011;343:d3795.
75. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet*. 2017;389:2105–2116.
76. Chapman MP, Moore EE, Moore HB, et al. Early TRAP pathway platelet inhibition predicts coagulopathic hemorrhage in trauma. *Shock*. 2015;43:33.
77. Scharf RE. Drugs that affect platelet function. *Semin Thromb Hemost*. 2012;38:865–883.
78. Connelly CR, Yonge JD, McCully SP, et al. Assessment of three point-of-care platelet function assays in adult trauma patients. *J Surg Res*. 2017;212:260–269.
79. Adamzik M, Görlinger K, Peters J, Hartmann M. Whole blood impedance aggregometry as a biomarker for the diagnosis and prognosis of severe sepsis. *Crit Care*. 2012;16:R204.
80. Tauber H, Streif W, Fritz J, et al. Predicting transfusion requirements during extracorporeal membrane oxygenation. *J Cardiothorac Vasc Anesth*. 2016;30:692–701.
81. Ranucci M, Baryshnikova E; For The Surgical And Clinical Outcome Research Score Group. The interaction between preoperative platelet count and function and its relationship with postoperative bleeding in cardiac surgery. *Platelets*. 2017;28:794–798.
82. Greene LA, Chen S, Seery C, Imahiyerobo AM, Bussell JB. Beyond the platelet count: immature platelet fraction and thromboelastometry correlate with bleeding in patients with immune thrombocytopenia. *Br J Haematol*. 2014;166:592–600.
83. Parastatidou S, Sokou R, Tsantes AG, et al. The role of ROTEM variables based on clot elasticity and platelet component in predicting bleeding risk in thrombocytopenic critically ill neonates. *Eur J Haematol*. 2021;106:175–183.
84. Sokou R, Piovani D, Konstantinidi A, et al. A risk score for predicting the incidence of hemorrhage in critically ill neonates: development and validation study. *Thromb Haemost*. 2021;121:131–139.
85. Wickramasinghe W, Alvitigala BY, Perera T, et al. Rotational thromboelastometry in critical phase of dengue infection: association with bleeding. *Res Pract Thromb Haemost*. 2022;6:e12704.
86. Henskens YMC, Gulpen AJW, van Oerle R, et al. Detecting clinically relevant rivaroxaban or dabigatran levels by routine coagulation tests or thromboelastography in a cohort of patients with atrial fibrillation. *Thromb J*. 2018;16:3.
87. Comuth WJ, Henriksen LO, van de Kerkhof D, et al. Comprehensive characteristics of the anticoagulant activity of dabigatran in relation to its plasma concentration. *Thromb Res*. 2018;164:32–39.
88. Schäfer ST, Wiederkehr T, Kammerer T, et al. Real-time detection and differentiation of direct oral anticoagulants (rivaroxaban and dabigatran) using modified thromboelastometric reagents. *Thromb Res*. 2020;190:103–111.
89. Groene P, Butte J, Thaler S, Görlinger K, Schäfer ST. Modified thromboelastometric tests provide improved sensitivity and specificity to direct oral anticoagulants compared to standard thromboelastometric tests in-vitro. *Thromb J*. 2022;20:40.
90. Beiderlinden M, Werner P, Bahlmann A, et al. Monitoring of argatroban and lepirudin anticoagulation in critically ill patients by conventional laboratory parameters and rotational thromboelastometry: a prospectively controlled randomized double-blind clinical trial. *BMC Anesthesiol*. 2018;18:18.
91. Teruya J, Hensch L, Bruzdowski K, Adachi I, Hui SR, Kostousov V. Monitoring bivalirudin therapy in children on extracorporeal circulatory support devices: Thromboelastometry versus routine coagulation testing. *Thromb Res*. 2020;186:54–57.
92. Mohammad A, Branicki F, Abu-Zidan FM. Educational and clinical impact of Advanced Trauma Life Support (ATLS) courses: a systematic review. *World J Surg*. 2014;38:322–329.
93. Roberts I, Shakur H, Coats T, et al. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. *Health Technol Assess*. 2013;17:1–79.
94. Gayet-Ageron A, Prieto-Merino D, Ker K, Shakur H, Ageron F-X, Roberts I; Antifibrinolytic Trials Collaboration. Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients. *Lancet*. 2018;391:125–132.
95. Stein P, Kaserer A, Sprengel K, et al. Change of transfusion and treatment paradigm in major trauma patients. *Anaesthesia*. 2017;72:1317–1326.
96. Carneiro JMGVM, Alves J, Conde P, et al. Factor XIII-guided treatment algorithm reduces blood transfusion in burn surgery. *Rev Bras Anestesiol*. 2018;68:238–243.
97. Levy JH, Goodnough LT. How I use fibrinogen replacement therapy in acquired bleeding. *Blood*. 2015;125:1387–1393.
98. Leal-Noval SR, Fernández Pacheco J, Casado Méndez M, Cuenca-Apolo D, Muñoz-Gómez M. Current perspective on fibrinogen concentrate in critical bleeding. *Expert Rev Clin Pharmacol*. 2020;13:761–778.

99. McQuilten ZK, Wood EM, Bailey M, Cameron PA, Cooper DJ. Fibrinogen is an independent predictor of mortality in major trauma patients: a five-year statewide cohort study. *Injury*. 2017;48:1074–1081.
100. McDonnell NJ, Browning R. How to replace fibrinogen in postpartum haemorrhage situations? (hint: don't use FFP!). *Int J Obstet Anesth*. 2018;33:4–7.
101. Callum J, Farkouh ME, Scales DC, et al; FIBRES Research Group. Effect of fibrinogen concentrate vs cryoprecipitate on blood component transfusion after cardiac surgery: the FIBRES randomized clinical trial. *JAMA*. 2019;322:1966–1976.
102. Grottke O, Mallaiah S, Karkouti K, Saner F, Haas T. Fibrinogen supplementation and its indications. *Semin Thromb Hemost*. 2020;46:38–49.
103. Khan S, Brohi K, Chana M, et al; International Trauma Research Network (INTRN). Hemostatic resuscitation is neither hemostatic nor resuscitative in trauma hemorrhage. *J Trauma Acute Care Surg*. 2014;76:561–7; .
104. Innerhofer P, Fries D, Mittermayr M, et al. Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC): a single-centre, parallel-group, open-label, randomised trial. *Lancet Haematol*. 2017;4:e258–e271.
105. Desborough M, Sandu R, Brunskill SJ, et al. Fresh frozen plasma for cardiovascular surgery. *Cochrane Database Syst Rev*. 2015;2015:CD007614.
106. Bolton-Maggs PH, Cohen H. Serious hazards of transfusion (SHOT) haemovigilance and progress is improving transfusion safety. *Br J Haematol*. 2013;163:303–314.
107. Steinbicker AU, Wittenmeier E, Goobie SM. Pediatric non-red cell blood product transfusion practices: what's the evidence to guide transfusion of the "yellow" blood products? *Curr Opin Anaesthesiol*. 2020;33:259–267.
108. Bulle EB, Klanderman RB, Pendergrast J, Cserti-Gazdewich C, Callum J, Vlaar APJ. The recipe for TACO: A narrative review on the pathophysiology and potential mitigation strategies of transfusion-associated circulatory overload. *Blood Rev*. 2022;52:100891.
109. Tung JP, Chiaretti S, Dean MM, Sultana AJ, Reade MC, Fung YL. Transfusion-related acute lung injury (TRALI): potential pathways of development, strategies for prevention and treatment, and future research directions. *Blood Rev*. 2022;53:100926.
110. Péju E, Litjens JF, Charpentier J, et al. Impact of blood product transfusions on the risk of ICU-acquired infections in septic shock. *Crit Care Med*. 2021;49:912–922.
111. Winearls J, Wullschlegel M, Wake E, et al. Fibrinogen Early In Severe Trauma study (FEISTY): results from an Australian multicentre randomised controlled pilot trial. *Crit Care Resusc*. 2021;23:32–46.
112. Levy JH, Szlam F, Tanaka KA, Sniecinski RM. Fibrinogen and hemostasis: a primary hemostatic target for the management of acquired bleeding. *Anesth Analg*. 2012;114:261–274.
113. Ozier Y, Hunt BJ. Against: fibrinogen concentrate for management of bleeding: against indiscriminate use. *J Thromb Haemost*. 2011;9:6–8.
114. Jensen NH, Stensballe J, Afshari A. Comparing efficacy and safety of fibrinogen concentrate to cryoprecipitate in bleeding patients: a systematic review. *Acta Anaesthesiol Scand*. 2016;60:1033–1042.
115. Erdoes G, Koster A, Meesters MI, et al. The role of fibrinogen and fibrinogen concentrate in cardiac surgery: an international consensus statement from the Haemostasis and Transfusion Scientific Subcommittee of the European Association of Cardiothoracic Anaesthesiology. *Anaesthesia*. 2019;74:1589–1600.
116. Beverly A, Ong G, Kimber C, et al. Drugs to reduce bleeding and transfusion in major open vascular or endovascular surgery: a systematic review and network meta-analysis. *Cochrane Database Syst Rev*. 2023;2:CD013649.
117. Baharoglu MI, Cordonnier C, Al-Shahi Salman R, et al; PATCH Investigators. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. *Lancet*. 2016;387:2605–2613.
118. Desborough MJ, Oakland KA, Landoni G, et al. Desmopressin for treatment of platelet dysfunction and reversal of antiplatelet agents: a systematic review and meta-analysis of randomized controlled trials. *J Thromb Haemost*. 2017;15:263–272.
119. Weber CF, Görlinger K, Byhahn C, et al. Tranexamic acid partially improves platelet function in patients treated with dual antiplatelet therapy. *Eur J Anaesthesiol*. 2011;28:57–62.
120. Kalbhenn J, Wittau N, Schmutz A, Zieger B, Schmidt R. Identification of acquired coagulation disorders and effects of target-controlled coagulation factor substitution on the incidence and severity of spontaneous intracranial bleeding during veno-venous ECMO therapy. *Perfusion*. 2015;30:675–682.
121. Muszbek L, Bagoly Z, Bereczky Z, Katona E. The involvement of blood coagulation factor XIII in fibrinolysis and thrombosis. *Cardiovasc Hematol Agents Med Chem*. 2008;6:190–205.
122. Rijken DC, Uitte de Willige S. Inhibition of fibrinolysis by coagulation factor XIII. *Biomed Res Int*. 2017;2017:1209676.
123. Durda MA, Wolberg AS, Kerlin BA. State of the art in factor XIII laboratory assessment. *Transfus Apher Sci*. 2018;57:700–704.
124. Schlimp CJ, Cadamuro J, Solomon C, Redl H, Schöchl H. The effect of fibrinogen concentrate and factor XIII on thromboelastometry in 33% diluted blood with albumin, gelatine, hydroxyethyl starch or saline in vitro. *Blood Transfus*. 2013;11:510–517.
125. van den Brink DP, Wirtz MR, Neto AS, et al. Effectiveness of prothrombin complex concentrate for the treatment of bleeding: a systematic review and meta-analysis. *J Thromb Haemost*. 2020;18:2457–2467.
126. Erdoes G, Koster A, Ortmann E, et al. A European consensus statement on the use of four-factor prothrombin complex concentrate for cardiac and non-cardiac surgical patients. *Anaesthesia*. 2021;76:381–392.
127. Bartoszko J, Callum J, Karkouti K; FIBRES Study Investigators. FIBRES study investigators. The association of prothrombin complex concentrates with postoperative outcomes in cardiac surgery: an observational substudy of the FIBRES randomized controlled trial. *Can J Anaesth*. 2021;68:1789–1801.
128. Katz DJ, Hira SK, Sison ML, Getrajdman CS. Impact of fibrinogen and prothrombin complex concentrate on clotting time in a model of obstetric hemorrhage. *J Clin Anesth*. 2022;78:110687.
129. Lier H, Vorweg M, Hanke A, Görlinger K. Thromboelastometry guided therapy of severe bleeding. Essener Runde algorithm. *Hamostaseologie*. 2013;33:51–61.
130. Sarode R, Milling TJ, Jr, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. *Circulation*. 2013;128:1234–1243.

131. Hanke AA, Joch C, Görlinger K. Long-term safety and efficacy of a pasteurized nanofiltrated prothrombin complex concentrate (Beriplex P/N): a pharmacovigilance study. *Br J Anaesth*. 2013;110:764–772.
132. Vigué B, Ract C, Tremey B, et al. Ultra-rapid management of oral anticoagulant therapy-related surgical intracranial hemorrhage. *Intensive Care Med*. 2007;33:721–725.
133. Tazarourte K, Riou B, Tremey B, Samama C-M, Vicaut E, Vigué B; EPAHK Study Group. Guideline-concordant administration of prothrombin complex concentrate and vitamin K is associated with decreased mortality in patients with severe bleeding under vitamin K antagonist treatment (EPAHK study). *Crit Care*. 2014;18:R81.
134. Steiner T, Poli S, Griebel M, et al. Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial. *Lancet Neurol*. 2016;15:566–573.
135. Goldstein JN, Refaai MA, Milling TJ, Jr, et al. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial. *Lancet*. 2015;385:2077–2087.
136. Ichikawa J, Kodaka M, Nishiyama K, Hirasaki Y, Ozaki M, Komori M. Reappearance of circulating heparin in whole blood heparin concentration-based management does not correlate with postoperative bleeding after cardiac surgery. *J Cardiothorac Vasc Anesth*. 2014;28:1003–1007.
137. Pailleret C, Jourdi G, Siguret V, et al. Modified ROTEM for the detection of rivaroxaban and apixaban anticoagulant activity in whole blood: A diagnostic test study. *Eur J Anaesthesiol*. 2019;36:449–456.
138. Kitchen S, Gray E, Mackie I, Baglin T, Makris M; BCSH Committee. BCSH committee. Measurement of non-Coumarin anticoagulants and their effects on tests of Haemostasis: Guidance from the British Committee for Standards in Haematology. *Br J Haematol*. 2014;166:830–841.
139. Favaloro EJ, Pasalic L, Curnow J, Lippi G. Laboratory monitoring or measurement of direct oral anticoagulants (DOACs): advantages, limitations and future challenges. *Curr Drug Metab*. 2017;18:598–608.
140. Milioglou I, Farmakis I, Neudeker M, et al. Prothrombin complex concentrate in major bleeding associated with DOACs: an updated systematic review and meta-analysis. *J Thromb Thrombolysis*. 2021;52:1137–1150.
141. Piran S, Khatib R, Schulman S, et al. Management of direct factor Xa inhibitor-related major bleeding with prothrombin complex concentrate: a meta-analysis. *Blood Adv*. 2019;3:158–167.
142. Dager WE, Roberts AJ, Nishijima DK. Effect of low and moderate dose FEIBA to reverse major bleeding in patients on direct oral anticoagulants. *Thromb Res*. 2019;173:71–76.
143. Getta B, Muller N, Motum P, Hsu D, Zebelman D, Rosenfeld D. Intermittent haemodialysis and continuous venovenous dialysis are effective in mitigating major bleeding due to dabigatran. *Br J Haematol*. 2015;169:603–604.
144. Røed-Undlien H, Schultz NH, Lunnan A, et al. In vitro apixaban removal by cytosorb whole blood adsorber: an experimental study. *J Cardiothorac Vasc Anesth*. 2022;36:1636–1644.
145. Artunc F, Muehlbacher T, Baumann D, et al. Removal of dabigatran is superior by sustained low efficient dialysis (SLED) compared to intermittent hemodialysis. *Blood Purif*. 2015;39:331–332.
146. Mair H, Jilek C, Haas B, Lamm P. Ticagrelor and rivaroxaban elimination with cytosorb adsorber before urgent off-pump coronary bypass. *Ann Thorac Surg*. 2020;110:e369–e370.
147. Hassan K, Brüning T, Caspary M, et al. Hemoadsorption of rivaroxaban and ticagrelor during acute type a aortic dissection operations. *Ann Thorac Cardiovasc Surg*. 2022;28:186–192.
148. Eikelboom JW, Quinlan DJ, van Ryn J, Weitz JL. Idarucizumab: the antidote for reversal of dabigatran. *Circulation*. 2015;132:2412–2422.
149. Connolly SJ, Crowther M, Eikelboom JW, et al; ANNEXA-4 Investigators. Full Study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2019;380:1326–1335.
150. Gómez-Outes A, Alcubilla P, Calvo-Rojas G, et al. Meta-analysis of reversal agents for severe bleeding associated with direct oral anticoagulants. *J Am Coll Cardiol*. 2021;77:2987–3001.