Novel approaches in management of perioperative coagulopathy

Kenichi A. Tanaka[a], *Stephen O. Bader*[a], *and Klaus Görlinger*[b]

Purpose of review
The recent advances in hemostatic monitoring, and discussion of the clinical implications of hemostatic therapies based on different blood components and factor concentrates.

Recent findings
Implementing suitable laboratory tests and transfusion protocols is highly recommended because the laboratory test guided, protocol-driven transfusion approach reduces blood component utilization, and possibly leads to improved outcomes. Timely assessment of coagulation has been difficult using conventional coagulation tests, but thrombocytopenia, fibrin polymerization defects, and fibrinolysis can be quickly assessed on thromboelastometry. The latter testing can be applied to guide the dosing of fibrinogen and prothrombin complex concentrate, which are selectively used to correct fibrinogen deficiency, and improve thrombin generation in acquired coagulopathy. These therapeutic approaches are novel, and potentially effective in reducing the exposure to allogeneic components (e.g., plasma and platelets) and side-effects of transfusion. Although the accessibility of different therapies among different countries, tranexamic acid is widely available, and is an effective blood conservation measure with a good safety profile in various surgical settings.

Summary
Our understanding of perioperative coagulopathy, diagnostic tools, and therapeutic approaches has evolved in recent years. Additional multidisciplinary efforts are required to understand the optimal combinations, cost-effectiveness, and safety profiles of allogeneic components, and available factor concentrates.

Keywords
coagulation, fibrinogen concentrate, monitoring, perioperative hemostasis, thromboelastometry, tranexamic acid

INTRODUCTION

The cause of perioperative bleeding is often multifactorial, and its dynamic nature (i.e., major deterioration in a matter of minutes) calls for rapid diagnosis and immediate interventions. Perioperative coagulopathy involves both procoagulant and anticoagulant proteins as well as cellular components (e.g., platelets and endothelium). Relatively long turn around time (TAT) for conventional hematological testing (>30–60 min) is adequate for managing chronic disorders, but it is crucial to have a faster TAT (<15–20 min) in perioperative, critically ill patients [1–4]. Laboratory-guided hemostatic component therapy has been shown to decrease blood component usage and overall costs of transfusion compared with unrestricted transfusion [5,6,7▪▪]. However, the practice of hemostatic transfusion widely varies depending on locally available hemostatic components and their costs [7▪▪,8,9], coagulation testing [point-of-care (POC) vs. central laboratory] [2,3,10], and patient demographics [11▪] in addition to surgical and anesthetic techniques [12]. In cases of major bleeding, allogeneic blood and plasma components are considered to be life-saving, but a number of inherent risks is

[a]Department of Anesthesiology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA and [b]Clinic of Anesthesiology and Intensive Care Medicine, University Hospital Essen, University Duisburg-Essen, Essen, Germany

Correspondence to Kenichi A. Tanaka, MD, M.Sc., Professor of Anesthesiology, University of Pittsburgh Medical Center, 200 Lothrop Street, PUH C-215, Pittsburgh, PA 15213, USA. Tel: +1 412 864 1612; e-mail: tanakak@upmc.edu

Curr Opin Anesthesiol 2014, 27:000–000
DOI:10.1097/ACO.0000000000000025

KEY POINTS

- Hemostatic component transfusion guided by laboratory coagulation assays or viscoelastic testing (ROTEM and TEG) can lead to less blood usage, and overall cost reduction.
- Fibrinogen concentrate is a new alternative to cryoprecipitate in the treatment of congenital afibrinogenemia or hypofibrinogenemia.
- Bleeding associated with vitamin K antagonist therapy can be acutely reversed with PCC, which contains therapeutic amounts of prothrombin, FVII, FIX, FX, protein C, and protein S.
- Targeted replacements of fibrinogen, and vitamin K-dependent factors in perioperative (often dilutional) coagulopathy are feasible under thromboelastometry guidance, but additional data are needed for their efficacy and safety against conventional transfusion.
- Antifibrinolytic therapy with tranexamic acid is effective in both congenital and acquired coagulopathy, and it can be administered via topical, oral, and intravenous route.

associated with allogeneic blood transfusion [13–15]. The indications, hematological effects, and potential side-effects of each component should be well understood to optimize the safety and efficacy of hemostatic interventions. In this review, we present an overview of the recent advances in coagulation monitoring, and discuss clinical implications of blood components and hemotherapeutic agents.

LABORATORY-GUIDED HEMOSTATIC THERAPY

The evaluation of coagulopathy is conventionally performed using prothrombin time [(PT) or international normalized ratio; (INR)], activated partial thromboplastin time (aPTT), fibrinogen level (Clauss method), and platelet count. These tests are universally available although the reference (normal) ranges vary among different assay reagents, methods, and devices. These tests are performed in isolated plasma (PT, aPTT, and fibrinogen), or in anticoagulated whole blood (platelet count). Laboratory-based testing offers excellent quality control for the devices and assays, so that reliable test results can be reported according to laboratory practice regulations and guidelines. However, typical TAT for these tests is about 30–60 min, and it could take longer when tests are repeated to confirm abnormal results (e.g., severe hypofibrinogenemia). Some laboratories have dealt with these logistic issues by modifying the stat test procedures. Chandler *et al.* [3] recently demonstrated that TAT for PT and fibrinogen can be reliably shortened to 14 min (range, 6–28 min) using a rapid centrifugation (2 min), and extended calibration ranges. Although it is possible to obtain several coagulation test results in a timely manner, the complex interactions of different coagulation elements (e.g., platelets and enzymatic factors) cannot be appreciated from isolated tests (i.e., no platelets in PT/aPTT). Further, hyperfibrinolysis can be triggered in a complex coagulopathy during major trauma and surgery, but profibrinolytic tendency is not readily detected by PT/aPTT or fibrinogen level [16]. Some of these limitations of traditional laboratory testing can be overcome by the use of viscoelastic coagulation testing in whole blood.

VISCOELASTIC TESTING

Thromboelastometry (ROTEM, TEM Innovations, Munich, Germany) and thrombelastography (TEG; Haemonetics, Niles, Illinois, USA) are the currently available viscoelastic test devices. Clot formation is assessed in whole blood by measuring the tensile (viscoelastic) force development between the cup and the immersed pin (Fig. 1). The viscoelastic signal is highly dependent on endogenous thrombin generation, fibrin polymerization, and fibrin interactions with platelet glycoprotein IIb/IIIa receptors. In cases of systemic fibrinolysis, early clot degradation by plasmin can be observed [17] (Fig. 2). As recently reviewed elsewhere [17–19], both ROTEM and TEG offer similar types of tests, and yield closely related clotting measurements, but these two systems are not interchangeable because of different types of reagents and blood samples (fresh whole blood or recalcified citrated blood) (Table 1) [19–24]. Heparinase cups are specifically requested for TEG, but the reagents for EXTEM, FIBTEM, and APTEM for ROTEM contain hexadimethrine (polybrene), which neutralizes heparin. In terms of the reference ranges, it is recommended that local values are set according to the specific patient population that is, adults or children, ethnicity, and disease types [20,25,26].

The most notable advance in hemostatic management using viscoelastic testing is a fibrin-specific clot assessment. The FIBTEM assay on the ROTEM allows a rapid assessment (TAT <5–10 min) of fibrin polymerization in whole blood, and it correlates with plasma fibrinogen levels [27–30]. In combination with EXTEM, FIBTEM can delineate hypofibrinogenemia from isolated thrombocytopenia, both of which decrease the overall clot strength (Fig. 2).

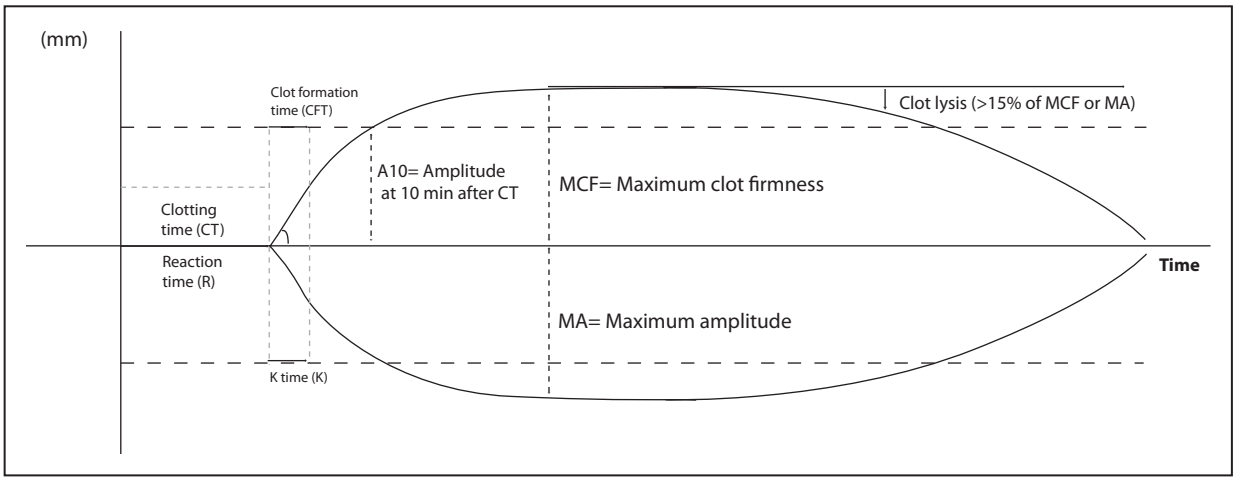

FIGURE 1. Changes in whole blood viscoelasticity are detected optically in ROTEM, and electromechanically in TEG and clot formation parameters are generated on ROTEM (upper panel) and TEG (lower panel). Plasmatic coagulation is reflected on CT and R time, and initial clot development is shown on CFT and K time (also on α angle). Maximal viscoelasticity is defined by MA or MCF for TEG and ROTEM, respectively. A_{10} or A_{15} (amplitude at 10 or 15 min after CT) may be preferably used to make early decision on ROTEM. Systemic fibrinolysis is suspected when clot breakdown (>15% of MA or MCF) is observed within 1 h. Adapted with permission from [17]. CT, clotting time; CFT, clot formation time; MA, maximum amplitude; MCF, maximum clot firmness.

Hypofibrinogenemia is assumed by the reduced α angle (<52°) on kaolin-TEG assay [31]. However, the TEG result is more likely to be interpreted as thrombocytopenia even if hypofibrinogenemia is the predominant cause of reduced clot strength [24]. The functional fibrinogen assay has been recently introduced for TEG, but few clinical data are available on the cut-off value for fibrinogen replacement [23].

Hyperfibrinolysis is suspected when the decrease of the amplitude over 1 h is more than 15% of the maximum amplitude on TEG or ROTEM (Table 1, Fig. 2). This is confirmed by using APTEM on ROTEM because the reagent contains aprotinin, which inhibits plasmin-induced fibrinolysis *in vitro* [16–19]. No confirmatory test for fibrinolysis is currently available for TEG, and platelet-induced clot retraction may be misinterpreted as fibrinolysis [32]. Early diagnosis of hyperfibrinolysis is important because ongoing fibrinolysis can exacerbate bleeding, and adversely affects therapeutic responses to hemostatic interventions including fibrinogen and recombinant activated factor VII (FVII) [33–35]. Although profibrinolytic states may be corrected with an antifibrinolytic agent, hyperfibrinolysis by viscoelastic testing underlie the severity of traumatic injury, and it is associated with high mortality (70–88%) [36,37,38▪].

Taken together, viscoelastic coagulation testing, particularly ROTEM, primarily focuses on the correction of hypofibrinogenemia, and, if any, fibrinolysis, which is followed by the correction of thrombocytopenia (or platelet dysfunction) and/or procoagulant factor deficiency. Several clinical studies have demonstrated the hemostatic effectiveness of this approach, and reduced the need for plasma transfusion [7▪▪,39,40,41▪▪,42].

FIBRINOGEN CONCENTRATE

Cryoprecipitate has been the mainstay therapy for fibrinogen replacement in congenital and acquired fibrinogen deficiency in North America. Human plasma-derived pasteurized fibrinogen concentrate (RiaStap; CSL Behring, Marburg, Germany) has been recently approved for the treatment of congenital afibrinogenemia or hypofibrinogenemia [43]. Fibrinogen concentrate has been indicated for the treatment of perioperative bleeding in many European countries where cryoprecipitate is unavailable [7▪▪,44]. In contrast to cryoprecipitate and plasma, fibrinogen concentrate is stored at room temperature for 30 months [43]. In addition, it can be reconstituted at bedside, and administered regardless of the blood type [44]. The fibrinogen content in each vial of fibrinogen concentrate is standardized (900–1300 mg per vial), whereas fibrinogen content is variable in the cryoprecipitate or plasma. The efficacy of fibrinogen concentrate (1 g in 50 ml) should be equivalent or superior to cryoprecipitate (~225 mg in 15 ml) [45], and far superior to plasma (~250 mg in 100 ml) [46].

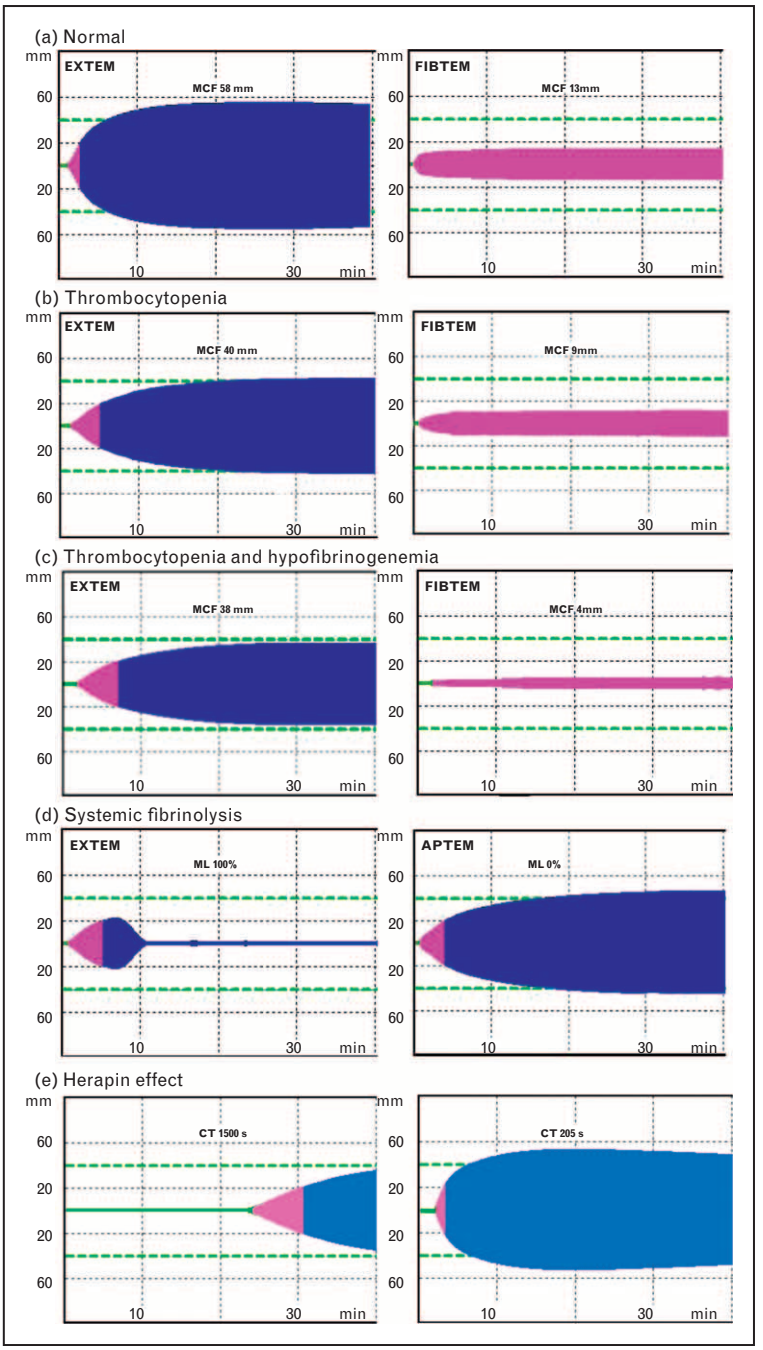

FIGURE 2. Normal EXTEM tracing is shown on the panels (a). Plasma fibrinogen level is presumably normal (>150 mg/dl), but thrombocytopenia is suspected on the panel (b). Thrombocytopenia and hypofibrinogenemia are suspected on EXTEM, and simultaneous FIBTEM on the panel (c) confirms hypofibrinogenemia. Systemic fibrinolysis is suspected on the panel (d) (ML: maximal lysis 100%), which can be confirmed by APTEM. Residual heparin or low coagulation factor levels are suspected on the panel (e), which can be confirmed by HEPTEM. Refer to Table 1 for reference ranges. Adapted with permission from [17].

In perioperative patients, fibrinogen replacement can be guided by the FIBTEM assay [7▪▪,40]. Görlinger *et al.* [40] reported that a 25 mg/kg dose of fibrinogen in an 80-kg patient (total 2 g of fibrinogen) generally results in a 4 mm increase in FIBTEM-MCF. They have generalized this finding according to the body weight (Table 2).

Solomon *et al.* [47] reported that FIBTEM-MCF was increased by 1 mm after the average fibrinogen dose of 7.6 mg/kg in adult cardiac surgical patients.

Table 1. Reference (normal) ranges for ROTEM and TEG tests

Test (activator)		CT/R (s)	CFT/K (s)	Angle α (°)	MCF/MA (mm)	Lysis (% of MA/MCF)
ROTEM	EXTEM (TF)	35–80	35–160	63–81	53–72	<15
	INTEM (ellagic acid)	100–240	35–110	71–82	53–72	<15
	FIBTEM (TF+cytochalasin D)				9–25	
TEG	RapidTEG (kaolin/TF)	86–118	34–138	68–82	52–71	<15
	Native (kaolin/TF)	78–110	30–118	66–82	54–72	<15
	KaoTEG (kaolin)	180–480	60–180	55–78	51–69	<15
	Native (kaolin)	240–480	60–240	47–74	55–73	<15
	Functional fibrinogen				11–24	
	Native (functional fibrinogen)				9–29	

Normal values according to the manufacturer of ROTEM and TEG for recalcified citrated blood samples, and for native blood samples (Native) on TEG. For rapidTEG, ACT values are shown instead of R time. EXTEM and FIBTEM reagents contain hexadimethrine, and are not susceptible to therapeutic levels of heparin. RapidTEG, kaoTEG, and INTEM are affected by heparin, and heparinase cup (TEG) or HEPTEM (ROTEM) should be considered to rule out residual heparin. For abbreviations of thromboelastographic parameters, refer to Fig. 1. ACT, activating clotting time; CT, clotting time; CFT, clot formation time; MA, maximum amplitude; MCF, maximum clot firmness; TF, tissue factor.

The dose can be approximated by the following formula:

$$\text{Dose} = [\text{target FIBTEM-MCF (mm)} - \text{current FIBTEM-MCF (mm)}] \times \text{Weight (kg)} \div 140$$

For example, if the FIBTEM-MCF were 4 mm in a 70-kg patient with clinical bleeding, and the target FIBTEM-MCF were 8 mm, the dose of fibrinogen can be calculated to be:

$$\text{Dose} = (8 - 4) \times 70 \div 140 = 2\,\text{g}$$

Per 1 g of fibrinogen administration, plasma fibrinogen is increased by approximately 25–28 mg/dl (median) in the adult bleeding case due to acquired hypofibrinogenemia [48,49].

In order to convert the dose of fibrinogen to the number of pooled units of cryoprecipitate, the calculated dose of fibrinogen is multiplied by a factor of 5 (assuming 1 g of fibrinogen in five pools of cryoprecipitate):

$$\text{Pools of cryoprecipitate} = (8 - 4) \times 70 \div 140 \times 5 = 10\,\text{U}$$

It is important to realize that FIBTEM-MCF can be affected by hematocrit, but the correlation between FIBTEM-MCF and fibrinogen level tends to improve under anemic state [30]. The target values of FIBTEM-MCF have been in the range of 8–10 mm [7▪▪,8,42], and FIBTEM-MCF of 10 mm approximates plasma fibrinogen of 200 mg/dl in post cardiopulmonary bypass (CPB) cases [30]. Clot firmness at 10 and 15 min after clotting time (CT) are designated as A_{10} and A_{15} respectively (Fig. 1), and these parameters can be used for early decision-making in severe coagulopathy [7▪▪,40,42]. The optimal target ranges of FIBTEM-MCF (alternatively A_{10} or A_{15}) should be locally determined by considering the pertinent patient population (e.g., neonate) [8,9], the extent of vascular injury and bleeding risk (e.g., replacement of aorta) [41▪▪], and by clinically evaluating therapeutic responses to available fibrinogen-rich components [45,47].

Fibrinogen concentrate is a plasma-derived product, but the risks of pathogen transmission, immunological, and allergic reactions are extremely low due to purification and pathogen inactivation processes [50,51]. Thromboembolic complications associated with fibrinogen concentrate are rare, but the estimated rate of thrombosis is presumably

Table 2. Dose of fibrinogen concentrate dosage and estimated changes in plasma fibrinogen and FIBTEM

Dose of fibrinogen (mg/kg)	25	50	75	100
Total (g) for 80-kg patient	2	4	6	8
Δ Fibrinogen level (mg/dl)	50	100	150	200
Δ FIBTEM-MCF (mm)	4	8	12	16

Note: The calculation is based on the assumption of normovolemia (blood volume of ~80 ml/kg body weight) and a hematocrit of about 30%. Actual fibrinogen recovery may vary due to volume status, extent of hemorrhage, and changes in hematocrit. No sufficient data exist for patients with a body weight less than 20 kg or more than 80 kg. MCF, maximum clot firmness.

Table 3. Commercial 3-factor and 4-factor prothrombin complex concentrate products

Product name	FII	FVII	FIX	FX	Protein C/S	Additive
Bebulin	120	13	100	139	N.R.	Heparin
Profilnine	148	11	100	64	N.R.	No heparin
Kcentra (Beriplex)	111	57	100	150	Yes	Heparin, AT
Octaplex	98	66	100	96	Yes	Heparin

Note: Other PCC products are also available in different countries. AT, antithrombin; N.R., not reported; Protein C/S, protein C/protein S; Yes, contains therapeutic amounts. Relative contents of vitamin K-dependent factors for different PCCs. The percentage (%) activity of each factor is shown relative to FIX activity (based on the prescribing information for each product; actual factor contents may vary for each vial). PCC, prothrombin complex concentrate.

3.48 events per 10^5 treatment based on 1 034 389 g of the usage over 22 years [52] The use of fibrinogen concentrate is potentially hazardous in disseminated intravascular coagulation (DIC) [5].

PROTHROMBIN COMPLEX CONCENTRATE

In acquired bleeding conditions, fibrinogen may not be the only factor that needs to be replaced. After fibrinogen replacement, other procoagulant factors and platelet count (or function) may remain abnormal, contributing to persistent microvascular bleeding [53,54]. Testing of agonist-specific platelet aggregation requires a separate set-up [7▪▪,11▪], but thrombocytopenia per se can be assessed by EXTEM-A_{10} (<40 mm) [7▪▪], EXTEM-A_{15} (<48 mm) [42], or TEG-maximum amplitude (maximum amplitude<50 mm) in the presence of normal fibrin polymerization (or fibrinogen level) [31,55]. Enzymatic defects of coagulation can be estimated by viscoelastic testing in the case of bleeding and hemodilution. EXTEM-CT (normal 42–74 s) is prolonged to more than 80 s on the ROTEM in the presence of vitamin K-dependent enzymatic deficiency. Prolonged (kaolin) reaction time (R-time >10 min) is used as a cut-off for hemostatic intervention on the TEG [31,55]. Prolonged CT and R-time have been traditionally addressed by the administration of plasma, but relatively large amounts of plasma (10–30 ml/kg) are required to correct enzymatic defects [31,56]. In a prospective randomized study of POC testing vs. central laboratory testing (control) for hemostastic management involving 100 cardiac surgical patients, Weber *et al.* [7▪▪] described the use of prothrombin complex concentrate [(PCC), 25 IU/kg)] according to EXTEM-CT over 80 s after restoring fibrin polymerization. In the control group, plasma transfusion was allowed if INR was more than 1.4 or after 4 units of erythrocytes were transfused (if INR value was unavailable). The frequency of plasma transfusion was reduced by half (40 vs. 80% with laboratory testing; $P<0.001$), whereas the frequency of PCC infusion was similar between two groups (44 vs. 52% with laboratory testing; $P=0.433$). The overall rate of adverse events (acute renal failure, sepsis, thrombotic complications, and allergic reactions) was also reduced in the POC group (8 vs. 38%; $P<0.001$). In their study, 4-factor PCC was used in the transfusion protocol, but similar findings have been reported with the post-CPB use of 3-factor PCC [57]. The main difference between 4-factor and 3-factor PCCs concerns the amount of FVII, which is considered to be therapeutic in 4-factor PCCs (Table 3).

One 4-factor product (Kcentra; CSL Behring, Marburg, Germany) has been recently approved by the Food and Drug Administration for the urgent reversal of vitamin K antagonists (e.g., warfarin) in adult patients with acute major bleeding [58,59]. Another 4-factor PCC (Octaplex; Octapharma, Lachen, Switzerland) has been available in Canada since 2006, and this product is expected to be available in the USA pending approval from the FDA. In patients receiving vitamin K antagonists, 4-factor PCC is preferably used according to the pretreatment INR (Table 4) [59]. The half-life of FVII is relatively short (4–6 h), and vitamin K (phytonadione, 5–10 mg slow i.v.) is usually administered before PCC to prevent a rebound increase in PT/INR [58].

Table 4. Treatment for acute warfarin reversal

INR	Treatment (i.v.)
2.0–3.9	PCC 25 IU/kg + vit K 5–10 mg
4.0–5.9	PCC 35 IU/kg + vit K 5–10 mg
>6.0	PCC 50 IU/kg + vit K 5–10 mg

Note: Dosing of 4-factor PCC based on the clinical trial of Kcentra (CSL Behring, Marburg, Germany) [59], and recommended dosing for other 4-factor and 3-factor PCC may be different (refer to the prescribing information for each PCC product). INR, international normalized ratio; PCC, prothrombin complex concentrate.

Thromboembolic complication is a possible risk of the administration of PCCs. The reported incidence of thrombotic complications after 4-factor PCCs is about 0.7–2% in the patients receiving vitamin K antagonists [60]. As previously mentioned, thromboelastometry-guided administration of PCC after normalizing fibrinogen level in post-cardiac surgical bleeding is effective, and it does not appear to increase thromboembolic complications [7▪▪]. The use of PCCs in patients with DIC unless anticoagulant reserve (e.g., antithrombin) is sufficiently restored before PCC administration [5]. Most PCCs (except for Profilnine and Cofact) contain trace amounts of heparin, and they should be avoided in patients with heparin-induced thrombocytopenia [5,59].

RECENT UPDATES ON TRANEXAMIC ACID

Antifibrinolytic therapy is routinely used for blood conservation in cardiac surgery (Society of Thoracic Surgeons guideline). Aprotinin is seldom used in current practice because of the concerns for higher risk of death indicated in the Blood Conservation Using Antifibrinolytics in a Randomized Trial [61]. Although the European Medicines Agency lifted the suspension of aprotinin in February 2012, ε-aminocaproic acid (EACA) and tranexamic acid are the mainstay antifibrinolytic therapy. Both EACA and tranexamic acid are lysine analogues, and are available in oral (tablet) and intravenous formulations. The numerous clinical uses of lysine analogues have been reported in the literature including bleeding treatment for congenital α_2-antiplasmin deficiency [62], hemophilia [63], and menorrhagia [63] as well as perioperative blood conservation (cardiac, liver, spinal/orthopedic, postpartum hemorrhage, and trauma) [64]. Clinical effectiveness of tranexamic acid was highlighted in a recent prospective randomized, placebo-controlled trial (Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage-2) involving 20 211 trauma patients [65]. The administered dose of tranexamic acid is lower (1 g loading followed by 1 g over 8 h i.v.) in trauma than in cardiac surgical setting (typically, 2 g bolus followed by 0.5 g/h i.v.) [66]. Their study demonstrated significant reductions in all-cause mortality [14.5 vs. 16.0%; relative risk (RR) 0.91; $P < 0.0035$], and deaths due to bleeding (4.9 vs. 5.7%; RR 0.85; $P < 0.0077$) [65]. Furthermore, no increase in vascular occlusive events was associated with tranexamic acid compared with the placebo. Thromboembolic complications seem to be rare with EACA and tranexamic acid in bleeding patients, but higher thrombotic risks are expected with DIC, pre-existing thrombophilia, oral contraceptive use, and postoperative hypercoagulability [67]. After hip and knee arthroplasties in elderly patients, there are substantial risks for deep vein thrombosis and pulmonary embolism without a proper thromboprophylaxis regimen (intermittent pneumatic compression, low-dose heparin, etc.) [68]. Blood loss and the need for blood transfusion could be reduced by antifibrinolytic therapy, but there is a remaining concern for thromboembolic events. Wong *et al.* [69▪▪] recently conducted a prospective randomized study comparing the topical application of tranexamic acid (1.5 or 3 g) vs. placebo in primary knee arthroplasties. One of two doses of tranexamic acid or placebo (in 100 ml physiological saline) was directly applied to the wound 5 min before closure. Both topical doses were shown to reduce postoperative bleeding by 20–25%, and 16–17% higher hemoglobin levels were maintained compared with the placebo. After topical application, mean plasma levels of tranexamic acid were 4.5 and 8.5 μg/ml (up to 120 μg/ml in cardiac surgery) [70,71] at which tranexamic acid is unlikely to exert systemic antifibrinolytic activity. This approach may be preferred in situations in which the wound is accessible, and any interference with venous thromboprophylaxis is undesirable. One precaution about this approach is that direct application of tranexamic acid to spinal cord (by accidental intrathecal injection) elicits an epileptogenic effect [72–74]. This effect is presumably triggered by competitive inhibition of glycine receptors and γ-aminobutyric acid receptors by tranexamic acid [75,76▪].

CONCLUSION

Our understanding of perioperative coagulopathy, diagnostic tools, and therapeutic approaches has evolved in the recent years. It is pivotal to ascertain timely diagnosis and therapeutic intervention(s) for coagulopathy resulting from major surgery, trauma, and postpartum bleeding [4,17,77,78]. It is highly recommended to implement suitable laboratory tests and transfusion protocols at each institution because laboratory test guided, protocol-driven transfusion approach reduces blood component utilization, and possibly leads to improved outcomes [5,6,7▪▪]. Perioperative coagulopathy is often multifactorial, and it can be rarely corrected with a single 'magic bullet'. Different blood components and pharmacological agents are often combined to achieve hemostasis. However, additional multidisciplinary efforts are required to understand the optimal combinations, cost-effectiveness, and safety profiles.

Although accessible hemostatic components and factor concentrates vary among different countries [7▪▪,44,79]. Tranexamic acid is a universally available, effective blood conservation measure with a good safety profile [65]. More information on the indication, dosing, and safety profiles of tranexamic acid should be available from several ongoing, large-scale trials in traumatic brain injury (Clinical Randomization of an Antifibrinolytic in Significant Head Injury-3 trial; ISRCTN15088122) [80], and postpartum hemorrhage (World Maternal Antifibrinolytic Trial trial; ISRCTN76912190) [81].

Acknowledgements

None.

Conflicts of interest

K.A.T. has served as a consultant for Tem International (Munich, Germany), Grifols Biologicals (Barcelona, Spain), and Octapharma (Vienna, Austria), and has previously received research support from CSL Behring (Marburg, Germany); none of the companies were involved in the article preparation. S.O.B. has served as a consultant for Grifols Biologicals. K.G. received honoraria for scientific lectures from CSL Behring and Octapharma; he is the Medical Director of TEM international since July 2012.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Plotkin AJ, Wade CE, Jenkins DH, *et al.* A reduction in clot formation rate and strength assessed by thrombelastography is indicative of transfusion requirements in patients with penetrating injuries. J Trauma 2008; 64:S64–S68.
2. Toulon P, Ozier Y, Ankri A, *et al.* Point-of-care versus central laboratory coagulation testing during haemorrhagic surgery. A multicenter study. Thromb Haemost 2009; 101:394–401.
3. Chandler WL, Ferrell C, Trimble S, Moody S. Development of a rapid emergency hemorrhage panel. Transfusion 2010; 50:2547–2552.
4. David JS, Godier A, Dargaud Y, Inaba K. Case scenario: management of trauma-induced coagulopathy in a severe blunt trauma patient. Anesthesiology 2013; 119:191–200.
5. Cross-sectional guidelines for therapy with blood compo nents and plasma derivatives: chapter 7 procoagulators. Transfus Med Hemother 2009; 36:419–436.
6. Ferraris VA, Brown JR, Despotis GJ, *et al.* 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg 2011; 91:944–982.
7. ▪▪ Weber CF, Gorlinger 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.

Clinical efficacies of laboratory coagulation testing vs. POC thromboelastometry/impedance platelet aggregometry were prospectively compared in moderate-to-high-risk cardiac surgical patients ($n = 50$ for each group). Fibrinogen and PCC were more effectively utilized in the POC group, resulting in reduced postoperative blood loss and clinical outcomes.

8. Haas T, Fries D, Velik-Salchner C, *et al.* Fibrinogen in craniosynostosis surgery. Anesth Analg 2008; 106:725–731.
9. Lee JW, Yoo YC, Park HK, *et al.* Fresh frozen plasma in pump priming for congenital heart surgery: evaluation of effects on postoperative coagulation profiles using a fibrinogen assay and rotational thromboelastometry. Yonsei Med J 2013; 54:752–762.
10. Avidan MS, Alcock EL, Da Fonseca J, *et al.* Comparison of structured use of routine laboratory tests or near-patient assessment with clinical judgement in the management of bleeding after cardiac surgery. Br J Anaesth 2004; 92:178–186.
11. ▪ Mahla E, Suarez TA, Bliden KP, *et al.* Platelet function measurement-based strategy to reduce bleeding and waiting time in clopidogrel-treated patients undergoing coronary artery bypass graft surgery: the timing based on platelet function strategy to reduce clopidogrel-associated bleeding related to CABG (TARGET-CABG) study. Circ Cardiovasc Interv 2012; 5:261–269.

The authors demonstrate that clopidogrel-induced platelet inhibition can be highly variable among preoperative cardiovascular patients, and platelet function testing can be utilized to shorten the waiting time by about 50% before coronary bypass grafting surgery.

12. Rahe-Meyer N, Solomon C, Tokuno ML, *et al.* Comparative assessment of coagulation changes induced by two different types of heart-lung machine. Artif Organs 2010; 34:3–12.
13. Holcomb JB, Wade CE, Michalek JE, *et al.* Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. Ann Surg 2008; 248:447–458.
14. Watson GA, Sperry JL, Rosengart MR, *et al.* Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome. J Trauma 2009; 67:221–227.
15. Kor DJ, Stubbs JR, Gajic O. Perioperative coagulation management: fresh frozen plasma. Best Pract Res Clin Anaesthesiol 2010; 24:51–64.
16. Levrat A, Gros A, Rugeri L, *et al.* Evaluation of rotation thrombelastography for the diagnosis of hyperfibrinolysis in trauma patients. Br J Anaesth 2008; 100:792–797.
17. Tanaka KA, Bolliger D, Vadlamudi R, Nimmo A. Rotational thromboelastometry (ROTEM)-based coagulation management in cardiac surgery and major trauma. J Cardiothorac Vasc Anesth 2012; 26:1083–1093.
18. Ganter MT, Hofer CK. Coagulation monitoring: current techniques and clinical use of viscoelastic point-of-care coagulation devices. Anesth Analg 2008; 106:1366–1375.
19. Bolliger D, Seeberger MD, Tanaka KA. Principles and practice of thromboelastography in clinical coagulation management and transfusion practice. Transfus Med Rev 2012; 26:1–13.
20. Lang T, Bauters A, Braun SL, *et al.* Multicentre investigation on reference ranges for ROTEM thromboelastometry. Blood Coagul Fibrinolysis 2005; 16:301–310.
21. Coakley M, Reddy K, Mackie I, Mallett S. Transfusion triggers in orthotopic liver transplantation: a comparison of the thromboelastometry analyzer, the thromboelastogram, and conventional coagulation tests. J Cardiothorac Vasc Anesth 2006; 20:548–553.
22. Venema LF, Post WJ, Hendriks HG, *et al.* An assessment of clinical interchangeability of TEG and RoTEM thromboelastographic variables in cardiac surgical patients. Anesth Analg 2010; 111:339–344.
23. Solomon C, Sorensen B, Hochleitner G, *et al.* Comparison of whole blood fibrin-based clot tests in thrombelastography and thromboelastometry. Anesth Analg 2012; 114:721–730.
24. Larsen OH, Fenger-Eriksen C, Christiansen K, *et al.* Diagnostic performance and therapeutic consequence of thromboelastometry activated by kaolin versus a panel of specific reagents. Anesthesiology 2011; 115:294–302.
25. Scarpelini S, Rhind SG, Nascimento B, *et al.* Normal range values for thromboelastography in healthy adult volunteers. Braz J Med Biol Res 2009; 42:1210–1217.
26. Haas T, Spielmann N, Mauch J, *et al.* Comparison of thromboelastometry (ROTEM®) with standard plasmatic coagulation testing in paediatric surgery. Br J Anaesth 2012; 108:36–41.
27. Rugeri L, Levrat A, David JS, *et al.* Diagnosis of early coagulation abnormalities in trauma patients by rotation thrombelastography. J Thromb Haemost 2007; 5:289–295.
28. Roullet S, Pillot J, Freyburger G, *et al.* Rotation thromboelastometry detects thrombocytopenia and hypofibrinogenaemia during orthotopic liver transplantation. Br J Anaesth 2010; 104:422–428.
29. Ogawa S, Szlam F, Chen EP, *et al.* A comparative evaluation of rotation thromboelastometry and standard coagulation tests in hemodilution-induced coagulation changes after cardiac surgery. Transfusion 2012; 52:14–22.
30. Ogawa S, Szlam F, Bolliger D, *et al.* The impact of hematocrit on fibrin clot formation assessed by rotational thromboelastometry. Anesth Analg 2012; 115:16–21.
31. Johansson PI, Stensballe J. Effect of haemostatic control resuscitation on mortality in massively bleeding patients: a before and after study. Vox Sang 2009; 96:111–118.
32. Katori N, Tanaka KA, Szlam F, Levy JH. The effects of platelet count on clot retraction and tissue plasminogen activator-induced fibrinolysis on thrombelastography. Anesth Analg 2005; 100:1781–1785.
33. Taketomi T, Szlam F, Levy JH, Tanaka KA. Warfarin reversal with prothrombin complex concentrate confers better antifibrinolytic activity compared with recombinant activated factor VII. Blood Coagul Fibrinolysis 2008; 19:106–108.

34. Bolliger D, Szlam F, Molinaro RJ, *et al.* Finding the optimal concentration range for fibrinogen replacement after severe haemodilution: an in vitro model. Br J Anaesth 2009; 102:793–799.

35. Dirkmann D, Gorlinger K, Gisbertz C, *et al.* 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.

36. Schochl H, Frietsch T, Pavelka M, Jambor C. Hyperfibrinolysis after major trauma: differential diagnosis of lysis patterns and prognostic value of thrombelastometry. J Trauma 2009; 67:125–131.

37. Ives C, Inaba K, Branco BC, *et al.* Hyperfibrinolysis elicited via thromboelastography predicts mortality in trauma. J Am Coll Surg 2012; 215:496–502.

38. ■ Cotton BA, Harvin JA, Kostousouv V, *et al.* Hyperfibrinolysis at admission is an uncommon but highly lethal event associated with shock and prehospital fluid administration. J Trauma Acute Care Surg 2012; 73:365–370.

The authors confirmed the previous finding by Schochl *et al.* [36] that hyperfibrinolysis on thrombelastography/metry on trauma admission (2% of 1966 cases) underscores the severity of injury, and is associated with high mortality (76%). Efficacy of antifibrinolytic therapy in this high-risk population is unknown.

39. Fenger-Eriksen C, Jensen TM, Kristensen BS, *et al.* Fibrinogen substitution improves whole blood clot firmness after dilution with hydroxyethyl starch in bleeding patients undergoing radical cystectomy: a randomized, placebo-controlled clinical trial. J Thromb Haemost 2009; 7:795–802.

40. Gorlinger K, Fries D, Dirkmann D, *et al.* Reduction of fresh frozen plasma requirements by perioperative point-of-care coagulation management with early calculated goal-directed therapy. Transfus Med Hemother 2012; 39:104–113.

41. ■■ Rahe-Meyer N, Solomon C, Hanke A, *et al.* Effects of fibrinogen concentrate as first-line therapy during major aortic replacement surgery: a randomized, placebo-controlled trial. Anesthesiology 2013; 118:40–50.

Hemostatic efficacy of fibrinogen concentrate ($n = 29$) vs. placebo ($n = 32$) was prospectively evaluated in the patients undergoing major aortic replacement surgery. The median fibrinogen dose of 8 g resulted in higher fibrinogen levels (260 vs. 189 mg/dl; $P < 0.001$), and clinically significant reductions of erythrocyte, plasma, and platelet transfusions ($P < 0.001$). The incidence of reexploration for bleeding, and adverse events during 45-day follow-up were not statistically different between two groups.

42. Fassl J, Matt P, Eckstein F, *et al.* Transfusion of allogeneic blood products in proximal aortic surgery with hyopthermic circulatory arrest: Effects of thromboelastometry-guided transfusion management. Journal of Cardiothoracic & Vascular Anesthesia 2013. [Epub ahead of print]. doi: 10.1053/j.jvca.2013.02.009.

43. RiaSTAP, fibirnogen concentrate (human). CSL Behring, Marburg, Germany: Prescribing Information; 2011.

44. Levy JH, Szlam F, Tanaka KA, Sniecienski RM. Fibrinogen and hemostasis: a primary hemostatic target for the management of acquired bleeding. Anesth Analg 2012; 114:261–274.

45. Theodoulou A, Berryman J, Nathwani A, Scully M. Comparison of cryoprecipitate with fibrinogen concentrate for acquired hypofibrinogenaemia. Transfus Apher Sci 2012; 46:159–162.

46. Rumph B, Bolliger D, Narang N, *et al.* In vitro comparative study of hemostatic components in warfarin-treated and fibrinogen-deficient plasma. J Cardiothorac Vasc Anesth 2010; 24:408–412.

47. Solomon C, Pichlmaier U, Schoechl H, *et al.* Recovery of fibrinogen after administration of fibrinogen concentrate to patients with severe bleeding after cardiopulmonary bypass surgery. Br J Anaesth 2010; 104:555–562.

48. Danes AF, Cuenca LG, Bueno SR, *et al.* Efficacy and tolerability of human fibrinogen concentrate administration to patients with acquired fibrinogen deficiency and active or in high-risk severe bleeding. Vox Sang 2008; 94:221–226.

49. Weinkove R, Rangarajan S. Fibrinogen concentrate for acquired hypofibrinogenaemic states. Transfus Med 2008; 18:151–157.

50. Groner A, Pereira A. Cryoprecipitate versus commercial fibrinogen concentrate in patients who occasionally require a therapeutic supply of fibrinogen: risk comparison in the case of an emerging transfusion-transmitted infection. Haematologica 2007; 92:846–849; Haematologica. 2008; 93: e24-6.

51. Sorensen B, Bevan D. A critical evaluation of cryoprecipitate for replacement of fibrinogen. Br J Haematol 2010; 149:834–843.

52. Dickneite G, Pragst I, Joch C, Bergman GE. Animal model and clinical evidence indicating low thrombogenic potential of fibrinogen concentrate (Haemocomplettan P). Blood Coagul Fibrinolysis 2009; 20:535–540.

53. Lance MD, Ninivaggi M, Schols SE, *et al.* Perioperative dilutional coagulopathy treated with fresh frozen plasma and fibrinogen concentrate: a prospective randomized intervention trial. Vox Sang 2012; 103:25–34.

54. Tanaka KA, Egan K, Szlam F, *et al.* Transfusion and hematologic variables after fibrinogen or platelet transfusion in valve replacement surgery: preliminary data of purified lyophilized human fibrinogen concentrate versus conventional transfusion. Transfusion 2013. [Epub ahead of print]. doi:10.1111/trf.12248.

55. Shore-Lesserson L, Manspeizer HE, DePerio M, *et al.* Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. Anesth Analg 1999; 88:312–319.

56. Chowdary P, Saayman AG, Paulus U, *et al.* Efficacy of standard dose and 30 ml/kg fresh frozen plasma in correcting laboratory parameters of haemostasis in critically ill patients. Br J Haematol 2004; 125:69–73.

57. Tanaka KA, Mazzeffi MA, Grube M, *et al.* Three-factor prothrombin complex concentrate and hemostasis after high-risk cardiovascular surgery. Transfusion 2013; 53:920–921.

58. Pabinger I, Brenner B, Kalina U, *et al.* Prothrombin complex concentrate (Beriplex P/N) for emergency anticoagulation reversal: a prospective multinational clinical trial. J Thromb Haemost 2008; 6:622–631.

59. Kcentra, prothrombin complex concentrate (human). CSL Behring, Marburg, Germany: Prescribing information; 2013.

60. Leissinger CA, Blatt PM, Hoots WK, Ewenstein B. Role of prothrombin complex concentrates in reversing warfarin anticoagulation: a review of the literature. Am J Hematol 2008; 83:137–143.

61. Fergusson DA, Hebert PC, Mazer CD, *et al.* A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med 2008; 358:2319–2331.

62. Aoki N, Saito H, Kamiya T, *et al.* Congenital deficiency of alpha 2-plasmin inhibitor associated with severe hemorrhagic tendency. J Clin Invest 1979; 63:877–884.

63. Hvas AM, Sorensen HT, Norengaard L, *et al.* Tranexamic acid combined with recombinant factor VIII increases clot resistance to accelerated fibrinolysis in severe hemophilia A. J Thromb Haemost 2007; 5:2408–2414.

64. Ortmann E, Besser MW, Klein AA. Antifibrinolytic agents in current anaesthetic practice. Br J Anaesth 2013; 111:549–563.

65. Shakur H, Roberts I, Bautista R, *et al.* Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet 2010; 376:23–32.

66. Ide M, Bolliger D, Taketomi T, Tanaka KA. Lessons from the aprotinin saga: current perspective on antifibrinolytic therapy in cardiac surgery. J Anesth 2010; 24:96–106.

67. Ogawa S, Richardson JE, Sakai T, *et al.* High mortality associated with intracardiac and intrapulmonary thromboses after cardiopulmonary bypass. J Anesth 2012; 26:9–19.

68. Falck-Ytter Y, Francis CW, Johanson NA, *et al.* Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141:e278S–325S.

69. ■■ Wong J, Abrishami A, El Beheiry H, *et al.* Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. J Bone Joint Surg Am 2010; 92:2503–2513.

Topical application of tranexamic acid (1.5–3 g) before the wound closure was proven to be effective in reducing postoperative blood loss, and erythrocyte transfusion in the primary knee arthroplasty. Systemic absorption of tranexamic acid was minimal.

70. Dowd NP, Karski JM, Cheng DC, *et al.* Pharmacokinetics of tranexamic acid during cardiopulmonary bypass. Anesthesiology 2002; 97:390–399.

71. Abou-Diwan C, Sniecinski RM, Szlam F, *et al.* Plasma and cerebral spinal fluid tranexamic acid quantitation in cardiopulmonary bypass patients. J Chromatogr B Analyt Technol Biomed Life Sci 2011; 879:553–556.

72. de Leede-van der Maarl MG, Hilkens P, Bosch F. The epileptogenic effect of tranexamic acid. J Neurol 1999; 246:843.

73. Yeh HM, Lau HP, Lin PL, *et al.* Convulsions and refractory ventricular fibrillation after intrathecal injection of a massive dose of tranexamic acid. Anesthesiology 2003; 98:270–272.

74. Garcha PS, Mohan CV, Sharma RM. Death after an inadvertent intrathecal injection of tranexamic acid. Anesth Analg 2007; 104:241–242.

75. Furtmuller R, Schlag MG, Berger M, *et al.* Tranexamic acid, a widely used antifibrinolytic agent, causes convulsions by a gamma-aminobutyric acid(A) receptor antagonistic effect. J Pharmacol Exp Ther 2002; 301:168–173.

76. ■ Lecker I, Wang DS, Romaschin AD, *et al.* Tranexamic acid concentrations associated with human seizures inhibit glycine receptors. J Clin Invest 2012; 122:4654–4666.

The authors provide evidence that a competitive inhibition of glycine (neurotransmitter) receptors by tranexamic acid is a plausible mechanism of convulsive seizures. Isoflurane, and to a lesser extent, propofol mitigate proconvulsant effects of tranexamic acid.

77. Gorlinger K, Shore-Lesserson L, Dirkmann D, *et al.* Management of hemorrhage in cardiothoracic surgery. J Cardiothorac Vasc Anesth 2013; 27:S20–S34.

78. Solomon C, Collis RE, Collins PW. Haemostatic monitoring during postpartum haemorrhage and implications for management. Br J Anaesth 2012; 109:851–863.

79. Levy JH, Tanaka KA, Dietrich W. Perioperative hemostatic management of patients treated with vitamin K antagonists. Anesthesiology 2008; 109:918–926.

80. Dewan Y, Komolafe EO, Mejia-Mantilla JH, *et al.* CRASH-3: tranexamic acid for the treatment of significant traumatic brain injury – study protocol for an international randomized, double-blind, placebo-controlled trial. Trials 2012; 13:87.

81. Shakur H, Elbourne D, Gulmezoglu M, *et al.* The WOMAN Trial (World Maternal Antifibrinolytic Trial): tranexamic acid for the treatment of postpartum haemorrhage – an international randomised, double blind placebo controlled trial. Trials 2010; 11:40.