**Role of coagulation factor concentrates in the operating room**

Cheng-Hock Toh M.D1,2,Yasir Alhamdi PhD1

1 Institute of Infection and Global Health, University of Liverpool, Liverpool L69 7BE, UK

2 Roald Dahl Haemostasis & Thrombosis Centre, Royal Liverpool University Hospital, Liverpool, L7 8XP, UK

**Correspondence:** Cheng-Hock Toh, Roald Dahl Haemostasis & Thrombosis Centre, Royal Liverpool University Hospital, Liverpool, L7 8XP, UK.

E-mail: [Toh@liverpool.ac.uk](mailto:Toh@liverpool.ac.uk)

**Key words:** Fibrinogen concentrate; fresh frozen plasma; prothrombin complex concentrate; coagulation monitoring; surgery

**Abstract**

The use of fresh frozen plasma (FFP), cryoprecipitate and platelets has been the mainstay of approaches to correct the coagulopathy that can arise in the peri-operative setting. Limitations include the time delays from obtaining results of coagulation screens to availability of thawed FFP and the potential of fluid overload. With advances in both global haemostatic testing and concentrates of coagulation factors, there is increasing opportunities for innovative practice. However, there remains a paucity of studies that can provide good quality unbiased evidence. These issues are elaborated here to form the basis for future study.

**Introduction**

Haemostasis is a natural defence against vascular injury and haemorrhage. In the context of elective surgery, the challenge to maintain adequate haemostasis is directly proportional to the nature and duration of the operation. The initiation trigger is via tissue factor exposure from sub-endothelial sites to cause factor VII activation, which then leads to amplification and propagation of the coagulation process (Figure 1).1 These pathways are well described elsewhere and the key enzymatic stages share the common template of requiring a vitamin K-dependent protein (e.g. factors VII, X or II) and a co-factor (e.g. tissue factor, factors VIIIa or Va) assembling on phospholipid surfaces in the presence of calcium.2 Such reactions, which are referred to as sevenase, tenase or prothrombinase respectively, accelerate coagulation activation by several 100,000 fold to ensure explosive thrombin generation.3

Thrombin is the key enzyme as it is not only essential for pro-coagulant consequences, through the conversion of fibrinogen into fibrin and the activation of platelets, but also in activating the protein C anti-coagulant pathway.4 This is particularly important at the margins of injury through thrombomodulin co-factor function to contain the extent of clot formation.4 The cross-linking of fibrin is the ultimate step in the coagulation cascade, with clot stabilization by thrombin-activated factor XIII. The action of thrombin-activatable fibrinolysis inhibitor also serves to reduce clot breakdown as part of thrombin-induced tissue-type plasminogen activator pro-fibrinolytic actions.5

From a physiological perspective, this would suggest a well-regulated homeostatic process involving equal and opposite reactions resulting from thrombin generation in vivo. So long as the surgical or traumatic insult is not excessive, exogenous haemostatic support is unlikely to be necessary peri- or post-operatively. However, in the event of unplanned surgery in the presence of infection such as in peritonitis or for major trauma, the haemostatic capacity may be compromised. This is true even in young patients with no medical history who develop significant coagulopathy peri-operatively after major trauma.6 The resulting coagulopathy in such circumstances presents a major challenge for anaesthetists and intensivists as it is typically multi-factorial and the clinical status can deteriorate rapidly. It is thus important to address this problem with prompt and comprehensive clinical assessments of coagulopathy with prompt and timely administration of haemostatic therapy. This review discusses the current issues around plasma transfusion support, current concepts in coagulation monitoring and understanding the roles played by non-activated coagulation factor concentrates as peri-operative therapy for achieving haemostasis. Activated prothrombin complex concentrates are not reviewed here as they are typically considered in the acquired haemophilia setting. The anticoagulant factor concentrates have certain indications in the operating room setting but are beyond the scope of this manuscript.

**Current issues in plasma transfusion support**

Primary haemostasis upon vascular injury is mediated by platelets and reinforced by coagulation factors. Transfusion of plasma and platelets has been the mainstay of haemostatic therapy for many decades. Therefore, delayed decision or administration of blood products after prolonged storage can exacerbate coagulopathy and potentially affect clinical outcomes,7primarily due to the risk of exsanguination, and secondarily, because clot formation is a defence mechanism against infection. Equally, premature and overzealous use of blood products can be harmful. For example, studies in intensive care patients have shown an increased risk of arterial thrombosis and death with platelet transfusions in the presence of consumptive thrombocytopaenia.8 This underscores the importance of timeliness in decision making and timeliness in its action.

Commonly used laboratory haemostasis assessment includes prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen level by Clauss method and platelet count. Typical turnaround time for these tests is in the region of 30–90 minutes which is not optimal in diagnosing coagulopathy or guiding haemostatic interventions. This is particularly an issue when multiple units of fresh frozen plasma (FFP) must be thawed according to laboratory procedure which adds 30-60 minutes of processing time.

FFP contain variable but near normal levels of pro- and anti-coagulant proteins and coagulation inhibitors. The relatively low concentrations of coagulation factors in therapeutic FFP (as compared to concentrates) makes it difficult to achieve a significant increase in patient’s circulating levels without administering large volumes. Based on rough guidance, as much as 2.5 L of plasma transfusion maybe required to improve clot times.9,10 On the other hand, coagulation factor concentrates enable larger increases without large infusion volumes.11 Large volumes of plasma transfusion are poorly tolerated in patients with limited cardiopulmonary reserve and can lead to intractable fluid overload. In addition, transfusion–related acute lung injury (TRALI) is a potential lethal complication of plasma transfusion although the preferential use of male donor plasma has significantly reduced its incidence.10,12

Although FFP has been available for approximately 60 years, evidence from randomised controlled trials (RCT) proving its efficacy and safety is lacking and recommendations in current guidelines (Table 1) are mainly based on observational studies.13-15 In addition, studies from Europe, Canada, US and Australia have shown that both the use of FFP and Cryoprecipitate are often inappropriate and for reasons outside clinical guidelines. 13,14 Furthermore, administering fresh frozen plasma in patients with minimally elevated INR values have been shown to be ineffective in producing meaningful corrections.9,16

**Rationale for using coagulation factor concentrates**

*Prothrombin complex concentrates:*

In view of the practical problems of administering FFP, prothrombin complex concentrates (PCC) could be advantageous because of the smaller volume required to replace deficient factors and the relative speed in reconstituting a lyophilised powder with 10-20ml of sterile water. However, PCC only contain the Vitamin K-dependent proteins, i.e. factors II, VII, IX, X, and acquired deficiency of factors V and VIII would not be remedied. Different formulations contain varying amounts of proteins C & S but PCC are mainly distinguished by their factor VII content.17 These are often referred to as three or four factor concentrates based on the levels of factor VII. PCC is licensed primarily for the management of bleeding in patients treated with vitamin K antagonists (VKA).15,18In Europe, there is a broad indication for PCC in the management of patients with low levels of factors II, VII, IX and X. In the peri-operative setting PCC is often used in the management of severe bleeding in patients undergoing cardio-vascular or other surgeries,19,20 especially those with prolonged PT.15 An advantage to their use is the reduced likelihood of TRALI due to the lack of antibodies in PCC. As to whether these products can induce further activation of coagulation and lead to adverse clinical outcomes, a meta-analysis of 27 studies for the reversal of vitamin K antagonists showed the overall incidence of thromboembolic complications as 1.4%.21 The authors concluded that there was a “low but quantifiable” risk of thromboembolic events in patients receiving PCC, but there was no direct comparison against a control (non-PCC treated group). The mortality rate was 10.6% and only few cases could be attributed to thromboembolic events. As such, a clear link between PCC use and mortality from thromboembolic complications could not be made.21Data from PCC infusion in a porcine model of liver injury indicates that a dose of 50 IU/kg precipitated thromboembolism in all tested animals with (DIC) observed in 44% of cases.22 These findings raise the prospect that high PCC concentrations might cause adverse clinical complications. However, current guidelines by American Society of Anesthesiologists Task Force on Perioperative Blood Management indicate that the overall risk of thromboembolic events following PCC transfusion is only 0.003% (evidence from observational studies).15 Close monitoring of PT and the clinical response is recommended with emphasis that the available evidence for using PCC in the managing peri-operative bleeding in patients not treated with VKA is weak (higher risk of thromboembolism is also suggested) compared to its primary indication in reversing VKA-associated bleeding.15,20

*Cryoprecipitate*

The use of cryoprecipitate (primarily to replenish fibrinogen) has been largely withdrawn by several European countries amid safety concerns, especially with regards to transmission of pathogens.23,24 Furthermore, current guidelines indicate that literature evidence is insufficient to evaluate the intra- or post-operative transfusion of cryoprecipitate in the management of bleeding.15As a replacement, fibrinogen concentrates are increasingly used to replenish depleted fibrinogen levels.25FFP may also be used to supplement fibrinogen in the absence of cryoprecipitate.

*Fibrinogen concentrates*

With regard to fibrinogen concentrates, there are distinct advantages over cryoprecipitate. Firstly, there is no requirement for ABO group matching.26,27 Secondly, its administration does not involve the time delay from thawing. Thirdly, higher amounts of fibrinogen is dissolvable in small volume infusions to enable administration within a short time period and also avoid the potential of fluid overload.27,28 The target fibrinogen level is usually set at 1g/l, based on the literature in congenital fibrinogen deficiency,29 but there has been a trend for earlier and higher targets of fibrinogen replacement in severe trauma.30-33 A fourth advantage is in terms of viral safety because of the ability to pasteurize and filter these concentrates in the manufacturing process.34 In a recent analysis of almost three decades of pharmacovigilance data related to fibrinogen concentrate transfusion, a small number of suspected viral transmission cases have been identified.35 However, it was concluded that a direct causal link to fibrinogen concentrates was unlikely as polymerase chain reaction results were negative and/or alternative explanations were found.35 As to contraindications to fibrinogen concentrate use, these include a history of anaphylactic reaction to the concentrate,36 and ongoing thrombosis or a high pro-thrombotic risk.28

As to approvals for the administration of fibrinogen concentrates in Europe, these are granted nationally and an approval by the European Medicines Agency does not exist. This reflects differing strategies both to the transfusion of blood products and the approval of blood products from across European countries.

**Current concepts in monitoring coagulation**While most guidelines on the use of FFP and cryoprecipitate are in reference to the degree of abnormality in PT, aPTT or fibrinogen, the availability of point-of-care testing using rotational thromboelastometry (ROTEM) or thrombo-elastography (TEG) in providing information would be important to examine for clinical value in the peri-operative setting.37The visco-elastic properties of whole blood clot formation, as assessed by ROTEM and TEG, are dependent on thrombin-mediated fibrin formation and its polymerisation. Indeed, the extent of fibrin polymerisation as an end-point would appear to offer an advantage because fibrin clot firmness cannot be assessed by PT, APTT or fibrinogen level. Different stages of ROTEM/TEG can give insights into (a) decrease or inhibition of the different coagulation factors that are required for thrombin formation (early phase), (b) kinetic interaction of platelets and fibrin that are required for enhancing clot strength (intermediate phase), (c) maximum clot strength (final phase). As such, ROTEM/TEG can monitor evolving changes in the coagulation profile and identify hypofibrinogenemic, hyperfibrinolytic and hypercoagulable states as well as the presence of low platelet/ factor levels (or their inhibition).38 This enables prompt transfusion decisions to be made, sometimes based on specific institutional algorithms, with fibrinogen concentrates, cryoprecipitate, FFP, platelets or tranexamic acid.38 The effect of the treatment is assessed soon after transfusion and depending on the TEG/ ROTEM results, further transfusions can be tailored to the patient’s specific needs. It must be emphasized that although ROTEM and TEG are based on similar principles, the results obtained with the two tests may not be interchangeable,39 because of differences in the activating reagents and operating characteristics. This may therefore result in different blood products being transfused based on which test was used.40 It has been suggested that in the surgical setting, ROTEM may be the most appropriate test because of its faster turnaround time.40 The new generation of viscoelastic coagulation monitoring devices with cartilage-based systems (TEG 6S, ROTEM sigma) might widen the use of these assays in the perioperative setting. The full-automation in these new devices will reduce variations in results related to pipetting, handling of blood and prior manipulation of reagents. Finally, it must be stated that the recent European guideline for managing major bleeding and coagulopathy following trauma highlighted that the usefulness of viscoelastic tests has been questioned and a number of significant limitations have been recently reported by several studies.41 Therefore, the guidelines indicate that more thorough studies are required in this area and emphasize that clinicians should use judgment when designing and implementing local policies.41

**Current peri-operative role for coagulation factor concentrates**  
Studies reviewed by Bolliger et al,42 included retrospective studies, case-control and RCT reported that administration of fibrinogen concentrate in patients undergoing cardiac surgery improved clot firmness as measured by ROTEM, significantly decreased the need for other blood products, such as red blood cells, FFP. Clinically, there were also significant reductions in post-operative bleeding drainage volume. However, several important issues relevant to clinical practice were unclear For example, FFP was often used in conjunction to make it difficult to assess the efficacy of fibrinogen concentrate alone in securing haemostasis in the bleeding patient.30,43-45 Also, minimum core outcome sets were not defined such as the length of follow up for adverse clinical events and for assessing the safety of such interventions.43-45

More recently, two randomized double-blinded placebo-controlled trials examined the efficacy of fibrinogen concentrates in the setting of complex cardiovascular surgery.46,47 The study by Ranucci et al found that in 116 patients, the infusion of fibrinogen concentrates (dose calculated according to fibrin‐based thromboelastometry test “FIBTEM” readings) can significantly reduce subsequent allogenic blood product transfusions as compared to placebo.47 However, the more recent study by Rahe-Meyer et al reported an opposite result whereby fibrinogen concentrates infusion (after a 5 minute bleeding mass of 60-250 g) resulted in increased requirement for further allogenic blood products.46 This discrepancy suggests that differences in timing of transfusion, baseline fibrinogen level before transfusion as well as variability in algorithms used to guide doses and requirements for further transfusion,48 can have major impact on outcomes. Although further robust RCTs are required to resolve the conflict, it must be emphasized that doses of fibrinogen concentrates as well as the requirement for other blood products are best adjusted according to the individual patient’s needs. Coagulation factor concentrate therapy when coupled with point-of-care peri-operative testing algorithm in a manner that is tailored to the patient’s needs was found to reduce the requirement for FFP and other blood products.49,50

Other systematic reviews have been published in the last few years.27,51 These have adopted a standardised analytical approach using Preferred reporting items for systematic reviews and meta-analysis. The Population Intervention Comparison Outcome and Study Design (PICOS) approach was used to define inclusion. Few studies comparing FFP to fibrinogen in a peri-operative or massive trauma setting,51 involved prospective high quality methodologies. In general, fibrinogen was found to be superior to FFP for half of the outcomes that were investigated including reducing blood loss, need for allogeneic transfusions, length of intensive care unit and hospital stay and increasing plasma fibrinogen levels.51 FFP on the other hand, showed a positive and negative effects for 28% and 22% of outcomes, respectively with limited evidence that FFP reduced mortality.51 In a prospective cohort study of 144 trauma patients, the use of factor concentrates (fibrinogen or PCC) alone was found to be associated with corrected coagulopathy, reduction in the need for further allogenic blood product transfusions and reduction in the development of multiple organ failure, whereas additional FFP transfusions did not confer further haemostatic correction and was associated with higher requirement for platelets and RBC transfusions.52 Collectively, this suggested that there was no strong evidence to support the clinical merit of FFP for surgical and/or massive trauma patients. Peri-operatively, there was a trend towards improved outcome measures with fibrinogen concentrate treatment but solid conclusions remain difficult to draw without further robust prospective studies.51

Another review by Warmuth et al27 focused on fibrinogen concentrate substitution in adults in the peri-operative setting and with massive hemorrhage. It utilised a broader search of several databases beyond Medline, yielding 772 results between 1985 and 2010. In two RCT and two non-RCT studies encompassing 74 patients in total, it was indicated that the administration of fibrinogen concentrate was associated with improved outcomes such as reduction in the substitution of red blood cells, FFP and platelet concentrates as well as significantly reduced post-operative bleeding.27 More recent systematic reviews agree that fibrinogen concentrates reduce the need for allogenic blood products transfusion in trauma and bleeding patients,53-55 but the consensus is that the current studies are of low quality and the need for further well-designed RCTs to address the gaps in knowledge is emphasized.53-55

An important point to be highlighted was that some studies used maximum clot firmness as an endpoint30 which is not a clinical outcome, but a laboratory outcome. Furthermore, Clauss fibrinogen method measurements are less sensitive to crystalloid-induced coagulation defects whereas ROTEM is more reliable at detecting this disturbance.56 In one study,57 when specimens drawn from patients during major surgery were tested in parallel using both methods, transfusion decisions based on Clauss results would result in no fibrinogen concentrate treatment in the 36 patients. Conversely, 36% of patients would have received fibrinogen concentrate if transfusion decisions were based on ROTEM guidance.57 This stresses the critical influence of methodology on transfusion practice.

Another systematic review looked at both fibrinogen concentrates and PCC in the peri-operative setting.17 All studies included small sample sizes consisting of highly selective patients. However, focusing on the cardiac surgery group, prospective studies indicated that fibrinogen concentrate and/or PCC administration was associated with less allogeneic blood transfusion and reduced chest tube drainage.17 As far as safety outcomes are concerned, it was clear that reporting was not uniform across different studies. Therefore, more robust trials with sound methodology and sufficient power are required to assess the efficacy of PCC and fibrinogen concentrates for the management of peri-operative coagulopathy in bleeding patients.

Finally, Table 1 provides a concise summary of the main indications for different factor-based blood products (allogenic and factor concentrates) transfusion in the peri-operative setting, as adapted from current guidelines.15

**Conclusion**

In summary, there is a need to better evidence the role of coagulation factor concentrates in the operating room to achieve optimal haemostasis and improve clinical outcome. The requirements include point-of-care tests that are simple to perform, rapid in result generation and robust in providing an accurate status of *in vivo* coagulation. These could then lead to improved evidence and stronger transfusion guidelines that can be better standardized across Europe with wider applicability.

**Disclaimer:** The authors declare no conflict of interest.

**Figure legends**

**Figure 1: Schematic representation of how coagulation factor replacement promotes haemostasis.** Initiation of coagulation activation via the tissue factor (TF) pathway leads to the tenase and prothrombinase reactions to generate thrombin (IIa). This can then amplify the process through thrombin-mediated generation of factors IXa, VIIa and Va. Thrombin conversion of fibrinogen (Fgn) to fibrin is then propagated. Fresh frozen plasma contains all these coagulation factors in unactivated form whereas available coagulation factor concentrates provide the vitamin K dependent ones; i.e. factors II, VII, IX and X, with VII being the most variable between products.

**References**

1. Butenas S, Orfeo T, Mann KG. Tissue factor in coagulation: Which? Where? When? *Arterioscler Thromb Vasc Biol*. 2009;29(12):1989-1996.

2. Versteeg HH, Heemskerk JW, Levi M, Reitsma PH. New fundamentals in hemostasis. *Physiol Rev*. 2013;93(1):327-358.

3. Nesheim ME, Tracy RP, Mann KG. "Clotspeed," a mathematical simulation of the functional properties of prothrombinase. *J Biol Chem*. 1984;259(3):1447-1453.

4. Rezaie AR. Regulation of the protein C anticoagulant and antiinflammatory pathways. *Curr Med Chem*. 2010;17(19):2059-2069.

5. Wang W, Boffa MB, Bajzar L, Walker JB, Nesheim ME. A study of the mechanism of inhibition of fibrinolysis by activated thrombin-activable fibrinolysis inhibitor. *J Biol Chem*. 1998;273(42):27176-27181.

6. Ozaki H, Tachibana H, Ishikawa S, Yusa K, Kitabatake K, Iino M. Disseminated Intravascular Coagulation after Surgery for Facial Injury. *Case Rep Dent*. 2016;2016:6053652.

7. van Straten AH, Soliman Hamad MA, Martens EJ, et al. Effect of storage time of transfused plasma on early and late mortality after coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2011;141(1):238-243 e231-232.

8. Goel R, Ness PM, Takemoto CM, Krishnamurti L, King KE, Tobian AA. Platelet transfusions in platelet consumptive disorders are associated with arterial thrombosis and in-hospital mortality. *Blood*. 2015;125(9):1470-1476.

9. Abdel-Wahab OI, Healy B, Dzik WH. Effect of fresh-frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities. *Transfusion*. 2006;46(8):1279-1285.

10. Yazer MH. The how's and why's of evidence based plasma therapy. *Korean J Hematol*. 2010;45(3):152-157.

11. Collins PW, Solomon C, Sutor K, et al. Theoretical modelling of fibrinogen supplementation with therapeutic plasma, cryoprecipitate, or fibrinogen concentrate. *Br J Anaesth*. 2014;113(4):585-595.

12. Triulzi DJ, Kleinman S, Kakaiya RM, et al. The effect of previous pregnancy and transfusion on HLA alloimmunization in blood donors: implications for a transfusion-related acute lung injury risk reduction strategy. *Transfusion*. 2009;49(9):1825-1835.

13. De Backer D, Vandekerckhove B, Stanworth S, et al. Guidelines for the use of fresh frozen plasma. *Acta Clin Belg*. 2008;63(6):381-390.

14. Schofield WN, Rubin GL, Dean MG. Appropriateness of platelet, fresh frozen plasma and cryoprecipitate transfusion in New South Wales public hospitals. *Med J Aust*. 2003;178(3):117-121.

15. Apfelbaum J, Nuttall G, Connis R. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management. *Anesthesiology*. 2015;122:241-275.

16. Holland LL, Brooks JP. Toward rational fresh frozen plasma transfusion: The effect of plasma transfusion on coagulation test results. *Am J Clin Pathol*. 2006;126(1):133-139.

17. Lin DM, Murphy LS, Tran MH. Use of prothrombin complex concentrates and fibrinogen concentrates in the perioperative setting: a systematic review. *Transfus Med Rev*. 2013;27(2):91-104.

18. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e152S-184S.

19. Griffee MJ, Deloughery TG, Thorborg PA. Coagulation management in massive bleeding. *Curr Opin Anaesthesiol*. 2010;23(2):263-268.

20. Colomina MJ, Diez Lobo A, Garutti I, Gomez-Luque A, Llau JV, Pita E. Perioperative use of prothrombin complex concentrates. *Minerva Anestesiol*. 2012;78(3):358-368.

21. Dentali F, Marchesi C, Giorgi Pierfranceschi M, et al. Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists. A meta-analysis. *Thromb Haemost*. 2011;106(3):429-438.

22. Grottke O, Braunschweig T, Spronk HM, et al. Increasing concentrations of prothrombin complex concentrate induce disseminated intravascular coagulation in a pig model of coagulopathy with blunt liver injury. *Blood*. 2011;118(7):1943-1951.

23. Sorensen B, Bevan D. A critical evaluation of cryoprecipitate for replacement of fibrinogen. *Br J Haematol*. 2010;149(6):834-843.

24. Ahmed S, Harrity C, Johnson S, et al. The efficacy of fibrinogen concentrate compared with cryoprecipitate in major obstetric haemorrhage--an observational study. *Transfus Med*. 2012;22(5):344-349.

25. Yang L, Stanworth S, Baglin T. Cryoprecipitate: an outmoded treatment? *Transfus Med*. 2012;22(5):315-320.

26. 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(5):555-562.

27. Warmuth M, Mad P, Wild C. Systematic review of the efficacy and safety of fibrinogen concentrate substitution in adults. *Acta Anaesthesiol Scand*. 2012;56(5):539-548.

28. Tanaka KA, Esper S, Bolliger D. Perioperative factor concentrate therapy. *Br J Anaesth*. 2013;111 Suppl 1:i35-49.

29. Bornikova L, Peyvandi F, Allen G, Bernstein J, Manco-Johnson MJ. Fibrinogen replacement therapy for congenital fibrinogen deficiency. *J Thromb Haemost*. 2011;9(9):1687-1704.

30. 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(5):795-802.

31. Schochl H, Nienaber U, Hofer G, et al. Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. *Crit Care*. 2010;14(2):R55.

32. 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(3):531-547.

33. 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(1):40-50.

34. Groner A. Reply. 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;92:846-9. *Haematologica*. 2008;93(2):e24-26; author reply e27.

35. Solomon C, Groner A, Ye J, Pendrak I. Safety of fibrinogen concentrate: analysis of more than 27 years of pharmacovigilance data. *Thromb Haemost*. 2015;113(4):759-771.

36. Behring C. Kcentra prothrombin complex concentrate (human). *Prescribing Information*. 2013.

37. Whiting D, DiNardo JA. TEG and ROTEM: technology and clinical applications. *Am J Hematol*. 2014;89(2):228-232.

38. Abdelfattah K, Cripps MW. Thromboelastography and Rotational Thromboelastometry use in trauma. *Int J Surg*. 2015.

39. Nielsen VG. A comparison of the Thrombelastograph and the ROTEM. *Blood Coagul Fibrinolysis*. 2007;18(3):247-252.

40. Christie A, Greilich PE, Sarode R. Comparison Of Thromboelastography (TEG) With Rotational Thromboelastrometry (ROTEM) In Surgical Patients. *Blood*. 2013;122(21):3659-3659.

41. Rossaint R, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. *Crit Care*. 2016;20:100.

42. Bolliger D, Tanaka KA. Roles of thrombelastography and thromboelastometry for patient blood management in cardiac surgery. *Transfus Med Rev*. 2013;27(4):213-220.

43. Karlsson M, Ternstrom L, Hyllner M, et al. Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery. A prospective randomised pilot study. *Thromb Haemost*. 2009;102(1):137-144.

44. Rahe-Meyer N, Pichlmaier M, Haverich A, et al. Bleeding management with fibrinogen concentrate targeting a high-normal plasma fibrinogen level: a pilot study. *Br J Anaesth*. 2009;102(6):785-792.

45. Rahe-Meyer N, Solomon C, Winterhalter M, et al. Thromboelastometry-guided administration of fibrinogen concentrate for the treatment of excessive intraoperative bleeding in thoracoabdominal aortic aneurysm surgery. *J Thorac Cardiovasc Surg*. 2009;138(3):694-702.

46. Rahe-Meyer N, Levy JH, Mazer CD, et al. Randomized evaluation of fibrinogen vs placebo in complex cardiovascular surgery (REPLACE): a double-blind phase III study of haemostatic therapy. *Br J Anaesth*. 2016;117(1):41-51.

47. Ranucci M, Baryshnikova E, Crapelli GB, et al. Randomized, double-blinded, placebo-controlled trial of fibrinogen concentrate supplementation after complex cardiac surgery. *J Am Heart Assoc*. 2015;4(6):e002066.

48. Schochl H, Voelckel W, Grassetto A, Schlimp CJ. Practical application of point-of-care coagulation testing to guide treatment decisions in trauma. *J Trauma Acute Care Surg*. 2013;74(6):1587-1598.

49. Gorlinger K, Fries D, Dirkmann D, Weber CF, Hanke AA, Schochl H. Reduction of Fresh Frozen Plasma Requirements by Perioperative Point-of-Care Coagulation Management with Early Calculated Goal-Directed Therapy. *Transfus Med Hemother*. 2012;39(2):104-113.

50. Gorlinger 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(6):1179-1191.

51. Kozek-Langenecker S, Sorensen B, Hess JR, Spahn DR. Clinical effectiveness of fresh frozen plasma compared with fibrinogen concentrate: a systematic review. *Crit Care*. 2011;15(5):R239.

52. Innerhofer P, Westermann I, Tauber H, et al. The exclusive use of coagulation factor concentrates enables reversal of coagulopathy and decreases transfusion rates in patients with major blunt trauma. *Injury*. 2013;44(2):209-216.

53. Wikkelso A, Lunde J, Johansen M, et al. Fibrinogen concentrate in bleeding patients. *Cochrane Database Syst Rev*. 2013(8):CD008864.

54. Aubron C, Reade MC, Fraser JF, Cooper DJ. Efficacy and safety of fibrinogen concentrate in trauma patients--a systematic review. *J Crit Care*. 2014;29(3):471 e411-477.

55. Lunde J, Stensballe J, Wikkelso A, Johansen M, Afshari A. Fibrinogen concentrate for bleeding--a systematic review. *Acta Anaesthesiol Scand*. 2014;58(9):1061-1074.

56. Fenger-Eriksen C, Moore GW, Rangarajan S, Ingerslev J, Sorensen B. Fibrinogen estimates are influenced by methods of measurement and hemodilution with colloid plasma expanders. *Transfusion*. 2010;50(12):2571-2576.

57. Urwyler N, Theiler L, Hirschberg M, Kleine-Brueggeney M, Colucci G, Greif R. Standard vs. point-of-care measurement of fibrinogen: potential impact on clinical decisions. *Minerva Anestesiol*. 2012;78(5):550-555.