

## Fibrinogen as a therapeutic target for bleeding: a review of critical levels and replacement therapy

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Fibrinogen plays a critical role in achieving and maintaining hemostasis and is fundamental to effective clot formation. There is increasing awareness of the important role of fibrinogen as a key target for the treatment and prevention of acquired bleeding. Fibrinogen is the first coagulation factor to fall to critically low levels (<1.0 g/L) during major hemorrhage (normal plasma fibrinogen levels range from 2.0 to 4.5 g/L), and current guidelines recommend maintaining the plasma fibrinogen level above 1.5 g/L. Fibrinogen supplementation can be achieved using plasma or cryoprecipitate; however, there are a number of safety concerns associated with these allogeneic blood products and there is a lack of high-quality evidence to support their use. Additionally, there is sometimes a long delay associated with the preparation of frozen products for infusion. Fibrinogen concentrate provides a promising alternative to allogeneic blood products and has a number of advantages: it allows a standardized dose of fibrinogen to be rapidly administered in a small volume, has a very good safety profile, and is virally inactivated as standard. Administration of fibrinogen concentrate, often guided by point-of-care viscoelastic testing to allow individualized dosing, has been successfully used as hemostatic therapy in a range of clinical settings, including cardiovascular surgery, postpartum hemorrhage, and trauma. Results show that fibrinogen concentrate is associated with a reduction or even total avoidance of allogeneic blood product transfusion. Fibrinogen concentrate represents an important option for the treatment of coagulopathic bleeding; further studies are needed to determine precise dosing strategies and thresholds for fibrinogen supplementation.

**F**ibrinogen is an essential protein for hemostasis and circulates at the highest concentration of all the coagulation proteins.<sup>1</sup> After hemostatic activation, thrombin cleaves fibrinogen and catalyzes fibrin polymerization to form a structural network critical for effective clot formation. After acute blood loss and volume resuscitation, dilutional coagulopathy can occur causing fibrinogen, a critical substrate for clot formation, to fall to low levels.<sup>2</sup> There is increasing awareness regarding the important role of fibrinogen during acute bleeding and as a target for the treatment and prevention of bleeding, especially in perioperative settings. However, in many centers, fibrinogen is not routinely monitored in the critically bleeding patient, despite growing evidence from clinical studies suggesting that fibrinogen is a vital target.<sup>3-5</sup>

Clinical data examining the efficacy and safety of fibrinogen concentrate for the treatment of acquired coagulopathy are reviewed here, as is the current evidence on appropriate plasma threshold levels and dosing across a range of clinical settings.

### THE CRITICAL ROLE OF FIBRINOGEN IN CLOT FORMATION AND HEMOSTASIS

Major blood loss represents a significant challenge across critical care settings, often resulting in coagulopathy and

**ABBREVIATIONS:** CABG = coronary artery bypass graft; CPB = cardiopulmonary bypass; FP24 = plasma frozen within 24 hours of collection; MCF = maximum clot firmness; MTP(s) = massive transfusion protocol(s); PCC = prothrombin complex concentrate; PPH = postpartum hemorrhage; ROTEM = thromboelastometry; TACO = transfusion-associated circulatory overload.

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**TRANSFUSION** \*\*,\*,\*\*.\*.

reducing patient survival rates.<sup>6</sup> Fibrinogen is fundamental to effective clot formation, playing a critical role in achieving and maintaining hemostasis, and is the first clotting factor to fall to critically low levels during major bleeding.<sup>2,6</sup> Treatment of fibrinogen deficiency is important for survival,<sup>7,8</sup> and the amount of fibrinogen administered to trauma patients has been positively correlated with reductions in mortality.<sup>9</sup>

Fibrinogen is a 340-kDa plasma glycoprotein synthesized in the liver<sup>10</sup> and is the physiological substrate of three enzymes: thrombin, Factor (F)XIIIa, and plasmin.<sup>11</sup> Fibrinogen has a mean half-life of 3.74 days (range, 3.00-4.08 days).<sup>12</sup> During coagulation, thrombin cleaves the fibrinogen molecule, producing a soluble fibrin monomer. These monomers are able to form a loose network in which red blood cells (RBCs) become trapped and a clot begins to form. Cross-linking of the fibrin polymers, induced by FXIIIa, is fundamental to the coagulation process, increasing the elasticity of the clot and its resistance to fibrinolysis. Fibrinogen also acts as the ligand for glycoprotein IIb/IIIa receptors, found on the platelet (PLT) surface, which are responsible for PLT aggregation.<sup>10</sup> These PLTs then become enmeshed within the fibrin strands, stabilizing the growing clot.

There are a number of causes that may contribute to a decrease in fibrinogen concentration and function during major bleeding. For example, fibrinogen metabolism exceeds fibrinogen synthesis during major hemorrhage.<sup>13</sup> In addition, hemodilution after blood loss and subsequent volume replacement leads to reduced fibrinogen levels,<sup>14</sup> impairing the polymerization of fibrin (if synthetic colloids are used to replace volume) and reducing clot stability.<sup>15</sup> Thus, fibrinogen supplementation to restore plasma fibrinogen is key to normalizing clotting function.<sup>16-18</sup>

It should be noted that fibrinogen is not the only coagulation factor to fall to low levels during bleeding; prothrombin, FV, and FVII are all significantly reduced after blood loss and subsequent volume replacement.<sup>2</sup> Correction of these deficiencies may also be important for achieving and maintaining hemostasis and may be addressed using other coagulation factor concentrates, such as prothrombin complex concentrate (PCC).<sup>19</sup> Other causes of coagulopathy, such as hypoperfusion<sup>20</sup> or the consumption or dilution of PLTs,<sup>21</sup> may also need to be addressed.

## WHAT IS THE CRITICAL LEVEL OF FIBRINOGEN FOR THERAPY?

Hypofibrinogenemia is the term used to describe a deficiency of fibrinogen and generally implies a level below the normal range (2.0-4.5 g/L in the healthy individual<sup>22</sup>). Low plasma fibrinogen levels have been shown to be a risk factor for perioperative bleeding in a number of settings,

including cardiovascular surgery,<sup>3,23</sup> trauma,<sup>9</sup> and obstetrics.<sup>24</sup> However, the threshold that triggers fibrinogen concentrate administration to treat hypofibrinogenemia is both variable and opinion-based.

Historically, a threshold level of 1.0 g/L was established for fibrinogen supplementation in patients with congenital fibrinogen deficiency. This was deemed sufficient to prevent excess bleeding and to secure hemostasis in these patients<sup>25</sup> as they are not usually suffering from any other coagulation factor deficiency or hemostatic impairment. Supplementing fibrinogen to above 1.0 g/L may appear to confer no further apparent benefit to the congenital fibrinogen deficiency patient when no other abnormalities exist. Importantly, due to method-related limitations, fibrinogen concentrations of less than 1.0 g/L are also associated with a prolongation of conventional laboratory tests (such as prothrombin time or activated partial thromboplastin time),<sup>26</sup> which is not to be interpreted as additional coagulopathy to the congenital fibrinogen deficiency. For patients without congenital fibrinogen deficiency, but who acquire a relative fibrinogen deficit due to major bleeding during trauma or surgery, there is insufficient evidence available to establish a definitive trigger threshold. The 2007 European trauma guidelines<sup>27</sup> recommended a threshold of 1.0 g/L, and the 2006 guidelines from the American Society of Anesthesiologists<sup>28</sup> recommended a threshold of 0.8 to 1.0 g/L; however, current expert opinion suggests that this may be too conservative and a higher target level may be necessary to enable effective clot formation<sup>29</sup> and to improve clinical outcomes during cardiac surgery.<sup>30</sup> It has been shown that clot strength increases linearly with fibrinogen concentration, even above the normal plasma fibrinogen range (up to 10 g/L),<sup>26,31</sup> with a minimum threshold of 2.0 g/L required in vitro for the optimal rate of clot formation to be achieved.<sup>32</sup> These results therefore suggest that fibrinogen supplementation increases clot strength regardless of plasma fibrinogen level.

One study found that 25 coagulopathic trauma patients had a mean plasma fibrinogen level of 0.9 g/L, associated with a mean maximum clot firmness (MCF; measured by the thromboelastometric FIBTEM test) of just 6 mm (normal range, 9-25 mm<sup>33</sup>). In contrast, 71 healthy volunteers had a mean FIBTEM MCF of 14 mm, and only 2.5% had a FIBTEM MCF of less than 7 mm.<sup>34</sup> The revised European trauma guidelines, published in 2013,<sup>35</sup> recommend fibrinogen supplementation for patients with a plasma fibrinogen level of below 1.5 to 2.0 g/L (Table 1).

In different settings, it may be necessary to derive revised threshold levels to account for the patient's altered coagulation state. For example, during pregnancy, the normal plasma fibrinogen level increases to approximately 5 g/L,<sup>43,44</sup> with fibrinogen levels of less than 2.0 g/L having a positive predictive value for evolution to severe postpartum hemorrhage (PPH) of 100%.<sup>45</sup> Therefore, a

**TABLE 1. Target plasma fibrinogen levels in treatment guidelines**

Guidelines	Scope of guidelines	Target or trigger plasma fibrinogen level
American Society of Anesthesiologists <sup>28</sup>	Perioperative blood transfusion	Trigger: <0.8-1 g/L
British Committee for Standards in Haematology <sup>5</sup>	Massive blood loss	Trigger: <1 g/L
UK Blood Services <sup>36</sup>	Transfusion medicine	Trigger: 1 g/L
Scandinavian guidelines <sup>37</sup>	Massive bleeding	Target: >1 g/L
German Medical Association <sup>38</sup>	Therapy with blood components and plasma derivatives	Trigger: 1 g/L
Austrian Society of Anesthesiology, Resuscitation and Intensive Care Medicine (OGARI) <sup>39</sup>	Trauma-related massive bleeding	Target: 1.5-2 g/L
Association of Anaesthetists of Great Britain and Ireland <sup>40</sup>	Massive hemorrhage	Trigger: <1 g/L
Italian Society of Transfusion Medicine <sup>41</sup>	Massive hemorrhage	No target level specified; recommend 3 g of fibrinogen concentrate or 10 U of cryoprecipitate to increase plasma level by 1 g/L
Task Force for Advanced Bleeding Care in Trauma <sup>35</sup>	Bleeding after major trauma	Trigger: <1.5-2 g/L
European Society of Anaesthesiology <sup>42</sup>	Severe perioperative bleeding	Trigger: <1.5-2.0 g/L

higher plasma fibrinogen target level may be necessary for pregnant patients. In addition, fibrinogen concentration can also increase with age, with one study reporting values of 2.7 g/L in healthy volunteers under the age of 30, 3.0 g/L for those aged 30 to 60, and 3.3 g/L for those aged over 60.<sup>46</sup> Hence, specific plasma fibrinogen target levels for the pediatric and geriatric populations may also be necessary.

### APPROACHES TO FIBRINOGEN SUPPLEMENTATION

The available therapeutic approaches to the supplementation of fibrinogen differ from country to country. In North America, cryoprecipitate is used to supplement fibrinogen whereas in European countries, with the exception of the United Kingdom, cryoprecipitate is used only sporadically or is not available at all, and supplementation of fibrinogen is often performed using lyophilized fibrinogen concentrates. Three different approaches to fibrinogen supplementation are reviewed below (see Table 2 for a comparison).

### THERAPEUTIC PLASMA

One of the most important innovations in transfusion medicine has been the invention of the plastic blood bag, facilitating the development of component therapy, in which whole blood is separated into its component parts (RBCs, PLTs, cryoprecipitate, and plasma) and the possibility of blood from one donor benefitting several recipients.<sup>61</sup> However, recent reviews have found no consistent evidence of benefit for the prophylactic or therapeutic use of plasma across a range of clinical indications.<sup>62-64</sup>

There is almost no strong evidence that plasma infusion has a positive impact on morbidity and mortality,

except perhaps in the trauma setting.<sup>65</sup> In contrast, studies have reported increased morbidity associated with transfusion of plasma products, such as multiorgan system failure.<sup>66</sup> To date, there is a paucity of Level 1 evidence (from controlled clinical trials) indicating any impact on patient outcomes.

A number of different therapeutic plasma preparations are available, each with its own distinct properties (Table 2). The variety of products stems mainly from different approaches to pathogen removal and/or inactivation or different methods of storage. Virally inactivated products, such as solvent/detergent (S/D)- or methylene blue-treated plasma, aim to minimize the risk of pathogen transmission. S/D-treated pooled plasma, recently approved by the US Food and Drug Administration, has the added advantage of a substantially reduced risk of transfusion-related acute lung injury (TRALI).<sup>67</sup> However, these products may be less effective than standard plasma as they contain subphysiological levels of fibrinogen;<sup>56</sup> methylene blue-treated plasma contains approximately 30% less fibrinogen than standard plasma<sup>68</sup> and may have a fibrinogen concentration of below 1 g/L.<sup>69</sup> Freeze-dried plasma offers the advantage of rapid reconstitution, avoiding the need for thawing before administration, and can undergo pathogen inactivation processes,<sup>53</sup> but there is an almost complete lack of evidence supporting its use.<sup>54</sup> Plasma products vary between centers, and in many cases nonvirally inactivated single-donor fresh-frozen plasma (FFP), plasma frozen within 24 hours of collection (FP24), and thawed plasma (used within 5 days of initial thaw) are the available products; for the purpose of this review, the term “plasma” will be used for FFP, FP24, and thawed plasma.

Frozen plasma is the most commonly inventoried form of plasma in the United States, with more than 4 million units transfused per year.<sup>70</sup> Once frozen, plasma

**TABLE 2. Comparison of approaches to fibrinogen supplementation**

Therapeutic option	Preparation	Storage	Administration	Reported fibrinogen concentration	Viral inactivation/removal
Liquid (never frozen) plasma <sup>22</sup>	Removed from liquid whole blood up to 5 days after the expiration of the whole blood	Stored at 1-6°C for up to 5 days after the parent whole blood expires	Must be cross-matched for compatibility with the recipient	Up to 4.5 g/L	[Options as follows] Viral reduction: Nanofiltration Viral inactivation: Heat treatment/pasteurization Treatment with methylene blue, S/D, amotosalen, or riboflavin
Frozen plasma <sup>47</sup>	FFP, placed at -18°C within 8 hr of phlebotomy; FP24, placed at -18°C within 24 hr of phlebotomy	Can be stored at -18°C for up to 12 months; once thawed (at 30-37°C), must be stored at 1-6°C and used within 24 hr	Must be thawed and cross-matched for compatibility with the recipient	1-3 g/L	Can be made from virally inactivated or reduced-liquid plasma
Thawed plasma <sup>48</sup>	Once FFP or FP24 has been thawed for more than 24 hr, it can be relabeled as "thawed plasma"	Must be stored at 1-6°C and used within 5 days	Must be cross-matched for compatibility with the recipient (NB. Many hospitals keep an inventory of thawed plasma for rapid use in emergency situations—this is usually universal donor AB plasma and can be administered to any patient without the need for cross-matching) <sup>49-52</sup>	1-3 g/L	Can be made from virally inactivated or reduced-liquid plasma
Freeze-dried plasma <sup>53-55</sup>	Plasma is frozen at -40°C under high pressure. Product is stabilized by the addition of glycine.	Can be stored at room temperature for up to 2 years	Must be reconstituted in sterile water	2.6 ± 0.3 g/L	Can be made from virally inactivated or reduced-liquid plasma
Methylene blue-treated plasma <sup>56</sup>	Liquid plasma is treated with methylene blue, exposed to visible light, and then purified and placed at -30°C	Can be stored at -30°C for up to 2 years; once thawed (at 37°C), should be used immediately	Must be thawed (at 37°C) and cross-matched for compatibility with the recipient	1.80 g/L (compared to 2.77 g/L before treatment)	Pathogens inactivated with methylene blue and exposure to visible light; methylene blue is then removed
S/D-treated plasma <sup>56</sup>	Liquid plasma is treated with S/D and then purified and placed at -18°C	Can be stored at -18°C for up to 4 years; once thawed (at 30-37°C) can be stored for up to 8 hr at 4°C or 4 hr at room temperature before use	Must be thawed (at 30-37°C) and cross-matched for compatibility with the recipient	2.32 g/L (compared to 2.77 g/L before treatment)	Virus inactivation is carried out using 1% TNBP and 1% Triton X-100. These S/D reagents are removed during the purification process.
Amotosalen-treated plasma <sup>56</sup>	Liquid plasma (single unit up to 635 mL) is treated with amotosalen, exposed to ultraviolet light, and then purified and frozen	Can be stored at -25°C for up to 2 years or between -18 and -25°C for up to 1 year	Must be thawed and cross-matched for compatibility with the recipient	2.09 g/L (compared to 2.90 g/L before treatment)	Pathogens are inactivated with amotosalen; amotosalen is then removed by absorption.
Riboflavin-treated plasma <sup>56</sup>	Liquid plasma is treated with riboflavin, exposed to ultraviolet light, and then frozen	Can be stored at -30°C for up to 2 years	Must be thawed and cross-matched for compatibility with the recipient	2.67 g/L (compared to 3.45 g/L before treatment)	Pathogens inactivated with riboflavin; subsequent removal of riboflavin not required
Cryoprecipitate <sup>9,57</sup>	After thawing at 1-6°C, plasma is centrifuged at 5000 × g for 6 min. Precipitated proteins are resuspended in 10-15 mL of plasma and are refrozen.	Can be stored at -18°C for up to 12 months	Must be thawed and cross-matched for compatibility with the recipient	Approx. 15 g/L	Can be made from virally inactivated or reduced-liquid plasma
Fibrinogen concentrate <sup>58-60</sup>	Manufactured from human plasma into a lyophilized powder	Some concentrates can be stored at room temperature (2-25°C)	Must be reconstituted in sterile water	15-20 g/L	Made from plasma that has undergone viral inactivation/removal steps, such as: Cryoprecipitation Glycine precipitation Pasteurization Nanofiltration TNBP/polysorbate 80 Dry heat

TNBP = tri(n-butyl)phosphate.

must be stored at  $-18^{\circ}\text{C}$  and can be kept at this temperature for up to 12 months. After thawing (at  $30\text{--}37^{\circ}\text{C}$ ), it must be kept at  $1$  to  $6^{\circ}\text{C}$  and transfused within 24 hours.<sup>71</sup> If it is not used within this time frame, it can be relabeled as “thawed plasma” and stored for a further 4 days.

Reported values for the fibrinogen concentration of FFP range from  $1$  to  $3$  g/L.<sup>47</sup> Such variability is attributable to physiological differences between donors. The low concentration of fibrinogen in plasma means that large doses are often required; if the target fibrinogen level (e.g.,  $3.6$  g/L;  $22$  mm FIBTEM MCF) is above the fibrinogen concentration found in plasma, then it cannot be reached using plasma.<sup>72,73</sup> In one study, patients receiving a median FFP dose of  $12.2$  mL/kg showed an increase in plasma fibrinogen concentration of only  $0.4$  g/L; a dose of  $33.5$  mL/kg was required to achieve an increase of  $1.0$  g/L.<sup>74</sup> Large doses introduce a risk of hypervolemia and transfusion-associated circulatory overload (TACO). A recent study found a high incidence (6%) of TACO in critical care patients.<sup>75</sup> Plasma is also associated with TRALI.<sup>76</sup> This is the leading cause of transfusion-related death in the United States,<sup>77</sup> although the AABB has recently introduced TRALI mitigation strategies, including only using plasma from female donors with no history of pregnancy and from male donors.<sup>78</sup>

Extensive preparation time is needed before plasma is ready to administer. First, patient blood type must be determined, and the donor unit must be compatible with the recipient. The appropriate number of units must be thawed and transported to the bedside. Overall, it can take 60 to 90 minutes before plasma is available for transfusion,<sup>79–81</sup> which can be an unacceptable delay in emergency situations. Some centers ensure that they have a constant supply of thawed, universally compatible plasma; however, this can lead to plasma units being wasted. In addition, the levels of coagulation factors in thawed plasma decrease over time, with the activity of FVIII falling by more than 50% over 5 days.<sup>82</sup> A 2012 systematic review of FFP highlighted numerous concerns regarding the lack of a high-quality evidence base for its clinical use and suggested that further research into its efficacy and safety is required.<sup>62</sup>

## CRYOPRECIPITATE

Cryoprecipitate is manufactured from plasma, using a method designed to precipitate high-molecular-weight proteins, such as FVIII, von Willebrand factor, and fibrinogen. After being thawed at  $1$  to  $6^{\circ}\text{C}$ , FFP is centrifuged at  $5000 \times g$  for 6 minutes, and the supernatant is removed; this supernatant is labeled “cryoreduced/cryopoor plasma.” The precipitated proteins are resuspended in  $10$  to  $15$  mL of plasma and refrozen within the hour, and the resulting cryoprecipitate can be stored at  $-18^{\circ}\text{C}$  for up to

12 months.<sup>83</sup> The product can also be prepared and pooled on demand.

Cryoprecipitate contains a much higher concentration of fibrinogen than plasma, typically around  $15$  g/L,<sup>9</sup> enabling more effective supplementation of plasma fibrinogen levels. Cryoprecipitate is currently used in the United States and the United Kingdom for fibrinogen supplementation in cases of perioperative bleeding. Interestingly, as stated by Bevan<sup>85</sup> and Sorensen and Bevan,<sup>85</sup> this represents a double standard since cryoprecipitate, a multidonor product with no antiviral processing,<sup>86</sup> is no longer used in hereditary bleeding disorders. Furthermore, cryoprecipitate has been withdrawn from a number of European countries due to safety concerns. As with plasma, cryoprecipitate needs to be screened for blood group compatibility and requires time for thawing before transfusion.

The AABB 2013 Circular of Information recommends the use of coagulation factors other than cryoprecipitate for treatment of patients with hemophilia A and von Willebrand disease; it also states that cryoprecipitate should not be used in these clinical settings if virally inactivated or recombinant factor preparations are available.<sup>87</sup> Evidence for the use of cryoprecipitate is limited,<sup>88,89</sup> and guidelines state that cryoprecipitate should not be used to control bleeding related to low fibrinogen levels if specific factor concentrates are available.<sup>90</sup>

## FIBRINOGEN CONCENTRATE

Fibrinogen concentrate is manufactured from human plasma and is commercially available as a pasteurized, lyophilized powder. During the manufacturing process, the plasma from which fibrinogen concentrate is derived is subject to a number of viral inactivation and removal processes, which inactivate all currently known virus types, including enveloped and nonenveloped viruses.<sup>91</sup> Thus, fibrinogen concentrate may be considered safer than standard (nonvirally inactivated) cryoprecipitate and FFP with regard to pathogen transmission. The viral inactivation and removal processes also remove antibodies and antigens, greatly reducing the risk of immunological and allergic reactions.<sup>91</sup>

Fibrinogen concentrate must be reconstituted in sterile water for injection to a final vial concentration of approximately  $20$  g/L.<sup>92</sup> The packet insert indicates a range of  $900$  to  $1300$  mg fibrinogen per 1-g vial; this range is the permitted degree of variation and does not represent the actual low level of variation between vials.<sup>93</sup> Therefore, unlike plasma or cryoprecipitate, fibrinogen concentrate delivers a standardized dose of fibrinogen. Fibrinogen concentrate does not need to be screened for blood type and can be stored at room temperature ( $2\text{--}25^{\circ}\text{C}$ ). Therefore, fibrinogen concentrate is available for almost immediate use, and relatively large doses can be

administered in a few minutes. The packet insert states that reconstitution in water should be completed in 5 to 10 minutes (and within a maximum of 15 min), and although the manufacturer recommends an infusion rate of no more than 5 mL/min, it is possible to infuse 1 g in less than 20 seconds in cases of severe bleeding.<sup>93,94</sup>

Fibrinogen concentrate has been shown to be effective and well tolerated in a number of clinical trials;<sup>22,95</sup> fears of an increased risk of thromboembolic events appear to be unfounded.<sup>94,96,97</sup> Studies across a variety of settings have reported the safety profile of fibrinogen concentrate as excellent<sup>3,98,99</sup> and more than 3,000,000 g has been administered since 1985.<sup>95</sup> A postmarketing surveillance study of fibrinogen concentrate, conducted between 1986 and 2008, found only nine voluntary reports of possibly related thrombotic events for 1,034,389 g of fibrinogen concentrate administered. Assuming an average dose of 4 g per treatment episode, this equates to 3.48 events per 10<sup>5</sup> treatment episodes (95% confidence interval, 1.59-6.61).<sup>96</sup> However, further clinical studies including long-term follow-up are required.

Currently, there is only one fibrinogen concentrate that is globally available under different trade names; it represents the standard of care for acquired hypofibrinogenemia in Austria, Germany, and Switzerland and is also licensed in Argentina, Brazil, Bulgaria, the Czech Republic, Hungary, Iran, Kuwait, the Netherlands, Portugal, Romania, Taiwan, Tunisia, and Turkey for acquired hypofibrinogenemia and congenital a-, dys-, and hypofibrinogenemia.<sup>22,95</sup> The same product is indicated for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia, in Australia, Canada, Israel, Mexico, New Zealand, Puerto Rico, the United States, and several countries across the European Union.<sup>4,22</sup> Other fibrinogen concentrate products with more limited availability are licensed in specific countries such as China, Japan and France.<sup>22</sup> Fibrinogen concentrate may also be used on a named-patient basis in a number of countries.<sup>22,100</sup> Four fibrinogen concentrates are currently available;<sup>10</sup> these are compared in Table 3.

## FIBRINOGEN CONCENTRATE DOSING

Studies have shown that it is possible to individualize the dosing of fibrinogen concentrate, based on the level of bleeding and initial plasma fibrinogen concentration.<sup>73,93,104</sup> The manufacturer recommends an initial dose of 1 to 2 g, with subsequent administration dependent on bleeding status. For example, in case of severe hemorrhage, larger doses of 4 to 8 g may be required. The dose can be estimated as follows:

$$\begin{aligned} & \text{Fibrinogen concentrate dose (g)} \\ &= \text{desired increase in plasma fibrinogen level (g/L)} \\ & \quad \times \text{plasma volume (L)}. \end{aligned}$$

A number of studies have shown that the exact dose of fibrinogen required to increase the plasma level by a specified amount depends on the underlying clinical condition of the patient. A prophylactic dose of 70 mg/kg raised fibrinogen levels by a mean of 1.0 g/L in the setting of congenital afibrinogenemia.<sup>105</sup> In one observational study of 39 patients with diffuse bleeding after cardiopulmonary bypass (CPB) surgery, median plasma fibrinogen levels increased by 0.28 g/L per 1 g of fibrinogen concentrate administered;<sup>106</sup> similar results were observed in a prospective study of 20 CPB patients (median fibrinogen increment of 0.3 g/L per 1 g of fibrinogen concentrate administered).<sup>107</sup> In the setting of obstetric hemorrhage, a median increase in plasma fibrinogen concentration of 0.36 g/L per 1 g of fibrinogen administered was observed in a case series of six patients.<sup>108</sup> Another observational study of 43 patients experiencing massive hemorrhage found that a 2-g dose of fibrinogen concentrate raised median plasma fibrinogen levels by 1.01 g/L<sup>4</sup> (see Table 4 for a comparison of studies).

Point-of-care testing using thromboelastometry (ROTEM) or thrombelastography enables various aspects of clotting in whole blood to be monitored in almost real time at, or very near to, the patient's bedside. This allows individualized patient management, with specific, targeted, and rapid supplementation of depleted coagulation factors.<sup>8,115</sup> More specifically, tests that measure the fibrin or fibrinogen contribution to clot strength, such as the thromboelastometric FIBTEM test (ROTEM device, TEM International, Munich, Germany), can be used to determine the most appropriate dose of fibrinogen concentrate.

MCF, measured using this test, has been used in a number of studies to calculate an individualized dose of fibrinogen concentrate.<sup>3,73,93</sup> The dose can be calculated as follows:

$$\begin{aligned} & \text{Fibrinogen concentrate dose (g)} \\ &= (\text{target FIBTEM MCF [mm]} \\ & - \text{actual FIBTEM MCF [mm]}) \times (\text{body weight [kg]}/70) \\ & \quad \times 0.5 \text{ g/mm}. \end{aligned}$$

Using this formula, a patient of 70 kg would require a dose of approximately 0.5 g fibrinogen concentrate to increase the FIBTEM MCF by 1 mm. The normal range for MCF values is 9 to 25 mm;<sup>33</sup> a high-normal target MCF of 22 mm has been used in the setting of aortic replacement surgery (achieved using median fibrinogen concentrate doses of 8<sup>3</sup> and 7.8 g<sup>73</sup> and a mean dose of 5.7 g<sup>104</sup>). Another recent study in cardiovascular surgery used a different FIBTEM parameter, A10 (clot amplitude reached after 10 min), as a marker for fibrinogen supplementation, with a target A10 of more than 15 mm (normal range, 7-23 mm).<sup>98</sup> A median dose of 3.2 g fibrinogen concentrate was administered; doses were calculated using the

**TABLE 3. Fibrinogen concentrates and their availability**

Brand name	Manufacturer	Availability	Indications	Contraindications	Viral inactivation	Fibrinogen content
*Haemocomplettan p4,22,58,95,101	CSL Behring	Argentina Austria Brazil Bulgaria Czech Republic Germany Hungary Iran Kuwait Netherlands Portugal Romania Switzerland Taiwan Tunisia Turkey Israel	<i>Therapy and prophylaxis of hemorrhagic diatheses in:</i> <ul style="list-style-type: none"> <li>• Congenital hypo-, dys- or afibrinogenemia</li> <li>• Acquired hypofibrinogenemia resulting from                             <ul style="list-style-type: none"> <li>– disorders of synthesis in cases of severe liver parenchyma damage</li> <li>– increased intravascular consumption e.g. as a result of disseminated intravascular coagulation, hyperfibrinolysis</li> <li>– increased loss</li> </ul> </li> </ul>	Anaphylactic or severe reactions to Haemocomplettan P or its components	Pasteurization at 60°C, 20 hr	900-1300 mg/50 mL
*RiaSTAP <sup>42,58,59</sup>	CSL Behring	Canada Puerto Rico United States Australia Belgium Cyprus Denmark Finland France Germany Great Britain Greece Iceland Ireland Italy Luxembourg Malta Mexico New Zealand Norway Poland Slovak Republic Slovenia Spain Sweden France	Treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia (not indicated for dysfibrinogenemia) Treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia (not indicated for dysfibrinogenemia) Treatment of bleeding in patients with congenital hypofibrinogenemia, or afibrinogenemia with bleeding tendency	Anaphylactic or severe reactions to RiaSTAP or its components	Pasteurization at 60°C, 20 hr	900-1300 mg/50 mL
Clottagen/ Clottafact <sup>25,58,60,102</sup>	LFB Biomedicaments	Japan Sweden France	Constitutional hypo-, dys-, or afibrinogenemia in patients with spontaneous or post-traumatic hemorrhage. Hypofibrinogenemia acquired during: – Severe acute hemorrhage associated with a secondary reduction in the circulating fibrinogen levels, e.g., severe acute PPH, or hemorrhages associated with dilutional coagulopathy, in surgical or trauma settings – Hemorrhagic syndrome associated with a reduction in heparin fibrinogen synthesis in patients with hepatic impairment or secondary to treatment with L-asparaginase Treatment of bleeding in patients with congenital fibrinogen deficiency (e.g., afibrinogenemia, hypofibrinogenemia)	Recent thrombosis or myocardial infarction History of thromboembolic diseases Hypersensitivity to the active substance or any of its ingredients	TNBP/polysorbate 80, 35-nm nanofiltration	1.5 mg/100 mL
Fibrinogen HT <sup>25,58</sup>	Benesis	Japan	Hemorrhagic states associated with: Congenital hypofibrinogenemia, dysfibrinogenemia, or afibrinogenemia Acquired hypofibrinogenemia owing to: Failure of fibrinogen synthesis in severe liver disorders Increased intravascular consumption of fibrinogen in DIC and hyperfibrinolysis	None stated	TNBP/polysorbate 80; dry heat, 60°C, 72 hr, 35-nm nanofiltration TNBP/polysorbate 80; dry heat	Unknown
FibroRAAS <sup>22,58,103</sup>	Shanghai RAAS	China Japan	Hemorrhagic states associated with: Congenital hypofibrinogenemia, dysfibrinogenemia, or afibrinogenemia Acquired hypofibrinogenemia owing to: Failure of fibrinogen synthesis in severe liver disorders Increased intravascular consumption of fibrinogen in DIC and hyperfibrinolysis	Should be administered in DIC and hyperfibrinolysis only in conjunction with other appropriate measures intended to eliminate the cause of the condition	TNBP/polysorbate 80; dry heat, 60°C, 72 hr, 35-nm nanofiltration TNBP/polysorbate 80; dry heat	0.5 mg/25 mL

\* Haemocomplettan P and RiaSTAP are different trade names for the same medicinal product.  
 DIC = disseminated intravascular coagulation; TNBP = tri(n-butyl)phosphate.  
 [Correction added after online publication 9-Oct-2013: the availability and indications for Haemocomplettan and RiaSTAP have been updated.]

**TABLE 4. Overview of clinical studies detailing fibrinogen concentrate administration**

Study	Design	Number of patients receiving fibrinogen concentrate	Trigger for administering fibrinogen concentrate	Target level (fibrinogen level or FIBTEM)	Fibrinogen dose	Mean fibrinogen level or FIBTEM MCF before and after treatment	Conclusions
<b>Trauma</b> Brenni et al. 2010 <sup>26</sup> <i>Acta Anaesthesiol Scand</i>	Case report	1	Hyperfibrinolysis and afibrinogenemia	N/S	16 g	Before treatment 2.1 g/L After treatment 2.5 g/L	Fibrinogen concentrate corrected coagulopathy and stabilized the patient with no need for PLTs or FFP
Innerhofer et al. 2013 <sup>09</sup> <i>Injury</i>	Post hoc analysis of data from a prospective study	144 (66 coagulation factor concentrates only; 78 coagulation factor concentrates and FFP)	Fibrinogen concentration <1.5-2.0 g/L FIBTEM MCF <7 mm	N/S	Coagulation factor concentrates only, 2 g; coagulation factor concentrates plus FFP, 4 g	Plasma fibrinogen maintained rather than increased, larger increases in FIBTEM MCF seen in patients also receiving FFP	The use of coagulation factor concentrates alone corrected coagulopathy in patients with severe blunt trauma and decreased allogeneic transfusion
Schöchl et al. 2010 <sup>08</sup> <i>Crit Care</i>	Retrospective	128	Severe bleeding; FIBTEM MCF < 10 mm	FIBTEM MCF 10-12 mm	Median 7 g	Before treatment 1.26 g/L; 6 mm After treatment 1.50 g/L; 9 mm	Fibrinogen concentrate is an effective and rapid first-line hemostatic therapy for severe trauma-induced bleeding
Schöchl et al. 2011 <sup>10</sup> <i>Crit Care</i>	Retrospective	681 (80 fibrinogen concentrate, 601 FFP)	FIBTEM MCF < 10 mm	FIBTEM MCF 10-12 mm	Median 6 g	Before treatment 1.4 g/L After treatment 1.8 g/L	Fibrinogen concentrate as first-line therapy, in conjunction with PCC, reduced RBC and PLT exposure
<b>Cardiovascular and vascular surgery</b> Karlsson et al. 2009 <sup>07</sup> <i>Thromb Haemost</i>	RCT	10	Plasma fibrinogen level <3.8 g/L	N/S	2 g	Before treatment 2.9 g/L Mean increase 0.6 g/L	Fibrinogen concentrate administered prophylactically reduced postoperative blood loss in CABG patients
Rahe-Meyer et al. 2009 <sup>04</sup> <i>J Thorac Cardiovasc Surg</i>	Prospective vs. retrospective	6	5-min bleeding mass from the surgical field: 60-250 g	FIBTEM MCF 22 mm	Mean 7.8 g	Before treatment 8.3 mm After treatment 22.7 mm	Fibrinogen concentrate reduced transfusion requirements and postoperative bleeding after TAA surgery
Rahe-Meyer et al. 2009 <sup>73</sup> <i>Br J Anaesth</i>	Prospective	10	5-min bleeding mass from the surgical field: 60-250 g	FIBTEM MCF 22 mm	Mean 5.7 g	Before treatment 11 mm After treatment 20 mm	Fibrinogen concentrate reduced transfusion requirements and postoperative bleeding after AV-AA surgery
Rahe-Meyer et al. 2013 <sup>3</sup> <i>Anesthesiology</i>	RCT	29	5-min bleeding mass from the surgical field: 60-250 g	FIBTEM MCF 22 mm	Median 8 g	Before treatment 1.57 g/L; 9.7 mm After treatment 2.6 g/L; 16.5 mm	Reduction of allogeneic transfusion after fibrinogen concentrate in patients undergoing aortic replacement surgery under CPB
Solomon et al. 2010 <sup>93</sup> <i>Br J Anaesth</i>	Retrospective	39	Diffuse bleeding	FIBTEM MCF 22 mm	Mean 6.5 g	Before treatment 1.9 g/L; 10.1 mm After treatment 3.6 g/L; 20.7 mm	Fibrinogen concentrate increased plasma fibrinogen and contributed to correction of bleeding after cardiovascular surgery
Solomon et al. 2012 <sup>106</sup> <i>Scand J Clin Lab Invest</i>	Prospective consecutive cohort	10	Diffuse bleeding	N/S	Median 6 g	Before treatment 2.1 g/L; 10.5 mm After treatment 3.8 g/L; 20.5 mm	Fibrinogen concentrate resulted in overall decreased transfusion
<b>Radical cystectomy</b> Fenger-Eriksen et al. 2009 <sup>11</sup> <i>J Thromb Haemost</i>	RCT	20 radical cystectomy patients (10 fibrinogen concentrate, 10 placebo)	30% hemodilution (i.e., 30% reduction from baseline in hematocrit)	N/S	45 mg/kg BW	Before treatment 1.74 g/L After treatment 2.41 g/L	Fibrinogen concentrate improved clot strength after hemodilution and reduced RBC transfusion requirements

TABLE 4. Continued

Study	Design	Number of patients receiving fibrinogen concentrate	Trigger for administering fibrinogen concentrate	Target level (fibrinogen level or FIBTEM)	Fibrinogen dose	Mean fibrinogen level or FIBTEM MCF, before and after treatment	Conclusions
<b>Orthopedic surgery</b> Haas et al. 2008 <sup>112</sup> <i>Anesth Analg</i>	Retrospective	9	FIBTEM MCF $\leq$ 7 mm	FIBTEM MCF of 8-10 mm and total clot strength of $>$ 45 mm	Mean 680 mg (76 mg/kg)	Before treatment 1.32 g/L; 7 mm After treatment 1.90 g/L; 10 mm	Fibrinogen concentrate prevented the need for FFP or PLTs
Mittermayr et al. 2007 <sup>113</sup> <i>Anesth Analg</i>	Prospective	60 orthopedic patients (13 received fibrinogen concentrate)	FIBTEM MCF $<$ 7 mm	Plasma fibrinogen concentration 1.5 g/L	30 mg/kg BW	N/S	Fibrinogen concentrate reversed dilutional coagulopathy during orthopedic surgery
<b>Obstetric hemorrhage</b> Bell et al. 2010 <sup>108</sup> <i>Int J Obstet Anesth</i>	Case series	6	Hemorrhage and hypofibrinogenemia ( $<$ 2 g/L)	N/S	Median 3 g	Before treatment 0.8 g/L After treatment 1.8 g/L	Fibrinogen concentrate normalized laboratory coagulation measurements and improved hemorrhage
Glover et al. 2010 <sup>114</sup> <i>Anaesthesia</i>	Case report	1	Low plasma fibrinogen	N/S	4 g	Before treatment 0.9 g/L After treatment 1.5 g/L	Fibrinogen concentrate reversed coagulopathy
Kreuz et al. 2005 <sup>105</sup> <i>Transfus Apher Sci</i>	Prospective	5	Afibrinogenemia or severe hypofibrinogenemia ( $\leq$ 14 mg/dL)	N/S	70 mg/kg	Median increase 1.0 g/L	Fibrinogen concentrate normalized or near normalized preinfusion coagulation tests
<b>Various settings</b> Fenger-Eriksen et al. 2008 <sup>4</sup> <i>Br J Anaesth</i>	Retrospective	43	Hypofibrinogenemia ( $<$ 2 g/L)	$>$ 2 g/L	2.0 g (adults) 0.35 g (children)	Mean increase 1.0 g/L	Fibrinogen concentrate significantly reduced blood loss and transfusion requirements for RBC, FFP, and PLT concentrate

AV-AA = aortic valve and ascending aorta; BW = body weight; N/S = none stated; RCT = randomized controlled trial; TAA = thoracic aortic aneurysm.

rationale that 25 mg/kg fibrinogen concentrate increases FIBTEM A10 by 4 mm.<sup>116</sup>

Maximum amplitude, an equivalent variable to MCF, can be measured using the functional fibrinogen assay on the thrombelastography device (Haemonetics Corp., Braintree, MA). This assay could potentially be used in the clinical setting in the same way as the FIBTEM assay. However, the functional fibrinogen assay has a tendency to report higher values than the FIBTEM test, indicating that MCF and maximum amplitude are not interchangeable.<sup>117</sup> Specific threshold and target values for this parameter need to be determined before this test is adopted in clinical practice, as use of the existing values determined for the FIBTEM assay could potentially result in inappropriate intervention.

For trauma patients with a plasma fibrinogen level of less than 1.5 to 2.0 g/L, the European trauma guidelines<sup>35,118</sup> recommend an initial fibrinogen concentrate dose of 3 to 4 g. Further dosing should then be guided by ROTEM or laboratory assessment of plasma fibrinogen level. Furthermore, the guidelines recommend administration of 2 g tranexamic acid during the early phase of trauma care. In a recent *in vitro* study, a very small dose of tranexamic acid (0.4 µg/mL) administered alongside fibrinogen concentrate was sufficient to stabilize clots against fibrinolysis.<sup>119</sup> Further research in this area is warranted, but the existing evidence suggests that fibrinogen concentrate and tranexamic acid given in combination may provide better hemostatic management than fibrinogen concentrate alone.

## PROPHYLAXIS

Preoperative plasma fibrinogen concentration has been shown to predict bleeding volume and transfusion requirements in several different settings. In a study of 97 coronary artery surgery patients, preoperative fibrinogen level was significantly correlated with chest tube drainage over the 48-hour period after sternotomy closure ( $r = -0.897$ ,  $p < 0.001$ ).<sup>23</sup> A similar correlation between preoperative fibrinogen concentration and 24-hour postoperative chest tube bleeding volume was reported in 98 patients undergoing surgery with CPB.<sup>120</sup> Fibrinogen level after surgery also correlated with bleeding volume. Another cardiovascular surgery study, involving 170 coronary artery bypass graft (CABG) patients, showed preoperative fibrinogen level to be an independent predictor of both 12-hour postoperative chest tube bleeding volume and postoperative transfusion of allogeneic blood products.<sup>121</sup> Significant correlation was observed between preoperative fibrinogen level and bleeding volume ( $r = -0.53$ ,  $p < 0.001$ ). In a study of 323 trauma patients, plasma fibrinogen concentration upon admission to the emergency room was shown to predict the likelihood of massive transfusion ( $\geq 10$  U RBCs in 24 hr).<sup>5</sup> The optimum

threshold for sensitivity and specificity of fibrinogen concentration was 1.48 g/L. Another large trauma study (517 patients) showed that fibrinogen level upon admission to hospital is an independent predictor of 24-hour and 28-day mortality ( $p < 0.001$ ).<sup>122</sup> A study of 82 girls (mean age 15 years) undergoing scoliosis surgery reported significant correlation between preoperative plasma fibrinogen concentration and total perioperative bleeding volume ( $r = -0.31$ ,  $p = 0.005$ ).<sup>123</sup> Fibrinogen has also been established as an important hemostatic marker in the management of PPH, with early measurement able to predict the risk of severe bleeding;<sup>45</sup> this risk is increased 2.63-fold with each 1 g/L decrease in fibrinogen concentration.

These data suggest that prophylactic fibrinogen supplementation before elective surgery (or as early as possible in emergency situations) has the potential to delay the onset of coagulopathy and thus improve patient outcomes. In a randomized controlled study of 20 CABG patients with preoperative fibrinogen level below 3.8 g/L, Karlsson and coworkers<sup>107</sup> showed that prophylactic administration of 2 g fibrinogen concentrate reduced postoperative bleeding by 32% ( $p = 0.010$ ); there was no evidence of hypercoagulability.

It would be valuable to ascertain which patients might benefit most from prophylactic fibrinogen, and it may be necessary to determine a ceiling fibrinogen concentration above which patients would not receive fibrinogen. The target fibrinogen concentration for prophylaxis also needs to be defined; this might differ from the target level when attempting to control coagulopathic bleeding, and also between different clinical settings.

## CLINICAL STUDIES EVALUATING THE EFFICACY OF FIBRINOGEN CONCENTRATE: SELECTED SETTINGS

Use of fibrinogen concentrate to restore fibrinogen levels during cases of acquired bleeding has been reported in a number of clinical settings, including trauma, surgery, and obstetrics. The key data are reviewed below (see also Table 4).

### TRAUMA

Trauma is the leading cause of mortality among children and young adults,<sup>124,125</sup> with coagulopathy responsible for 40% of trauma-related deaths.<sup>6</sup>

Case reports have shown that fibrinogen concentrate can be used successfully as first-line hemostatic treatment for coagulopathy resulting from major trauma.<sup>115,126</sup> In both cases, coagulopathy was corrected without the use of FFP or PLTs, indicating a potential role for fibrinogen concentrate in reducing transfusion of allogeneic blood products.

Clinical studies have shown that coadministration of fibrinogen concentrate with other coagulation factor concentrates is a potentially effective management protocol for trauma patients. A retrospective analysis of 131 patients with acquired bleeding demonstrated that goal-directed coagulation management with fibrinogen concentrate and PCC improved survival rates as compared with those predicted by the Trauma Injury Severity Score (TRISS).<sup>8</sup> In another retrospective study, significantly more of the 601 patients who received FFP without factor concentrates required transfusion with RBCs or PLT concentrate, compared with 80 trauma patients who received fibrinogen concentrate and/or PCC.<sup>110</sup> These results were corroborated by a prospective study of 144 patients with major blunt trauma, in which the use of coagulation factor concentrates alone effectively corrected coagulopathy and reduced requirement for RBCs and PLTs, compared with those also receiving FFP.<sup>109</sup> This study showed that patients who received only factor concentrates were significantly less likely to develop multiorgan failure or sepsis when compared with patients receiving FFP.

A retrospective study of 294 trauma patients further evaluated whether administration of fibrinogen concentrate is associated with improved outcomes.<sup>127</sup> Although 6-hour mortality was significantly reduced in the fibrinogen concentrate group, overall mortality was not significantly different between groups. In contrast to other studies, RBC requirement was not reduced in the fibrinogen concentrate group.

The majority of clinical data to date suggest that fibrinogen concentrate plays a key role as a primary hemostatic agent in trauma patients. Its administration can enable successful treatment of trauma-related bleeding with reduced or even no requirement for allogeneic blood products. Further prospective, randomized studies are required to confirm these data and to establish effective management protocols using this approach, such as that recently developed by Schöchl et al.<sup>128</sup> On the US clinical trials register (ClinicalTrials.gov), there are currently two ongoing European trials investigating the use of fibrinogen concentrate in trauma.

## CARDIOVASCULAR AND VASCULAR SURGERY

Complex cardiovascular and vascular surgical procedures are often accompanied by excessive bleeding, usually as a result of coagulation system impairment, inadequate surgical hemostasis, or both.<sup>129</sup> Perioperative bleeding is associated with increased morbidity and mortality rates<sup>130</sup> and represents a significant health burden.

Recently, results of a prospective, placebo-controlled, double-blind study of patients undergoing elective cardiac surgery involving CPB have been published.<sup>3</sup> Fibrinogen concentrate or placebo was administered to 61

patients, guided by the FIBTEM test conducted at the point of care, for patients who had clinically relevant coagulopathic bleeding immediately after removal from CPB and completion of surgical hemostasis. Patients in the fibrinogen concentrate group required significantly fewer allogeneic blood product transfusions when compared with patients in the placebo group (2 U vs. 13 U, respectively). In addition, total avoidance of transfusion was achieved in nearly half of patients who received fibrinogen concentrate compared with none of those who received placebo.

Other prospective and retrospective studies have also shown that administration of fibrinogen concentrate during cardiac surgery is associated with reduction in transfusion of allogeneic blood products and incidence of postoperative bleeding.<sup>73,93,104,106,107</sup> In a study of 42 patients undergoing elective aortic valve operation or ascending aorta replacement, those receiving fibrinogen concentrate before algorithm-based therapy required significantly fewer units of allogeneic blood products and displayed reduced 24-hour postoperative bleeding.<sup>73</sup> Similar results were seen in a retrospective study of fibrinogen concentrate (guided by point-of-care FIBTEM results) as an initial treatment for postbypass bleeding in patients who had undergone thoracoabdominal aortic aneurysm repair.<sup>104</sup> The need for subsequent blood product transfusion was reduced in these patients, as was 24-hour drainage volume. Moreover, a prospective study demonstrated that in patients undergoing CPB grafting with bleeding after CPB, FIBTEM-guided administration of fibrinogen concentrate resulted in overall decreased rates of transfusion, compared with administration of allogeneic blood products.<sup>106</sup> This study also demonstrated that administration of fibrinogen concentrate increased fibrin clot quality and helped achieve hemostasis.<sup>106</sup>

The evidence suggests that fibrinogen concentrate reduces both bleeding and transfusion of allogeneic blood products in cardiovascular and vascular surgery. Given the high incidence of mortality resulting from coagulopathy acquired during these complex procedures, the use of fibrinogen concentrate has the potential to become first-line treatment in this setting.

## OBSTETRIC HEMORRHAGE

Obstetric hemorrhage remains a major cause of mortality and morbidity in childbirth.<sup>131,132</sup> Increased uterine arterial blood flow during labor means that obstetric hemorrhage can rapidly result in life-threatening blood loss, requiring volume resuscitation and allogeneic blood transfusion.

A study detailing six cases of severe hemorrhage showed that addition of fibrinogen concentrate to existing therapies was effective in the treatment of peripartum blood loss associated with hypofibrinogenemia.<sup>108</sup> In all

cases, coagulation variables were rapidly normalized and severe hemorrhage was arrested. A case study also reported successful control of major antenatal obstetric hemorrhage associated with disseminated intravascular coagulopathy, through use of fibrinogen concentrate alone.<sup>114</sup>

These findings suggest that infusion of fibrinogen concentrate can rapidly control bleeding during obstetric hemorrhage. Given the need for an effective, timely therapy and the increasing evidence linking fibrinogen levels with PPH progression, large randomized, controlled trials in this setting are urgently needed. One such trial is nearing completion, the FIB-PPH trial, which aims to compare transfusion requirements in 245 women receiving fibrinogen concentrate or placebo.<sup>133</sup>

### RADICAL CYSTECTOMY

Radical cystectomy involves removal of the entire bladder and part of nearby organs. The effectiveness of fibrinogen concentrate for treating coagulopathy during radical cystectomy was investigated in a prospective, randomized, placebo-controlled trial of patients who had received 30% dilution with hydroxyethyl starch.<sup>111</sup> Compared with placebo, fibrinogen concentrate significantly improved ROTEM MCF, and the number of patients requiring post-operative allogeneic blood product transfusion was significantly lower in the fibrinogen concentrate group.

### ORTHOPEDIC SURGERY

Orthopedic surgery is associated with blood loss and consumption of coagulation factors, and thus volume replacement with colloids and/or crystalloids is often administered. However, this carries a risk of dilutional coagulopathy and impaired fibrin polymerization.<sup>134-136</sup>

The effect of fibrinogen concentrate during orthopedic surgery was examined in a prospective study of 66 patients who received volume resuscitation with synthetic colloids or crystalloids.<sup>113</sup> This study showed that fibrinogen concentrate maintained clot firmness even in cases of continuing blood loss and further colloid transfusion. In another study of children with dilutional coagulopathy undergoing surgical craniostomy repair, repeated doses of fibrinogen concentrate sufficiently restored hemostasis in all patients, without requirement for FFP or PLT transfusion.<sup>112</sup> In both studies, administration of fibrinogen concentrate increased both the rate of formation and the strength of the fibrin-based clot.<sup>112,113</sup>

### OTHER SETTINGS AND AREAS OF INTEREST

Although there is a growing body of evidence to support the use of fibrinogen concentrate in the settings described

above, further research is warranted. In trauma, a large number of centers employ massive transfusion protocols (MTPs), whereby RBCs, plasma, and PLTs are administered in a set ratio, usually 1:1:1. As there is evidence to suggest that patients treated with MTPs are frequently suffering from a fibrinogen deficiency,<sup>137</sup> it may be of interest to conduct a study in which fibrinogen concentrate was administered as an early component of an MTP. However, recent evidence from a feasibility study suggests that although fixed-ratio transfusion protocols are clinically feasible, they lead to plasma wastage when compared to goal-directed transfusion.<sup>138</sup> Larger trials are required to clarify the role of a 1:1:1 transfusion strategy and to determine the safety and efficacy of such protocols.

There is little to no evidence regarding the use of fibrinogen concentrate in clinical settings other than those discussed above. Further areas of interest include the pediatric population and cancer patients. Further trials should be conducted to study the use of fibrinogen concentrate as first-line hemostatic therapy in these settings, and further research is required to determine appropriate trigger and/or target fibrinogen levels and dosing strategies.

### SUMMARY

Fibrinogen has a critical role during acute bleeding and is an important target for both prevention and cessation of bleeding. As the precursor to fibrin and a mediator of PLT aggregation, fibrinogen is fundamental to clotting. Fibrinogen levels can be supplemented using a number of therapies, including plasma, cryoprecipitate, and fibrinogen concentrate. However, allogeneic blood products are associated with a high number of adverse events and long preparation and administration times. Moreover, little high-quality clinical evidence exists to support their use as hemostatic therapy in acquired major bleeding.

Fibrinogen concentrate has been reported to supplement fibrinogen levels in a variety of clinical settings and appears to be effective and well tolerated. Fibrinogen concentrate has the potential to reduce allogeneic blood product transfusion and improve outcomes, with no evidence of an increased risk of adverse events. It will be necessary to determine a definitive set of target plasma fibrinogen levels, with specific targets needed for certain patient populations.

Fibrinogen concentrate has a number of advantages over alternative therapies: it is available for administration almost immediately, can be administered in very small volumes, has a very good safety profile, and is virally inactivated as standard. Unlike plasma and cryoprecipitate, which contain variable amounts of fibrinogen, fibrinogen concentrate can be used to deliver a standardized dose. Furthermore, standard laboratory tests, or increasingly, viscoelastic testing, allow for individualized dosing based

on pretreatment fibrinogen level and current hemostatic capacity. Fibrinogen concentrate is often perceived to be more expensive than plasma or cryoprecipitate. However, prospective comparison of the direct and indirect costs of allogeneic blood products and fibrinogen concentrate are required before any conclusions can be made regarding cost-effectiveness.<sup>85,139,140</sup>

Fibrinogen concentrate represents an important option for treating coagulopathic bleeding, allowing reduction or even total avoidance of allogeneic blood product transfusion. Further multicenter studies in different clinical settings are needed to determine precise dosing strategies and thresholds for fibrinogen supplementation.

**CONFLICT OF INTEREST**

JHL serves on a steering committee for CSL Behring for aortic surgery.

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