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Published on: 30 Dec 2015 - Seminars in Thrombosis and Hemostasis (Semin Thromb Hemost)

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DOI: <https://doi.org/10.1055/s-0035-1564841>

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ZORA URL: <https://doi.org/10.5167/uzh-127770>

Journal Article

Accepted Version



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Originally published at:

Stein, Philipp; Spahn, Gabriela; Spahn, Donat (2016). Indications and Risks of Fibrinogen in Surgery and Trauma. *Seminars in Thrombosis and Hemostasis*, 42(02):147-154.

DOI: <https://doi.org/10.1055/s-0035-1564841>

Indications and Risks of Fibrinogen in Surgery and Trauma.

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Abstract

Fibrinogen has a central role in coagulation. Following trauma and perioperatively low fibrinogen levels have been found to be risk factors for exaggerated bleeding, transfusion needs and adverse outcome. Conversely, treatment with exogenous fibrinogen in critically bleeding patients with low fibrinogen levels has been shown to decrease transfusion needs. Since following trauma and in many perioperative situations fibrinogen is the first coagulation “element” to become critically low, it appears reasonable to target fibrinogen in clinical coagulation algorithms aiming at early specific and goal-directed treatment. A low fibrinogen can be a low plasma concentration or a low functional fibrinogen as assessed by point-of-care techniques like thromboelastography or thromboelastometry. This review summarizes the evidence base for perioperative algorithm based fibrinogen administration including the exact thresholds for fibrinogen administration used in the different algorithms. Algorithm based individualized goal-directed use of fibrinogen resulted in highly significant reduction of transfusion needs, adverse outcomes, in certain studies even mortality and where investigated reduced costs, with high safety levels at the same time. Best evidence exists in cardiac surgery, followed by trauma, postpartum hemorrhage and liver transplantation. The introduction of these concepts is highly demanding and requires a tremendous educational effort to familiarize all health care workers with the necessary knowledge and the skills of how to run thromboelastometry / thromboelastography tests. Future research is needed to compare the efficacy, safety and costs of different al-

gorithms. This, however, should not prevent us from introducing these expedient point-of-care based algorithms clinically today.

Keywords: Fibrinogen, Blood Coagulation, Algorithms, Patient Blood Management

Introduction

Fibrinogen has a central role in coagulation. It links platelets and is the substrate of the plasmatic coagulation resulting in a mesh network which is essential for clot strength¹⁻³. Following trauma⁴⁻⁸ and perioperatively⁹⁻¹³ low fibrinogen levels have been found to be risk factors for exaggerated bleeding, transfusion needs and adverse outcome. Conversely, treatment with exogenous fibrinogen in critically bleeding patients with low fibrinogen levels has been shown to decrease transfusion needs highly significantly^{10,14-17}. Fibrinogen molecules are consumed for the developing clot whereas most other coagulation factors are reusable enzymes. Therefore fibrinogen is the first coagulation factor to become critically low during activation of coagulation and bleeding¹⁸⁻²⁰.

Consequently targeting fibrinogen as a central element in critical bleeding for early specific and goal-directed treatment appears reasonable. The optimal way of quickly detect critically low fibrinogen levels, however, is still a matter of debate. At certain centers laboratory based fibrinogen concentration measurements are the only way of detecting low fibrinogen levels. However, turnaround times of 60-90 min^{21,22} are too high in a critically bleeding patient, fibrinogen concentration measurements vary by up to 80% between laboratories²³ and may be influenced by the presence of artificial colloids^{24,25}. Hence thromboelastographic / thromboelastometric techniques are increasingly used to monitor coagulation quickly following trauma and during critical bleeding perioperatively^{4,5,10,12,15-17,26}. These monitoring techniques allow a comprehensive evaluation of the coagulation within 10-20 min with a specific focus on fibrinogen activity including the compromis-

ing effect of artificial colloids on coagulation^{25,27-30}. In the following a “low fibrinogen level” thus may be based on a low fibrinogen concentration measured in the central laboratory or a low fibrinogen activity based on thromboelastographic / thromboelastometric evaluation.

While some may argue that the evidence is still limited justifying the use of fibrinogen for the early goal-directed treatment of coagulopathy or critical bleeding³¹, we are going to present the emerging concepts in different fields of trauma and surgery including their limitation and safety aspects. We are also going to characterize the difference between the prospective randomized study vs. a pragmatic algorithm introduction approach in the complex and highly dynamic field of coagulopathy and critical bleeding^{32,33}.

Trauma

Trauma is a major health care issue resulting in the annual death of 5-8 million people worldwide²⁰. Bleeding in trauma is due to vascular damage but in approximately 30% of patients also due to coagulopathy of trauma^{20,34,35} which develops already at scene before any medical intervention³⁶ and which results in a several fold increased mortality^{34,35,37}. Besides hyperfibrinolysis^{20,38-40} a low fibrinogen level is the hallmark of the coagulopathy of trauma^{4-8,20,41}.

Early detection and characterization of coagulopathy following trauma is essential for early goal-directed treatment based on algorithms³³. Such algorithms go far beyond describing indications for the administration of fibrinogen. They rather define the type of coagulation monitoring used and the treatment of all significant

alterations of the coagulation system following trauma including targets for the interior milieu (pH, temperature, and hemoglobin level), the administration of tranexamic acid, prothrombin complex concentrate (PCC), factor XIII and labile allogeneic blood products such as red blood cells, plasma and platelets^{20,26,42}.

In addition, such point-of-care based algorithms also define when and how to monitor the success of the initiated treatment and how to capture the evolution of the case over time. This is particularly important in the highly dynamic period following trauma. Fibrinogen is a key element in such algorithms (table 1) but the success cannot be ascribed to one single measure. Nevertheless such algorithms are successful in improving coagulation tests⁴³ reducing the need for allogeneic blood transfusions^{15,16,44}, reducing the incidence of post-traumatic multi-organ failure, shortening length of hospital stay¹⁶ and they may improve survival^{15,17}. The recent study of Nardi et al.¹⁵ deserves special mentioning. They describe the institutional switch from a rigid 1:1 RBC:plasma transfusion scheme to an individualized thromboelastometry and fibrinogen / PCC based early treatment algorithm. With this algorithm they could decrease transfusions of allogeneic blood products highly significantly with a trend towards improved survival¹⁵.

At current time, we are unaware of a prospective randomized study assessing the effect of the administration of fibrinogen in trauma patients. However, there is a prospective randomized study in trauma patients comparing a 1:1:1 RBC:plasma:platelet transfusion scheme with a laboratory based individualized treatment algorithm⁴⁵. Although conceptualized as a feasibility trial Nascimento

at al. found a near significant two-fold reduction in mortality from 32% to 14% of patients treated according to an individualized treatment algorithm ⁴⁵.

The use of algorithms or the administration of fibrinogen has to our knowledge not resulted in any specific adverse effect in trauma. However, some wonder, whether the administration of exogenous fibrinogen would not result in exaggerated high postoperative / posttraumatic fibrinogen levels. Post-traumatic fibrinogen levels indeed increase significantly in the first week but this increase is not any higher in patients treated with exogenous fibrinogen during the initial treatment ⁴⁶.

Cardiac surgery

The success of a thromboelastometry, fibrinogen and PCC based coagulation algorithm was first shown in a single center study by Görlinger et al. ⁴⁷. They compared the traditional period before (2004) with the period after the introduction of their algorithm (2009) and found a significant reduction in the use allogeneic blood products by 20%, particularly RBC (-19%) and plasma (-94%) with a slight but significant increase in platelet transfusion (+29%); at the same time, however, the percentage of patients on dual platelet antagonists increased by >400%. Even more importantly, massive transfusion (-50%), surgical re-exploration (-47%) and thrombotic adverse events (-45%) decreased significantly ⁴⁷. A similar algorithm was then tested in a prospective randomized 2-center trial in patients with diffuse bleeding after cardiopulmonary bypass and heparin reversal against a traditional algorithm (table 1) ⁴⁸. Again, a highly significant reduction

on RBC transfusions (from 5 to 3) and plasma (from 5 to 0) and the use of recombinant factor VIIa (from 24% to 2%) was found while the use of fibrinogen concentrate was similar in both groups. Interestingly also the total costs of hemotherapy (factor concentrates, allogeneic blood products and coagulation test costs) were significantly reduced from 3'109 Euro to 1'658 Euro per patient. The most important findings, however, were a significantly reduced rate of adverse events (from 38% to 8%) and a reduction in 6 month mortality (from 20% to 4%) in patients treated by the thromboelastometry, fibrinogen and PCC based coagulation algorithm⁴⁸. Also in patients after aortic surgery with clinically relevant coagulopathic bleeding after cardiopulmonary bypass and heparin reversal, the effect of high dose fibrinogen administration based on thromboelastometry resulted in a highly significant reduction in total exposure to allogeneic blood products from 13 to 2 units per patient and a concomitant increase of the percentage of patients totally avoiding any blood products from 0% to 45%⁴⁹. In this study no trigger level for the administration of fibrinogen was used but a thromboelastometry test (FIBTEM) was done 20 min prior to the end of cardiopulmonary bypass. Based on this test and aiming for a FIBTEM MCF of 22 mm the individual dose of fibrinogen (median 8 g (IQR 6 – 9 g)) was calculated. In general complex cardiac surgery the same approach was followed in a recent prospective randomized double-blind study in 116 patients⁵⁰. Also in this study the percentage of patients avoiding all allogeneic blood products was significantly higher (67% vs. 45%) and the amounts of RBCs, plasma and platelet transfused as well as postoperative bleeding was significantly lower in the treatment arm⁵⁰.

There are also prospective randomized studies on the prophylactic use of fibrinogen in cardiac surgery. Karlsson et al. found in a small study of 20 patients that a preoperative 2 gr dose of fibrinogen (vs. placebo) in patients undergoing CABG surgery reduced postoperative blood loss and increased the Hb concentration at postoperative day one without effect on transfusion rate ⁵¹. A similar approach was chosen by Sadeghi et al. ⁵². In 60 patients undergoing CABG surgery they administered 1 gr of fibrinogen (vs. placebo) after anesthesia induction and found reduced postoperative bleeding. There was a trend towards fewer patients needing postoperative RBC transfusions but the difference was not statistically significant ⁵². Finally, Tanaka et al. studied 20 patients following valve surgery with signs of coagulopathic bleeding ⁵³. They compared a 4 g dose of fibrinogen vs. the administration of one unit of apheresis platelets. Patients in the fibrinogen group received fewer platelet transfusions and had a lower total donor exposure than patients in the platelet group ⁵³.

No safety issues have been detected in any of the above studies. In contrast, in two studies a significant reduction of major adverse events was found ^{47,48} and in one study even mortality was significantly reduced ⁴⁸. A minor issue is the question of whether the intraoperative administration of fibrinogen would result in exaggerated fibrinogen levels postoperatively. This has been specifically assessed and clearly shown that the postoperative fibrinogen levels similarly in patients with and without intraoperative fibrinogen administration ⁵⁴.

Until today it is unclear which algorithm element (thrombelastometry, fibrinogen or PCC administration) is most important for the success. Interestingly, already

the implementation of any type of thromboelastography and thromboelastometry coagulation algorithm results in a significant reduction in the use of allogeneic blood products in cardiac surgery⁵⁵⁻⁵⁷. Nevertheless the study by Weber et al., in which an algorithm using primarily fibrinogen and PCC rather than plasma and platelets resulting in improved outcome, indicates that factor concentrates may significantly contribute to the observed benefit in reduced major adverse events and improved survival⁴⁸. Another important aspect of such advanced coagulation algorithms is the repeated monitoring of the coagulation status of the patient. This allows early and specific intervention with a sufficient but moderate dose. The effect is then quickly verified and additional drugs may be given if necessary. In any case an overtreatment with consecutive hypercoagulability is avoided which may explain a reduction in thrombotic complications in some of the studies^{47,48}.

A study similar the one of Rahe-Meyer et al.⁴⁹ has recently been performed in aortic surgery as a prospective randomized multi-center study (<https://clinicaltrials.gov/ct2/show/NCT01475669>, accessed June 21, 2015). However, at current time the results have not been formally published.

Liver surgery and transplantation

Liver transplantation remains an operation with major blood loss and substantial need of allogeneic blood product transfusion, because blood coagulation is altered and often compromised in the recipient⁵⁸⁻⁶³. Since blood loss and blood product transfusions remain significant independent risk factors for mortality and

adverse outcome⁶⁴, ways of detecting and characterizing coagulation problems using thromboelastography / thromboelastometry have been sought since many years (table 1)^{61,62,65}. Thromboelastography / thromboelastometry, fibrinogen and PCC based algorithms were developed and resulted in conflicting results: Rollet et al. could not decrease their need for allogeneic blood products⁶⁰, while Leon-Justel et al. succeeded in reducing their transfusion needs highly significantly⁶⁶. Kirchner et al. have shown the safety of such a treatment concept. They searched prospectively for hepatic artery and portal vein thrombosis, pulmonary embolism, stroke and myocardial infarction and did not find a difference between the groups⁵⁸.

To our knowledge, there are no prospective randomized studies on the efficacy of fibrinogen in liver surgery and transplantation published.

Postpartum hemorrhage

Postpartum hemorrhage (PPH) is a major cause of maternal morbidity and mortality worldwide^{67,68} and the incidence is increasing in the Western countries^{69,70}. PPH has recently be defined as “*active bleeding of >1'000 ml within the 24 hours following birth that continues despite the use of initial measures including first-line uterotonic agents and uterine massage*”⁷¹. Pathophysiology of PPH is a combination of the following main factors: Uterine atony, trauma to the birth canal, placental problems (retained, abnormal implantation) and coagulopathy characterized by hyperfibrinolysis and low fibrinogen^{71,72}. For non-obstetricians it is important to understand that all these factors are present and intertwined, and as a

consequence, need to be addressed at the same time, ideally in a common algorithm between obstetricians, anesthesiologists and hematologists. Equally important is implementing a process to detect women with PPH early.

The first step in the treatment of PPH related coagulopathy is to stop hyperfibrinolysis with tranexamic acid. A first pivotal study was performed by Ducloy-Bouthors et al. in women with >800 ml of PPH ⁷³. Women randomized to receive 4 gr of tranexamic acid had less blood loss, less progression to severe PPH and received fewer RBC transfusions. Based on this and many other studies the World Health Organization recommends treating women with PPH with tranexamic acid

(http://apps.who.int/iris/bitstream/10665/75411/1/9789241548502_eng.pdf?ua=1, accessed June 21, 2015). The optimal dose of tranexamic acid is unknown at the current time but 1-2 gr may be adequate ⁷². The WOMEN trial in 15'000 women with PPH is using assessing a dose of 1 gr followed by 1 gr if bleeding continues ⁷⁴. This study is still recruiting (<https://clinicaltrials.gov/ct2/results?term=NCT00872469&Search=Search>, accessed June 21, 2015).

A low fibrinogen level was first detected as an independent risk factor for the development of severe PPH in 2007 ⁷⁵. A fibrinogen concentration < 2 g/l predicted severe PPH with a positive predictive value of 100% ⁷⁵. However, the association of a low fibrinogen level with PPH has been challenged recently ⁷⁶. Nevertheless fibrinogen treatment in severe PPH was at least as efficacious as the administration of cryoprecipitate ⁷⁷.

Also in PPH, thromboelastography / thromboelastometry guided algorithms are feasible, efficient and successful. Such an algorithm has been published recently (table 1)¹⁰. By the implementation of their algorithm Mallaiah et al. succeeded highly significantly in decreasing the total number of allogeneic blood products and major adverse outcomes in women with at least 1'500 ml of blood loss after delivery¹⁰.

At current time there is only one prospective randomized study addressing fibrinogen application in patients with PPH⁷⁸. Wikkelse et al. randomized 249 patients with PPH to receiving a pre-emptive dose of 2 gr fibrinogen or placebo. The fibrinogen concentration before treatment was 4.5 g/l in both groups which is normal for pregnant women^{76,79}. Since largely women without coagulopathy were included, transfusion outcome was identical in both groups⁷⁸. A clinically more relevant prospective randomized study is underway⁸⁰ in which women with severe PPH and signs of (low) fibrinogen related coagulopathy in thromboelastometry after treatment with tranexamic acid (1 gr) will be randomized to receive fibrinogen (4-8 gr) or placebo⁸⁰. Despite the formal lack of high-quality proof of efficacy of fibrinogen treatment in severe PPH in women with low fibrinogen levels and / or signs of fibrinogen related coagulopathy, fibrinogen is recommended by the PPH-Consensus Group in Europe^{81,82}.

Risk

Safety issues and specific benefits in the various surgical settings and following trauma have been presented in the respective chapters above. In addition, pre-

clinical safety animal data was published ⁸³ and also extensive post-marketing pharmacovigilance data was analyzed recently ⁸⁴. Over a period of 27 years and over 2'611'294 g of fibrinogen, representing 652'824 patients across a wide range of clinical settings 383 adverse drug reactions were reported ⁸⁴. Anaphylaxis and severe allergic reactions were reported in 20 cases. Five fatal outcomes were described but only one case of death was associated with the anaphylactic reaction. There were 28 cases of thromboembolic complications of which 16 were described in the setting of acquired and 12 in congenital fibrinogen deficiency. In 13 of these 16 cases of acquired fibrinogen deficiency, patients received other pro-thrombotic products in complex clinical situations. Finally, there were 21 cases of suspected viral transmission. With the exception of one case with insufficient data, a causal relationship was considered unlikely, because polymerase chain reaction tests were non-reactive (negative) for the concerned batches and other ways of transmission were probable. Such pharmacovigilance data may be criticized for incomplete reporting. However, also the reporting of adverse events due to allogeneic blood transfusion is known to be largely incomplete. In a study on pulmonary adverse effects of allogeneic blood products none of 24 cases of expert adjudicated transfusion related lung injury or transfusion associated circulatory overload was reported to the blood bank ⁸⁵. Therefore the incidence of potential side effects cannot be assessed by such analyses. Safety of fibrinogen or thromboelastometry / thromboelastography, fibrinogen and PCC based algorithms can only be assessed in direct comparisons as described in detail in the different surgery chapters above.

Outlook

Thromboelastometry / thromboelastography, fibrinogen and PCC based algorithms are highly promising concepts enabling quick and specific treatment of coagulation problems perioperatively and after trauma. However, some argue that these concepts had never been tested prospectively in a randomized, double-blind multi-center study and thus would not be valid. It is certainly crucial to assess efficacy and safety of these concepts. However, the introduction of these concepts is highly demanding and requires a tremendous educational effort to familiarize all health care workers with the necessary knowledge including the skills of how to run thromboelastometry / thromboelastography tests. When achieved, an equally demanding continuous educational effort aiming at maintaining knowledge and skills and a long learning curve start until this concept works at its best. Once all this is achieved, switching back and forth between a traditional allogeneic blood product based treatment concept and a thromboelastometry / thromboelastography and coagulation factor based algorithm is utterly impossible.

Therefore comparing periods before and after introduction (and learning curve) of algorithms is pragmatically more appropriate. An important topic for future studies is the comparison of different intervention thresholds of specific algorithms. One example might be, comparing a maximum clot firmness value in the FIBTEM of 7 mm vs. 12 mm in trauma patients. Such types of studies could be performed as a prospective randomized multi-center study.

Conclusions

Fibrinogen has a central role in coagulation and low fibrinogen levels are associated with exaggerated bleeding and transfusion needs. Thromboelastography / thromboelastometry, fibrinogen and PCC based algorithms are capable of decreasing the need for allogeneic transfusions and improving clinical outcome with lower mortality and morbidity in certain situations. This has clearly been shown in cardiac surgery and has a high evidence level in trauma. Interestingly, in liver transplantation the scientific evidence is not so clear, although thromboelastography / thromboelastometry based treatment algorithms have been introduced over 30 years ago in this very context. In postpartum hemorrhage evidence is emerging that the above mentioned concepts are efficacious as well. Therefore future research is warranted, which, however, should not prevent us from introducing these expedient point-of-care based algorithms clinically now.

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Conflict-of-interest statement (past 5 years): Donat R. Spahn

Dr. Spahn's academic department is receiving grant support from the Swiss National Science Foundation, Berne, Switzerland, the Ministry of Health (Gesundheitsdirektion) of the Canton of Zurich, Switzerland for Highly Specialized Medicine, the Swiss Society of Anesthesiology and Reanimation (SGAR), Berne, Switzerland, the Swiss Foundation for Anesthesia Research, Zurich, Switzerland, Bundesprogramm Chancengleichheit, Berne, Switzerland, CSL Behring, Berne, Switzerland, Vifor SA, Villars-sur-Glâne, Switzerland.

Dr. Spahn was the chairman of the ABC Faculty and is the co-chairman of the ABC-Trauma Faculty, which both are managed by Physicians World Europe GmbH, Mannheim, Germany and sponsored by unrestricted educational grants from Novo Nordisk Health Care AG, Zurich, Switzerland, CSL Behring GmbH, Marburg, Germany and LFB Biomédicaments, Courtaboeuf Cedex, France.

In the past 5 years, Dr. Spahn has received honoraria or travel support for consulting or lecturing from the following companies: Abbott AG, Baar, Switzerland, AMGEN GmbH, Munich, Germany, AstraZeneca AG, Zug, Switzerland, Bayer (Schweiz) AG, Zürich, Switzerland, Baxter AG, Volketswil, Switzerland, Baxter S.p.A., Roma, Italy, B. Braun Melsungen AG, Melsungen, Germany, Boehringer Ingelheim (Schweiz) GmbH, Basel, Switzerland, Bristol-Myers-Squibb, Rueil-Malmaison Cedex, France and Baar, Switzerland, CSL Behring GmbH, Hattersheim am Main, Germany and Berne, Switzerland, Curacyte AG, Munich, Germany, Daiichi Sankyo (Schweiz) AG, Thalwil, Switzerland, Ethicon Biosurgery, Sommerville, New Jersey, USA, Fresenius SE, Bad Homburg v.d.H., Germany, Galenica AG, Bern, Switzerland (including Vifor SA, Villars-sur-Glâne, Switzerland), GlaxoSmithKline GmbH & Co. KG, Hamburg, Germany, Janssen-Cilag AG, Baar, Switzerland, Janssen-Cilag EMEA, Beerse, Belgium, Merck Sharp & Dohme AG, Luzern, Switzerland, Novo Nordisk A/S, Bagsvård, Denmark, Octapharma AG, Lachen, Switzerland, Organon AG, Pfäffikon/SZ, Switzerland, Oxygen Biotherapeutics, Costa Mesa, CA, Photonics Healthcare B.V., Utrecht, Netherlands, ratiopharm Arzneimittel Vertriebs-GmbH, Vienna, Austria,

Roche Diagnostics International Ltd, Reinach, Switzerland, Roche Pharma (Schweiz) AG, Reinach, Switzerland, Schering-Plough International, Inc., Kenilworth, New Jersey, USA, Tem International GmbH, Munich, Germany, Verum Diagnostica GmbH, Munich, Germany, Vifor Pharma Deutschland GmbH, Munich, Germany, Vifor Pharma Österreich GmbH, Vienna, Austria, Vifor (International) AG, St. Gallen, Switzerland.

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No conflicts of interest to be declared

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No conflicts of interest to be declared

Table 1: Trigger values for the administration of fibrinogen concentrate in different clinical settings. Please note that the algorithms in the various studies were not limited to the administration of fibrinogen. They also contained information on the monitoring of coagulation and the indication for other coagulation products including (in most) the use of allogeneic blood products (RBC, plasma and platelets).

Clinical setting	Trigger	Fibrinogen dose	Reference
Trauma	FIBTEM MCF \leq 7 mm	2-4 g	Nardi et al. ¹⁵
Trauma	FIBTEM MCF \leq 10 mm	2-4 g	Schöchl et al. ¹⁷
Trauma	FIBTEM MCF $<$ 7 mm	2-4 g	Theusinger et al. ²⁶
Trauma	Fibrinogen $<$ 1.5-2 g/L	3-4 g	Spahn et al. ²⁰
Trauma	Fibrinogen $<$ 1.5-2 g/L	2-4 g	Nienaber et al. ⁴⁴
Trauma	FIBTEM A10 $<$ 7 mm	3 – 8 g	Schöchl et al. ⁴⁶
Cardiac surgery	FIBTEM A10 \leq 10 mm (early after CPB) or FIBTEM A10 $<$ 15 mm (late ongoing bleeding)	25 – 50 (75) mg/kg	Görlinger et al. ⁴⁷
Cardiac surgery	FIBTEM A10 \leq 10 mm (early after CPB) or FIBTEM A10 $<$ 15 mm (late ongoing bleeding)	25 – 50 (75) mg/kg	Weber et al. ⁴⁸
Cardiac surgery (CABG)	Prophylactic preoperatively	2 g	Karlsson et al. ⁵¹
Cardiac surgery (CABG)	Prophylactic preoperatively	1 g	Sadeghi et al. ⁵²
Cardiac surgery (valve replacement)	Moderate bleeding	4 g fibrinogen	Tanaka et al. ⁵³

Cardiac surgery (pediatric)	FIBTEM A10 \leq 5 mm	20 ml/kg FFP	Nakayama et al. ⁵⁶
Liver transplantation	FIBTEM MCF \leq 6 mm	n/a	Kirchner et al. ⁵⁸
Liver transplantation	FIBTEM MCF \leq 6 mm or Fibrinogen $<$ 1 g/L	50 mg/kg	Roullet et al. ⁶⁰
Obstetric	Fibrinogen $<$ 2 g/L	n/a	Abdul-Kadir et al. ⁷¹
Obstetric	Fibrinogen \leq 2 g/L	4 g	Ahmed et al. ⁷⁷
Obstetric	Severe PPH with blood loss of $>$ 1 liter	2 g	Wikkelso et al. ⁷⁸
Obstetric	Fibrinogen $<$ 1.5 g/L	2 – 4 g	Girard et al. ⁸¹
Obstetric	FIBTEM A5 $<$ 7 mm or Fibrinogen \leq 1.5 g/L	3 g initial dose	Mallaiah et al. ¹⁰
General	Fibrinogen $<$ 1.5-2 g/L	25 – 50 mg/kg	Kozek-Langenecker et al. ⁴²
General pediatric surgery	FIBTEM MCF $<$ 7 mm or Fibrinogen $<$ 1.5-2 g/L	30 – 50 mg/kg	Kozek-Langenecker et al. ⁴²
General	Fibrinogen \leq 2 g/L	1-2 g	Fenger-Eriksen et al. ¹⁴