Human Fibrinogen Concentrate (RiaSTAP and Fibryga)

Number: 0792

Policy

Notes: Precertification Required.

Precertification of human fibrinogen concentrate is required of all Aetna participating providers and members in applicable plan designs. For precertification, call Aetna's Special Case Precert Unit at (855) 888-9046.

Aetna considers human fibrinogen concentrate (RiaSTAP and Fibryga) medically necessary for the treatment of acute bleeding episodes in persons with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.

Aetna considers continuation of human fibrinogen concentrate therapy medically necessary for persons who meet all initial medical necessity criteria.

Aetna considers human fibrinogen concentrate experimental and investigational for the treatment of the following indications (not an all-inclusive list) because its effectiveness for these indications has not been established.

Policy History

Last Review
01/13/2021
Effective: 08/21/2009
Next Review: 01/14/2021

Definitions

Additional Information

Clinical Policy Bulletin
Notes
• Acquired hypofibrinogenemia (acquired fibrinogen deficiency)
• Bleeding associated with aortic reconstruction and deep hypothermic circulatory arrest
• Dysfibrinogenemia
• Obstetric hemorrhage including post-partum hemorrhage in persons without congenital fibrinogen deficiency
• Peri-operative (pre-operative, intra-operative, and post-operative) hemorrhage in persons without congenital fibrinogen deficiency
• Trauma-associated hemorrhage in persons without congenital fibrinogen deficiency.

**Dosing Recommendations**

When the fibrinogen level is known:

**RiaSTAP**:  
Target fibrinogen level (mg/dl) – measured fibrinogen level (mg/dL)  
1.7 (mg/dL per mg/kg body weight)

**Fibryga**:  
Target fibrinogen level (mg/dl) – measured fibrinogen level (mg/dL)  
1.8 (mg/dL per mg/kg body weight)

When the fibrinogen level is not known: 70mg/kg body weight for RiaSTAP and Fibryga.

Background

U.S. Food and Drug Administration (FDA)-Approved Indications

- Fibryga is indicated in adults and adolescents with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia, for the treatment of acute bleeding episodes.
- Fibryga is not indicated for dysfibrinogenemia.
- RiaSTAP is indicated in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia, for the treatment of acute bleeding episodes.

Fibrinogen, also known as Factor I, is synthesized in the liver and circulates in the blood with a normal plasma concentration of 250 to 400 mg/dL (2.5 to 4.0 g/L). It plays an important role in clotting of the blood. Diminished concentrations of fibrinogen limit the body's ability to form a clot. Congenital fibrinogen deficiency (CFD) is a rare, potentially life-threatening bleeding disorder. Individuals with CFD are unable to make sufficient amounts of fibrinogen. There are 2 types of hereditary fibrinogen disorders: (i) type I deficiencies (quantitative defects) such as afibrinogenemia and hypofibrinogenemia – with low or unmeasurable levels of immunoreactive protein; and (ii) type II deficiencies (qualitative defects) such as dysfibrinogenemia and hypodysfibrinogenemia – with normal or altered antigen levels associated with reduced coagulant activity. While dysfibrinogenemias are in most cases autosomal dominant disorders, type I deficiencies are generally inherited as autosomal recessive traits. Patients affected by congenital afibrinogenemia or severe hypofibrinogenemia may experience bleeding manifestations varying from mild to severe (Asselta et al, 2006).
Congenital fibrinogen deficiency affects an estimated 1 person per 1,000,000, with an estimated prevalence of 150 to 300 people in the United States. It is usually diagnosed at birth when newborns bleed from their umbilical cord site. Al-Mondhiry and Ehmann (1994) noted that diagnosis of congenital afibrinogenemia is usually established by demonstrating trace or absent immunoreactive fibrinogen in the plasma. Patients with hypofibrinogenemia are usually asymptomatic, unless exposed to trauma. Furthermore, Berube (2009) stated that disorders involving fibrinogen are rare but should be considered in any patient with a history of hemorrhage or thrombosis in whom most of the common causes have been ruled out. Blood coagulation tests such as prothrombin time (PT) that is often reported as the International Normalized Ratio (INR), activated partial thromboplastin time (APTT), and thrombin clotting time (TCT) or thrombin time (TT) all require the production of a fibrin clot as an end point, and will be abnormally prolonged in patients with hypofibrinogenemia or afibrinogenemia. Abnormal laboratory results in patients with afibrinogenemia will correct completely following administration of normal plasma or purified fibrinogen. Accordingly, these tests are sensitive for the presence of a fibrinogen disorder, but lack specificity.

Verhovsek and colleagues (2008) provided examples of methods and findings for commonly used laboratory tests for afibrinogenemia and hypofibrinogenemia:

Table: Methods and findings for afibrinogenemia and hypofibrinogenemia

<table>
<thead>
<tr>
<th>Afibrinogenemia</th>
<th>Hypofibrinogenemia</th>
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<table>
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<tr>
<th>Clinical Problem</th>
<th>Trauma-related intracranial hemorrhage at age 40. Subsequent trauma-related and surgery-related bleeding</th>
<th>Recurrent pregnancy loss from placental abruptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (normal: 11 to 14 sec)</td>
<td>No clot detected</td>
<td>14.2</td>
</tr>
<tr>
<td>INR (normal: 0.8 to 1.2)</td>
<td>No clot detected</td>
<td>1.2</td>
</tr>
<tr>
<td>APTT (normal: 22 to 35 sec)</td>
<td>No clot detected</td>
<td>32</td>
</tr>
<tr>
<td>TCT or TT (normal: 20 - 30 sec)</td>
<td>No clot detected</td>
<td>46</td>
</tr>
<tr>
<td>Reptilase time (normal: 15 - 27 sec)</td>
<td>&gt; 60</td>
<td>33</td>
</tr>
<tr>
<td>Clottable fibrinogen (normal: 160 - 420 mg/dL)</td>
<td>&lt; 20</td>
<td>60</td>
</tr>
<tr>
<td>Fibrinogen antigen (normal: 160 - 420 mg/dL)</td>
<td>&lt; 10</td>
<td>60</td>
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Individuals with CFD are advised to curtail physical activities because of risk of bleeding from minor trauma. If bleeding occurs in the brain or other organs and is left untreated, it may lead to blood loss, organ damage and death. The standard approach for replacement of fibrinogen in patients with CFD is cryoprecipitate; but more recently, a pasteurized human fibrinogen concentrate has become available.

In an open, multi-center, non-controlled, retrospective study, Kreuz and co-workers (2005) examined the effectiveness and tolerability of a pasteurized human fibrinogen concentrate in patients with CFD. Hemostatic efficacy was assessed by laboratory investigation as well as clinical observation. A total of 12 patients (afibrinogenemia, n = 8; hypofibrinogenemia, n = 3; dysfibrinogenemia combined with hypofibrinogenemia, n = 1) were included in the study. Fibrinogen substitution was indicated for one of the following reasons: (i) to stop an ongoing bleed; (ii) as prophylaxis before surgery; or (iii) for routine prophylaxis to prevent spontaneous bleeding. A total of 151 fibrinogen infusions were recorded. The median single dosage was 63.5 mg/kg body weight of the drug for bleeding events or surgery and 76.9 mg/kg for prophylaxis. The median total dose per event for bleeding events or surgery was 105.6 mg/kg. Fibrinogen was administered in 26 bleeding episodes; 11 surgical operations; and 89 prophylactic infusions, of which 86 were received by 1 patient. The median response (n = 8) was 1.5 mg/dL per substituted mg of fibrinogen per kg body weight (0.8 to 2.3). The median in vivo recovery (n = 8) was 59.8 % (32.5 to 93.9). Clinical efficacy was very good in all events with the exception of one surgical procedure, where it was moderate. No intercurrent bleeding
occurred during prophylaxis. All but 1 infusion was well-tolerated; the patient, who was administered 86 prophylactic infusions, experienced an anaphylactic reaction after the 56th infusion. In addition, one patient developed deep vein thrombosis and nonfatal pulmonary embolism with treatment for osteosynthesis after collum femoris fracture. Fibrinogen substitution could not be excluded as a contributing factor in this high-risk patient. The authors concluded that substitution with pasteurized human fibrinogen concentrate in patients with CFD is efficient and generally well tolerated.

A review by de Moerloose and colleagues (2013) stated that "Depending on the country of residence, patients receive fresh frozen plasma (FFP), cryoprecipitate, or fibrinogen concentrates. Fibrinogen concentrate preparation includes safety steps for inactivation/removal of viruses, so concentrates are safer than cryoprecipitate or FFP".

Bevan (2009) stated that congenital abnormalities of fibrinogen are rare disorders classified as quantitative (afibrinogenemia and hypofibrinogenemia) or qualitative types (dysfibrinogenemia and hypodysfibrinogenemia). Fibrinogen is essential to hemostasis as the substrate for fibrin clot formation and also acts in primary hemostasis as a key ligand in platelet aggregation. Quantitative deficiency of fibrinogen can result in severe bleeding, or arterial and venous thromboembolism, and poor wound healing. Dysfibrinogenemia is characterized by functional abnormalities of fibrinogen, which may be asymptomatic (in 50% of cases), or cause bleeding (25%) or thrombosis (25%). Replacement of the deficient or abnormal fibrinogen with frozen plasma, cryoprecipitate, or fibrinogen concentrate has been found to be effective in practice in treating hemostatic complications of these disorders. Although cryoprecipitate is the most commonly used replacement material, pathogen-reduced fibrinogen concentrates have several advantages, most importantly a lower potential risk of viral transmission and standardized fibrinogen content allowing accurate dosing.
They also avoid transfusing unwanted clotting factors, platelet micro-particles and immunoglobulins, and can be administered rapidly without thawing. The use of fibrinogen concentrate to treat congenital fibrinogen disorders is strongly supported in principle and increasingly by practical experience and evidence.

Levy et al (2012) noted that there currently is a lack of awareness among physicians regarding the significance of fibrinogen during acute bleeding and, at many medical centers, fibrinogen is not monitored routinely during treatment. These investigators reviewed current studies that demonstrate the importance of considering fibrinogen replacement during the treatment of acquired bleeding across clinical settings. If depleted, the supplementation of fibrinogen is key for the rescue and maintenance of hemostatic function; however, the threshold at which such intervention should be triggered is currently poorly defined. Although traditionally performed via administration of fresh frozen plasma or cryoprecipitate, the use of lyophilized fibrinogen (concentrate) is becoming more prevalent in some countries. Recent reports relating to the efficacy of fibrinogen concentrate suggest that it is a viable alternative to traditional hemostatic approaches, which should be considered.

Levy et al (2014) stated that 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
successfuly used as hemostatic therapy in a range of clinical settings, including cardiovascular surgery, post-partum hemorrhage, and trauma. Results showed 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.

Elliott and Aledort (2013) stated that fibrinogen plays a key role in the coagulation process, and therefore maintaining adequate quantities of fibrinogen is an essential step in achieving satisfactory hemostasis in patients with acquired hypofibrinogenemia. Potential options for treating acquired hypofibrinogenemia in patients with uncontrolled bleeding include the use of cryoprecipitate or fibrinogen replacement therapy. These investigators provided a brief overview of the hemostatic process and the methods for assessing coagulopathy and discussed the safety and effectiveness of cryoprecipitate and fibrinogen concentrate in restoring fibrinogen levels, achieving hemostasis and reducing transfusion requirements in different patient populations requiring rapid hemostasis. Other issues relevant to the clinical use of these agents in restoring hemostasis, including variations in product composition, preparation time and cost, were also examined. The authors also noted that “Although it has been shown that fibrinogen concentrate offers a more rigorous viral inactivation process and has the potential for more rapid and predictable dosing than cryoprecipitate, there remains a clear need for prospective, randomized studies to establish the precise role of fibrinogen concentrate in achieving hemostasis, reducing transfusion requirements, and, more importantly, improving hard clinical outcomes such as morbidity and mortality in patients with acquired coagulopathies. Moreover, these studies need to further elucidate the threshold for fibrinogen concentrate treatment and the most appropriate dosages in different patient
populations requiring rapid hemostasis. Finally, these prospective, randomized studies need to confirm the optimal timing of intervention with fibrinogen concentrate”.

An UpToDate review on "Disorders of fibrinogen" (Berube, 2014) states that "Sources of fibrinogen for clinical use include cryoprecipitate, fresh frozen plasma (FFP), and fibrinogen concentrates; the latter, if available, is the preferred product".

Fenger-Eriksen and colleagues (2008) noted that patients experiencing massive hemorrhage are at high risk of developing coagulopathy through loss, consumption, and dilution of coagulation factors and platelets. It has been reported that plasma fibrinogen concentrations may reach a critical low level relatively early during bleeding, calling for replacement fibrinogen therapy. These researchers audited the effects of fibrinogen concentrate therapy on laboratory and clinical outcome in patients with massive hemorrhage. They identified 43 patients over the previous 2 years to whom a fibrinogen concentrate had been administered as treatment for hypofibrinogenemia during serious hemorrhage. Platelet count, plasma fibrinogen, activated partial thromboplastin time (APTT), prothrombin time (PT), D-dimer, and volume of blood lost were obtained from medical and laboratory records. Numbers of units of red blood cells (RBC), fresh frozen plasma (FFP), and pooled platelet concentrates were recorded before and after fibrinogen substitution. A significant increase in plasma fibrinogen concentration was observed after fibrinogen concentrate therapy. Platelet counts and fibrin D-dimer values remained unchanged, whereas the APTT and PT improved significantly. Requirements for RBC, FFP, and platelets were significantly reduced; blood loss decreased significantly. The authors concluded that fibrinogen substitution therapy with a fibrinogen concentrate generally improved global laboratory coagulation results; and as supplementary intervention, appeared to reduce the requirements for RBC, FFP, and platelet substitution in this patient cohort.
On January 16, 2009, the Food and Drug Administration (FDA) licensed RiaSTAP (human fibrinogen concentrate) for the treatment of acute bleeding in patients with CFD. RiaSTAP is a purified fibrinogen concentrate made from the plasma of healthy human donors that undergoes virus inactivation and removal for safety assurance. It was developed under the FDA’s accelerated approval regulations for orphan drugs. There have been more than 1,000,000 units sold worldwide (outside the United States, RiaSTAP is marketed under the trade name of Haemocomplettan). RiaSTAP is indicated for the treatment of acute bleeding episodes in patients with CFD including afibrinogenemia and hypofibrinogenemia; it is not indicated for dysfibrinogenemia.

The licensing of RiaSTAP was based on a phase II, prospective, open-label, safety and pharmacokinetic study using maximum clot firmness (MCF) as a surrogate endpoint for hemostatic efficacy. A total of 15 patients with afibrinogenemia achieved the target level of fibrinogen expected to prevent bleeding after they received 70 mg/kg body weight of the drug. In addition, plasma from 14 of the 15 patients showed a highly significant (p < 0.0001) mean improvement in MCF from baseline to 1 hour post-infusion following RiaSTAP treatment. The most serious adverse reactions that have been reported in clinical studies or through post-marketing surveillance following RiaSTAP treatment are allergic-anaphylactic reactions and thromboembolic episodes, including myocardial infarction, pulmonary embolism, deep vein thrombosis and arterial thrombosis. The most common adverse reactions that have been reported after RiaSTAP therapy are allergic reactions and generalized reactions such as chills, fever, headache, as well as nausea and vomiting.

In addition to the treatment of CFD, human fibrinogen concentrate has also been employed in the management of other hypofibrinogenemic conditions such as acquired hypofibrinogenemia and post-operative hemorrhage. Clinical
data for the use of human fibrinogen concentrate in acquired hypofibrinogenenic states are scarce. Weinkove and Rangarajan (2008) evaluated the safety and effectiveness of Haemocomplettan in patients with acquired hypofibrinogenemia. Demographical and pre-treatment clinical data of patients treated with Haemocomplettan were retrospectively reviewed. Pre- and post-treatment fibrinogen levels, transfusion requirements, outcomes and adverse reactions were recorded. A total of 30 adult patients who received Haemocomplettan for acquired hypofibrinogenemia (plasma fibrinogen concentration less than 1.5 g/L) were included in the study. Causes of hypofibrinogenemia included placental abruption, disseminated intravascular coagulation as a result of massive blood loss and transfusion, liver failure and cardiac surgery. Following a median dose of 4 g Haemocomplettan, median Clauss fibrinogen level rose from 0.65 to 2.01 g/L, with a median fibrinogen increment of 0.25 g/L per 1 g fibrinogen concentrate administered. It was reported that 46 % of patients stopped bleeding with blood components and Haemocomplettan alone, and a further 29 % stopped bleeding with surgical or endoscopic intervention. Inpatient mortality was 40 %; no venous thromboses were observed. A total of 4 patients with massive perioperative hemorrhage and hypotension (including 3 post-cardiothoracic surgery) had arterial ischemic events, however, none of which was attributable to over-replacement of fibrinogen. The cost of Haemocomplettan was comparable with that of cryo­precipitate. The authors concluded that purified human fibrinogen concentrate appears effective in the management of acquired hypofibrinogenemia.

Bleeding diathesis after aortic valve operation and ascending aorta replacement (AV-AA) is usually managed with FFP and platelet concentrates. In a pilot study, Rahe-Meyer et al (2009) compared hemostatic effects of conventional transfusion management and FIBTEM (thromboelastometry test)-guided fibrinogen concentrate administration. A blood­product transfusion algorithm was developed with
retrospective data from 42 elective patients (group A). Two
units of platelet concentrate were transfused after
cardiopulmonary bypass, followed by 4 units of FFP if bleeding
persisted, if platelet count was less than or equal to 100 x 10
(3) microl(-1) when removing the aortic clamp, and vice versa
if platelet count was greater than 100 x 10(3) microl(-1). The
trigger for each therapy step was greater than or equal to 60 g
blood absorbed from the mediastinal wound area by dry swabs
in 5 mins. Assignment to two prospective groups was neither
randomized nor blinded; group B (n = 5) was treated according
to the algorithm, group C (n = 10) received
Haemocomplettan/RiaSTAP before the algorithm-based
therapy. A mean of 5.7 (0.7) g fibrinogen concentrate
decreased blood loss to below the transfusion trigger level in
all group C patients. Group C had reduced transfusion [mean
of 0.7 (range of 0 to 4) units versus 8.5 (5.3) units in group A
and 8.2 (2.3) units in group B] and reduced post-operative
bleeding [366 (199) ml versus 793 (560) ml in group A and 716
(219) ml in group B]. The authors concluded that in this pilot
study, FIBTEM-guided fibrinogen concentrate administration
was associated with reduced transfusion requirements and 24­
hr post-operative bleeding in patients undergoing AV-AA.

In a prospective randomised pilot study, Karlsson et al (2009)
examined if prophylactic infusion of fibrinogen concentrate
may reduce post-operative bleeding. A total of 20 elective
coronary artery bypass graft (CABG) patients with pre­
operative plasma fibrinogen levels of less than 3.8 g/L were
included in this study. Patients were randomized to receive an
infusion of 2 g fibrinogen concentrate (FIB group) or no
infusion before surgery (control group). Primary endpoint was
safety with clinical adverse events and graft occlusion
assessed by multi-slice computed tomography. Pre-defined
secondary endpoints were post-operative blood loss, blood
transfusions, hemoglobin levels 24 hrs after surgery, and
global hemostasis assessed with thromboelastometry, 2 and
24 hrs after surgery. Infusion of 2 g fibrinogen concentrate
increased plasma levels of fibrinogen by 0.6 +/- 0.2 g/L. There
were no clinically detectable adverse events of fibrinogen infusion. Computed tomography revealed 1 sub-clinical vein graft occlusion in the FIB group. Fibrinogen concentrate infusion reduced post-operative blood loss by 32 % (565 +/- 150 versus 830 +/- 268 ml/12 hrs, p = 0.010). Hemoglobin concentration was significantly higher 24 hrs after surgery in the FIB group (110 +/- 12 versus 98 +/- 8 g/L, p = 0.018). Prophylactic fibrinogen concentrate infusion did not influence global post-operative hemostasis as assessed by thromboelastometry. The authors concluded that in this pilot study pre-operative fibrinogen concentrate infusion reduced bleeding after CABG without evidence of post-operative hypercoagulability. They stated that larger studies are needed to ensure safety and confirm efficacy of prophylactic fibrinogen treatment in cardiac surgery.

Mercier and Bonnet (2010) reviewed the optimal use of blood products and clarified the indications for prohemostatic drugs in obstetric hemorrhage. The literature emphasizes the usefulness of transfusing packed red blood cells, fresh frozen plasma and platelets earlier and in defined ratios to prevent dilutional coagulopathy during obstetric hemorrhage. It seems reasonable to use blood products for transfusion earlier and in a 1:1 fresh frozen plasma: red blood cell ratio during acute obstetric hemorrhage; however, this analysis is mainly based on trauma literature. Fibrinogen concentrate should be added if the fibrinogen plasma level remains below 1.0 g/L and perhaps even as soon as it falls below 1.5 to 2.0 g/L; the addition of tranexamic acid (1 g) is cheap, likely to be useful and appears safe. Data on the proactive administration of platelets are insufficient to recommend this practice routinely. Presently, recombinant factor VIIa (60 to 90 microg/kg) is advocated only after failure of other conventional therapies, including embolization or conservative surgery, but prior to obstetric hysterectomy. The authors stated that prospective randomized controlled trials are highly desirable to examine the use of clotting factors and other prohemostatic drugs for the management of obstetric hemorrhage.
Wikkelsoe and colleagues (2012) described the protocol of a randomized controlled trial (FIB-PPH trial) to examine the effects of fibrinogen concentrate as initial treatment for post-partum hemorrhage (PPH). In this placebo-controlled, double-blind, multi-center trial, parturients with primary PPH are eligible following vaginal delivery in case of manual removal of placenta (blood loss [greater than or equal to] 500 ml) or manual exploration of the uterus after the birth of placenta (blood loss [greater than or equal to] 1,000 ml). Caesarean sections are also eligible in case of peri-operative blood loss [greater than or equal to] 1,000 ml. The exclusion criteria are known inherited hemostatic deficiencies, pre-partum treatment with anti-thrombotics, pre-pregnancy weight less than 45 kg or refusal to receive blood transfusion. Following informed consent, patients will be randomly allocated to either early treatment with 2 g fibrinogen concentrate or 100 ml isotonic saline (placebo). Hemostatic monitoring with standard laboratory coagulation tests and thrombo-elastography (TEG, functional fibrinogen and RapidTEG) is performed during the initial 24 hours. Primary outcome is the need for blood transfusion. To examine a 33 % reduction in the need for blood transfusion a total of 245 patients will be included. Four university affiliated public tertiary care hospitals will include patients during a 2-year period. Adverse events including thrombosis are assessed in accordance with International Conference on Harmonisation (ICH) - good clinical practice (GCP). The authors concluded that a widespread belief in the benefits of early fibrinogen substitution in cases of PPH has led to increased off-label use. The FIB-PPH trial is investigator-initiated and aims to provide an evidence-based platform for the recommendations of the early use of fibrinogen concentrate in PPH.

Schochl et al (2010) reported the treatment of major trauma using mainly coagulation factor concentrates. This retrospective analysis included trauma patients who received greater than or equal to 5 units of red blood cell concentrate within 24 hours. Coagulation management was guided by
thromboelastometry (ROTEM). Fibrinogen concentrate was given as first-line hemostatic therapy when maximum clot firmness (MCF) measured by FibTEM (fibrin-based test) was less than 10 mm. Prothrombin complex concentrate (PCC) was given in case of recent coumarin intake or clotting time measured by extrinsic activation test (EXTEM) greater than 1.5 times normal. Lack of improvement in EXTEM MCF after fibrinogen concentrate administration was an indication for platelet concentrate. The observed mortality was compared with the mortality predicted by the trauma injury severity score (TRISS) and by the revised injury severity classification (RISC) score. Of 131 patients included, 128 received fibrinogen concentrate as first-line therapy, 98 additionally received PCC, while 3 patients with recent coumarin intake received only PCC. Twelve patients received FFP and 29 received platelet concentrate. The observed mortality was 24.4 %, lower than the TRISS mortality of 33.7 % (p = 0.032) and the RISC mortality of 28.7 % (p > 0.05). After excluding 17 patients with traumatic brain injury, the difference in mortality was 14 % observed versus 27.8 % predicted by TRISS (p = 0.0018) and 24.3 % predicted by RISC (p = 0.014). The authors concluded that ROTEM-guided hemostatic therapy, with fibrinogen concentrate as first-line hemostatic therapy and additional PCC, was goal-directed and fast. A favorable survival rate was observed. Moreover, they stated that prospective, randomized trials to investigate this therapeutic alternative further appear warranted.

Wafaisade et al (2012) examined if blood component transfusion and hemostatic drug administration during acute trauma care have changed in daily practice during the recent years. The multi-center trauma registry of the German Society for Trauma was retrospectively analyzed for primarily admitted patients older than 16 years with an Injury Severity Score greater than or equal to 16 who had received at least 5 red blood cell (RBC) units between emergency room arrival and intensive care unit admission. Administration of FFP and platelet units has been documented since 2002, and use of
hemostatic drugs since 2005. From 2002 to 2009 (n = 2,813), the FFP:RBC ratio increased from 0.65 to 0.75 (p = 0.02) and the platelet:RBC ratio from 0.04 to 0.09 (p < 0.0001). A constant increase was also observed regarding the overall use of hemostatic drugs (n = 1,811; 2005 to 2009) as these were administered to 43.4% of the patients in 2005 and to 60.7% in 2009 (p < 0.0001). In particular, the administration of fibrinogen concentrate (2005: 17.0%, 2009: 45.6%; p < 0.0001) and recombinant factor VIIa (2005: 1.9%, 2009: 6.3%; p = 0.04) showed a marked increase. However, mortality rates remained unchanged during the 8-year study period. The authors concluded that therapy of bleeding trauma patients has changed in Germany during the recent years toward more aggressive coagulation support. This development continues although grades of evidence are still low regarding most of the changes reported in this study. They stated that randomized controlled trials are needed with respect to blood component therapy using pre-defined ratios and to the administration of hemostatic drugs commonly used for the severely injured.

Grottke (2012) noted that trauma-induced coagulopathy is a frequent complication in severely injured patients. To correct coagulopathy and restore hemostasis, these patients have traditionally been treated with fresh frozen plasma, but in the last decade, there has been a shift from empirical therapy to targeted therapy with coagulation factor concentrates and other hemostatic agents. This investigator highlighted emerging therapeutic options and controversial topics. Early administration of the anti-fibrinolytic medication tranexamic acid was shown in the multi-center CRASH-2 trial to be an effective and inexpensive means of decreasing blood loss. Numerous retrospective and experimental studies have shown that the use of coagulation factor concentrates decreases blood loss and may be useful in reducing the need for transfusion of allogeneic blood products. In particular, early use of fibrinogen concentrate and thrombin generators has a positive impact on hemostasis. However, the use of
prothrombin complex concentrate to correct trauma-induced coagulopathy has also been associated with a potential risk of serious adverse events. The author concluded that current evidence in trauma resuscitation indicated a potential role for coagulation factor concentrates and other hemostatic agents in correcting trauma-induced coagulopathy. They stated that despite a shift towards such transfusion strategy, there remains a shortage of data to support this approach.

Ziegler et al (2013) stated that use of allogeneic blood products to treat pediatric trauma may be challenged, particularly in relation to safety. These researchers reported successful treatment of a child with severe abdominal and pelvic injuries with preemptive fibrinogen supplementation followed by rotational thromboelastometry (ROTEM)-guided, goal-directed hemostatic therapy. Fibrinogen concentrate was administered (total dose: 2 g), while transfusion of fresh frozen plasma and platelet concentrate was avoided. Activated partial thromboplastin time was prolonged and Quick values were low but ROTEM clotting time values remained normal, therefore, no thrombin-generating drugs were considered necessary. The authors concluded that this case showed the potential for hemostatic treatment with coagulation factor concentrates to be applied to pediatric trauma.

Wafaisade et al (2013) examined if the administration of fibrinogen concentrate (FC) in severely injured patients was associated with improved outcomes. Patients documented in the Trauma Registry of the German Society for Trauma Surgery (primary admissions, Injury Severity Score [ISS] greater than or equal to 16) who had received FC during initial care between emergency department (ED) arrival and intensive care unit admission (FC+) were matched with patients who had not received FC (FC-). The matched-pairs analysis yielded two comparable cohorts (n = 294 in each group) with a mean ISS of 37.6 ± 13.7 (FC+) and 37.1 ± 13.3 (FC-) (p = 0.73); the mean age was 40 ± 17 versus 40 ± 16 (p = 0.72), respectively. Patients were predominantly male (71.1
% in both groups, p = 1.0). On ED arrival, hypotension (systolic blood pressure, less than or equal to 90 mm Hg) occurred in 51.4 % (FC+) and 48.0 % (FC-) (p = 0.41), and base excess was -7.4 ± 5.3 mmol/L for FC+ and was -7.5 ± 6.2 mmol/L for FC- (p = 0.96). Patients were administered 12.8 ± 14.3 (FC+) versus 11.3 ± 10.0 (FC-) packed red blood cell units (p = 0.20). Thromboembolism occurred in 6.8 % (FC+) versus 3.4 % (FC-) (p = 0.06), and multi-organ failure occurred in 61.2 % versus 49.0 % (p = 0.003), respectively. Whereas 6-hour mortality was 10.5 % for FC+ versus 16.7 % for FC- (p = 0.03), the mean time to death was 7.5 ± 14.6 days versus 4.7 ± 8.6 days (p = 0.006). The overall hospital mortality rate was 28.6 % versus 25.5 % (p = 0.40), respectively. The authors concluded that this was the first study to investigate the effect of FC administration in bleeding trauma. In this large population of severely injured patients, the early use of FC was associated with a significantly lower 6-hour mortality and an increased time to death, but also an increased rate of multi-organ failure. A reduction of overall hospital mortality was not observed in patients receiving FC.

In a single-center, prospective, placebo-controlled, double-blind study, Rahe-Meyer et al (2013) examined if fibrinogen concentrate can reduce blood transfusion when given as intra-operative, targeted, first-line hemostatic therapy in bleeding patients undergoing aortic replacement surgery. Patients aged 18 years or older undergoing elective thoracic or thoraco-abdominal aortic replacement surgery involving cardiopulmonary bypass were randomized to fibrinogen concentrate or placebo, administered intra-operatively. Study medication was given if patients had clinically relevant coagulopathic bleeding immediately after removal from cardiopulmonary bypass and completion of surgical hemostasis. Dosing was individualized using the fibrin-based thrombo-elastometry test. If bleeding continued, a standardized transfusion protocol was followed. A total of 29 patients in the fibrinogen concentrate group and 32 patients in the placebo group were eligible for the efficacy analysis.
During the first 24 hours after the administration of study medication, patients in the fibrinogen concentrate group received fewer allogeneic blood components than did patients in the placebo group (median, 2 versus 13 U; p < 0.001; primary endpoint). Total avoidance of transfusion was achieved in 13 (45 %) of 29 patients in the fibrinogen concentrate group, whereas 32 (100 %) of 32 patients in the placebo group received transfusion (p < 0.001). There was no observed safety concern with using fibrinogen concentrate during aortic surgery. The authors concluded that hemostatic therapy with fibrinogen concentrate in patients undergoing aortic surgery significantly reduced the transfusion of allogeneic blood products. Moreover, they stated that larger multi-center studies are needed to confirm the role of fibrinogen concentrate in the management of peri-operative bleeding in patients with life-threatening coagulopathy.

In a prospective, randomized, open-label study, Tanaka et al (2014) compared hematologic and transfusion profiles between the first-line acquired fibrinogen (FIB) replacement and platelet transfusion in post-cardiac surgical bleeding. A total of 20 adult patients who underwent valve replacement or repair and fulfilled preset visual bleeding scale were randomized to 4 g of FIB or 1 unit of apheresis platelets. Primary end-points included hemostatic condition in the surgical field and 24-hour hemostatic product usage. Hematologic data, clinical outcome, and safety data were collected up to the 28th day post-operative visit. In patients who received the first-line FIB concentrate (n = 10), the visual bleeding scale improved after intervention, and the incidence of platelet transfusion and total plasma donor exposure were lower compared to the platelet group (n = 10). Post-intervention FIB level was statistically higher (209 mg/dL versus 165 mg/dL) in the FIB group than in the platelet group, but platelet count and prothrombin were lower. There were no statistical differences in the post-operative blood loss and red blood cell transfusion between 2 groups. The authors concluded that these preliminary data indicated that the
primary FIB replacement may potentially reduce the incidence of platelet transfusion and the number of donor exposures. These preliminary findings need to be validated by well-designed studies.

Gielen et al (2014) performed a systematic review and meta-analysis to define the association between fibrinogen levels and blood loss after cardiac surgery. A database search (January 2013) was performed on publications assessing the association between pre- and post-operative fibrinogen levels and post-operative blood loss in adult patients undergoing cardiac surgery. Cohort studies and case-control studies were eligible for inclusion. The main outcome was the pooled correlation coefficient, calculated via Fisher's Z transformation scale, in a random-effects meta-analysis model stratified for the time-point at which fibrinogen was measured. A total of 20 studies were included. The pooled correlation coefficient of studies (n = 9) concerning pre-operative fibrinogen levels and post-operative blood loss was -0.40 (95 % confidence interval [CI]: -0.58 to -0.18), pointing towards more blood loss in patients with lower pre-operative fibrinogen levels. Among papers (n = 16) reporting on post-operative fibrinogen levels and post-operative blood loss, the pooled correlation coefficient was -0.23 (95 % CI: -0.29 to -0.16). The authors concluded that the findings of this meta-analysis indicated a significant but weak-to-moderate correlation between pre- and post-operative fibrinogen levels and post-operative blood loss in cardiac surgery. They stated that this moderate association calls for appropriate clinical studies on whether fibrinogen supplementation will decrease post-operative blood loss.

Aubron et al (2014) summarized the available literature evaluating the use of FC in the management of severe trauma. Studies reporting the administration of FC in trauma patients published between January 2000 and April 2013 were identified from MEDLINE and from the Cochrane Library. The systematic review identified 12 articles reporting FC usage in trauma patients: 4 case reports, 7 retrospective studies, and 1
prospective observational study; 3 of these were not restricted to trauma patients. The authors concluded that despite methodological flaws, some of the available studies suggested that FC administration may be associated with a reduced blood product requirement. They stated that randomized controlled trials (RCTs) are needed to determine whether FC improves outcomes in pre-hospital management of trauma patients or whether FC is superior to another source of fibrinogen in early hospital management of trauma patients.

In June 2017, Fibryga, a human fibrinogen concentrate, was approved by the U.S. Food and Drug Administration for the treatment of acute bleeding episodes in adults and adolescents with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. However, Fibryga is not indicated for dysfibrinogenemia.

Two clinical trials (FORMA 01 and FORMA 02) formed the basis for the safety and efficacy for Fibryga. The FORMA 01 was a randomized, phase 2 crossover study in which 22 subjects (ranging in age 12 to 53 years; 6 adolescents and 16 adults) with congenital fibrinogen deficiency compared the pharmacokinetics (PK) and pharmacodynamics (PD) of Fibryga to the comparable U.S. licensed fibrinogen concentrate product, RiaSTAP. Each subject received a single intravenous 70 mg/kg dose of Fibryga and the comparator product. Blood samples were drawn from the subjects to determine the fibrinogen activity at baseline and up to 14 days after the infusion. The incremental in vivo recovery (IVR) was determined from levels obtained up to 4 hours post-infusion. The median incremental IVR was a 1.8 mg/dL (range 1.1 – 2.6 mg/dL) increase per mg/kg. The median in vivo recovery indicated that a dose of 70 mg/kg will increase patients’ fibrinogen plasma concentration by approximately 125 mg/dL. No difference in fibrinogen activity was observed between males and females. There was no difference in the pharmacokinetics of Fibryga between adults and adolescents (12-17 years of age) (FDA, 2017).
An interim analysis of the FORMA 02 was used for the FDA-approved indications of Fibryga. The FORMA 02 is an ongoing prospective, uncontrolled phase 3, open-label, multicenter clinical study involving 13 patients (ranging in age 13 to 53 years; 2 adolescents and 11 adults) with congenital fibrinogen deficiency (afibrinogenemia and hypofibrinogenemia), and was used to establish safety and efficacy of Fibryga. Of the 22 evaluable bleeding events, 21 (95%) were rated as having a good or excellent efficacy. For 1 bleeding event, the investigator's assessment was missing. The median number of infusions for the bleeding events was 1. Two (9%) bleeding events required 2 infusions. None of the bleeding events required more than 2 infusions. The most common adverse reactions observed in more than one subject in the clinical study (> 5%) were vomiting, weakness and pyrexia (FDA, 2017).

According to the prescribing information, the dosing, duration, and frequency of administration for Fibryga should be individualized based on the extent of bleeding, laboratory values, and the clinical condition of the patient. The recommended target fibrinogen plasma level is 100 mg/dL for minor bleeding and 150 mg/dL for major bleeding. The patient's fibrinogen level should be monitored during treatment with Fibryga. Additional infusions of Fibryga should be administered if the plasma fibrinogen level is below the accepted lower limit (80 mg/dL for minor bleeding, 130 mg/dL for major bleeding) of the target level until hemostasis is achieved. (FDA, 2017). See appendix for additional dosing information.

**Bleeding Associated with Aortic Reconstruction and Deep Hypothermic Circulatory Arrest**

Hanna and associates (2016) noted that human FC (HFC) is approved by the FDA for use at 70 mg/kg to treat congenital afibrinogenemia. In a prospective, pilot, off-label study, these
researchers examined if this dose of HFC increases fibrinogen levels in the setting of high-risk bleeding associated with aortic reconstruction and deep hypothermic circulatory arrest (DHCA). A total of 22 patients undergoing elective proximal aortic reconstruction with DHCA were administered 70 mg/kg HFC upon separation from cardio-pulmonary bypass (CPB). Fibrinogen levels were measured at baseline, just before, and 10 minutes after HFC administration, on skin closure, and the day after surgery. The primary study outcome was the difference in fibrinogen level immediately after separation from CPB, when HFC was administered, and the fibrinogen level 10 minutes following HFC administration. Additionally, post-operative thromboembolic events were assessed as a safety analysis. The mean baseline fibrinogen level was 317 ± 49 mg/dL and fell to 235 ± 39 mg/dL just before separation from CPB. After HFC administration, the fibrinogen level rose to 331 ± 41 mg/dL (p < 0.001) and averaged 372 ± 45 mg/dL the next day. No post-operative thromboembolic complications occurred. The authors concluded that administration of 70 mg/kg HFC upon separation from CPB raised fibrinogen levels by approximately 100 mg/dL without an apparent increase in thrombotic complications during proximal aortic reconstruction with DHCA. Moreover, they stated that further prospective study in a larger cohort of patients will be needed to definitively determine the safety and evaluate the effectiveness of HFC as a hemostatic adjunct during these procedures.

Individuals with Acquired Fibrinogen Deficiency Undergoing Abdominal Surgery

Roy and colleagues (2019) noted that cytoreductive surgery (CRS) with hyper-thermic intra-peritoneal chemotherapy for pseudomyxoma peritonei (PMP) is associated with excessive bleeding and acquired fibrinogen deficiency. Maintaining plasma fibrinogen may support hemostasis. In a prospective, off-label, single-center, randomized, controlled phase-II clinical trial, these researchers compared the safety and efficacy of human fibrinogen concentrate (HFC) versus cryoprecipitate as
fibrinogen sources for bleeding patients with acquired fibrinogen deficiency undergoing PMP CRS. Patients undergoing PMP surgery with predicted intra-operative blood loss of greater than or equal to 2 L received human fibrinogen concentrate (HFC; 4 g) or cryoprecipitate (2 pools of 5 units, containing approximately 4.0 to 4.6 g fibrinogen), repeated as needed. The primary end-point was a composite of intra-operative and post-operative efficacy, graded using objective 4-point scales and adjudicated by an independent committee. One hundred percent of patients receiving HFC (95 % CI: 83.9 to 100.0, n = 21) or cryoprecipitate (84.6 to 100.0, n = 22) achieved hemostatic success. HFC demonstrated non-inferior efficacy (p = 0.0095; post-hoc) and arrived in the operating room 46 mins faster. There were significantly greater mean increases with HFC versus cryoprecipitate in plasma fibrinogen (0.78 versus 0.35 g/L; p < 0.0001) and FIBTEM A20 (3.33 versus 0.93 mm; p = 0.003). Factor XIII, factor VIII, and von Willebrand factor activity were maintained throughout surgery. Only RBC were transfused intra-operatively (median units: HFC group, 1.0; cryoprecipitate group, 0.5). Thrombo-embolic events were detected with cryoprecipitate only. Safety was otherwise comparable between groups. The authors concluded that human fibrinogen concentrate was effective in maintaining hemostasis in patients with acquired fibrinogen deficiency undergoing CRS for PMP. HFC is available for use faster than cryoprecipitate and has a comparable safety profile, with the possible exception of thrombo-embolic events, which were observed only with cryoprecipitate. Owing to the generalizability of the clinical model used, these results have implications for other surgical settings in which patients acquire fibrinogen deficiency and experience acute bleeding. These researchers stated that further studies are needed to examine potential differences between the safety profiles of the 2 products. Moreover, the authors stated that although the findings of this phase-II study demonstrated comparable hemostatic efficacy and non-inferiority of HFC to cryoprecipitate, a confirmatory multi-center study would further strengthen these findings.
Peri-Operative Hemorrhage (e.g., Cardiovascular Surgery)

In a randomized, placebo-controlled, double-blind, clinical trial Bilecen and associates (2017) examined if fibrinogen concentrate infusion dosed to achieve a plasma fibrinogen level of 2.5 g/L in high-risk cardiac surgery patients with intra-operative bleeding reduces intra-operative blood loss. This study was conducted in the Netherlands (February 2011 to January 2015), involving patients undergoing elective, high-risk cardiac surgery (i.e., combined coronary artery bypass graft [CABG] surgery and valve repair or replacement surgery, the replacement of multiple valves, aortic root reconstruction, or reconstruction of the ascending aorta or aortic arch) with intra-operative bleeding (blood volume between 60 and 250 ml suctioned from the thoracic cavity in a period of 5 minutes) were randomized to receive either fibrinogen concentrate or placebo. Subjects received intravenous, single-dose administration of fibrinogen concentrate (n = 60) or placebo (n = 60), targeted to achieve a post-infusion plasma fibrinogen level of 2.5 g/L. The primary outcome was blood loss (in mls) between intervention (i.e., after removal of cardio-pulmonary bypass) and closure of chest. Safety variables (within 30 days) included: in-hospital mortality, myocardial infarction (MI), cerebrovascular accident (CVA) or transient ischemic attack (TIA), renal insufficiency or failure, venous thromboembolism (VTE), pulmonary embolism (PE), and operative complications. Among 120 patients (mean age of 71 [standard deviation [SD], 10] years, 37 women [31 %]) included in the study, combined CABG and valve repair or replacement surgery comprised 72 % of procedures and had a mean (SD) cardiopulmonary bypass time of 200 minutes (83) minutes. For the primary outcome, median blood loss in the fibrinogen group was 50 ml (inter-quartile range [IQR], 29 to 100 ml) compared with 70 ml (IQR, 33 to 145 ml) in the control group (p = 0.19), the absolute difference 20 ml (95 % CI: -13 to 35 ml). There were 6 cases of stroke or TIA (4 in the fibrinogen group); 4 MI (3 in the fibrinogen group); 2 deaths (both in the fibrinogen group); 5 cases with renal insufficiency or failure (3
in the fibrinogen group); and 9 cases with re-operative thoracotomy (4 in the fibrinogen group). The authors concluded that among patients with intra-operative bleeding during high-risk cardiac surgery, administration of fibrinogen concentrate, compared with placebo, resulted in no significant difference in the amount of intra-operative blood loss.

Karkouti and co-workers (2018) stated that coagulopathic bleeding is a serious complication of cardiac surgery to which an important contributor is acquired hypofibrinogenemia (plasma fibrinogen less than 1.5 to 2.0 g/L). The standard intervention for acquired hypofibrinogenemia is cryoprecipitate, but purified fibrinogen concentrates are also available. There is little comparative data between the 2 therapies and RCTs are needed. FIBrinogen REplenishment in Surgery (FIBRES) is a multi-center, randomized (1:1), active-control, single-blinded, phase-III clinical trial in adult cardiac surgical patients experiencing clinically significant bleeding related to acquired hypofibrinogenemia. The primary objective is to demonstrate that fibrinogen concentrate is non-inferior to cryoprecipitate. All patients for whom fibrinogen supplementation is ordered by the clinical team within 24 hours of cardiopulmonary bypass will receive 4 g of fibrinogen concentrate or 10 units of cryoprecipitate (dose-equivalent to 4 g), based on random allocation and deferred consent. The primary outcome is total RBC, platelet and plasma transfusions administered within 24 hours of bypass. Secondary outcomes include major bleeding, fibrinogen levels and adverse events (AEs) within 28 days. Enrolment of 1,200 patients will provide greater than 90% power to demonstrate non-inferiority. One pre-planned interim analysis will include 600 patients. The pragmatic design and treatment algorithm align with standard practice, aiding adherence and generalizability.

Li and co-workers (2018) noted that post-operative bleeding remains a frequent complication after cardiovascular surgery and may contribute to serious morbidity and mortality. Observational studies have suggested a relationship between
low endogenous plasma fibrinogen concentration and increased risk of post-operative blood loss in cardiac surgery. Although the transfusion of fibrinogen concentrate has been increasing, potential benefits and risks associated with peri-operative fibrinogen supplementation in cardiovascular surgery are not fully understood. In a meta-analysis, these investigators evaluated the effects of fibrinogen concentrate in cardiovascular surgery. PubMed, Cochrane Library, Ovid Medline, Embase, Web of Science, and China National Knowledge Infrastructure were searched on January 15, 2017, with automated updates searched until February 15, 2018, to identify all RCTs of fibrinogen concentrate, whether for prophylaxis or treatment of bleeding, in adults undergoing cardiovascular surgery. All RCTs comparing fibrinogen infusion versus any other comparator (placebo/standard of care or another active comparator) in adult cardiovascular surgery and reporting at least 1 pre-defined clinical outcome were included. The random-effects model was used to calculate risk ratios and weighted mean differences (MDs; 95% CI) for dichotomous and continuous variables, respectively. Subgroup analyses by fibrinogen dose and by baseline risk for bleeding were pre-planned. A total of 8 RCTs of fibrinogen concentrate in adults (n = 597) of mixed risk or high risk undergoing cardiovascular surgery were included. Compared to placebo or inactive control, peri-operative fibrinogen concentrate did not significantly impact risk of all-cause mortality (RR, 0.41; 95% CI: 0.12 to 1.38; I = 10%; p = 0.15). Fibrinogen significantly reduced incidence of allogeneic RBC transfusion (RR, 0.64; 95% CI: 0.49 to 0.83; I = 0%; p = 0.001). No significant differences were found for other clinical outcomes. Subgroup analyses were unremarkable when analyzed according to fibrinogen dose, time of infusion initiation, mean cardiopulmonary bypass time, and rotational thrombo-elastometry/fibrinogen temogram use (all p values for subgroup interaction were non-significant). The authors concluded that current evidence remained insufficient to support or refute routine peri-operative administration of fibrinogen concentrate in patients undergoing cardiovascular
surgery. Fibrinogen concentrate may reduce the need for additional allogeneic blood product transfusion in cardiovascular surgery patients at high risk or with evidence of bleeding. However, no definitive advantage was found for reduction in risk of mortality or other clinically relevant outcomes. They stated that the small number of clinical events within existing randomized trials suggested that further well-designed studies of adequate power and duration to measure all-cause mortality, stroke, MI, re-operation, and thrombo-embolic events should be conducted. They also stated that future studies should address cost-effectiveness relative to standard of care.

On behalf of the Hemostasis and Transfusion Scientific Subcommittee of the European Association of Cardiothoracic Anesthesiology, Erdoes and colleagues (2019) provided an international consensus statement on “The role of fibrinogen and fibrinogen concentrate in cardiac surgery”. These investigators stated that currently data regarding the safety and efficacy of administering fibrinogen concentrate in cardiac surgery are limited. Studies are limited by their low sample size and large heterogeneity with regard to the patient population, by the timing of fibrinogen concentrate administration, and by the definition of transfusion trigger and target levels. Assessment of fibrinogen activity using viscoelastic point-of-care testing shortly before or after weaning from cardiopulmonary bypass in patients and procedures with a high risk of bleeding appeared to be a rational strategy. In contrast, the use of Clauss fibrinogen test for determination of plasma fibrinogen level can no longer be recommended without restrictions due to its long turn-around time, high inter-assay variability and interference with high heparin levels and fibrin degradation products. Administration of fibrinogen concentrate for maintaining physiological fibrinogen activity in the case of microvascular post-cardiopulmonary bypass bleeding appeared to be indicated. The authors stated that available evidence does not suggest aiming for supra-normal levels, however; and the use of
cryoprecipitate as an alternative to fibrinogen concentrate might be considered to increase plasma fibrinogen levels. They noted that although conclusive evidence is lacking, fibrinogen concentrate does not seem to increase adverse outcomes (i.e., thrombo-embolic events). These researchers stated that large, prospective, multi-center studies are needed to better define the optimal peri-operative monitoring tool, transfusion trigger and target levels for fibrinogen replacement in cardiac surgery.

**Post-Partum Hemorrhage**

In a multi-center, double-blinded, parallel RCT, Wikkelso and colleagues (2015) hypothesized that pre-emptive treatment with FC reduces the need for RBC transfusion in patients with PPH. These investigators assigned subjects with severe PPH to a single dose of FC or placebo (saline). A dose of 2 g or equivalent was given to all subjects independent of body weight and the FC at inclusion. The primary outcome was RBC transfusion up to 6 weeks post-partum; secondary outcomes were total blood loss, total amount of blood transfused, occurrence of re-bleeding, hemoglobin of less than 58 g/L, RBC transfusion within 4 hours, 24 hours, and 7 days, and as a composite outcome of “severe PPH”, defined as a decrease in hemoglobin of greater than 40 g/L, transfusion of at least 4 units of RBCs, hemostatic intervention (angiographic embolization, surgical arterial ligation, or hysterectomy), or maternal death. Of the 249 randomized subjects, 123 of 124 in the fibrinogen group and 121 of 125 in the placebo group were included in the intention-to-treat analysis. At inclusion the subjects had severe PPH, with a mean blood loss of 1,459 (S.D. of 476) ml and a mean FC of 4.5 (S.D. of 1.2) g/L. The intervention group received a mean dose of 26 mg/kg FC, thereby significantly increasing FC compared with placebo by 0.40 g/L (95 % CI: 0.15 to 0.65; p = 0.002). Post-partum blood transfusion occurred in 25 (20 %) of the fibrinogen group and 26 (22 %) of the placebo group (relative risk [RR], 0.95; 95 % CI: 0.58 to 1.54; p = 0.88). These researchers found no
difference in any pre-defined secondary outcomes, per-protocol analyses, or adjusted analyses. No thromboembolic events were detected. The authors concluded that there is no evidence to support the use of 2 g FC as pre-emptive treatment for severe PPH in patients with normofibrinogenemia.

**Trauma-Associated Hemorrhage**

Mengoli and colleagues (2017) stated that hemorrhage following injury is associated with significant morbidity and mortality. The role of fibrinogen concentrate in trauma-induced coagulopathy has been the object of intense research in the last 10 years and has been systematically analyzed in this review. A systematic search of the literature identified 6 retrospective studies and 1 prospective one, involving 1,650 trauma patients. There were no randomized trials. Meta-analysis showed that fibrinogen concentrate had no effect on overall mortality (RR: 1.07, 95 % CI: 0.83 to 1.38). Although the meta-analytic pooling of the current literature evidence suggested no beneficial effect of fibrinogen concentrate in the setting of severe trauma, the quality of data retrieved was poor and the final results of ongoing randomized trials will help to further elucidate the role of fibrinogen concentrate in traumatic bleeding.

Curry and associates (2018) conducted a blinded, randomized, placebo-controlled trial at 5 UK major trauma centers with adult trauma patients with active bleeding who required activation of the major hemorrhage protocol. Participants were randomized to standard major hemorrhage therapy plus 6 g of fibrinogen concentrate or placebo; 27 of 39 participants (69 %; 95 % CI: 52 to 83 %) across both arms received the study intervention within 45 minutes of admission. There was some evidence of a difference in the proportion of participants with fibrinogen levels of greater than or equal to 2 g/L between arms (p = 0.10). Fibrinogen levels in the fibrinogen concentrate (FgC)-arm rose by a mean of 0.9 g/L.
(SD, 0.5) compared with a reduction of 0.2 g/L (SD, 0.5) in the placebo-arm and were significantly higher in the FgC-arm (p<0.0001) at 2 hours. Fibrinogen levels were not different at day 7. Transfusion use and thromboembolic events were similar between arms. All-cause mortality at 28 days was 35.5 % (95 % CI: 23.8 to 50.8 %) overall, with no difference between arms. The authors concluded that early delivery of fibrinogen concentrate within 45 minutes of admission was not feasible. Although evidence pointed to a key role for fibrinogen in the treatment of major bleeding, researchers need to recognize the challenges of timely delivery in the emergency setting. Moreover, they stated that future studies must explore barriers to rapid fibrinogen therapy, focusing on methods to reduce time to randomization, using “off-the-shelf” fibrinogen therapies (such as extended shelf-life cryoprecipitate held in the emergency department or fibrinogen concentrates with very rapid reconstitution times) and limiting the need for coagulation test-based transfusion triggers.

Peralta and Chowdary (2019) noted that uncontrolled bleeding in trauma secondary to a combination of surgical bleeding and trauma-induced complex coagulopathy is a leading cause of death; PCCs, recombinant activated factor seven (rFVIIa) and recombinant human prothrombin act as procoagulants by increasing thrombin generation and fibrinogen concentrate aids stable clot formation. These investigators summarized the current evidence for procoagulant use in the management of bleeding in trauma, and data and evidence gaps for routine clinical use. Retrospective and prospective studies of PCCs (± fibrinogen concentrate) have demonstrated a decreased time to correction of trauma coagulopathy and decreased RBC transfusion with no obvious effect on mortality or thromboembolic outcomes. PCCs in a porcine model of dilutional coagulopathy demonstrated a sustained increase in thrombin generation, unlike recombinant human prothrombin, which showed a transient increase and has been studied only in animals. In other retrospective studies, there was a suggestion that lower doses of PCCs may be effective in the
setting of acquired coagulopathy. The authors concluded that there is increasing evidence that early correction of coagulopathy has survival benefits, and the use of procoagulants as first-line therapy has the potential benefit of rapid access and timely treatment. This requires confirmation in prospective studies.

Seebold and colleagues (2019) stated that fibrinogen is one of the first coagulation factors to be depleted during traumatic hemorrhage, and evidence suggested hypo-fibrinogenemia resulted in poor outcomes. A number of fibrinogen replacement products are currently available, with no clear consensus on the ideal product to use in severe traumatic hemorrhage. These researchers hypothesized that it will be possible to rapidly administer fibrinogen concentrate (FC) guided by rotational thrombo-elastometry (ROTEM) FIBTEM A5 in patients presenting with trauma hemorrhage. They examined 36 consecutive patients with trauma admitted to a level 1 trauma center in Australia who received FC as part of their initial resuscitation. ROTEM analysis was conducted at various time-points from emergency department (ED) admission to 48 hours after admission. The primary outcome was time to administration of FC after identification of hypo-fibrinogenemia using ROTEM FIBTEM A5. Data were collected on quantity and timing of product transfusion, demographics, Injury Severity Score and laboratory values of coagulation. Spearman rank order correlation was used to determine the correlation between FIBTEM A5 and Clauss fibrinogen (FibC). A total of 36 patients received FC as their initial form of fibrinogen replacement during the study. Patients were hypo-fibrinogenemic by both FIBTEM A5 (6 mm) and FibC (1.7 g/L) on presentation to the ED. It took a median of 22 mins (IQR, 17 to 30 mins) from time of a FIBTEM A5 analysis to FC administration. Both parameters increased significantly (p < 0.05) by 24 hours after admission. The authors concluded that the findings of this study suggested that administration of FC represented a rapid and feasible method to replace fibrinogen in severe traumatic hemorrhage.
However, the optimal method for replacing fibrinogen in traumatic hemorrhage is controversial and large multi-center RCTs are needed to provide further evidence. This study provided baseline data to inform the design of further clinical trials examining fibrinogen replacement in traumatic hemorrhage.

Appendix

RiaSTAP is available as single-use vials containing 900 to 1,300 mg lyophilized fibrinogen concentrate powder for reconstitution. Actual fibrinogen potency for each lot is printed on vial label and carton. The dosing of RiaSTAP is as follows (Israels, 2009; CSL Behring US Package Insert, 2009):

**Adult**

- Administer intravenously, not to exceed injection rate of 5 ml/min.
- Dose (mg/kg) = (Target level [mg/dL] - measured level [mg/dL]) divided by 1.7; if fibrinogen level unknown, use 70 mg/kg body weight.
- Maintain target fibrinogen level of 100 mg/dL until hemostasis is obtained.

**Pediatric**

- Data limited; clinical trials included 4 children less than 16 years of age.
- Children exhibited shorter half-life (69.9 +/- 8.5 hrs) and faster clearance (0.7 +/- 0.1 mg/L) than adults (half-life = 82.3 +/- 20.0 hrs; clearance = 0.53 +/- 0.1 mg/L), but limited number of children restricts statistical interpretation of these data.
Fibryga is available as lyophilized powder in single-use bottles containing approximately 1 g fibrinogen concentrate per bottle.

The dosing of Fibryga is as follows (FDA, 2017):

**Adult**

- Administer intravenously, not to exceed injection rate 5 mL/min.
- Dose (mg/kg) = [Target level (mg/dL) – measured level (mg/dL)] divided by 1.8 (mg/dL per mg/kg body weight); if fibrinogen level unknown, use 70 mg/kg body weight.
- Maintain target fibrinogen level of 100 mg/dL for minor bleeding, and 150 mg/dL for major bleeding.

**Pediatric**

- Data limited; an ongoing prospective phase 3 trial included 2 adolescents
- There was no difference in the pharmacokinetics of Fibryga between adults and adolescents (12-17 years of age).

**CPT Codes / HCPCS Codes / ICD-10 Codes**

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

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<td>Other CPT codes related to the CPB:</td>
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<td>Fibrinogen; activity</td>
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<td>85385</td>
<td>antigen</td>
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<tr>
<td>96374</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug</td>
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<tr>
<td>Code</td>
<td>Code Description</td>
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<td>96375</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); each additional sequential intravenous push of a new substance/drug (List separately in addition to code for primary procedure)</td>
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<td>96376</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); each additional sequential intravenous push of the same substance/drug provided in a facility (List separately in addition to code for primary procedure)</td>
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**HCPCS codes covered if selection criteria are met:**

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<td>J7178</td>
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**ICD-10 codes covered if selection criteria are met:**

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**ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):**

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<td>O72.0 - O72.3</td>
<td>Postpartum hemorrhage</td>
</tr>
<tr>
<td>O86.0, O90.2</td>
<td>Other complications of obstetrical surgical wounds</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:

5. Berube C. Disorders of fibrinogen. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed June 2014.


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AETNA BETTER HEALTH® OF PENNSYLVANIA
Amendment to Aetna Clinical Policy Bulletin Number: 0792 Human Fibrinogen Concentrate (RiaSTAP and Fibryga)
For the Pennsylvania Medical Assistance plan RiaSTAP is only considered experimental and investigational for bleeding associated with aortic reconstruction and deep hypothermic circulatory arrest in persons without congenital fibrinogen deficiency.

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