Haemocomplettan® P alone or in combination with Fibrogammin® P in acquired hypofibrinogenemia

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Health Technology Assessment

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1.1 Background

Haemostasis is a complex process employing a multitude of cells, blood coagulation factors (clotting factors), co-factors, and regulators (activators and inhibitors) following the damage of a blood vessel in order to stop bleeding. Fibrinogen – coagulation factor I – is activated by thrombin which leads to the conversion to fibrin. In addition, thrombin converts fibrin-stabilising factor – coagulation factor XIII – into its active form XIIIa[1]. Fibrin monomers aggregate to fibrin polymers and are being cross-linked and hence stabilised by factor XIIIa. Therefore, both factors I and XIII are essential in building a fibrin clot.

haemostasis is a complex process resulting in a three-dimensional fibrin network

Clotting factor deficiencies may be inherited through mutations of genes encoding the respective coagulation factor. The gene for fibrinogen is located on chromosome 4, that of factor XIII on both chromosomes 6 and 1. Such deficiencies occur rarely - estimations range from 1 per 500,000 to 1 per 2,000,000 individuals [1]. More frequently, a lack of fibrinogen is acquired through impaired synthesis, increased loss, or increased consumption caused by various underlying clinical conditions, such as disseminated intravascular coagulopathy (DIC), hepatic insufficiency, life-threatening bleeding, dilutional coagulopathy, severe trauma, or long-term corticosteroid therapy [2]. Similarly, a lack of factor XIII may be acquired through major surgery, DIC, sepsis, chronic inflammatory bowel diseases, Purpura Schönlein-Hennoch, hepatic insufficiency, and systematic haematologic diseases. [3].

congenital or acquired clotting factor deficiencies

1.2 Haemocomplettan® P[2]

1.2.1 Fibrinogen

The normal plasma concentration of fibrinogen ranges from 2.0 to 4.5 g/L (gram per litre). Its plasma half-life[3] is 3 to 5 days [4]. As an acute phase protein its concentration is subject to variability and may be increased for different reasons, such as inflammation, tumors, pregnancy, or after surgery. In massive haemorrhage, crystalloids and colloids are being substituted, leading to the development of dilutional coagulopathy with a drop of fibrinogen below a critical level [5, 6]. This critical level, however, is highly disputed. In several guidelines, a fibrinogen level of less than 1.0 g/L is considered as a threshold for substitution of blood products [6-10]. The German Medical Association defined an additional threshold of <1.5 g/L in severe haemor-

normal plasma concentration 2.0 to 4.5 g/L

disputed threshold for fibrinogen substitution: <1 g/L; <1.5 g/L; <1.5 to 2 g/L

[1] a = activated

[2] P = pasteurised

[3] half-life = the time it takes for a substance to decrease by half

rhage [10]. The Task Force for Coagulation of the Austrian Society of Anesthesiology, Resuscitation and Intensive Care Medicine (ÖGARI) "strongly recommends" to maintain a fibrinogen level of 1.5 to 2 g/L in trauma-related massive bleeding [11]. Recently, one study suggested that women with a fibrinogen concentration of less than 2 g/L may already be at high risk of severe bleeding in post-partum haemorrhage [12].

substitution of fibrinogen preventively or according to plasma fibrinogen level

Depending on the urgency in massive haemorrhage, fibrinogen might be substituted either preventively or according to plasma fibrinogen levels as determined by conventional coagulation tests, such as the Clauss assay, or ROTEM® rotational thrombelastometry, a recently developed point-of-care device. The rationale behind this approach is the fact that in massive haemorrhage depletion of fibrinogen occurs early during progression of coagulopathy [5, 6].

1.2.2 Sources of fibrinogen

Fibrinogen may be substituted as fresh frozen plasma (FFP), Octaplas® SD[4], cryoprecipitate, or fibrinogen concentrate.

FFP

FFP: single donor, test ABO-compatiblility

FFP is derived from whole blood or by plasmapheresis from a single donor's blood after removing blood cells. It is stored at minus 30°C[5] and has to be thawed at 37°C before it can be used, which takes at least 30 minutes. One unit of FFP contains all coagulation factors, including 2 to 5 g/L fibrinogen, dissolved in about 150 to 400 millilitre (mL) of plasma. The recommended dose is 10 to 15 (millilitre per kilogram (mL/kg) body weight but depends upon the individual blood loss. AB0 blood group typing is necessary before FFP can be orderd and transfused to a patient [5].

Octaplas® SD

Octaplas® SD: multiple donors, virus inactivated, test ABO-compatiblility

Octaplas® SD is solvent-detergent treated human plasma derived from multiple donors and is used for the same indications and at the same dosage as FFP. Similar to FFP, it has to be thawed and ABO-blood group compatibility has to be tested before administration. The clotting factor content of Octaplas® SD is lower than that of FFP due to the virus inactivation process. One 200 mL bag of Octaplas® SD contains 9 to 14 g human plasma proteins. The specific amount of fibrinogen, however, depends on the fibrinogen concentration of the respective donor(s) [13].

Cryoprecipitate

Cryoprecipitate: by thawing FFP, production not standardised

Cryoprecipitate is derived from FFP, when thawed at 1°C to 6°C. It can be refrozen but should be used within 12 months. One unit contains 100 to 350 mg fibrinogen (6.7 to 23 g/L), FXIII, FVIII, von Willebrand factor, fibronection, albumin, immunglobulin (Ig) G and IgM, dissolved in typically 15 mL

[4] SD = solvent detergent

[5] C = Celsius

of plasma. It has to be thawed before administration as well but it can be thawed more quickly than FFP because of the smaller volume. The dose is calculated individually and depends upon the current fibrinogen level, the desired increase in fibrinogen level, and the plasma volume of the respective patient [5, 14, 15]. Although cryoprecipitate is not very frequently used in Europe (but is common in Northern America), it can be easily prepared by most blood banks.

Fibrinogen concentrate (Haemocomplettan® P)

multiple donors, standardised fibrinogen content

Fibrinogen concentrates are produced from pooled human plasma (derived from selected donors) under highly controlled and standardised conditions by pharmaceutical companies with high experience in the production of blood products. Due to sophisticated virus inactivation procedures the risk of pathogen transmission is low [16]. The products come as lyophilized dry powder with an exactly defined amount of purified fibrinogen (1 or 2 g per vial). Before administration (as a slow injection) it has to be dissolved in 50 to 100 mL of water for injection, resulting in a fibrinogen concentration of 20 g/L [13]. The low volume does not lead to volume overload and allows the administration of high amounts of fibrinogen within a short time.

1.2.3 Indication

approved 1994/ 2004

In Austria Haemocomplettan® P is licensed for the prevention of haemorrhagic diathesis in congenital afibrinogenemia, hypofibrinogenemia, and dysfibringoenemia as well as for acquired hypofibrinogenemia due to impaired synthesis, increased consumption, or increased loss of fibrinogen. First approval was granted in 1994 with renewal of approval in 2004 [13].

1.2.4 Regulatory Status

Haemocomplettan® P and RiaSTAP™ produced by CSL Behring GmbH

The World Federation of Hemophilia provides an overview of clotting factor concentrates available throughout the world [17]. The fibrinogen concentrates Haemocomplettan® P and RiaSTAP™ are being manufactured by CSL Behring GmbH, Marburg, Germany [17]. The manufacturers and its predecessors have been producing and marketing fibrinogen for the use in congenital and acquired fibrinogen deficiencies since the mid 1950s. In 1977, however, the United States Food and Drug Administration (FDA) revoked all licenses for fibrinogen concentrates – affecting several companies, including CSL Behring - due to the risk of hepatitis transmission and lack of evidence regarding the effectiveness of fibrinogen [18, 19]. By contrast, in Japan fibrinogen concentrate was administered for the treatment of obstetric bleeding until 1988, resulting in about 10,000 cases of hepatitis C infection [19]. Since then the manufacturing process has been improved, particularly with regard to the pasteurisation step, when plasma is being heated at 60°C for 20 hours in order to inactivate a number of viruses, such as hepatitis C virus and HIV [18].

no EMEA approval, only national licensure

FDA approval for RiaSTAP™ 2009

The trade name Haemocomplettan® P was introduced by CSL Behring in 1985. Fibrinogen concentrate is licensed as Haemocomplettan® P in some European countries, such as Austria, Germany, Switzerland, Portugal and the Netherlands. Moreover, it is available on a patient-name basis in 11 European countries, including Iceland, Norway, Sweden, Finland, Denmark, United Kingdom, Belgium, France, Spain, Italy and Greece [20]. Licensures were granted nationally, however, an approval by the European Medicines Agency (EMEA) does not exist. In addition, fibrinogen concentrate is licensed as Clottagen in France, Fibrinogen HT in Japan, and FIBRORAAS in China. Furthermore, fibrinogen concentrate has been licensed as RiaSTAP™ in the United States since January 2009 [17].

1.2.5 Estimated performance and costs

clinical use of Haemocomplettan® P ranges from 146 vials/ 100 beds to 26 to 69 vials/ 100 beds

An assessment[6] revealed that between January 2009 and June 2009 the consumption of Haemocomplettan® P varied remarkably within selected Austrian hospitals, including the General Hospital Vienna and St. Anna Children's Hospital, University Hospital Graz, University Hospital Innsbruck, General Hospital Salzburg, General Hospital Klagenfurt, Hospitals Wels and Grieskirchen, and Hospital St. Pölten. During this time period the highest consumption in one of the hospitals was 146 vials of Haemocomplettan® P, containing one gram of fibrinogen, per 100 beds, whereas in all other hospitals it ranged from 26 to 69 vials per 100 beds (personal communication).

7-fold increase in use, 24-fold increase in costs since 2001

Within all public hospitals in one Austrian province, the consumption of Haemocomplettan® P has been increasing steadily since 2001. It rose more than seven-fold from 484 gram (g) in 2001 –with a short decline in 2002 – to 3,576 g in 2008. Similarly, the costs increased more than 24-fold from €[7] 36,036 in 2001 to € 878,737 in 2008. In the largest of these hospitals, which is a University Hospital, 2,456 g of Haemocomplettan® P were used in 2008[8], 59% and 37% of which were administered in the operating theatre and the intensive care unit, respectively. The remaining 4% were given to patients on the ward and in the outpatient clinic. In comparison, 322 g of Haemocomplettan® P were used in this hospital in 2001[5] (personal communication).

5-fold increase in use and costs since 2001

A University Hospital in another Austrian province, shows the same trend regarding Haemocomplettan® P consumption. It increased constantly from 797 g in 2001[9] – with a short decline in 2003 – to 3,501 g in 2008 and is expected to reach 4,132 g in 2009[6]. Since in Austria one vial of Haemocomplettan® P, containing one gram of fibrinogen, is € 352.4 [13], the costs for the

[6] In this assessment the hospital with the highest consumption of Haemocomplettan® P is known and is compared anonymously to the other hospitals.

[7] € = Euro

[8] According to the studies identified in our review with the amount of fibrinogen concentrate administered being between 2 to 8 gram, between approximately 300 and 1200 patients must have been treated in 2008. In comparison, between 40 and 160 patients must have been treated in 2001.

[9] According to the studies identified in our review with the amount of fibrinogen concentrate administered being between 2 to 8 gram, between approximately 100 and 400 patients must have been treated in 2001. However, this figure is estimated to increase to about 500 to 2000 patients in 2009.

substitution of fibrinogen are estimated to reach € 1,456,117 in 2009 - a more than 5-fold increase since 2001.

In comparison, the price for FFP ranges from € 73.45 to € 81.86 (personal communication). Furthermore, one bag of 200ml Octaplas® SD human plasma solution for intravenous infusion is between € 87.1 and € 91.05, depending on the ABO-blood group [13].

1.3 Fibrogammin® P

1.3.1 Factor XIII

The normal plasma concentration of factor XIII is 0.02 g/L [4]. Effective haemostasis may be achieved with as little as 1% of enzymatic activity [21]. In addititon, its half-life is 9 to 10 days [4]. There are different assays in use for determining factor XIII activity [22] and usually results from the laboratory are available within one week. Factor XIII concentration is expressed as units per millilitre (U/mL), whereby 1 U/mL equals 100% factor XIII activity of a normal control plasma.

normal plasma concentration 0.02 g/L, 1% of normal enzymatic activity is sufficient for hemostasis

In severe haemorrhage, clotting factor XIII might be administered preventively without prior determining its plasma concentration because this is not part of routine coagulation tests [3].

1.3.2 Sources of factor XIII

Factor XIII may be substituted as FFP, Octaplas® SD, cryoprecipitate, or factor XIII concentrate.

FFP/ Octaplas® SD/ Cryoprecipitate

A detailed description of FFP, Octaplas® SD, and cryoprecipitate is available at 1.2.2. The specific amount of factor XIII in these blood products, however, depends on the factor XIII activity of the respective donor(s).

Factor XIII concentrate (Fibrogammin® P)

Factor XIII concentrate is produced from pooled human plasma (derived from selected donors) under highly controlled and standardised conditions by pharmaceutical companies with high experience in the production of blood products. Due to sophisticated virus inactivation procedures the risk of pathogen transmission is low [16]. The product comes as lyophilised dry powder in vials containing either 250 units (U) or 1,250 U of factor XIII. The content of these 250 U and 1,250 U vials is being dissolved in 4 mL and 20 mL of water for injection, respectively, prior to administration as a slow injection. The recommended dosage is at least 15 to 20 U per kg body weight [13].

multiple donors, standardised factor XIII content

1.3.3 Indication

approved 2000/ 2005

In Austria Fibrogammin® P is licensed for the treatment of patients with congenital factor XIII deficiency and resulting haemorrhagic diathesis, haemorrhage, and wound healing disorders. In addition, it is approved for the treatment of patients with hemorrhagic diathesis due to acquired factor XIII deficiency, for supportive care of wound healing disorders, and to improve consolidation of bone fractures. First approval was granted in 2000 with renewal of approval in 2005 [13].

1.3.4 Regulatory Status

produced by CSL Behring GmbH

Factor XIII concentrate is manufactured by CSL Behring GmbH, Marburg, Germany and is licensed as Fibrogammin® P in Austria and several other countries within the European Union as well as in Japan. However, it is not available in the United States, where factor XIII deficiencies are being treated with FFP and cryoprecipitate [2].

1.3.5 Estimated performance and costs

substantial variability in clinical use and costs

Among all public hospitals in one Austrian province, the consumption of Fibrogammin® P varied consideraby between 2001 and 2008. It ranged from 69,000 U to 91,250 U between 2001 and 2006, increased steeply to 139,250 U in 2007 and plummeted to 63,750 U in 2008. Costs for Fibrogammin® P ranged from € 13,168 to € 66,026 during this time period (personal communication).

19-fold increase in use and costs since 2002

In a University Hospital in another Austrian province the consumption of Fibrogammin® P rose from 18,250 U in 2002 - with a short decrease in 2003 - to 279,500 U in 2008 and is estimated to reach 354,000 U in 2009, equalling a more than 19-fold increase since 2002. One vial of Fibrogammin® P, containing 250 U of fibrin-stabilising factor, is € 154.6 [13]. One vial of 1,250 U is € 648.05. Hence, the costs for the substitution of fibrin-stabilising factor are estimated to reach between € 183,528 and € 218,914 in 2009 – a more than 19-fold increase since 2002 (personal communication).

2 Guidelines for the transfusion of blood products

lack of national Austrian transfusion guidelines

In Austria, national transfusion guidelines do not exist, which leads to a considerable variability in the substitution of blood products among different institutions.

ÖGARI-recommendations not evidence based

Recommendations for coagulation management in trauma-related massive bleeding have been issued by the Task Force for Coagulation of the ÖGARI [11]. These include recommendations on the substititution of fibrinogen concentrate and factor XIII concentrate in this specific setting. According to these guidelines, the substitution of fibrinogen concentrate should be guided by ROTEM® rotational thrombelastometry or, if this is not achievable, a fibrinogen level of 1.5 to 2 g/L should be maintained. In addition, factor XIII concentrate should be administered empirically without prior measurement of factor XIII activity at a dosage of 30 U per kg body weight in low clot strength as estimated by ROTEM® analysis.

departmental guidelines, not evidence based

Likewise, local guidelines for one University Hospital in Austria have been launched by two authors who are also part of the Task Force for Coagulation of the ÖGARI [23]. These guidelines contain similar recommendations for the administration of fibrinogen concentrate. The settings, however, have been extended to perioperative use, severly ill patients, and critically ill intensive care unit patients. The substitution of factor XIII concentrate is not accounted for in these guidelines.

conflicting guidelines from Canada, Great Britain, and Europe

Further guidelines for the transfusion of blood products are availabale from Canada, Great Britain, Germany, and a European Expert Group [6-10]. Nevertheless, these recommendations are subject to substantial variability regarding indications, settings, cut-off levels, and dosages of different blood products. The German Medical Association issued guidelines for the substitution of fibrinogen in acquired fibrinogen deficiency [10]. According to these guidelines, the threshold for the occurrence of spontaneous haemorrhage is a fibrinogen level of < 1 g/L. This threshold, however, increases to < 1.5 g/L in severe haemorrhage. Furthermore, it is emphasised that the fibrinogen level should be determined specifically. The fibrinogen dosage can be calculated and depends on the desired increase in fibrinogen level and the plasma volume of the respective patient, which in turn depends on the body weight. The required dose for adults is 3 to 6 g. After fibrinogen replacement, the fibrinogen plasma level should be controlled and should be above the critical level of about < 1 g/L [10].

German guidelines

European guidelines

The multidisciplinary Task Force for Advanced Bleeding Care in Trauma developed European guidelines for the management of haemorrhage in trauma patients [9]. According to these, fibrinogen should be subtituted in severe bleeding with a plasma fibrinogen level of < 1g/L. The recommended dosage is 3 to 4 g of fibrinogen concentrate or 50 mg/kg body weight of cryoprecipitate initially, followed by further administration according to the fibrinogen level as determined by laboratory tests.

inadequate administration of blood products in Boston, Canada, New South Wales

Studies have been conducted assessing the appropriateness of blood product substitution, particularly of FFP and cryoprecipitate [14, 24-26]. Overall, there is lack of evidence from randomised controlled trials confirming the effectiveness of FFP infusion in various underlying clinical conditions, such as liver diseases, cardiovascular diseases, or DIC, and current guidelines are mainly based on observational studies [24]. A number of audits showed that in many cases the administration of cryoprecipitate and other blood products was inadequate. In a tertiary care medical centre in Boston, 24% (12/51) of patients received cryoprecipitate for the wrong indication over a period of 19 weeks [14]. In 25 hospitals in Canada about one third (34%) of cryoprecipitate transfusions during eight weeks were considered inappropriate. Furthermore, another 42% of cryoprecipitate transfusions may have been done for wrong indications but this could not be established [26]. In New South Wales the percentage of cryoprecipitate substitutions assessed as having been inappropriate was 62% over a period of 8 months. In addition, 33% of platelets and 37% of FFP transfusions were considered inadequate [25].

3 Technical comparison of Clauss fibrinogen assay and ROTEM® rotational thrombelastometry

Clauss method since 1957, ROTEM® method since 1995

The Clauss method has been employed for determining plasma fibrinogen concentrations since 1957 [27]. As it has been suggested to be the most reliable of the laboratory methods used for determining the fibrinogen level [28], we considered it the "gold standard". However, there is a variety of laboratory tests available for quantifying the fibrinogen level [28, 29]. Rotational thrombelastometry ROTEM® evolved from thrombelastographic methods first described by Hartert in 1948 [30, 31] and was launched in 1995 [32]. Table 3-1 shows a comparison of Clauss functional fibrinogen assay and the ROTEM® rotational thrombelastometry method.

Table 3-1: Clauss fibrinogen assay versus ROTEM® method for estimating fibrinogen activity

	Clauss fibrinogen assay	ROTEM® [33]	
Introduced	1957 [27]; considered as "gold standard", reference test	1995 [32]; based on thrombelastography introduced by Hartert in 1948 [30, 31]	
Setting	laboratory	point-of-care	
Sample	cell-free citrated plasma sample [27]	citrated whole-blood sample [34]	
Duration	30-50 min.[1] [35] including centrifugation and sample transport	10-30 min. [30, 35-37], depends on parameter assessed; FIBTEM[2]: 10 min. [35]	
Type of assay	quantitative assay	qualitative test	
Unit	g/L[3]	mm[4] sec[5] °[6] % of MCF[7]	MCF, CA[8]
Analyser/ reagent/ assay protocol	various analysers (including machines), reagents and assay protocols [28, 38]	dedicated device and reagents [28]	
Calibration	against commercial reference standards [28, 38]	against reference individuals [36, 37] or plasma quality control standards provided by manufacturer [39]	
Establishing reference ranges	should be done in each laboratory [28]	should be done in each laboratory [37]	
Inter-centre/ analyser variability for reference preparations/ reference ranges	no significant differences in reference preparations between centres or analysers [38]	comparable reference ranges between centres [37]	
Repeatability (within-run imprecision)	-	coefficient of variation depends upon individual test and parameter, between 2% and 13% [37]	
Costs per single analysis	€[9] 14.43 (Clinical Department for Medical and Chemical Laboraroy Diagnostics, Medical University of Vienna)	£[10] 4 [40]/ €[9] 5 [41]	

[1] *min = minutes*
[2] *FIBTEM = one test of ROTEM®*
[3] *g/L = gram per litre*
[4] *mm = millimetre*
[5] *sec = seconds*
[6] *° = grade*
[7] *MCF = maximum clot firmness*
[8] *CA = clot amplitude*
[9] *€ = Euro*
[10] *£ = United Kingdom Pounds*

Clauss fibrinogen assay is "gold standard"

The *Clauss fibrinogen assay* is conducted in the laboratory at 37°C [27]. For measuring the fibrinogen concentration with the Clauss method blood is drawn into tubes filled with trisodium citrate and centrifuged to obtain platelet poor plasma. Following dilution of plasma, thrombin in high concentrations is added and the clotting time is measured. This time is converted into the level of functional fibrinogen (in g/L) using a normogram obtained from a reference sample [27, 28]. Including the centrifugation procedure it takes about 30 minutes to run this assay [35]. The Clauss method may be performed manually or by automated coagulometers [28]. A variety of analysers (including machines), reagents and assay protocols is available and in use [38]. Calibration is done against commercial reference standards, national, or international standards [28, 38] and should be done daily. An evaluation of commercial reference preparations in the United Kingdom found no significant differences in the variability of reference standards between centres or analysers [38]. As necessary for nearly all coagulation assays, it has been recommended to establish reference ranges for each laboratory by testing at least 40 healthy males and females of various age groups [28]. According to the Department for Medical and Chemical Laboratory Diagnostics of the Medical University of Vienna, the cost for a single analysis is about €14.34.

measures level of functional fibrinogen in g/L; takes about 30 minutes

MCF in FIBTEM is considered representative for fibrinogen

ROTEM® rotational thrombelastometry is marketed by Pentapharm GmbH, Munich, Germany [33]. It employs six different tests for the measurement of coagulation disorders, including INTEM, EXTEM, FIBTEM, HEPTEM, APTEM, and NATEM that assess distinct parameters of both the extrinsic and intrinsic pathway of the coagulation and therefore require various activators and inhibitors [30, 33, 42]. The analyser consists of four independent, temperature-controlled measurement channels [37, 42]. For determining the fibrinogen-dependent component of blood coagulation, whole blood drawn into trisodium citrate is used. Because whole blood samples are employed in this method, results depend on the hematocrit level. With the FIBTEM method, the maximum clot firmness (MCF) and the clot amplitude after 5 or 10 minutes runtime are considered to best estimate fibrinogen activity. ROTEM® is a point-of-care device yielding results within 10 to 30 minutes [30, 35-37], depending on the parameter assessed [35]. Calibration is done against reference individuals [36, 37] or plasma quality control standards provided by the manufacturer [39]. It should be done daily and takes about 15 minutes [35]. A multi-centre investigation on reference ranges for ROTEM® found no differences between centres in Austria, Germany and France. However, it has been recommended to establish reference ranges in each laboratory [37]. Moreover, the repeatability (within-run imprecision) seems to depend on the parameter assessed and has been shown coefficients of variation ranging from 2% to 13% [37]. In the FIBTEM test of ROTEM® the single contribution of fibrinogen to the clot firmness is assessed by inhibiting platelets, allowing inferences about the fibrinogen concentration and function [34]. The cost for a single analysis is about €5 [41].

point-of-care device

measures surrogate parameters; takes 10 to 30 minutes

4 Literature search and selection

4.1 PICO-Question

PICO-questions

i) Efficacy and safety of Haemocomplettan® P alone or in combination with Fibrogammin® P in acquired hypofibrinogenemia in children and adults compared to FFP/ Octaplas® SD/ Cryoprecipitate.

ii) Accuracy of ROTEM® point-of-care testing compared to standard laboratory tests for determining the need for the transfusion of blood products in acquired hypofibrinogenemia.

4.2 Inclusion Criteria

Inclusion criteria for relevant studies are outlined in table 4.2-1.

Table 4.2-1: Inclusion Criteria

Population	children and adults with acquired hypofibrinogenemia/ fibrinogen deficiency/ fibrinogen defect
Intervention	Question i) ✲ Haemocomplettan® P ✲ Fibrogammin® P Question ii) ✲ ROTEM® point-of-care testing
Control	Question i) ✲ Fresh Frozen Plasma (FFP) ✲ Octaplas® SD ✲ Cryoprecipitate Question ii) ✲ standard laboratory haematosis tests ✲ Clauss assay
Outcomes	Question i) ✲ bleeding/ haemorrhage ✲ necessity of substitution of blood products other than clotting factors I and XIII ✲ reduction in the use of blood products other than clotting factors I and XIII, particularly FFP/ Octaplas® SD Question ii) ✲ correlation ROTEM®/ standard laboratory tests
Study design	Question i) ✲ for efficacy: all prospective, controlled studies ✲ for safety: all studies

4.3 Search strategy

systematic literature search in several databases

We conducted a systematic literature search in the following databases on 29 October 2009:

- Medline via Ovid
- Embase
- INAHTA – CRD (DARE -NHS EED- HTA)
- The Cochrane Library

additional search on websites

In addition, we searched for assessments on the following websites:

- WHO Health Evidence Network (http://www.euro.who.int/HEN)
- Canadian Agency for Drugs and Technologies in Health (http://www.cadth.ca/index.php/en/home)
- National Coordinating Centre for Health Technology Assessment (http://www.hta.nhsweb.nhs.uk/)
- NHS Institute for Health and Clinical Excellence (http://guidance.nice.org.uk/)

limits: English and German language, 1985 to 2009

827 references

We limited the literature search to articles published in English and German between 1985 and 2009. After deduplication the search yielded 531 results. Furthermore, we conducted a hand search, adding up to 827 references after deduplication. The detailed search strategy is available on request from the LBI-HTA.

contacting of industry and Austrian approval agency

We requested information regarding Haemocomplettan® P and Fibrogammin® P from CSL Behring, Germany. In addition, we asked the Austrian Agency for Health and Food Safety (AGES) PharmMed for information on the national licensure of Haemocomplettan® P and Fibrogammin® P. Moreover, we contacted Pentapharm, Germany for information on the ROTEM system but did not receive a response. We contacted several hospitals in Austria and Germany requesting guidelines for haemostasis management in the perioperative setting.

4.4 Literature Selection

Overall, the literature search yielded 827 results. Two reviewers independently screened, assessed and included the abstracts. In cases of disagreement, we achieved consensus either through discussion or by involving a third person. The selection process is displayed in figure 4.4-1:

827 references, independently selected by 2 reviewers

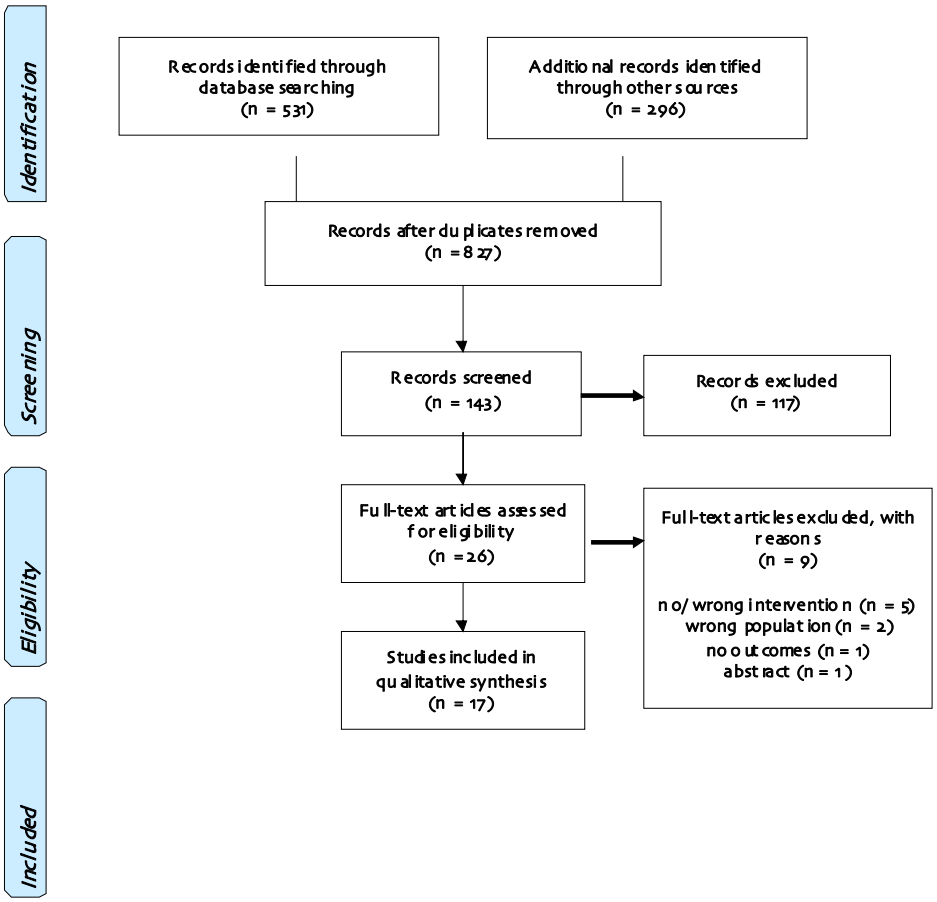

Figure 4.4-1: Selection process (PRISMA Flow Diagram)

5 Evaluating the quality of studies

Two reviewers independently assessed the internal validity of the studies. In cases of disagreement, we achieved consensus either through discussion or by involving a third person. A detailed description of the criteria for assessing the internal validity of individual studies can be found in the Internal Manual of the LBI-HTA [43].

independently by 2 reviewers

6 Extraction of data

One person extracted the data and a second person reviewed the extracted data regarding completeness and accurateness.

6.1 Study results

Overall, we found four studies concerning the efficacy of Haemocomplettan® P [44-47], nine studies assessing the safety of Haemocomplettan® P [45-54], and one trial regarding Fibrogammin® P [55]. In addition, we identified three studies comparing ROTEM® rotational thrombelastometry and standard laboratory haemostasis tests [32, 35, 36]. Moreover, two studies assessed the consumption of blood products before and after ROTEM® implementation [40, 41].

overall 17 studies included

6.1.1 Haemocomplettan® P

Efficacy

Four comparative studies could be identified, two of which were prospective, randomised controlled trials and the remaining two were cohort studies [44-47]. The four studies are summarised in table 6.1.1-1 and table 6.1.1-2. One of the cohort studies consisted of a prospective study group and a historical control, the other one comprised a prospective intervention group and both a prospective and a retrospective control group. Overall, 74 patients – 37 in the intervention and 37 in the control groups - were included in the studies.

4 studies, 74 patients, 37 each in intervention and control arm

Table 6.1.1-1: Studies concerning the efficacy of Haemocomplettan® P in acquired hypofibrinogenemia

author, year, reference no.	funding/ setting	aim	study design/ study population	intervention	primary/ secondary outcomes
Rahe-Meyer N et al., 2009 [46]	CSL Behring, Marburg, Germany/ Hannover Medical School, Germany	assess the efficacy of infusion of fibrinogen concentrate in patients pts.[1] undergoing elective TAAA[2] surgery	comparative study with historical control; I[3]: prospective n[4]=6 vs.[5] C[6]: retrospective n=12	I: administration of Haemocomplettan® P prior to standard transfusion algorithm; trigger: intraoperative blood loss between 60 and 250g[7]; mean amount of fibrinogen substituted 7.8±2.7g C: standard transfusion algorithm (PC[8] and/or FFP[9], if needed)	primary: transfusion of allogeneic blood products intraoperatively and during 24h[10] postoperatively; no transfusion triggers pre-defined; secondary: number of pts. without any transfusion 24h postoperatively; 24h postoperative drainage volume
Rahe-Meyer N et al., 2009 [45]	CSL Behring, Marburg, Germany/ Hannover Medical School, Germany	compare haemostatic effects of conventional transfusion management and fibrinogen concentrate administration in pts. undergoing AV-AA[11]	comparative, prospective study; no randomisation, no blinding; I: n=10 vs. C: n=5	I: administration of Haemocomplettan® prior to standard transfusion algorithm; trigger: intraoperative blood loss between 60 and 250g; mean amount of fibrinogen substituted 7.5g (0.7g SD[12]) C: standard transfusion algorithm (PC and/or FFP, if needed)	primary: transfusion of allogeneic blood products after CPB[13] during 24h postoperatively; no transfusion triggers predefined; secondary: 24h postoperative drainage volume
Karlsson M et al., 2009 [47]	CSL Behring, Marburg, Germany; Sahlgrenska University Hospital, Sweden; Swedish Heart & Lung Foundation/ Sahlgrenska University Hospital, Sweden	assess the feasibility of prophylactic infusion of fibrinogen concentrate to CABG[14] pts.	prospective, randomised controlled phase I-II study; I: n=10 vs. C: n=10	I: pre-operative infusion of 2g fibrinogen concentrate C: no infusion before surgery	primary: i) clinical adverse events: signs of central or peripheral thrombembolism, respiratory or circulatory failure; allergic reactions; ii) graft occlusion assessed by CT[15] 3-4 days after surgery; secondary: i) postoperative bleeding (total amount of chest tube drainage after closure of the sternum and during the first 12 postoperative hours); ii) transfusion of blood products according to predefined transfusion triggers; iii) haemoglobin concentration 24h after surgery; iv) effects of fibrinogen infusion on global haemostasis 2h and 24h after surgery by assessing clot formation via ROTEM®

Fenger-Eriksen C et al., 2009 [44]	CSL Behring, Marburg, Germany; University of Aarhus Research Foundation; A. P. Møller and Hustru Chastine Mc Kinney Møllers Foundation/ Department of Urology, Aarhus University Hospital, Skejby, Denmark	investigate the likelihood of coagulopathy after haemodilution with HES[16] 130/0.4 and evaluate hemostatic effect of concentrated fibrinogen infusion in pts. undergoing radical cystectomy	prospective, double-blind, randomised, placebo-controlled study; I: n=11 vs. C: n=10; overall, 20 pts. were evaluated, 10 each in the I and C; no ITT[17] analysis	I: IV[18] administration of 45mg/kg[19] Haemocomplettan®; trigger: 30% reduction in hematocrit level after dilution with HES[20] 130/0.4 C: IV administration of placebo = 2.25mg/kg isotonic saline 0.9%	primary: MCF[21] as determined by ROTEM®; secondary: i) other thrombelastometric variables; ii) platelet function; iii) thrombin generation; iv) bleeding; v) requirement for peri- and postoperative blood product transfusion according to pre-defined transfusion triggers

[1] *pts = patients*
[2] *TAAA = thoracoabdominal aortic aneurysma*
[3] *I = intervention group*
[4] *n = number*
[5] *vs = versus*
[6] *C = control group*
[7] *g = gram*
[8] *PC = platelet concentrate*
[9] *FFP = fresh frozen plasma*
[10] *h = hours*
[11] *AV-AA = aortic valve operation and ascending aorta replacement*
[12] *SD = standard deviation*
[13] *CPB = cardio-pulmonary bypass*
[14] *CABG = coronary artery bypass graft*
[15] *CT = computed tomography*
[16] *HES = hydroxyethyl starch*
[17] *ITT = intention-to-treat*
[18] *IV = intravenous*
[19] *mg/kg = milligram per kilogram*
[20] *HES = hydroxyethyl starch*
[21] *MCF = maximum clot firmness*

Table 6.1.1-2: Results of efficacy studies of Haemocomplettan® P in acquired hypofibrinogenemia

author, year, reference no.	Results							
	primary outcomes	intervention	control	p-value	secondary outcomes	intervention	control	p-value
Rahe-Meyer N et al., 2009 [46]	total concentrates (u[1]) RBC[2] (u) FFP[3] (u) PC[4] (u)	2.5±4.3 1.0 1.0 0.5	16.4±4.8 4.1 9.1 3.2	<0.05 <0.05 <0.05 <0.05	no transfusion drainage volume (mL[5])	4 (67%) 449±182	0 1093±594	<0.05 <0.05
Rahe-Meyer N et al., 2009 [45]	total concentrates (u) RBC (u) FFP (u) PC (u)	0.7±1.5 0.5±1.1 0.2±0.6 0.0	8.2±2.3 2.4±1.1 4.2±1.1 1.6±0.9	<0.05 <0.05 <0.05 <0.05	drainage volume (mL)	366±199	716±219	<0.05
Karlsson M et al., 2009 [47]	i) <u>signs of thromboembolism:</u> perioperative MI[6] peripheral pulmonary embolus (subclincally) ii) <u>graft occlusion:</u> LIMA LAD[7] graft patency vein graft patency	 0 1 100% 94% (16/17)	 1 0 100% 100% (20)	 0.46	i) postoperative bleeding (mL/12h[8]) ii) blood transfusion (number of pts.[9]) iii) haemoglobin concentration (g/L[10]) iv) global haemostasis	565±150 1/10 (10%) 110±12 no significant differences in ROTEM® variables between I[11] and C[12] at any point in time	830±268 3/10 (30%) 98±8	<0.01 0.29 0.018
Fenger-Eriksen C et al., 2009 [44]	MCF[13]	according to authors significantly better in I versus C but not further specified			i) maximum velocity of clot formation ii) platelet function iii) thrombin generation iv) perioperative blood loss v) <u>blood product transfusion</u> perioperative RBC (u) postoperative RBC during 48h (u) pts. transfused with RBC during 48 h	according to authors significantly better in I versus C but not further specified no data provided according to authors comparable between I and C but not further specified 2.0 (0-6) 1.5 (0-2) 20% (2/10)	 2.5 (0-5) 0 (0-2) 80% (8/10)	 0.91 <0.05 <0.05

[1] *u = units*
[2] *RBC =red blood cells*
[3] *FFP = fresh frozen plasma*
[4] *PC =platelet concentrate*
[5] *mL = millilitre*
[6] *MI = myocardial infarction*
[7] *LIMA LAD = left internal mammary artery/ left anterior descending coronary artery*
[8] *h = hours*
[9] *pts = patients*
[10] *g/L = gram per litre*
[11] *I = intervention group*
[12] *C= control group*
[13] *MCF = maximum clot firmness*

18 pts, 6 in intervention group, TAAA surgery; cohort study

Rahe-Meyer N et al. (2009) [46] assessed the efficacy of fibrinogen concentrate infusion in patients undergoing elective thoracoabdominal aortic aneurysma (TAAA) surgery in a cohort study consisting of a prospective study group (n[10]=6) and a retrospective control group (n=12). The historical control encompassed all patients who underwent elective TAAA surgery at Hannover Medical School in 2006. The characteristics of the study groups at the beginning of the study were similar with regard to age, weight, BMI, sex, and comorbidities. However, the intraoperative cardiopulmonary bypass time differed substantially between the intervention (111 ± 35 minutes) and the control group (139 ± 79 minutes, p-value not stated). The study group received fibrinogen concentrate (Haemocomplettan® P) prior to a standard transfusion algorithm, if intraoperative blood loss was between 60 and 250 g, a threshold empirically set by the authors. Dosing of fibrinogen concentrate was calculated by applying a formula in order to obtain a MCF of 22 mm in the ROTEM® FIBTEM test, which – according to the authors – translates into a plasma fibrinogen level of 3.6 g/L. The mean amount of fibrinogen administered was 7.8 ± 2.7 g. The historical control had received blood products, including platelet concentrates and FFP, according to a standard transfusion algorithm. The primary outcome measures were transfusion of allogeneic blood products during surgery and 24 hours (h) postoperatively. Secondary outcomes encompassed the number of patients without any transfusion during 24 h postoperatively and 24 h postoperative drainage volume. Overall, the intervention group needed significantly less blood products, including RBC concentrates, platelets, and FFP, than the historical control. In addition, all patients (100%) in the control group were in need of transfusion of blood products during 24 h postoperatively as compared to only 33% in the intervention group. This difference was statistically significant as was the difference in 24 h postoperative drainage volume in favour of the intervention group.

mean fibrinogen substitution 7.8 ± 2.7 g

100% in control vs. 33% in intervention group were in need of transfusion

15 pts, 10 in intervention group, AV-AA surgery; cohort study

Rahe-Meyer N et al. (2009) [45] compared the haemostatic effects of conventional transfusion management and fibrinogen concentrate administration in patients undergoing aortic valve operation and ascending aorta replacement (AV-AA) in a cohort study. Both the study group (n=10) and the control group (n=5) were assessed prospectively, whereas data from a historical control (n=42), including all patients who underwent elective AV-AA in 2006, were used to develop a standard transfusion algorithm. There were no significant differences between the three study groups with respect to age, weight, BMI, sex, and comorbidities. However, hours spent in the intensive care unit differed significantly ($p<0.05$) between the study (20 h; 5 h SD[11]) and the control group (31 h; 21 h SD). In addition, patients in the intervention group spent a mean of 10 days (2 days SD) in hospital, whereas individuals in the control group spent a mean of 12 days (12 days SD) in hospital. The intervention group received fibrinogen concentrate (Haemocomplettan® P) prior to the standard transfusion algorithm, if intraoperative blood loss was between 60 and 250 g, a threshold empirically set by the authors. Fibrinogen concentrate dosing was calculated according to a formula with the aim of obtaining a MCF in the ROTEM® FIBTEM test of about 22 mm. The mean amount of fibrinogen substituted was 5.7 g (0.7 g SD). Patients in the prospective control group were transfused according to the standard transfusion algorithm. Primary outcome was transfusion requirements of allogeneic

mean fibrinogen substitution 5.7 g (0.7 g SD)

[10] n = number

[11] SD = Standard Deviation

decreased transfusion requirements in intervention group

blood products during 24 h postoperatively. Secondary outcome was the 24 h postoperative drainage volume. Both the transfusion of allogeneic blood products, including RBC concentrates, platelets and FFP, as well as the 24 h postoperative drainage volume were significantly decreased in the intervention compared to the control group.

20 pts, 10 in intervention group, CABG surgery; randomised controlled phase I-II study

Karlsson M et al. (2009) [47] explored the feasibility of prophylactic infusion of fibrinogen concentrate to patients who underwent coronary artery bypass graft (CABG) surgery at Sahlgrenska University Hospital, Sweden between September and December 2006 in a prospective, randomised controlled phase I-II study comprising ten patients each in the intervention and the control group. Baseline characteristics between the two groups were comparable with regard to age, BMI, sex, smoking status, preoperative aspirin/clopidogrel treatment, and euroSCORE risk stratification index. Participants allocated to the intervention group received 2 g fibrinogen concentrate intravenously prior to surgery, whereas individuals in the control group neither received fibrinogen nor placebo. The primary outcome was clinical adverse events, including signs of central or peripheral thrombembolism, respiratory or circulatory failure, or allergic reactions. Secondary endpoints encompassed postoperative bleeding, transfusion of blood products, haemoglobin concentration 24 h postoperatively, and effects of fibrinogen infusion on global haemostasis 2 h and 24 h postoperatively. Regarding primary outcomes, one patient in the control group developed a myocardial infarction perioperatively. One participant allocated to the intervention group experienced a subclinical – as detected by computed tomography – peripheral pulmonary embolus. There were no statistically significant differences in the LIMA LAD[12] graft patency and the vein graft patency between the two groups. In terms of secondary outcomes, the intervention group showed decreased postoperative bleeding and increased haemoglobin concentration compared to the control group. No significant differences, however, could be observed in the requirement of blood transfusions in the first 12 h postoperatively as well as the global haemostasis 2 h and 24 h postoperatively between the two groups.

2 g fibrinogen prior to surgery

no differecens in postoperative transfusion requirements

[12] LIMA LAD = left internal mammary artery/ left anterior descending coronary artery

Fenger-Eriksen C et al. (2009) [44] assessed the hemostatic effect of fibrinogen concentrate substitution in coagulopathy after haemodilution with hydroxyethyl starch (HES) 130/0.4 in patients undergoing elective radical cystectomy in a sinlge-centre, prospective, double-blind, randomised placebo-controlled trial. The intervention (n=11) and control group (n=10) were comparable at baseline with regard to age and body mass index. In all patients perioperative blood loss was substituted with HES 130/0.4 until hematocrit levels were reduced by 30% compared to baseline values. Then, participants were randomly allocated to either the intervention or the control arm. Patients in the intervention group received 45 milligram per kilogram (mg/kg) fibrinogen concentrate, whereas patients in the control group received 2.25 mg/kg isotonic saline 0.9%. The primary outcome measure was MCF as determined by ROTEM® thrombelastometry. Secondary outcomes encompassed further ROTEM® variables, platelet function, thrombin generation, bleeding, and peri- and postoperative blood products transfused. The authors state that MCF was significantly better in the intervention than in the control group. In terms of secondary endpoints, the maximum velocity of clot formation was significantly better in the fibrinogen group than in the placebo group, whereas blood loss was comparable between the two arms. No data is provided on platelet function and thrombin generation. Regarding transfusion requirements for RBC, FFP, and platelets, thresholds were predefined according to internal and national guidelines, respecitvely. 80% (8/10) of patients in the placebo group were in need of RBC within 48 h postoperatively compared to 20% (2/10) in the intervention group ($p<0.05$). Furthermore, significantly less units of RBC were administered postoperatively to the intervention group compared to the control group, whereas perioperatively this figure was not different between groups. In terms of FFP substitution, both intraoperatively and postoperatively no differences were observed between the two arms. No patients in either group needed platelets.

21 pts, 11 in intervention group, radical cystectomy; double-blind RCT

45 mg/kg fibrinogen concentrate vs. 2.25 mg/kg isotonic saline 0.9%

decreased postoperative transfusion requirements in intervention group

Safety and Mortality

Overall, we identified nine studies [45-54], assessing the safety and mortality of administration of fibrinogen concentrate in patients with acquired hypofibrinogenemia. The results of these studies are outlined in table 6.1.1-3 and in table 6.1.1-4.

9 studies

Table 6.1.1-3: Safety of Haemocomplettan® P in acquired hypofibrinogenemia

author, year, reference no.	Adverse events			Mortality		
	events	intervention	control	cause	intervention	control
Rahe-Meyer N et al., 2009 [46]	re-exploration for bleeding major neurological events renal failure postoperative atrial fibrillation	0 0 0 0	4 (33%) 2 (17%) 2 (17%) 1 (8%)	30-day mortality	0	2 (17%)
Rahe-Meyer N et al., 2009 [45]	re-exploration for bleeding major neurological events postoperative atrial fibrillation	0 0 1 (10%)	1 (20%) 0 1 (20%)	30-day mortality	0	0
Karlsson M et al., 2009 [47]	myocardial infarction (subclinical) peripheral pulmonary embolus	0 1	1 0			

adverse events and deaths only in the control group

In the cohort study *by Rahe-Meyer N et al.* (2009) [46] of patients undergoing TAAA surgery neither adverse events nor deaths occurred in the prospective intervention group (n=6). In comparison, in the historical control in 33% (4/12) of patients re-exploration for bleeding had to be done, 17% (2/12) experienced a major neurological event, 17% (2/12) had a renal failure, and another 8% (1/12) had postoperative atrial fibrillation. In addition, 30 days postoperatively 17% (2/12) of patients had died.

postoperative atrial fibrillation in 1/10 pts in intervention group

In the second cohort study conducted by *Rahe-Meyer N et al.* (2009) of patients undergoing AV-AA the only adverse event in the intervention group was postoperative atrial fibrillation in 10% (1/10) of patients as compared to 20% (1/5) of patients in the control arm. Moreover, 20% (1/5) of patients in the control were in need of re-exploration for bleeding. No major neurological events occurred in either group. 30 days after surgery all individuals, regardless of the assigned group, were alive

subclinical peripheral pulmonary embolus in 1/10 pts in intervention group

In the study by *Karlsson M et al.* (2009) [47] of CABG patients one participant in the intervention group (n=10) developed a subclinical peripheral pulmonary embolus and one patient in the control group (n=10) experienced a perioperative myocardial infarction.

Table 6.1.1-4: All safety studies of Haemocomplettan® P in acquired hypofibrinogenemia

author, year, reference no.	study design/ dose of fibrinogen administered	funding	patient population	number of patients	adverse events	mortality	comments
Rahe-Meyer N et al., 2009 [46]	prospective/ mean 7.8±2.7g[1]	CSL Behring, Marburg, Germany	TAAA[2] surgery	6	0	0	adverse events and deaths in the control possibly related to more severely ill pts.[3] included in the control group
Rahe-Meyer N et al., 2009 [45]	prospective/ mean 7.5g (0.7g SD[4])	CSL Behring, Marburg, Germany	AV-AA[5] surgery	10	1	0	adverse events in the control possibly related to more severely ill pts. included in the control group
Karlsson M et al., 2009 [47]	prospective/ 2g	CSL Behring, Marburg, Germany; Sahlgrenska University Hospital, Sweden; Swedish Heart & Lung Foundation	CABG[6] patients	10	1	not specified	randomised controlled trial
Dickneite G et al., 2009 (CSL Behring) [48]	retrospective/ not specified	CSL Behring, Marburg, Germany	congenital and acquired hypofibrinogenemia	not specified	9	not specified	parmacosurveillance over 22 years
Weinkove R et Rangarajan S (2008) [49]	retrospective/median 4g	no information provided	placental abruption, massive blood loss and transfusion, liver failure, postcardiac surgery, others	30	10 (33%)	12 (40%)	one death prior to fibrinogen concentrate administration; not specified whether adverse events and deaths were related to fibrinogen substitution
Farriols Danés A et al. (2008) [50]	retrospective/median 4g	CSL Behring, Marburg, Germany	sepsis, upper gastrointestinal tract hemorrhage, gynaecological diseases, surgery/trauma, haematological malignancy, liver transplantation, liver insufficiency, other	69	0	30 (44.2%)	according to authors higher plasma fibrinogen levels were associated with increased survival; causes of death not specified
Fenger-Eriksen C et al. (2008) [51]	retrospective/2g in adults, 0.35g in children	no information provided	obstetric complications, paediatric, cardiothoracic bleeding, intra-abdominal bleeding, trauma, other	43	2 (5%)	9 (21%)	according to authors no serious adverse events related to fibrinogen substitution, causes of death: bleeding (8), not specified (1)
Haas T et al. (2008) [52]	retrospective/ 76 (67 ; 100) mg/kg[6]	no information provided	craniosynostosis surgery	9	0	0	children: median age 12 months (25th; 75th percentile: 8; 22)
Schopen G et al. (1994) [54]/ Bonik K et al. (1996) [53]	retrospective/mean 5.6g/ mean 5.2g	Behringwerke AG, Liederbach, Germany/ Centcom Pharma GmbH, Liederbach, Germany	hemorrhages, liver insufficiency, disseminated intravascular coagulation, hyperfibrinolysis, leukaemias	51/ 94	0/ 2 (2%)	16 (31%)/ 20 (21%)	according to authors none of the deaths is related to fibrinogen concentration administration but causes of death are not stated

[1] *g = gram*
[2] *TAAA = thoracoabdominal aortic aneurysma*
[3] *pts = patients*
[4] *SD = standard deviation*
[5] *CABG = coronary artery bypass graft*
[6] *mg/kg = milligram per kilogram*

1,034,389 gram of Haemocomplettan® P distributed over 22 years

Recently pharmacosurveillance data published by *Dickneite G et al.* (CSL Behring) (2009) [48] has become available. According to this report , between 1 January 1986 and 31 August 2008, overall 1,034,389 g of Haemocomplettan® P were handed out across 21 European, Asian, and African countries, equalling around € 364.5 million, if calculated with Austrian prices.

9 cases of thrombosis in 22 years – 3.48 per 100,000 treatment episodes

Over these 22 years, nine cases of central or peripheral thrombosis suspected to be related to fibrinogen concentrate administration were reported, two of which occurred in patients with acquired hypofibrinogenemia. One of these patients was an adult who recovered, the other one was a neonate who died subsequently. The authors estimated the incidence of thrombosis as having been 3.48 (95% CI[13]: 1.59; 6.61) per 100,000 treatment episodes.

30 pts, 33% adverse events, 12% deaths – 6/ 30 died from persistent bleeding

Weinkove R et Rangarajan S (2008) [49] retrospectively reviewed data of a heterogeneous population of 30 adults with acquired hypofibrinogenemia who had received Haemocomplettan® P in a single institution. Overall, of the 30 adults, 12 (40%) patients died in hospital and 10 individuals (33%) experienced adverse events. Causes of death included persistent bleeding (6), sepsis (2), myocardial infarction (2, of which one occurred prior to fibrinogen concentrate administration), liver failure (1), and disseminated carcinoma (1). Adverse events encompassed ischaemic cerebrovascular events (3) and myocardial infarction (1), all of which occurred between 4 and 12 days following fibrinogen administration. However, according to the authors those four ischaemic events were not related to fibrinogen administration. Furthermore, in 4 (50%) women with placental abruption the foetus died in utero, and another 2 (25%) had to undergo an emergency hysterectomy.

69 pts, no adverse events, 44% died within 72 hours

Farriols Danés A et al. (2008) [50] retrospectively assessed the therapeutic effect of fibrinogen concentrate administration in 69 patients with acute as well as chronic acquired hypofibrinogenemia due to various underlying clinical conditions in a third-level hospital. 58% of individuals were female. Causes of acute fibrinogen deficiency comprised sepsis, upper gastrointestinal tract haemorrhage, gynaecological diseases, surgery/ trauma, and others. Chronic fibrinogen deficiency encompassed various underlying diseases, such as haematological malignancies, liver transplantation, and hepatic insufficiency. 32.3% and 44.2% of individuals had died in hospital after 24h and 72h, respectively. According to the authors, no severe adverse events occurred.

43 pts, 5% adverse events, 21 % inpatient deaths

Fenger-Eriksen C et al. (2008) [51] retrospectively explored the effects of fibrinogen concentrate administration in a heterogeneous population of 43 patients with acquired hypofibrinogenemia in serious hemorrhage in a single centre. 65% of individuals were female. Of the 43 patients, 8 (18%) had died intraoperatively and another one had died the day after surgery, adding up to 9 (21%) inpatient deaths. A further two (5%) patients experienced adverse events, including jitter and snoring respiration as well as attacks of shivering.

9 children, no adverse events, no deaths

Haas T et al. (2008) [52] audited fibrinogen concentrate administration in 9 children who had undergone surgery for craniosynostosis repair in a single institution. According to the authors, no bleeding complications or thrombembolic events occurred in any of the children during their hospital stay.

67 pts, no adverse events, 31% of pts died

Schopen G et al. (1994) [54] carried out an interim-analysis of a post-marketing drug monitoring study on Haemocomplettan® P in 67 patients with acquired hypofibrinogenemia, of whom 51 males and females were evaluated. The authors state that no adverse events, particularly no throm-

[13] CI = confidence interval

bembolic complications, occurred. Nevertheless, 16 (31%) individuals died. According to the authors, these deaths were not caused by fibrinogen concentrate administration. However, causes of death are not specified.

96 pts, 2% adverse events, 21% of pts died

In the final analysis of this postmarketing drug monitoring study 96 patients with acquired hypofibrinogenemia across 36 hospitals in Germany were evaluated by *Bonik K et al.* (1996) [53]. However, 94 individuals were finally assessed for tolerability of fibrinogen concentrate. 20 (21%) patients died and a further two (2%) experienced adverse events, namely elevated body temperature. The authors claim that none of the deaths was related to fibrinogen concentrate administration but causes of death remain unclear.

6.1.2 Fibrogammin® P

Efficacy

1 study, 22 pts

One prospective, randomised, double-blind, placebo-controlled study [55] encompassing 22 patients could be found. Information on the trial is summarised in table 6.1.2-1 and in table 6.1.2-2.

22 pts, surgery for gastrointestinal cancer; double-blind, placebo-controlled study

Korte WC et al. (2009) [55] evaluated whether preoperative administration of factor XIII has positive effects on clot firmness and therefore prevents patients from blood loss. Patients undergoing various elective surgical procedures for gastrointestinal cancer who were at increased risk of intraoperative blood loss, defined as elevated preoperative fibrin monomer level of more than 3 microgram per litre (μg/L), were included. A pre-planned interim analysis was done on 22 patients as an intention-to-treat analysis. Seven out of these 22 patients were female (32%). According to the authors, the characteristics of the study groups at the beginning of the study were similar with regard to body mass index, age and American Society of Anaesthesiology physical status classification scores. The intervention group received Fibrogammin (30U/kg) intravenously (IV) 15 minutes into surgery, whereas placebo (Albumin) was administered to the control group. The primary outcome measure was the reduction in MCF 195 minutes into surgery as determined by ROTEM® thrombelastometry. A range of secondary endpoints was assessed as well. Regarding the primary endpoint, the difference in the reduction in MCF 195 minutes into surgery was statistically significant (p=0.004) and was 7% in the intervention as compared to 38% in the placebo group. In terms of secondary outcomes, significant differences were observed for median overall blood loss which was 750 mL in the intervention and 1050 mL in the control group (p=0.041), and for fibrinogen consumption at 195 minutes showing a decrease by 28% in the study group compared to the placebo group (p=0.01). All other secondary outcomes, such as transfusion of blood products, volume support, and length of surgery besides others, did not show significant differences between the two arms.

30U/kg Fibrogammin® P versus Albumin

no differences in transfusion requirements

Table 6.1.2-1: Efficacy of Fibrogammin® P

author, year, reference no.	funding/ setting	aim	study design/ study population	intervention	primary/ secondary outcomes
Korte C et al., 2009 [55]	CSL Behring, Bern, Switzerland; CSL Behring, Hattersheim, Germany; Dade Behring, Marburg, Germany; Pentapharm, Basel, Switzerland; Novo Nordisk, Zurich, Switzerland; Institute for Clinical Chemistry and Haematology and Institute for Anesthesiology, Kantonsspital St. Gallen, St. Gallen, Switzerland/ Kantonsspital St. Gallen, St. Gallen, Switzerland	proof of concept study in order to confirm that pts.[1] at high risk for intraoperative blood loss show reduced loss of clot firmness when factor XIII is administered early during surgery	prospective, randomised, double-blind, placebo-controlled; pts. undergoing elective gastro-intestinal cancer surgery at increased risk for intraperative blood loss as measured by preoperative fibrin monomer levels >3µg/L[2] (n[3]=22)	I[4]: study medication = factor XIII (Fibrogammin) 30U/kg[5]; trigger: 15min[7]. after beginning of surgery C[6]: placebo = Albumin	primary: maximum clot firmness (MCF) assessed by ROTEM®; secondary: median factor XIII activity; prothrombin conversion as measured by F1+2[8]; fibrinogen level; reduction in red blood cell support and infusion volume; lowest ph and lowest body temperature; length of surgery; median overall blood loss

[1] *pts = patients*
[2] *µg/L = microgram per litre*
[3] *n = number*
[4] *I = intervention group*
[5] *U/kg = units per kilogram*
[6] *C = control group*
[7] *min = minutes*
[8] F_{1+2} *=prothrombin fragments*

Table 6.1.2-2: Results of efficacy of Fibrogammin® P

author, year, reference no.	Results							
	primary outcome	intervention	control	p-value	secondary outcomes	intervention	control	p-value
Korte C et al., 2009 [55]	reduction in MCF[1] after 195min.[2]	7%	38%	0.004	median overall blood loss (mL[3])	750; (-29%)	1050	0.041
					fibrinogen consumption at 195min.	-28%		0.01
					no statistically significant differences between the intervention and the control group with regard to prothrombin conversion, IV[4] fluids, transfusion of RBC[5], FFP[6], or platelets, pH, body temperature and length of surgery			

[1] *MCF = maximum clot firmness*
[2] *min = minutes*
[3] *mL = millilitre*
[4] *IV = intravenous*
[5] *RBC = red blood cells*
[6] *FFP = fresh frozen plasma*

Safety and Mortality

adverse events in 3/ 22 pts

As can be seen in table 6.1.2-3, in the study by *Korte WC et al.* (2009) a total of three out of 22 patients experienced adverse events, all of whom were assigned to the intervention group. According to the authors, these adverse events were unlikely to be related to the administration of factor XIII. Observed side effects included one episode of hypotension following the administration of Fibrogammin® P in one patient. Furthermore, one patient developed a deep vein thrombosis one week after surgery. Another patient developed postoperative ascites and pleural empyema with sepsis and died from a myocardial infarction 30 days after surgery. In terms of mortality, three patients had died in each of the two groups after a median follow-up of 340 days. The cause of mortality is only stated for one patient in the intervention group, who died from myocardial infarction 30 days after surgery. No information is provided about the causes of death in the other five patients.

6 pts died

Table 6.1.2-3: Safety of Fibrogammin® P

author, year, reference no.	Adverse events			Mortality		
	events	intervention	control	cause	intervention	control
Korte C et al., 2009 [55]	overall	3	0	overall	3	3
	hypotension	1	0	not stated	2	3
	deep vein thrombosis	1	0	myocardial infarction	1	0
	postoperative ascites	1	0			
	pleural empyema with sepsis	1	0			
	myocardial infarction	1	0			

6.1.3 Comparison ROTEM® rotational thrombelastometry/standard laboratory hemostasis tests

3 studies, 147 pts, liver transplant, trauma, postpartum haemorrhage

Three studies were identified evaluating the ability of rotational thrombelastometry in detecting coagulation disorders and guiding blood transfusions, respectively, as well as exploring correlations between ROTEM® and standard laboratory hemostasis tests [32, 35, 36]. Results of the studies are shown in table 6.1.3-1. Two of these – both published in 2006 - are prospective, observational, single-arm studies. The remainder – published in 2009 - is a comparative observational study with a prospective intervention and a historical control group. In total, 147 patients were assessed, comprising a heterogeneous patient population, including patients undergoing orthotopic liver transplantation (OLT), trauma patients and women experiencing postpartum haemorrhage (PPH).

Table 6.1.3-1: Use of ROTEM® rotational thrombelastometry to detect fibrinogen deficiency in acquired hypofibrinogenemia

author, year, reference no.	funding	aim	study design/ study population	cut-off values Clauss fibrinogen assay	cut-off values ROTEM® FIBTEM	test accuracy		correlation/ agreement
Coakley M et al., 2006 [32]	no information provided	compare extent to which administration of blood products would be indicated using ROTEM®/ conventional coagulation tests in pts.[1] undergoing OLT[2]	prospective, observational, single-arm, n[3]=20 OLT pts.	fibrinogen <1 g/L[4]; met in 39% of samples	FIBTEM MA[5]=MCF[6] <8mm; met in 55% of samples	not specified		Pearson's correlation: significant correlation r=0.75; p[7]≤0.01 Kappa-analysis: moderate agreement k=0.42; p≤0.05
Rugeri L et al., 2006 [36]	BIODIS, Signes, France	assess ability of ROTEM® to detect various coagulation disorders in trauma pts. and its usefulness in guiding transfusion of blood products	prospective, observational, single-arm, n=90 trauma pts.	fibrinogen <1 g/L	CA_{10}[8]-FIBTEM=5mm[9]	sensitivity specificity PPV[10] NPV[11]	91% (72; 93) 85% (84; 86) 55% (45; 60) 99% (97; 100)	Spearman's rank test: significant correlation r=0.85; p≤0.001
Huissoud C et al., 2009 [35]	none	evaluate ability of ROTEM® to early detect decrease in fibrinogen levels in PPH[12]	prospective, observational, n=91 women: prospective study group with PPH, n=37; retrospective control group without PPH, n=54	fibrinogen <1 g/L	CA_{5}[13]/ CA_{15}[14]-FIBTEM= 4mm/ 5mm	sensitivity specificity PPV NPV	100/ 100% 86% (76; 96)/ 88% (79; 97) 13% (3; 22)/ 14% (5; 24) 100/ 100%	Spearman's rank test: fibrinogen/CA_5 r= I[15]: 0.86; p<0.0001 vs.[16] C[17]: 0.83; p<0.0001 fibrinogen/CA_{15} r= I: 0.84; p<0.0001 vs. C: 0.83; p<0.0001

[1] *pts = patients*
[2] *OLT = orthotopic liver transplantation*
[3] *n = number*
[4] *g = gram per litre*
[5] *MA = maximum amplitude*
[6] *MCF = maxiumum clot firmness*
[7] *p = p-value*
[8] *CA_{10} = clot amplitude at 10 minutes*
[9] *mm = millimetre*
[10] *PPV= positive predictive value*
[11] *NPV = negative predictive value*
[12] *PPH = postpartum hemorrhage*
[13] *CA_5 = clot amplitude at 5 minutes*
[14] *CA_{15} = clot amplitude at 15 minutes*
[15] *I = intervention group*
[16] *vs = versus*
[17] *C = control group*

Coakley M et al. (2006) [32] employed both ROTEM® thrombelastostometry and conventional coagulation tests in 20 patients undergoing OLT in a prospective, observational, single-arm study. Overall, there was a significant correlation between ROTEM® FIBTEM maximum amplitude (MA) = MCF and Clauss fibrinogen ($r=0.75$; $p\leq0.01$) but only moderate agreement between ROTEM® FIBTEM MA results and Clauss fibrinogen results as to when substitute fibrinogen ($k=0.42$; $p\leq0.05$). ROTEM® FIBTEM met criteria for fibrinogen transfusion – defined as FIBTEM MA/MCF <8mm - in 55% of blood samples, whereas Clauss fibrinogen assay met criteria for replacement of fibrinogen – defined as <1 g/L – in only 39% of blood samples taken.

20 liver transplant pts

fibrinogen cut-off <1 g/L: Clauss 39% vs. ROTEM® 55% of samples suggest substitution

Rugeri L et al. (2006) [36] compared ROTEM® thrombelastostometry and conventional coagulation tests in a prospective, observational, single-arm study comprising 90 trauma patients, 23% of whom were female. The authors defined normal ROTEM® values based on blood samples taken from 70 healthy individuals, 30% of whom were female. Correlations were assessed for fibrinogen level and clot amplitude at 10 minutes (CA_{10})-FIBTEM ($r=0.85$; $p<0.001$), prothrombin time (PT) and clot amplitude at 15 minutes (CA_{15}) -EXTEM ($r=0.66$; $p<0.001$), activated partial thromboplastin time (aPTT) and clot formation time (CFT)-INTEM ($r=0.91$; $p<0.001$) as well as for platelet count and CA_{15}-INTEM ($r=0.57$; $p<0.001$). The ROTEM® cut-off parameter for fibrinogen was CA_{10}-FIBTEM of 5 mm corresponding to a fibrinogen level as determined by Clauss assay of <1 g/L. ROTEM® FIBTEM showed a sensitivity of 91% and a specificity of 85%. Although the test had a high NPV of 99%, indicating that in 99% of negative test results a fibrinogen level <1g/L can be ruled out, the PPV was only 55%. Therefore, in only 55% of positive test results the fibrinogen level truly was less than 1 g/L.

90 trauma pts

ROTEM® FIBTEM: PPV 55%, i.e. in only 55% of positive tests the fibrinogen level truly was <1 g/L

Huissoud C et al. (2009) [35] conducted an observational study with a prospective intervention group consisting of 37 women experiencing PPH and a historical control group of 54 women without PPH. The authors explored correlations between ROTEM® FIBTEM test results and fibrinogen level as determined by Clauss assay. A negative correlation could be found between fibrinogen level and FIBTEM clotting time (CT) in both the intervention and the control group but it was only significant in the control group. Furthermore, positive and statistically significant correlations were found between fibrinogen level and FIBTEM CA_5/CA_{15}, and MCF in both arms. Cut-off values for CA_5-FIBTEM were 6/5/4 mm and for CA_{15}-FIBTEM 8/6/5 mm according to Clauss fibrinogen levels of <2/1.5/1 g/L. The sensitivity of ROTEM® FIBTEM was 100% in all cut-off values chosen for FIBTEM in PPH, whereas the specificity ranged from 84% to 88%. The NPV was 100% in all cut-off values but the PPV decreased steadily from 50/46% in CA_5-/CA_{15}-FIBTEM 6/8 mm – according to fibrinogen levels of <2 g/l - to only 13/14% in CA_5-/CA_{15}-FIBTEM 4/5 mm – corresponding to fibrinogen levels of <1 g/L.

37 postpartum hemorrhage pts

ROTEM® FIBTEM: PPV 50% (according to fibrinogen level <2 g/L) decreased to 13% (according to fibrinogen level <1 g/L)

6.1.4 Comparison transfusion requirements and costs before/ after implementation of ROTEM® rotational thrombelastometry

2 studies, 2412 pts

Two studies [40, 41] – comprising 2412 patients overall - could be identified comparing transfusion requirements, including number of patients transfused with blood products as well as units of blood products transfused, patient-relevant outcomes, and costs, during six months before and after implementation of ROTEM® rotational thrombelastometry in two cardiac surgery units. The results of these studies are summarised in table 6.1.4-1 and in table 6.1.4-2.

990 pts, cardiac intensive care unit

Anderson L et al. (2006) [40] evaluated the reduction in the consumption of RBC, FFP and platelets associated with the implementation of ROTEM® thrombelastometry for postoperative transfusion management in 990 sequential patients in a cardiac intensive care unit in 2001/ 2002. The authors showed statistically significant decreases both in the number of patients transfused with RBC, FFP, and platelets as well as in the units of blood products transfused after ROTEM® implementation compared to the period before its use. However, no significant differences were observed in patient-relevant outcomes, including discharge haemoglobin level, length of stay in intensive care unit and hospital, and surgical re-exploration.

no difference in patient-relevant outcomes

1422 cardiosurgical pts

Spalding GJ et al. (2007) [41] assessed the reduction in treatment costs of 1422 cardiosurgical patients associated with ROTEM® implementation in a single institution within one year. The authors concluded that there was a significant decrease in the monthly consumption of platelets and FXIII but not in the use of RBC and FFP, along with an increase in fibrinogen consumption. Furthermore, overall monthly costs for blood products and factor concentrates decreased from € 125,828 to € 55,925. Declines could be seen in the costs for RBC, FFP, platelets, and FXIII, whereas at the same time costs for fibrinogen rose almost four-fold from € 4,025 before to € 15,812 after ROTEM® implementation.

reduced overall costs

Table 6.1.4-1: Comparison of transfusion requirements and costs in acquired hypofibrinogenemia in cardiosurgical patients before and after ROTEM® implementation

author, year, reference no.	funding	aim	study design/ study population	inclusion/exclusion criteria	characteristics of the study groups at the beginning of the study	primary outcomes
Anderson L et al., 2006 [40]	Scottish National Blood Transfusion Serivce	evaluate the reduction in the consumption of RBC, FFP and platelets associated with the implementation of ROTEM® thrombelastometry	before/after study; retrospective analysis; n=990 sequential pts. period 1 = before implementation of ROTEM® = July 2001 to December 2001; n=488 pts. period 2 = after implementation of ROTEM® = February 2002 to July 2002; n=502 pts.	postoperative transfusion management in a cardiac intensive care unit: inclusion period 1: excessive bleeding postoperatively as defined by fulfilling certain criteria, if requested by the surgeon or anaesthesist vs. period 2: not specified	no significant differences between the two groups with regard to age, gender, preoperative haemoglobin concentration, platelet count, fibrinogen concentration, and INR, valve surgery, cross clamp time; significant differences between the two groups with regard to EuroSCORE risk index, preoperative PTT, coronary artery bypass grafting, combined valve/bypass surgery, time in theatre, bypass time	discharge Hb (g/dL) length of stay in intensive care unit (hours) length of stay in hospital (days) surgical re-exploration
Spalding GJ et al., 2007 [41]	no information provided	evaluate the reduction in treatment costs of cardiosurgical patients associated with the implementation of ROTEM®	before/after study period 1 = before implementation of ROTEM®; n=729 pts. period 2 = after implementation of ROTEM®; n=693 pts.	all pts. undergoing cardiac surgery in a single institution within one year	no significant differences between the two groups with regard to age, gender, cardiac surgery procedure, early mortality, early resternotomy significant difference between the two groups with regard to EuroSCORE risk index	not specified

Table 6.1.4-2: Results of studies assessing transfusion requirements and costs before and after ROTEM®implementation

Results					
author, year, reference no.	**transfusion requirements, patient-relevant outcomes, costs**		**before ROTEM®-implementation**	**after ROTEM®-implementation**	**p-value**
Anderson L et al., 2006 [40]	number of pts.[1] transfused with	RBC[2]	294/488 (60%)	270/502 (53%)	0.04
		FFP[3]	81/488 (17%)	60/502 (12%)	0.037
		platelets	77/488 (16%)	56/502 (11%)	0.033
	units transfused (number)	RBC	1094	931	0.003
		FFP	343	271	0.036
		platelets	96	75	0.032
	patient-relevant outcomes	discharge Hb[4] (g/dL[5])	10±1.2	9.9±1.2	n. s.[6]
		length of stay in intensive care unit (hours)	23	24	n. s.
		length of stay in hospital (days)	7	7	n. s.
		surgical re-exploration	19/488 (4%)	16/502 (3%)	n. s.
Spalding GJ et al., 2007 [41]	monthly consumption	RBC (unit)	439	368	n. s.
		PltC[7] (unit)	59	28	0.000
		FFP (unit)	118	116	n. s.
		PCC[8] (500 IU[9])	130	27	0.000
		Fibrinogen (1g[10])	14	55	n. s.
		rFVIIa[11] (120 IU)	11	1	0.000
		FXIII[12] (1250 IU)	17	8	0.001
		Aprotinin (2.5 Mio IU)	109	43	0.000
		Desmopressin (40µg[13])	22	39	0.000
	monthly costs in Euro	cumulative	€ 125,828	€ 55,925	
		RBC (1 unit á €[14] 70)	€ 30,730	€ 25,620	
		PltC (1 unit á € 500)	€ 29,500	€ 14,000	
		FFP (1 unit á € 51)	€ 6,018	€ 5,916	
		PCC (500 IU á € 120)	€ 15,600	€ 3,240	
		Fibrinogen (1g á € 287.5)	€ 4,025	€ 15,812	
		rFVIIa (120 IU á €1,512)	€ 16,632	€ 604	
		FXIII (1250IU á € 405)	€ 6,885	€ 3,240	
		Aprotinin (2.5 Mio IU á € 123.75)	€ 13,488	€ 5,321	
		Desmopressin (40µg á 134.12)	€ 2,950	€ 5,230	

[1] *pts = patients*
[2] *RBC = red blood cells*
[3] *FFP = fresh frozen plasma*
[4] *Hb = haemoglobin*
[5] *g/dL = gram per decilitre*
[6] *ns = not significant*
[7] *PltC = platelet concentrate*
[8] *PCC = prothrombin complex concentrate*
[9] *IU = international units*
[10] *g = gram*
[11] *rFVIIa = recombinant clotting factor VIIa (activated)*
[12] *FXIII = clotting factor XIII*
[13] *µg = microgram*
[14] *€ = Euro*

7 Quality of studies

7.1 Haemocomplettan® P

few studies, small sample sizes, poor quality of studies

We assessed the methodological quality of the two cohort studies by *Rahe-Meyer N et al.* [45, 46] according to the criteria for the evaluation of cohort studies outlined in the Internal Manual of the LBI-HTA [43]. In addition, we evaluated the methodological quality of the two randomised controlled trials by *Karlsson M et al.* [47] and *Fenger-Eriksen et al.* [44] according to the CONSORT statement for improving the quality of reports of parallel-group randomised trials [56]. Overall, the quality of the studies identified is poor. On the one hand, results could have been flawed by introducing systematic errors. On the other hand, results could have been obtained simply by chance as well due to small sample sizes, ranging from 6 to 10 participants in the intervention groups and 5 to 10 individuals in the control groups.

selection bias

The major flaw in the study by *Rahe-Meyer N et al.* (2009) [46] appears to be the introduction of selection bias. Although the historical control group seems to be a consecutive cohort of patients recruited in a single institution during 2006, it remains unclear whether the intervention group was selected consecutively as well. Exclusion criteria are clearly stated by the authors and the same criteria were applied to both groups. Nevertheless, the historical control may have been different from the intervention group because they were recruited at different points in time and therefore could have been influenced by different confounding factors, ultimately leading to selection bias. The differences in cardio-pulmonary bypass time, complication rates and in-hospital mortality between the two groups suggest that they may have been different at baseline, particularly with regard to the severity of TAAA with the control group being more severely ill than the intervention group. However, baseline data regarding the severity of TAAA to overcome that suspicion is lacking. The introduction of measurement bias cannot be ruled out as the level of bleeding was assessed differently in the two groups. The primary outcome parameter of the trial was the amount of blood products substituted postoperatively and it could be shown that less blood products were transfused in the intervention group compared to the control group. However, given the lack of pre-defined transfusion triggers, this endpoint might not have been objective. The authors neither specify the length of follow-up nor the number of patients lost to follow-up in each group which could, particularly if different between the two groups, introduce systematic errors. Small sample sizes in both groups may have led to results that could have been obtained simply by chance as well. Finally, the causes of death in two patients in the control group are not stated.

different confounding factors

more severly ill pts in control group?

measurement bias

small sample size: results obtained by chance?

selection bias

different groups at baseline?

lack of blinding

small sample sizes

In the second cohort study identified by *Rahe-Meyer N et al.* (2009) [45] selection bias could have arisen as well. It seems that the historical control of 42 participants was recruited consecutively in a single hospital during 2006 but this remains unclear for both the prospective intervention and control group. Detailed inclusion criteria are not provided, exclusion criteria are described in-depth and were applied equally to all groups. Although the authors emphasise that the study groups were similar at baseline, they do not provide information regarding the severity of the underlying condition. Moreover, hours spent in the intensive care unit differed significantly ($p<0.05$) between the study (20 h; 5 h SD) and the control group (31 h; 21 h SD). In addition, patients in the intervention group spent a mean of 10 days (2 days SD) in hospital, whereas individuals in the control group spent a mean of 12 days (12 days SD) in hospital suggesting that the study group might have consisted of healthier individuals overall. Time periods of recruitment varied between groups and this may have introduced selection bias. In addition, lack of blinding may have led to measurement bias. No information is provided on length of follow-up and number of patients lost to follow-up which could potentially have led to systematic errors, particularly if different between the groups. Finally, small sample sizes in both groups may have led to results that could have been obtained simply by chance as well.

selection bias

underpowered study

lack of blinding

intention-to-treat analysis?

In the randomised controlled trial conducted by *Karlsson M et al.* (2009) [47] no information is provided on how randomisation to either the intervention or the control group was achieved. In addition, allocation concealment using blank envelopes is considered inadequate. Baseline characteristics were similar between the two groups. However, the small sample size may have resulted in the introduction of random errors. Not only is an explanation about how the sample size was determined missing but the authors also state that due to the small sample size the study is underpowered to confirm the efficacy and safety of administration of fibrinogen concentrate to CABG patients. Lack of blinding, particularly of those administering the study drug and assessing the outcomes, and failure to administer placebo to the control group could have influenced treatment decisions during surgery and subsequently outcomes. Neither the period of follow-up, nor the number of individuals lost to follow-up in each group is specified. As an intention-to-treat analysis is not mentioned at all, it remains questionable whether analysis of results was done adequately or not.

In the second randomised placebo-controlled trial by *Fenger-Eriksen et al.* (2009) [44] the study manuscript was developed according to the CONSORT statement [56]. Inclusion and exclusion criteria were well defined and equally applied to all study participants. Randomisation was done intraoperatively using blank envelopes. However, it remains unclear who was in charge of conducting the randomisation. The authors claim that the groups were similar at baseline with regard to age, body mass index, and some laboratory parameters but no further information is provided, particularly in terms of severity of the underlying condition. Considering that only two out of 20 participants were female without knowing which group they were allocated to, the two arms might have been intrinsically different at the beginning of the trial. Blinding of the study staff was achieved by preparing and administering the study drugs by another person. No information is provided about who assessed the outcomes and whether this person was blinded to group assignment. Allocation concealment seems to have been done appropriately. Thresholds for transfusion of blood products, including RBC, FFP, and platelets were pre-defined. The period of follow-up is not stated. Although at first 11 participants had been allocated to the intervention group, final analysis was done on ten patients only. Hence, analysis was not done as an intention-to-treat analysis. In terms of outcomes, data presented were not compared between the intervention and the control group but between two different points in time – at baseline and before administration of fibrinogen concentrate or placebo. However, the authors claim that the primary outcome MCF and maximum velocity of clot formation were significantly better in the fibrinogen than in the placebo group without providing supporting data. In addition, it remains questionable whether this difference would have been significant, if done as an intention-to-treat analysis. Regarding safety, neither adverse events nor side effects are mentioned at all.

selection bias

different groups at baseline?

outcome assessor blinded to group assignment?

no intention-to-treat analysis

no data for primary outcome provided

no safety data presented

single institution, small studies, retrospective, heterogeneous patient population, multiple underlying clinical conditions, critically ill pts

In terms of safety and mortality of Haemocomplettan® P administration[45-54], the available evidence is challenging for various reasons. The majority of the studies were conducted in a single institution, encompassing a considerably heterogeneous patient population with multiple underlying clinical conditions leading to hypofibrinogenemia and bleeding, such as surgery, trauma, obstetric complications, liver insufficiency, haematological malignancies, besides others. Most of the studies included a small number of severely ill patients, ranging from six to 94 individuals. The amounts of fibrinogen administered vary considerably. Follow-up periods are either not stated, or short, or differ between studies. Most importantly, in most of the trials data was reviewed retrospectively which might have led to biased results. Pharmacosurveillance data, collected over 22 years by CSL Behring, only revealed nine cases of thrombosis overall, of which two occurred in acquired fibrinogen deficiency. It remains unclear how many patients had been treated over this time period but the authors estimated the incidence of thrombosis as being 3.48 (95% CI: 1.59; 6.61) per 100,000 treatment episodes. However, these figures are most-likely underestimated due to underreporting which is very likely not only in developed European countries but particularly in developing countries in Asia and Africa, where there might not even be a system for reporting of adverse events in place. Remarkable differences in terms of adverse events between the studies, ranging from zero to 33%, and mortality, ranging from zero to 44%, suggest that these figures may also depend on the severity of the underlying condition and do not allow inferences about an association with fibrinogen concentrate administration. In addition, because of the variety of underlying diseases included, no conclusion can be drawn on a specific sub-population of patients.

underlying clinical condition is essential; adverse events: 0 to 33%, mortality 0 to 44%

7.2 Fibrogammin® P

selection bias

22 pts overall, but how many in intervention vs. control?

no comparison between intervention and control at baseline

We assessed the quality of the study conducted by *Korte WC et al.* (2009) [55] according to the CONSORT statement for improving the quality of reports of parallel-group randomised trials [56]. Although the authors describe in detail inclusion and exclusion criteria for participant recruitment, they do not provide information about the setting, location, or time period of recruitment and data collection. Overall, 22 patients were enrolled in the study but no information is given about who enrolled participants and how many participants were allocated to each the study group and the placebo group. Despite the small sample size, randomisation was done in a blockwise manner but no information about the block size is provided. Hence, selection bias may have been introduced. Allocation concealment is not mentioned at all. Baseline demographics and clinical characteristics of patients are sparse with lack of a comparison between intervention group and control group. Blinding appears to have been done

adequately. It remains unclear who assessed the outcomes and how assessors had been trained. Dates and time periods of follow-up are not stated. Although the surrogate endpoint MCF was significantly better in the intervention than in the control group, no differences could be observed in patient-relevant endpoints, such as transfusion requirements or length of surgery, most likely because the study was underpowered to detect such differences. Causes of death are poorly reported with stating the cause of death for one out of six patients only. The generalisability of the study results is questionable because of the high-risk population undergoing a variety of surgical procedures. Overall, due to major flaws in the quality of the study, the possible introduction of bias cannot be excluded jeopardising both the internal and external validity of study results.

underpowered study

causes of death not reported for 5 out of 6 pts

7.3 ROTEM® rotational thrombelastometry versus standard laboratory hemostasis tests

We assessed the methodological quality of the studies [32, 35, 36] according to the STARD statement for the reporting of studies of diagnostic accuracy [57, 58].

In the study by *Coakley M et al*. (2006) [32] selection bias could have been introduced because important information on detailed inclusion as well as exclusion criteria is missing and it remains unclear whether a consecutive series of patients was recruited or not. Baseline characteristics are sparse and are confined to the Child's classification of the severity of liver cirrhosis. Another possible source of bias in this trial is measurement bias because the tests were performed at different points in time. Furthermore, information about the persons conducting the tests is lacking, particularly about their expertise and whether they were blinded or not. In addition, the authors do not provide information on test accuracy, namely sensitivity, specificity, positive predictive value and negative predictive value of ROTEM® FIBTEM.

no inclusion/ exclusion criteria

sparse baseline data

measurement bias, lack of blinding

In the study by *Rugeri L et al*. (2006) [36] patients were enrolled consecutively into the study. Characteristics of the participants at the beginning of the trial are not stated. No information is provided on who executed the coagulation tests and whether this person was blinded to the results of the respective other test. The authors provide detailed information on the test accuracy.

baseline characteristics not stated, blinding?

Although a consecutive series of women were enrolled into the intervention group in the study by *Huissoud C et al.* (2009) [35], selection bias may have arisen by comparing a prospective intervention group and a historical control group because participants were selected at different points in time. Baseline characteristics of the two study groups are sparse and include maternal age and term of pregnancy only. The introduction of measurement bias may have been possible because measurement of ROTEM® values was conducted by three clinicians. The authors provide in-depth information on the test accuracy.

sparse baseline characteristics

measurement bias

7.4 Transfusion requirements and costs before/after implementation of ROTEM® rotational thrombelastometry

2 studies, single institution, cardiosurgical pts

The two studies identified [40, 41] were both conducted in a single institution and solely focused on patients undergoing cardiosurgical procedures.

transfusion requirements

Anderson et al. (2006) [40] showed that although the number of patients transfused as well as the number of units of blood products substituted decreased after ROTEM® implementation, patient-relevant outcomes, including discharge haemoglobin (Hb), length of stay in intensive care unit (ICU) and in hospital, and surgical re-exploration for bleeding, were not affected.

costs for blood products

Spalding GJ et al. (2007) [41] concluded that ROTEM® implementation decreased monthly costs for most blood products, except for fibrinogen, for which monthly costs increased almost four-fold. Therefore, it can only be said that ROTEM® implementation was a cost-effective strategy in these two specific settings but no conclusions can be drawn on other sub-populations of patients. Nevertheless, patient-relevant outcomes should be given priority over cost-reduction strategies and benefits should be carefully weighed against possible harms.

8 Discussion

Haemocomplettan® P and Fibrogammin® P have been licensed in Austria since 1994 and 2000, respectively, although there is a lack of studies assessing the efficacy and safety of these drugs. In this systematic review we identified only sparse evidence, mainly from clinical trials in highly selected individuals, that patients may benefit from substitution of fibrinogen and factor XIII in certain circumstances. However, important questions regarding evidence-based substitution of fibrinogen and factor XIII remain unclear:

approved in Austria since 1994 and 2000

What is the threshold for substitution of fibrinogen?

In all clinical trials assessed, fibrinogen was substituted regardless of fibrinogen plasma levels [44-47]. Therefore, we were not able to identify cut-off values for administration of fibrinogen, i.e. certain plasma levels at which substitution of fibrinogen would be indicated.

threshold level for fibrinogen substitution not established

Acquired hypofibrinogenemia frequently occurs due to impaired synthesis, increased loss, or increased consumption of fibrinogen for various reasons. In massive haemorrhage the substitution of crystalloids and colloids lead to the development of dilutional coagulopathy with fibrinogen being the first clotting factor to reach a critical level [5, 6]. This critical level is discussed controversially. Recent guidelines from Great Britain, Canada, Germany and from a European Critical Care Expert Group suggest empirically set thresholds of less than 1 g/L for fibrinogen substitution [6-10]. The German Medical Assciation sets an additional threshold at less than 1.5 g/L in severe bleeding [10]. Only the Austrian ÖGARI guidelines for trauma-related massive bleeding propose a cut-off of less than 1.5 to 2 g/L: However, the higher the cut-off level, the more patients will be eligible for fibrinogen substitution and the more fibrinogen concentrate will be consumed, increasing costs. Overall, for none of the empirically defined thresholds there is any evidence for the "appropriate" fibrinogen substitution in any patient population.

different thresholds in guidelines from GB, Canada, Europe and Austria

highest cut-offs in ÖGARI-guidelines

Which amount of fibrinogen needs to be substituted?

In the studies identified, the total amount of fibrinogen administered varied considerably between the trials, ranging from about 2 to 8 g per patient. The amount of fibrinogen substituted may depend upon the underlying clinical condition and the magnitude of blood loss. Therefore, the variability in fibrinogen dosage may have been associated with the heterogeneous patient populations assessed. However, there is lack of evidence both proving the effect-size to be dose-dependent and providing maximum dosage cut-offs. There is not even a reasoning provided for the different dosages.

no established dosing guidelines

dose-dependent effect-size? maximum dosage cut-off?

In two of the four efficacy studies of Haemocomplettan® P[45, 46] MCF was assessed by ROTEM® FIBTEM to guide fibrinogen transfusion. The rationale behind measuring MCF was to draw conclusions on intraoperative fibrinogen plasma levels. However, MCF values were chosen arbitrarily. In the study by *Karlsson et al.* (2009) [47] all patients in the intervention group received 2 g of fibrinogen, regardless of plasma fibrinogen levels or ROTEM® values. In the remaining study by *Fenger-Eriksen et al* (2009) [44] fibrinogen concentrate was administered according to body weight to all patients in the intervention group, regardless of plasma fibrinogen levels or ROTEM® values.

surrogate parameter MCF, arbitrarily chosen MCF cut-off values

As for the substitution of other coagulation factors, such as factors VIII or IX in haemophilia, or the prothrombin time in prothrombin-complex therapy, dosing of fibrinogen or factor XIII substitution should be guided by plasma levels and recovery. The gold standard for fibrinogen measurement is the Clauss assay, ROTEM® has been proven not to be effective for a reliable estimation of fibrinogen activity (see below).

How accurate is ROTEM® FIBTEM in predicting the need for fibrinogen transfusion?

ROTEM® rotational thrombelastometry seems to have some advantages over conventional laboratory hemostasis tests, particularly in the setting of massive bleeding, because it may be performed on-site and more quickly than the Clauss assay.

sensitivity, specificity, NPV were good or fair but PPV was poor - 13 to 55%

We identified two studies, providing information about the test accuracy of ROTEM® FIBTEM in estimating fibrinogen plasma levels by employing various FIBTEM values [35, 36]. Although the sensitivity, specificity, and NPV of ROTEM® FIBTEM were good or at least fair, the PPV only ranged between 13% and 55% with wide 95% CI for different FIBTEM test results. Therefore, only a small percentage of positive FIBTEM results - corresponding to a Clauss fibrinogen level <1 g/L - truly was in accordance with a fibrinogen concentration of less than 1 g/L.

sensitivity 91%, specificity 85%, NPV 99%, PPV 55%

In the study by *Rugeri L et al*. (2006) [36] ROTEM® FIBTEM showed a sensitivity of 91% with a wide 95% CI, ranging from 72% to 93%, indicating that 91% of patients with a CA_{10}-FIBTEM result of 5mm truly had a fibrinogen level <1 g/L. The specificity of 85% (95%CI: 84; 86%) suggests that 85% of individuals with a CA_{10}-FIBTEM result of 5mm truly did not have a fibrinogen level of <1 g/L. Although the test had a high NPV of 99% (95% CI: 97; 100%), indicating the proportion of tests with a negative test result which truly did not translate into a fibrinogen level of <1 g/L, the PPV was only 55% with a wide 95% CI ranging from 45% to 60%. Therefore, in only 55% of positive test results the fibrinogen level truly was <1 g/L. Hence, it remains questionable whether ROTEM® FIBTEM is an adequate test in the setting of haemorrhage in trauma patients because it may lead to unnecessary substitution of fibrinogen and transfusion of blood products.

sensitivity 100%, specificity 84 to 88%, NPV 100%, PPV 13% to 50%

Although ROTEM® FIBTEM showed a sensitivity of 100% in the study by *Huissoud C et al.* (2009) [35], the specificity only ranged from 84% to 88% with a wide 95% CI between 75% and 97%. Moreover, the NPV was 100% but the PPV decreased steadily from 50/46% in CA_5-/CA_{15}-FIBTEM 6/8mm – according to fibrinogen levels of <2 g/l - to only 13/14% in CA_5-/CA_{15}-FIBTEM 4/5mm – corresponding to fibrinogen levels of <1 g/L. In addition, the 95% CI of PPV in all cut-offs were wide. Hence, with decreasing fibrinogen levels, the PPV of ROTEM® FIBTEM CA_5/CA_{15} declined as well, indicating that in the 37 women who experienced PPH, the prevalence of fibrinogen levels below 2 g/L was low and decreased with declining fibrinogen levels. The lower the fibrinogen level in PPH falls, the smaller the proportion of women with a CA_5/CA_{15}-FIBTEM result indicating a fibrinogen level of <1/1.5/2 g/L, who are correctly diagnosed. Hence, those parameters may lead to fibrinogen substitution in patients who truly would not be in need for it. Using ROTEM® FIBTEM for guiding fibrinogen substitution leads to fibrinogen transfusion more often than would be required and may increase the rate of adverse events, such as thrombembolic complications.

decreased costs but no differences in patient-relevant outcomes

Although two further studies [40, 41] suggested that the implementation of ROTEM® led to a reduction in the transfusion of blood products, such as RBC, FFP, and platelets, as well as a decrease in monthly costs for blood products, no differences in patient-relevant outcomes were observed. On the one hand, this finding may be in favour of ROTEM®, indicating that although patients received less blood products after ROTEM® implementation, the discharge Hb remained the same. On the other hand, it may suggest that the use of ROTEM® did neither shorten length of stay in ICU or hospital, nor diminish the need for surgical re-exploration. Therefore, benefits should be weighed carefully against possible harms due to increased fibrinogen substitution.

What is the evidence regarding adverse events and mortality of Haemocomplettan® P?

conflicting evidence regarding adverse events and mortality

We discovered pharmacosurveillance data provided by CSL Behring [48] indicating nine adverse events over a period of 22 years, only two of which occurred in acquired hypofibrinogenemia. However, in the remaining studies identified [45-47, 49-54], the available evidence both regarding adverse events and mortality is conflicting, possibly due to small sample sizes, heterogeneous patient populations, varying dosages of fibrinogen administered, and mainly retrospective comparisons. In addition, causes of adverse events and death are often not stated and might have been influenced by the underlying clinical condition in these severely ill patients.

What is the evidence for substitution of Fibrogammin® P?

improved MCF but not patient-relevant outcomes

The administration of Fibrogammin® P improved MCF – a surrogate parameter – in a small group of individuals at high-risk of intraoperative bleeding but no differences were observed in patient-relevant outcomes, such as transfusion of blood products and length of surgery, most likely because the study was underpowered to detect such differences. Because of the specific sub-population assessed and the lack of evaluating patient-relevant outcomes, no conclusion can be drawn about the efficacy and safety of Fibrogammin® P.

Is there evidence for the combined administration of fibrinogen and factor XIII?

no evidence for combined administration

As no studies could be found regarding the combined administration of Haemocomplettan® P and Fibrogammin® P in patients with acquired fibrinogen deficiency, such as severe haemorrhage, there is no evidence at all for this approach.

Are there evidence based guidelines regarding fibrinogen and factor XIII substitution in Austria?

lack of national transfusion guidelines in Austria

Overall, there is a need for evidence-based transfusion guidelines in order to control both the substitution of fibrinogen and factor XIII. In Austria guidelines regarding the coagulation management in trauma-related massive bleeding have been published by the Task Force for Coagulation of the ÖGARI [11]. In addtition, in one University Hospital in Austria, internal guidelines for the administration of fibrinogen concentrate have been developed by two authors of the ÖGARI guidelines [23]. According to these guidelines, Haemocomplettan® P might

ÖGARI guidelines/ internal guidelines: neither based on manufacturer's recommendation nor on evidence

be substituted in massive haemorrhage as well as preventively in patients at high risk of bleeding. However, the recommended initial dose is almost twice the dose outlined in the manufacturer's summary of product characteristics. In addition, either the ROTEM® FIBTEM CA_{10} should be determined prior to fibrinogen substitution and should be less than 7mm, or the MCF should be less than 10 to 12mm, or the fibrinogen level as determined by Clauss assay should be less than 1.5 to 2 g/L. However, there is no underlying evidence for these recommendations and it appears that they are based on personal expertise of one group of anesthesists emphasising the urgent need for evidence based, national transfusion guidelines in Austria.

more unanswered questions

A number of questions regarding the substitution of fibrinogen and factor XIII, however, remain unclear:

- Is there a score assessing the necessity of fibrinogen or factor XIII substitution?

The development and implementation of a scoring tool in order to identify patients who will benefit from fibrinogen replacement would be useful. In addition, this would be helpful in achieving both a scientifically and economically justifiable use of this therapy. A score should include patient-specific and disease-specific parameters, laboratory values, and parameters estimating the bleeding risk. Such a scoring system would need to be validated in appropriately designed studies.

- What influence does the dynamic of the plasma fibrinogen or factor XIII levels have?

To the best of our knowledge, to date, no study has investigated the dynamic of fibrinogen or factor XIII plasma levels and its consequence for fibrinogen or factor XIII replacement in target patients. The clinical course of the underlying disorder could best be monitored by measuring the increase or decrease of fibrinogen or factor XIII plasma levels and by putting these values in context with other laboratory or clinical parameters.

- What is the appropriate dosage of fibrinogen or factor XIII concentrate in specific clinical settings, which are adequate intervals of administration, and how long is the appropriate duration of treatment?

Although the total amount of fibrinogen replacement was within a narrow range (see above), the available studies did not address the necessary number of infusions, the intervals between the infusions, and the appropriate duration of therapy. Furthermore, the target population was of considerable heterogeneity. Hence, in some patients a single infusion may be sufficient, whereas in others several days of therapy with two or three infusions daily may be adequate.

- Which would be adequate study designs to answer these questions?

Due to the heterogeneity of the possible target population the design of a randomized controlled trial with sufficient statistical power is cumbersome. The definition of inclusion and exclusion criteria, trigger events for substitution of fibrinogen or factor XIII, and clinical (amount of bleeding) as well as surrogate outcome parameters (Clauss fibrinogen level or ROTEM® values) all have a great impact on the message and clinical relevance of such a trial.

9 Conclusion

In conclusion, almost all studies identified in our systematic review were funded by CSL Behring GmbH, Marburg, Germany - the manufacturers of Haemocomplettan® P and Fibrogammin® P.

CSL Behring GmbH funded almost all studies

The results of these trials are not generalisable due to highly selected and very heterogeneous patient populations. In addition, only studies assessing the intraoperative administration of fibrinogen concentrate have been published. Therefore, the use outside the operating theatre is not supported by any evidence. There is lack of evidence about the efficacy of Haemocomplettan® P because fibrinogen concentrate administration was almost always combined with substitution of FFP. There is no evidence for definite substitution triggers for fibrinogen, such as fibrinogen plasma levels or certain amounts of blood loss. Furthermore, there are no certain cut-off levels for ROTEM guided transfusion of fibrinogen. However, once fibrinogen substitution has been decided on, the amount of fibrinogen concentrate that needs to be transfused remains unclear.

lack of evidence for fibrinogen replacement

Concerning Fibrogammin® P, there is lack of evidence about the use of this drug as we only identified one trial comprising a highly selected patient population.

no evidence for factor XIII replacement

The combined administration of Haemocomplettan® P and Fibrogammin® P is not supported by any evidence.

No evidence could be identified supporting the recommendations outlined in existing guidelines, namely internal guidelines in one University Hospital and ÖGARI guidelines, particularly regarding the indications, cut-off values, and dosages for fibrinogen substitution.

guidelines are not evidence based

Overall, given the lack of evidence regarding Haemocomplettan® P and Fibrogammin® P on the one hand and their steadily increasing consumption within Austrian hospitals on the other hand, prospective, (randomised) controlled trials of good quality and sufficient size, assessing patient-relevant outcomes, are urgently requested to investigate the efficacy and safety of these two drugs in acquired hypofibrinogenemia. In the meantime, it will be of utmost importance to demand thorough documentation of the use of Haemocomplettan® P and Fibrogammin® P, including recording of the setting, patient population, dosages, cut-off values, follow-up periods, adverse events and side-effects. In addition, the development of evidence based, national Austrian transfusion guidelines will be inevitable.

demand thorough documentation of use

development of national transfusion guidelines

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