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Human Fibrinogen Concentrate (RiaSTAP): Comparative Cost-Effectiveness Evaluation

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Human Fibrinogen Concentrate (RiaSTAP): Comparative Cost-Effectiveness Evaluation

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Authorship

Gord Blackhouse was responsible for conceptualizing the economic evaluation, conducted the economic evaluation, and wrote the methods and results sections of the economic evaluation.

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Kaitryn Campbell completed the literature search design and execution, drafted the literature search section, and reviewed and edited report revisions.

Ron Goeree contributed to the conception and design, data acquisition and analysis plan, the analysis, and the draft report.

All authors approved the final report.

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Conflicts of Interest

No conflicts of interest were declared.

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Disclaimer

This report is prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). This report contains a comprehensive review of existing public literature, studies, materials, and other information and documentation available to CADTH at the time it was prepared.

This report was produced, as part of a collaboration between CADTH and the Canadian Blood Services (CBS), to provide an economic evaluation of a new plasma product to supplement a CBS clinical evidence report. The scope of the research questions in this CADTH report was discussed in collaboration with CBS and clinical experts. Based on the scope, the clinical data needs were determined, and any gaps in the data in the CBS clinical evidence report were addressed through a systematic review. CADTH used these data to inform this report.

The information in this report is intended to be used by CBS, along with the CBS evidence report, to make recommendations to the provincial and territorial ministries of health on whether to purchase and distribute the new plasma product.

The information in this report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or as a result of the use (or misuse) of any information contained in or implied by the information in this report.

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ABBREVIATIONS

AFD	acquired fibrinogen deficiency
CADTH	Canadian Agency for Drugs and Technologies in Health
CEAC	cost-effectiveness acceptability curve
CFD	congenital fibrinogen deficiency
CI	confidence interval
DIC	disseminated intravascular coagulation
EQ-5D	EuroQol 5-D
FC	fibrinogen concentrate
FFP	fresh frozen plasma
FP	frozen plasma
mRS	modified Rankin Score
OR	odds ratio
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-years
RBC	red blood cell
RCT	randomized controlled trial
RR	relative risk
WTP	willingness to pay

EXECUTIVE SUMMARY

Context and Policy Issues

Fibrinogen deficiency disorders are categorized as congenital (genetic absence or deficiency of fibrinogen) and acquired (low levels of fibrinogen due to medical conditions that may result in the increased loss, increased consumption, or reduced concentration of this hematologic factor). Fibrinogen deficiency can be treated through administration of human fibrinogen concentrate (FC), cryoprecipitate, fresh frozen plasma (FFP), or antifibrinolytic agents (tranexamic acid).

In Canada, RiaSTAP (CSL Behring Canada Inc.) is a human FC that is indicated for the treatment of acute hemorrhage episodes in patients with congenital fibrinogen deficiency. However, given that the acquired forms of fibrinogen deficiency can lead to potentially serious clinical situations (e.g., hemorrhage due to trauma), off-label uses of human FC might be considered by clinicians as important therapeutic options. Therefore, the identification of such potential off-label uses, along with the assessment of the effectiveness of FC in treating these, needs to be considered in developing a reimbursement policy on RiaSTAP that also considers identifying the alternatives to FC for the treatment of fibrinogen deficiency disorders.

The Canadian Agency for Drugs and Technologies in Health (CADTH), in collaboration with Canadian Blood Services, was requested to perform an economic evaluation on RiaSTAP. This assessment complements a recent evaluation of the clinical evidence on RiaSTAP performed by CBS Therapeutic Drug Product Review Process expert reviewers; this assessment was done in the context of RiaSTAP, replacing the previously available FC product available in Canada, i.e., Haemocomplettan (CSL Behring Canada Inc.).

Objectives

To evaluate the cost-effectiveness of human FC products in the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiencies (CFDs) (afibrinogenemia or hypofibrinogenemia) and patients with acquired fibrinogen deficiencies (AFD). Based on expert opinion, four specific subpopulations of patients with AFD were identified as representative of the way human FC is used in clinical practice: obstetrical hemorrhage, trauma-related hemorrhage, prophylaxis for hemorrhage during cardiac surgery, and acute hemorrhage during cardiac surgery.

Methods

Based on findings from the Canadian Blood Services Medical Overview, an analysis of gaps in the clinical data was assessed based on the needs of the economic evaluation. The type of economic analysis varied based on data availability on the comparators in the selected indications (congenital and acquired) and patient subpopulations (afibrinogenemia, hypofibrinogenemia, obstetrical hemorrhage, trauma hemorrhage, prophylaxis for major cardiac surgery, and acute hemorrhage during major cardiac surgery). When available, a cost-utility analysis was used since it incorporates both mortality and quality of life implications of one treatment over another. However, in the absence of clinical outcomes, data cost-minimization analyses were conducted in which only costs are considered in the analysis and outcomes are

assumed to be the same between treatments. The economic model considered the cost of treatment (blood products), transfusions, hospital length of stay, and the long-term costs of thromboembolic events. The outcome of the cost-utility analysis was quality-adjusted life-years (QALYs) that were estimated based on episodic mortality and one-year mortality from thromboembolic events extrapolated over a 40-year time horizon.

Summary of Findings

Key Clinical Findings

The limited available evidence suggested: (1) a beneficial effect of FC on the amount of blood loss and the number and volume of necessary blood transfusions, as well as mortality and thromboembolic adverse events, when it was compared with "no-FC" or placebo in patients undergoing cardiac surgeries; (2) lower rate of blood loss and potentially fewer myocardial infarction events with FC, versus no-FC in patients undergoing pre-cardiac surgery prophylaxis, (3) a lower incidence of organ failure, and a lower mortality rate in early hours after trauma when compared with "no-FC"; and (4) no statistical difference in blood loss or transfusion requirements in post-partum hemorrhage when compared with cryoprecipitate. No data comparing FC with cryoprecipitate in cardiac surgery or trauma patients were identified.

Based on a literature search, no comparative head-to-head studies were identified for treatments in patients with CFD, those that would enable the comparison of FC with cryoprecipitate in trauma patients, or for patients who undergo major cardiac surgeries. Finally, comparing the effects of FC with tranexamic acid in any of the populations of interest was not possible due to insufficient data.

Key Economic Findings

No comparative studies that evaluated patients with CFD were found; therefore, no study-based economic evaluation for this study population was conducted. For AFD patients with obstetrical hemorrhage who were treated with FC, the product cost was $[redacted] more per patient compared with cryoprecipitate, and transfusion costs $[redacted] less, but hospital stay costs were $[redacted] with FC compared with cryoprecipitate, therefore resulting in total costs of $707 more for FC-treated patients compared with cryoprecipitate-treated patients. In AFD patients with trauma-related hemorrhage, treatment with FC resulted in costs of $7,412 more per patient and 0.64 QALYs fewer than with patients not treated with FC, therefore dominating FC (resulting in lower costs and higher QALYs). When used as a prophylactic for cardiac surgery, FC resulted in lower costs per patient ($1,005 versus $4,128) and higher QALY gains (7.13 versus 7.09) compared with no-FC treatments, resulting in FC dominating (producing lower costs and higher QALYs). In treating acute hemorrhage during cardiac surgery, FC resulted in cost savings of $2,718 and QALY gains of 1.19 per patient compared with placebo, indicating FC's dominance against placebo. Results were robust to one-way sensitivity analyses assuming a lower cost for FC and excluding thromboembolic events from the model. Probabilistic sensitivity analysis (PSA) results show that, for obstetrical hemorrhage, FC has a 0.76 probability of being more expensive than cryoprecipitate. The PSA results indicate that with a willingness to pay a threshold of $100,000 per QALY, the probability of FC being cost-effective in trauma-related hemorrhage and in cardiac surgery (prophylactic and acute treatment) is 0.15 and 0.97, respectively.

Key Limitations

There was a lack of data comparing FC with active comparators in many of the populations of interest. No comparative studies were found for treatments in patients with CFDs. Among the AFD populations, only in the obstetrical hemorrhage trials were there study data for an active comparator (cryoprecipitate). Differences in nearly all comparative outcomes that were used in the economic analyses were not statistically significant. For the populations for which randomized controlled trials (RCTs) were available, the sample sizes were small. For the other populations of interest, clinical data used in the economic analyses were obtained from observational studies. The included observational study comparing FC with cryoprecipitate in cardiothoracic surgery did not statistically compare the outcome measures between the study groups.

Conclusions and Implications for Decision- or Policy-Making

The clinical review found some trends in amount of blood loss, blood transfusion requirements, mortality, and thromboembolic events favouring FC. Economic analyses found FC to be cost-effective in certain populations (pre-cardiac-surgery prophylaxis, treating hemorrhage occurring during cardiac surgery) but not in others (treating hemorrhage related to trauma). The lack of comparative studies makes drawing conclusions about the clinical and cost-effectiveness of FC uncertain.

1 CONTEXT AND POLICY ISSUES

Fibrinogen (factor I) is a plasma protein, primarily synthetized by the liver, which plays an important part in primary hemostasis, clot formation, and wound healing.[1] Fibrinogen deficiency is categorized as either congenital or acquired. Congenital fibrinogen deficiency (CFD) is a rare genetic disorder characterized by the complete absence of fibrinogen (afibrinogenemia), low levels of fibrinogen (hypofibrinogenemia), or structurally or functionally deficient fibrinogen in the blood (dysfibrinogenemia).[1] Acquired fibrinogen deficiency (AFD) may result from decreased hepatic synthesis (e.g., in liver failure), increased loss (e.g., in massive hemorrhage), increased consumption (e.g., in disseminated intravascular coagulation [DIC]), or reduced concentration (e.g., during fluid replacement therapy) of fibrinogen.[1]

Replacement of plasma fibrinogen can be achieved through administration of human fibrinogen concentrate (FC), cryoprecipitate, or fresh frozen plasma (FFP).[2] Antifibrinolytic agents (tranexamic acid) may also be used in treatment of patients with dysfibrinogenemia, especially for local treatment of superficial bleeds or dental procedures.[1]

In Canada, RiaSTAP (CSL Behring Canada Inc.) is a human FC that is replacing Haemocomplettan (CSL Behring Canada Inc.), a previously available FC product with an identical pharmaceutical form and production process, except that Haemocomplettan is stabilized with a human albumin product that is not licensed in the United States.[3] RiaSTAP is indicated in Canada for the treatment of acute bleeding episodes in patients with CFD, including afibrinogenemia and hypofibrinogenemia. However, it is not indicated for dysfibrinogenemia. Given AFD accounts for potentially serious cases of fibrinogen deficiency (e.g., hemorrhage due to trauma) there is a significant potential for off-label uses of human FC. This needs to be considered in developing a reimbursement policy on RiaSTAP. Also relevant for developing the reimbursement policy on RiaSTAP is identifying the alternative(s) to FC for the treatment of fibrinogen deficiency states. These mainly include cryoprecipitate and plasma.[2]

1.1 Objectives of the Report

The objective of this study is to assess the cost-effectiveness of human FC products in the treatment of acute bleeding episodes in patients with CFD (afibrinogenemia or hypofibrinogenemia), and those with AFD.

2 RESEARCH QUESTIONS

1. In patients with CFD, what is the comparative clinical effectiveness of human FC versus:
   a. Cryoprecipitate?
   b. Plasma?

2. In patients with AFD, what is the comparative clinical effectiveness of human FC versus:
   a. Cryoprecipitate?
   b. Plasma?
   c. Placebo?
   d. Antifibrinolytic agents?
3. In patients with CFD, what is the comparative cost-effectiveness of human FC versus:
   a. Cryoprecipitate?
   b. Plasma?

4. In patients with AFD, what is the comparative cost-effectiveness of human FC versus:
   a. Cryoprecipitate?
   b. Plasma?
   c. Placebo?
   d. Antifibrinolytic agents?

3 METHODS

3.1 Clinical Review

3.1.1 Literature search strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2013, Issue 2), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Health technology assessments, systematic reviews, and meta-analyses were not limited to the human population, however all other publication types were limited to human studies, with no methodological filters. The search was also limited to English language documents published between January 1, 2008 and June 13, 2013. Additional targeted searching in PubMed and The Cochrane Library databases was performed in order to provide additional data for the economic model. The detailed search strategy is presented in Appendix 1.

3.1.2 Selection criteria and methods

One reviewer (NA) screened the titles and abstracts of search results for relevance using a predefined checklist (Appendix 2). Full-text copies of any items passing title/abstract screening were retrieved, and assessed by one reviewer (NA) for inclusion, based on explicit predetermined criteria (Table 1). A second reviewer (GB) was consulted, when necessary.

3.1.3 Data extraction strategy and critical appraisal of individual studies

Data extraction for each article was performed by one reviewer and accuracy of the abstracted data was confirmed by a second reviewer. The quality of the included studies was evaluated using the Downs and Black quality assessment checklist, which is applicable to both randomized and non-randomized comparative studies (Appendix 3).[4] This quality assessment tool contains a list of 27 criteria concerning external validity, bias, confounding factors, statistical power, and reporting. The checklist has a total score ranging from 0 to 27, with higher scores indicating a higher-quality study. For this review, a numeric score was not used in the quality appraisal of each study. Instead, the methodological quality of the included evidence was assessed based on reporting, external and internal validity, and risk of confounding, where appropriate, and its strengths and limitations were described.

3.1.4 Data analysis methods

A qualitative synthesis of data from the included studies was undertaken. The results are presented in the form of a structured narrative along with summary tables.

Table 1: Inclusion and Exclusion Criteria for Primary Studies	
Inclusion Criteria	
Patient Population	**CFD states:** • Afibrinogenemia • Hypofibrinogenemia. **AFD states:** • Obstetrical hemorrhage • Massive surgical hemorrhage, including post-cardiovascular surgery as well as non-cardiovascular surgery • Massive hemorrhage due to trauma • AFD-associated liver disorders, e.g., liver transplantation, ascites, hepatitis, hepatic cancer • AFD-associated gastrointestinal bleeding • Hyperfibrinolysis and other forms of increased loss of fibrinogen including hemorrhagic and septic shock, DIC, and microvascular hemorrhage due to DIC • Catastrophic bleeding thrombolysis, i.e., very serious bleeding associated with the use of thrombolytic agents such as alteplase or streptokinase • Presurgical hemorrhage prophylaxis.
Intervention	• Human fibrinogen concentrate
Comparators	• Cryoprecipitate • Plasma (including FP, FFP, and solvent/detergent plasma [Octaplasma]) • Antifibrinolytic agents (aminocaproic acid* and tranexamic acid) • Placebo. * Aminocaproic acid has not been available in Canada since 2005. It was, however, included in the list of comparators to ensure completeness of the information retrieval regarding antifibrinolytic agents.

Outcomes	• Plasma fibrinogen levels
	• Transfusion of RBC
	• Transfusion of other allogeneic components (e.g., RBC, plasma, platelets) or plasma protein concentrates
	• Clot firmness (including both mean and maximum clot firmness as well as measures of both TEG and ROTEM)
	• Control of bleeding episodes
	• Blood loss
	• Length of hospital stay
	• Mortality
	• Adverse events:
	  ○ Thromboembolic complications
	  ○ Transfusion-related viral contamination
	  ○ Other adverse events:
	  ▪ Plasma – volume overload
	  ▪ Allergy
	  ▪ TRALI

Study Design	• RCTs • Non-randomized trials or comparative observational studies.
Exclusion Criteria	
• Non-comparative clinical studies • Case reports • Pharmacokinetics/ pharmacodynamics studies • In-vitro or animal studies	

Table 1: Inclusion and Exclusion Criteria for Primary Studies
• Studies that used non-systemic fibrinogen concentrate (e.g., topical or intra-articular) • Duplicate publications of already included studies • Review articles or editorials.

AFD = acquired fibrinogen deficiency; CFD = congenital fibrinogen deficiency; DIC = disseminated intravascular coagulation; FFP = fresh frozen plasma; FP = frozen plasma; RBC = red blood cells; RCTs = randomized controlled trials; ROTEM = rotational thromboelastometry; TEG = thromboelastography; TRALI = transfusion-related acute lung injury.

3.2 Pharmacoeconomic Analysis

3.2.1 Type of economic evaluation

The type of economic analysis varied according to data availability for the various target populations and comparators of interest. The intent was to conduct cost-utility analyses for all target populations inclusive of all target comparators. A cost-utility analysis was used because it incorporates both mortality and quality of life implications of one treatment over another. Additionally, the cost per quality-adjusted life-year (QALY), which is used in cost-utility analyses, is commonly used in economic evaluations. Therefore, using this outcome allows for comparisons with cost-effectiveness findings for other treatments and disease areas. However, in the absence of clinical outcomes from comparative studies for specific populations and comparators, cost-minimization analyses were conducted. In a cost-minimization analysis, only costs are considered in the analysis and outcomes are assumed to be the same between treatments.

3.2.2 Target population

There were a number of target populations for this evaluation. These included individuals with CFD and patients with AFD. FC is currently indicated for patients with CFD. Patients with CFD are further subdivided into patients with afibrinogenemia and patients with hypofibrinogenemia. Patients with AFD are further subdivided into four subpopulations. These include women with obstetrical hemorrhage, patients treated for trauma-related hemorrhage, patients undergoing surgery that are given a prophylaxis against bleeding, and bleeding during major cardiac surgery. These represent populations in which FC is sometimes used for off-label use. A summary of the various populations of interest is provided below.

a) CFD:

- Afibrinogenemia
- Hypofibrinogenemia

b) AFD:

- Obstetrical hemorrhage
- Trauma hemorrhage
- Prophylaxis for major cardiac surgery
- Acute hemorrhage during major cardiac surgery

3.2.3 Treatments

The primary treatment of interest is the blood product FC sold in Canada under the brand name RiaSTAP. Relevant comparators of interest are:

a) cryoprecipitate
b) FFP
c) frozen plasma (FP)
d) Octaplasma
e) tranexamic acid
f) no intervention.

Aminocaproic acid, a fibrolytic agent, was not considered as it was taken off the Canadian market in 2005.

3.2.4 Perspective

The analysis was conducted from a third-party payer perspective, specifically a Canadian Ministry of Health.

3.2.5 Efficacy and safety

The primary outcome of the model was the expected quality-adjusted life-year (QALYs). In the model, QALYs are driven by mortality and thromboembolic events occurring during the acute episode. Mortality and thromboembolic-event data for the model were based on findings from the clinical review. For thromboembolic events, the one-year mortality impacts of patients suffering myocardial infarction (MI) or stroke were incorporated into the model. The short-term (one year) and long-term (two-plus years) annual costs and quality of life impacts for each of these events were also included in the model.

3.2.6 Time horizon

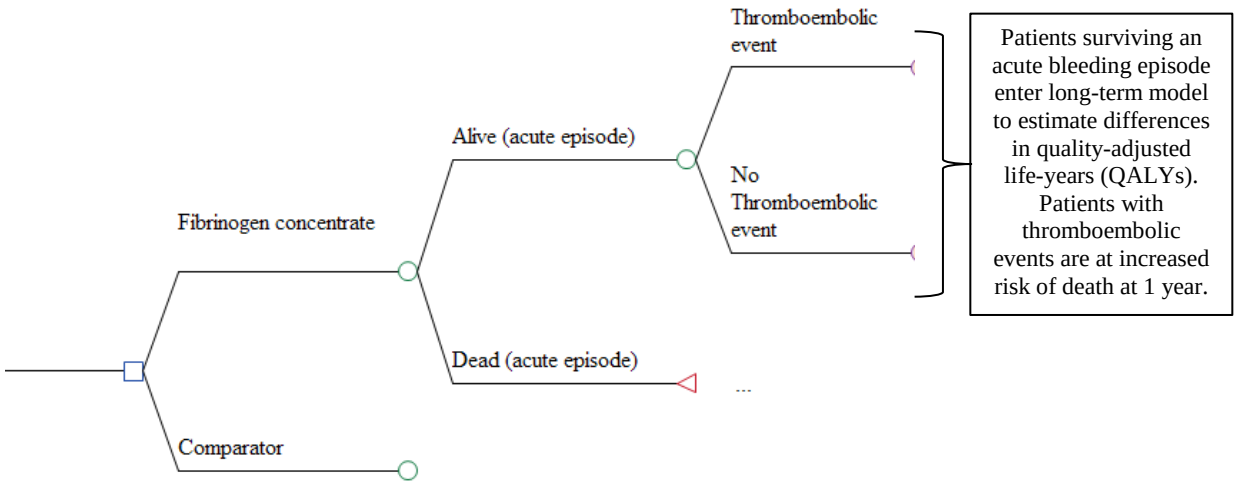
A 40-year time horizon was used in the analyses. A long-term time horizon was chosen in order to project short-term differences in mortality into long-term differences in QALYs between treatment groups.

3.2.7 Modelling

Figure 1 provides a graphical representation of the model used to evaluate the various populations of interest. The model begins with an acute bleeding episode in which patients are treated either with FC or with a comparator product. A proportion of patients will die during the acute episode while the remainder will remain alive. Among patients who are alive, a proportion will suffer a thromboembolic event during the acute episode whereas the remainder will not. Patients who survive enter a 40-year model where they are at risk of dying each year based on age- and gender-specific annual mortality rates. Acute-event mortality and thromboembolic event data were derived from findings from the clinical review. Patients who suffer a thromboembolic event during the acute episode are at increased risk of death the first year after the event. One-year mortality rates for thromboembolic events were derived from published literature. The model structure is identical for both acute treatment and prophylaxis populations.

Data from comparative studies identified in the clinical review were used to inform the model of short-term mortality, total length of stay, ICU length of stay, volume of the blood products transfused, thromboembolic events, average patient starting age, and dosage of FC and comparators.

Figure 1: Conceptual Design of Economic Model



Comparative studies used to inform model of:
1) mortality from bleeding episode
2) length of hospital stay (Total, ICU)
3) thromboembolic events (MI,stroke)
4) transfusion volume during episode (FFP, platelets, RBC,Octaplasma)
5) patient age
6) dosage.

3.2.8 Utility values

General population utility values were applied to patients who did not suffer a thromboembolic event each year that they were alive. Age- and gender-specific utility values were based on a utility study by Kind et al.[5] Table 2 provides the utility values by age used in the model.

Table 2: General Population Utility Values by Age and Gender		
Age Group	**Males**	**Females**
Under 25	0.94	0.94
25 to 34	0.93	0.93
35 to 44	0.91	0.91
45 to 54	0.84	0.85
55 to 64	0.80	0.81
65 to 74	0.78	0.78
75+	0.73	0.71

For patients suffering an MI, a utility decrement was applied to the general population utility values. The decrements are based on a study in which 2,950 patients who had survived an MI in the past filled out a survey that included a EuroQol 5-D (EQ-5D) questionnaire.[6] The average utility score was compared with that of the general population and decrements for MI survivors by age group were reported. The decrements for patients with an MI are provided in Table 3.

Table 3: Utility Decrements for Patients with MI by Age Group	
Age Group	**Utility Decrement**
45 to 54	- 0.06
55 to 64	- 0.051
65 to 74	- 0.025
75+	- 0.007

MI = myocardial infarction.

Data from two studies were used to derive stroke health-state utility weights. Rivero-Arias et al.[7] provided estimates of post-stroke utility scores according to modified Rankin Score (mRS). In a Canadian-based cohort study, Goeree et al.[8] reported the distribution of discharge-modified ranking score according to type of stroke (ischemic, hemorrhagic, transient ischemic attack). The mRS-specific utility values reported by Rivero-Arias et al.[7] were applied to the distribution of hospital discharge mRS reported by Goeree et al. in order to derive a weighted average utility weight for ischemic and hemorrhagic stroke. Based on these data the utility weight applied to patients post-ischemic and hemorrhagic stroke was 0.46 and 0.28, respectively.

3.2.9 Costs

a) Cost per episode

Costs considered during the acute episode include the cost of treatment (e.g., FC and comparators), hospital costs based on total length of stay and ICU length of stay, and the costs of transfusions of other blood products. For patients with thromboembolic events, separate costs were applied to patients the first year after the event and in subsequent (2+ years) after the event.

b) Cost of treatments

The cost of FC and its comparators was derived using a number of components. First, the cost per unit of each blood product was estimated. Next, the unit costs were applied to population-specific dosages estimated to be used for each product.

The unit cost assumed for each blood product evaluated is provided in Table 4. The unit cost for most of the blood products was provided by the Canadian Blood Services. The cost per unit for Octaplasma was based on the cost used in a recent CADTH report.[9] The cost per 500 mg pill of tranexamic acid was based on the BC PharmaCare reimbursement rate. The current cost per unit for FC is $[redacted] per gram. In sensitivity analysis, the cost of FC is assumed to be $[redacted] per gram instead of $[redacted] per gram. This alternative cost is based on an estimate by CBS on the cost of FC if a change in the manufacturing process of the product is undertaken. Although red blood cells (RBCs) and platelets are not considered as comparators in the analysis, their costs are provided here as they are considered part of transfusion costs in the analysis.

Table 4: Unit Costs for Blood Products

Blood Product	Cost	Source
Fibrinogen concentrate	$[redacted] per gram	CBS
Cryoprecipitate	$118 per unit	CBS
Fresh frozen plasma	$349 per unit	CBS
Frozen plasma	$34 per unit	CBS
Octaplasma	$141 per unit	CADTH Octaplas HTA[9]
Tranexamic acid	$4.66 per mL 100g/mL	BC PharmaCare
Platelets	$263 per unit	CBS
Red blood cells	$407 per unit	CBS

BC = British Columbia; CADTH = Canadian Agency for Drugs and Technologies in Health; CBS = Canadian Blood Services; HTA = health technology assessment.

Based on expert opinion, Canadian Blood Services provided an estimate of dosages for the blood products being compared by patient population. Specifically, dosages were provided for treatment of acute bleeding for patients with CFD, for treatment of acute hemorrhage, and as a prophylactic treatment for patients with AFD. Estimated dosages were based on an 80 kg patient. Table 5 presents the estimated dose for the various blood products by patient population.

c) Cost of treatment administration

The cost of intravenous drug administration was not taken into account in the analysis. It was assumed that the administration costs would be the same for all blood products and medications under analysis.

Table 5: Treatment Dosages by Blood Product and Population			
	Congenital	**Acquired**	
Blood Product	**Acute Hemorrhage**	**Acute Hemorrhage**	**Prophylactic**
Fibrinogen concentrate	7 g day 1 + 4 g every other day over 7 days = 19 g	4 g	2 g
Cryoprecipitate	10 units on day 1 + 10 units every other day over 7 days = 40 units	10 units	10 units
Fresh frozen plasma	3 units	3 units	3 units
Frozen plasma	5 units	5 units	5 units
Octaplasma	7 units	7 units	7 units
Tranexamic acid	n/a	n/a	2 g

G = gram; n/a = not available.

d) Cost of disease and complications management

The cost per ICU day ($2,337) and cost per non-ICU day ($907) used in the model were based on unit costs reported in a recent Canadian study.[10]

The costs of thromboembolic events were included in the model. The first-year and subsequent-year costs of MI were based on a Canadian study[11] that evaluated health care costs of individuals with various diabetes-related events. Costs were provided separately for patients with diabetes and matched with patients without diabetes. Costs were presented separately by years since diagnosis. The first-year cost of MI was $10,579 annually per patient. Costs beyond the first year were $2,798 per patient.

The first-year cost of stroke was estimated from a Canadian-based costing study.[8] In this study, the total one-year health care costs for patients suffering an ischemic stroke were found to be $53,576. The one-year cost following a hemorrhagic stroke was estimated to be $56,573 per patient. These costs were applied to the first year post-stroke in the current model. The annual cost of either hemorrhagic or ischemic stroke beyond the first year after the event was assumed to be $4,068[11] per patient.

3.2.10 Mortality

Patients who survive the acute episode are at risk of death each year of the model. The age- and gender-specific mortality rates used in the model were based on Canadian life tables.[12,13] Patients who suffer a thromboembolic event during the acute episode are at an increased risk of death at year one. A mortality rate of 6% was applied in the first year for patients suffering an MI during the acute episode. This was based on a longitudinal cohort study of 2,090 patients treated for MI.[14] The study reported both one-year mortality rates for overall mortality and one-year mortality rates for patients who were alive and discharged after MI. The one-year post-mortality mortality rate was reported to be 6%. The probability of dying one year after stroke was based on a Canadian study by Tu and Gong[15] This study reported mortality for patients hospitalized for acute stroke in Canada at 30 days (18.9%) and at one year (32.0%). In the model, it is assumed that all patients who suffer a thromboembolic event survive the acute episode. Therefore, using the 0.32 mortality rate would overestimate the post-discharge one-year mortality rate, as any of these patients would have died during the index event. Therefore, the one-year mortality rate

reported in Tu and Gong[15] was adjusted assuming that the 0.189 of patients who died in the first 30 days died during the index hospitalization. The one-year post-discharge stroke mortality rate used in the model was estimated as the proportion of patients surviving to 30 days who died within one year. The one-year mortality rate after stroke in the model was set equal to 0.16 (0.32 to.0.189)/(1 to 0.189).

3.2.11 Sensitivity analyses

a) Univariate sensitivity analysis

Sensitivity analysis was conducted assuming a lower price of FC. Specifically, the model was run assuming an FC cost of $[redacted] per gram instead of $[redacted], as this cost may be realized in the future if a change in the manufacturing process is made. Additionally, results were evaluated excluding thromboembolic events from the model. This sensitivity analysis was conducted because, unlike other model variables, the cost and mortality impact of mortality thromboembolic events are modelled beyond the acute bleeding episode.

b) Probabilistic sensitivity analysis/cost-effectiveness acceptability curves

In order to assess parameter uncertainty, PSA was conducted for all evaluations based on capacitive study data. One thousand Monte Carlo simulations were used to generate a distribution of incremental costs and QALYs. During each simulation model, parameters are varied based on a distribution of values for each model variable. For dichotomous variables such as mortality rates and thromboembolic event rates, beta distributions were used. If the relative risk of a dichotomous variable was published, a distribution on the relative risk using a lognormal distribution was used. For continuous variables such as transfusion volume and length of stay, normal distributions were used. Distributions were applied to transfusion volume and length of stay only if a measure of dispersion (e.g., standard error, standard deviation) showed no measure of uncertainty. Based on the Monte Carlo simulations, cost-effectiveness acceptability curves were used to show the probability that FC is cost-effective as a function of a decision-maker's willingness to pay for an additional QALY.

4 RESULTS

4.1 Selection of Primary Studies

A total of 857 potential citations was identified by the clinical search, with 793 citations being excluded during the title and abstract review based on irrelevance to the questions of interest. The full-text documents of the remaining 64 articles were retrieved; of those, 52 did not meet the eligibility criteria and were excluded. Although it had been planned a priori that studies reporting on laboratory variables (clot firmness and plasma fibrinogen levels) would be included in this review, it was decided to include only those studies reporting outcomes that were relevant to the economic evaluation. Three of the initially included articles merely reported effects of interventions on laboratory measurements,[16-18] with two articles[17,18] presenting data from already included studies.[19,20] Of these three articles, one[18] was used to extract data required for the economic model and two were excluded.[16,17] Twelve articles, reporting 11 studies (RCTs and seven observational studies), met the inclusion criteria and were included in this review. Appendix 4 describes the PRISMA flowchart of the included studies in the report.

4.2 Study and Patient Characteristics

A summary of individual study characteristics is presented in Appendix 5. As the appendix shows, five of the included articles were reports of four single-centre RCTs conducted in Germany,[20,21] the Netherlands,[22] Sweden,[19] and Denmark.[23] These studies compared FC with placebo or "no-FC,"[19-21,23] and FFP or platelets[20,22] when they were used as prophylactic (pre-surgical hemorrhage prophylaxis)[19] or therapeutic (fibrinogen replacement)[20-23] technologies in patients who underwent major surgeries.

The included observational studies originated from the UK,[24] Germany,[25-28] the Netherlands,[29] and Ireland.[30] These studies compared FC with "no-FC,[25,29] cryoprecipitate,[24,30] and allogeneic blood products (FFP, RBC, or platelets)[26-28] in patients undergoing thoracic and abdominal cardiovascular surgeries,[24,26-29] trauma patients requiring surgery,[25] or those with major postpartum hemorrhage.[30] Two studies retrospectively selected cohorts of patients who received allogeneic blood products as a comparison group,[27,28] one of which also recruited a prospective control group.[28]

4.3 Critical Appraisal of Included Studies

The methodological quality of the included RCTs and observational studies was assessed in terms of reporting, and external and internal validity. The key findings from the quality assessment (strengths and limitations) are summarized in Appendix 6.

All of the included studies described their objectives, interventions, comparators, and main outcomes clearly, and used at least one control group to compare the effects of the study intervention. All of the five included RCTs clearly described the randomization process, four of which also used an intervention assignment concealment method to blind study participants and evaluators.[20-23] No randomization or intervention assignment concealment methods were used in the remaining seven studies, which used an observational design.

All of the included studies reported the baseline characteristics of study participants that might serve as potential confounding factors. However, only one observational study adjusted for potential confounders in their analysis,[29] and one matched intervention and control groups for potential confounders.[25] None of the included studies compared the characteristics of the participants who were lost to follow-up in the study groups or considered attritions in their analyses.

Although participants in each of the included RCTs were recruited from a single university hospital, the study samples appeared to be representative of the general population. However, it was difficult to decide whether the academic health care settings were representative of the locations where patients would receive the treatment in a "real world" situation. None of the reviewed studies provided sufficient information on the representativeness of participants who were asked or those who agreed to participate in the study, and none seemed to experience major participant attrition that might affect their external validity.

Non-RCT study participants consisted of cohorts of patients who were recruited from university hospitals[24-29] or national databases.[30] Thus, the study samples could be considered as representative, except for the two non-RCTs[24, 25] that selected convenience samples of patients for whom infusion data were available. These samples might not be perfectly generalizable to the entire groups of patients who were treated in the study centres.

4.4 Summary of Findings of the Clinical Review

The summaries of the study outcomes and intervention-related adverse events are presented in Appendices 7 and 8.

4.4.1 Blood loss

The average amount of blood loss was estimated in two RCTs[19,20] and five non-randomized or observational studies.[24,27-30] These studies used different statistical measures and various durations of follow-up to report blood loss (Appendix 7). The results of the RCTs showed a statistically significant reduction in the amount of blood loss in cardiothoracic surgery patients treated with FC as compared with those who received one cycle of FFP or platelets ($P = 0.003$)[20] and those in placebo ($P < 0.001$)[20] groups.

Difference in amount of blood loss between the study groups was tested statistically in two of the non-RCTs.[29,30] In the remaining non-RCTs, no statistical comparisons were made to compare this outcome between the study groups. The univariate analysis performed by Bilecen et al.[29] showed a statistically significant reduction in blood loss in patients who underwent cardiac surgery, in favour of "no-FC" group ($P < 0.01$). However, there was no statistical difference between the two groups after adjustment for demographic and surgery-related variables as well as transfusion of other blood products (adjusted odds ratio [OR] = 1.02, 95% confidence interval [CI] 0.91 to 1.14). Ahmed et al.,[30] who included patients with major obstetric hemorrhage, reported no statistically significant difference between FC and cryoprecipitate groups in terms of blood loss after treatment.

4.4.2 Control of bleeding episodes

Two RCTs[21,22] and two non-RCTs[27,28] reported on post-treatment hemostasis (Appendix 7). "Avoidance of allogeneic blood transfusions" was used as a proxy measure for achieving hemostasis in three of these studies.[21,27,28] In the RCT by Rahe-Meyer et al.[21] a statistically higher proportion of patients in the FC group avoided allogeneic blood transfusions compared with those in placebo group ($P < 0.001$). Lance et al.[22] reported no statistical difference between FC and FFP groups in terms of post-treatment hemostasis. Both cohort studies, comparing FC with allogeneic blood products, reported statistically higher rates of hemostasis in favour of FC ($P < 0.05$ for all comparisons).[27,28]

4.4.3 Transfusion requirements

Need for the transfusion of blood products following study interventions was reported in three RCTs[19,21,23] and six non-RCTs.[25-30] As shown in Appendix 7a, the results of two of the RCTs[21,23] indicated a statistically lower need for the transfusion of blood products, including FFP, RBC, and platelets in the FC group 24 to 48 hours after surgery (but not during operation), when compared with the placebo or "no-FC" groups. The third RCT,[19] on the other hand, showed no statistical difference in the proportion of the patients who needed blood transfusion after surgery between the FC and "no-FC" groups.

The non-RCTs that compared FC to "no-FC" suggested a statistically lower need for FFP,[25,29] RBC,[29] or platelets[29] in FC-treated patients. Similarly, median volumes of blood products transfused were statistically lower in the FC group versus the groups who received allogeneic blood products (FFP, RBC, or platelets) in three other observational studies[26-28] (see Appendix 7b for details). Ahmed et al.,[30] who performed their study on the patients with major obstetric hemorrhage, reported no statistical difference between the FC and cryoprecipitate groups in terms of transfusion requirements.

4.4.4 Mortality

Mortality rates were reported in one RCT[21] and six observational studies.[25-30] The RCT by Rahe-Meyer et al.[21] reported a 3% intervention-related mortality in the FC-treated patients, compared with 13% in the "no-FC" group (relative risk [RR] = 0.3, 95% CI, 0.0 to 2.3).

No deaths were reported in three of the observational studies during the study period.[26,28,30] One study did not perform a statistical test to compare mortality rates between the study groups, most likely due to small sample sizes.[27] Bilecen et al.[29] reported no statistical difference between FC and "no-FC" groups in terms of 30-day mortality. The observational study by Wafaisade et al.[25] found a statistically lower mortality rate in the FC group during the first six hours after trauma surgeries (10.5% versus 16.7%; $P = 0.03$), while no significant difference was detected between FC and "no-FC" groups in 24-hour and 30-day follow-up periods, as well as overall mortality rates.

4.4.5 Intervention-related adverse events

The reported adverse events are shown in Appendix 8. Thromboembolic events were reported in two RCTs[19,21] and three non-RCTs.[25,26,29] Six studies including two RCTs[21,22] and four non-RCTs[25,27-29] reported on other adverse events that had been observed during their study periods.

These included operative hemorrhage, re-operation due to bleeding, pleural effusion, organ failures, arrhythmias, and infectious and neurologic events. Four of the studies did not use a statistical test to compare adverse events in the study groups.[21,22,27,28] Wafaisade et al.[25] reported statistically lower rates of organ failure in FC-treated trauma patients compared with those who received no-FC. They found no statistical difference between the two groups in terms of thromboembolic events and sepsis. In the study by Bilecen et al.[29] the observed thromboembolic events, renal failures, and infectious complications were comparable between FC and "no-FC" groups.

The included studies did not report any cases of volume overload, allergic reactions, or transfusion-related acute lung injury.

4.5 Pharmacoeconomic Evaluation

4.5.1 Base case analysis

a) Product costs based on assumed dosages for various products

Table 6 presents treatment costs for the comparators of interest by population. These estimates incorporate the unit cost for each product and the assumed dosages for each product. As shown for the treatment of acute hemorrhage in patients with CFD, treatment costs are estimated to be highest using FC ($[redacted]). Treatment cost with FC is estimated to be $[redacted] higher than the cost of treatment with cryoprecipitate ($4,720). Treatment costs are lowest with FP. For patients with AFD being treated for acute hemorrhage, FC has the highest estimated treatment cost ($[redacted]) followed by cryoprecipitate ($1,180) and fresh frozen plasma ($1,047). FC treatment costs are $[redacted] more than costs with cryoprecipitate. In patients with AFD given prophylactic treatment, cryoprecipitate has the highest estimated cost ($1,180) followed by FFP ($1,047) and Octaplasma ($990). In this population, tranexamic acid is estimated to have the lowest treatment cost. If product treatment cost were used solely to decide which treatment is optimal, FP would be the optimal treatment for acute hemorrhage for patients with either congenital or AFD. Tranexamic acid would be considered the optimal (cheapest) treatment as a prophylactic in patients with AFD.

Table 6: Product Costs Based on Estimated Dosage for Each Product

	Congenital	Acquired	
Blood Product	**Acute Treatment**	**Acute Treatment**	**Prophylaxis**
Fibrinogen concentrate	$[redacted]	$[redacted]	$[redacted]
Cryoprecipitate	$4,720	$1,180	$1,180
Fresh frozen plasma	$1,047	$1,047	$1,047
Fresh plasma	$150	$150	$150
Octaplasma	$990	$990	$990
Tranexamic acid	n/a	n/a	$93

b) Economic evaluations based upon findings from comparative studies

Economic analyses were conducted for different populations of interest based upon data identified in the clinical review of comparative studies. Analyses were conducted for specific populations if any of the following data were reported 1) mortality 2) transfusion volume 3)

hospital length of stay. No comparative studies were found for patients with CFD. Therefore, no further analysis was conducted for this population. Study data were identified for each of the four AFD populations (obstetrical hemorrhage, trauma-related hemorrhage, prophylaxis for cardiac surgery, and acute hemorrhage during major cardiac surgery). Therefore, study-data-based economic evaluations were conducted for these populations. The following sections summarize the study data used as inputs for each population along with the base case findings.

4.5.2 Congenital fibrinogen deficiencies

No comparative studies were found that evaluated patients with CFD. Therefore, no study-based economic evaluation for this study population was conducted.

4.5.3 Acquired fibrinogen deficiencies

a) Obstetrical hemorrhage

One observational study[30] was identified that evaluated patients with obstetrical hemorrhage. In this study, women with major obstetrical hemorrhage who were given FC were compared with patients given cryoprecipitate using retrospective chart review. Major obstetrical hemorrhage was defined as patients having: an estimated blood loss of at least 2.5 litres; transfusion of at least five units of RBCs; or the treatment of a coagulopathy during the acute episode. All patients in the study had an FC level of less than 2 g/L.

Table 7 provides information from Ahmed et al.[30] used as inputs into the economic evaluation of patients with obstetrical hemorrhage. Patients given FC were given a mean dose of 4 g. Cryoprecipitate-treated patients were given a mean dose of 11 units of the blood product. There were no maternal deaths in the study. FC-treated patients had longer total length of hospital stay than patients treated with cryoprecipitate did. Patients treated with FC had a lower mean volume of RBCs and Octaplasma transfused compared with patients treated with cryoprecipitate. Thromboembolic events were not reported in the study. The differences in length of stay and in transfusion volumes were not statistically significant. The *P*-value for the difference in total length of stay was 0.19. The *P*-value for the difference in ICU length of stay was 0.95. The *P*-values for the difference in RBCs and Octaplasma were reported to be 0.40 and 0.36, respectively.

Table 7: Data Inputs Used for Economic Evaluation in Obstetrical Hemorrhage Population

	Fibrinogen Concentrate (n = 20)	**Cryoprecipitate (n = 14)**	***p*-value**
Age	31	32.8	
Dose	4 g	11 units	
Mortality	0.0	0.0	
Thromboembolic events	NA	NA	
Length of hospital stay (days)	6.55	5.22	0.19
ICU length of stay (days)	1.40	1.42	0.95
Transfusions			
Red blood cells (units)	5.70	7.10	0.40
Octaplasma (units)	3.15	4.07	0.36

NA = Not available

The base case results of the economic evaluation in the obstetrical hemorrhage population are shown in Table 8. Based on findings from Ahmed et al.,[30] the product cost for FC is estimated to be $[redacted] per patient more than the product cost of cryoprecipitate. Patients treated with FC had $[redacted] fewer transfusion costs, but $[redacted] more in hospital length of stay costs. The total episodic costs were estimated to be $707 more for FC-treated patients compared with cryoprecipitate-treated patients. The QALYs were estimated to be the same for FC- and cryoprecipitate-treated patients. This is because no difference in maternal mortality or in thromboembolic events was found between FC- and cryoprecipitate-treated patients. It should be noted that the assumption of equivalence of mortality and thromboembolic events between FC and cryoprecipitate in this population is based solely on the findings of a single study.[30] Since QALYs are equivalent, the criterion for which treatment is optimal is based solely on cost (i.e., cost-minimization analysis). For this population, cryoprecipitate would be considered optimal, because the total cost for this treatment group is less than the total costs for the FC treatment group.

Table 8: Base Case Results: Obstetrical Hemorrhage – FC vs. Cryoprecipitate

Treatment	Product	Transfusion	LoS	Thrombo	Total	QALYs	$/QALY
	Costs						
FC	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$12,273	14.55	
Cryoprecipitate	$1,298	$3,510	$6,757	-	$11,565	14.55	
Incremental (FC-cryoprecipitate)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$707	0.00	n/a

FC = fibrinogen concentrate; LoS = length of stay; NA = Not available; QALY = quality-adjusted life-year; vs. = versus.

b) Trauma-related hemorrhage

One comparative study[25] was found that evaluated FC for treatment of trauma-related hemorrhage. In this matched pairs study, trauma patients were identified from a German trauma surgery database as either having been given FC or not given FC. Trauma patients not given FC were matched with trauma patients given FC on a number of criteria including age, gender, injury severity score, and trauma-associated severe hemorrhage (TASH) score.

Table 9 provides study data from this study[25] used as inputs into the economic evaluation of the trauma-related hemorrhage population. Information on the dose of FC given to patients was not provided in the study. The average dose of FC was assumed to be 4 grams. This was based on the mean dose of FC that would be given for acute treatment of AFD provided by expert opinion (see Table 5). A higher proportion of patients who were treated with FC died during the acute episode than patients who were not treated with FC (0.286 versus 0.255). A higher proportion of FC patients than no-FC patients had thromboembolic events (0.068 versus 0.034). Details on specific types of thromboembolic events suffered were not provided. In the model it was assumed that one third of all events were MI, one third were ischemic strokes, and one third were assumed to be hemorrhagic strokes. Patients who were treated with FC had both higher total length of hospital stay and ICU length of stay than patients not treated with FC. Patients treated with FC also had higher volumes of FFP, RBCs, and platelets transfused than patients not treated with FC. None of the differences between the treatment groups were statistically significant.

Table 9: Data Inputs Used for Economic Evaluation in Trauma Population			
	Fibrinogen Concentrate (n = 294)	**No Fibrinogen Concentrate (n = 294)**	***P*-value**
Age	40.3	40.0	
Dose	4 g	NA	
Mortality	0.286	0.255	0.40
Thromboembolic events	0.068	0.034	0.06
Length of hospital stay	34.6	32.8	0.96
ICU length of stay	17.6	17.3	0.68
Transfusions			
FFP (Units)	10.6	8.7	0.07
RBCs (Units)	12.8	11.3	0.20
Platelets (Units)	1.2	1.0	0.30

FFP = fresh frozen plasma; ICU = intensive care unit; NA = not available; RBCs = red blood cells.

Table 10 shows base case results for the trauma-related hemorrhage population. Based on the assumed dosage of 4 grams, the product cost for FC-treated patients was estimated to be $[redacted]. Patients treated with FC were also estimated to have $[redacted] more in transfusion costs, $[redacted] more in length of stay costs, and $[redacted] more in thromboembolic event costs compared with patients not treated with FC. Total costs were estimated to be $7,412 higher for patients treated with FC than for patients not treated with FC. Patients treated with FC are expected to have 0.64 less QALYs than patients not given FC. This difference was based on the higher mortality and thromboembolic events experienced by FC patients. As patients treated with FC have both higher expected costs and lower expected QALYs, FC would be considered to be dominated by treatment without FC. Therefore, treatment with FC would not be considered to be cost-effective regardless of how much decision-makers are willing to pay for an additional QALY.

Table 10: Base Case Results: Trauma-Related Hemorrhage Population – FC vs. No-FC							
Treatment	**Product**	**Transfusion**	**LoS**	**Thrombo**	**Total**	**QALYs**	**$/QALY**
	Costs						
FC	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$60,471	9.05	
No-FC	$0.00	$9,924	$40,430	$2,706	$53,059	9.69	
Incremental (FC – No-FC)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$7,412	–0.64	No-FC dominates

FC = fibrinogen concentrate; LoS = length of stay; QALY = quality-adjusted life-years; vs. = versus.

c) Prophylaxis for cardiac surgery

One comparative study was identified with relevant data that evaluated the use of FC as a prophylaxis against bleeding during major cardiac surgery.[19] In this study patients undergoing elective coronary artery bypass grafting were randomized to receive or not receive FC immediately before surgery. All patients in the study had a preoperative fibrinogen level less than or equal to 3.8 g/L.

Table 11 provides data inputs used in the economic evaluation of FC as a prophylaxis for hemorrhage during cardiac surgery. All patients in the FC group received 2 grams of FC. The

study did not report on mortality or hospital length of stay. A smaller proportion of patients given FC had an MI than patients not given FC (0.0 versus 0.10). This difference was based on a single patient in the no-FC group having an MI. The authors did not report the mean volume of blood transfusions for each group. However they did provide the number of units of FFP, RBC, and platelets given to patients who received transfusion in each group. The mean volume of FFP, RBC and platelets per patient for each group was estimated based on this data. Patients given FC has lower mean volume of FFP, RBCs, and platelets compared to patients not given prophylaxis FC. P-values were not reported for differences in rates of MI or for transfusion volumes.

Table 11: Data Inputs Used for Prophylactic for Cardiac Surgery Population

	Fibrinogen Concentrate (n = 10)	No Fibrinogen Concentrate (n = 10)	*p*-value
Age	66	68	
Dose	2 g	NA	
Mortality	NA	NA	
Thromboembolic events			
MI	0.00	0.10	NR
Length of hospital stay	NA	NA	
Transfusions			
FFP (Units)	0.2	0.7	NR
RBCs (Units)	0.3	0.8	NR
Platelets (Units)	0.0	0.4	NR

FFP = fresh frozen plasma; MI = myocardial infarction. NA = not available; NR = not reported; RBCs = red blood cells.

The base case results for the cardiac prophylaxis population are provided in Table 12. The cost of FC for patients in the FC group is estimated to be $[redacted]. Patients given prophylaxis FC incurred $[redacted] less transfusion costs and $[redacted] less lifetime thromboembolic event costs than patients not given prophylaxis FC. Because data on hospital length of stay were not reported, length of stay costs were not part of the analysis. The total cost for patients given FC is estimated to be $3,123 less than patients not given prophylaxis FC. Based on the lower thromboembolic event rate found in the FC-treated patients, FC patients were estimated to have 0.04 more expected QALYs than patients not treated with FC. Therefore, regardless of a decision-maker's willingness to pay for a QALY, treatment with FC would be considered cost-effective compared with no-FC treatment.

Table 12: Base Case Results: Prophylactic for Cardiac Surgery – FC vs. Cryoprecipitate							
	Product	**Transfusion**	**LoS**	**Thrombo**	**Total**	**QALYs**	**$/QALY**
Treatment	**Costs**						
FC	$[redacted]	$[redacted]	NA	$[redacted]	$1,005	7.13	
No-FC	$0	$775	NA	$3,354	$4,128	7.09	
Incremental (FC – no-FC)	$[redacted]	$[redacted]	NA	$[redacted]	-$3,123	0.04	FC dominates

FC = fibrinogen concentrate; LoS = length of stay; NA = not available; QALY = quality-adjusted life-year; vs. = versus.

d) Acute hemorrhage during cardiac surgery

One randomized controlled trial, reported in three separate publications,[18,20,21] and four comparative observational studies[26-29] for patients treated for hemorrhage during major cardiac surgery with data relevant for the economic evaluation, were identified in the literature review. Three of the four observational studies were conducted by the same research group that conducted the randomized controlled trial. Because of the preferable nature of RCT data, inputs for the model were based on data reported in the RCT.[18,20,21] Patients in this study were undergoing elective aortic replacement surgery and were randomly assigned to receive either FC or placebo. Patients who had bleeding in the range of 60 to 250 g/5 minutes after cardiopulmonary bypass were included in the study.

Table 13 provides the input data used for the economic evaluation of FC in patients hemorrhaging during cardiac surgery. The average dose of FC used in the study was 8 grams. Patients given FC had lower mortality than patients given placebo (0.03 versus 0.13). FC patients had longer total length of stay but shorter ICU length of stay. As for thromboembolic events, 3.4% of patients suffered an MI. Among placebo patients, 3.1% of patients suffered an ischemic stroke whereas 3.1% suffered a hemorrhagic stroke. One of the publications of the clinical trial[21] reported the median number of hospital-free days over 45 days as an outcome. These data were used to estimate the length of stay for each study. For example, the median number of hospital-free days over 45 postoperative days for FC patients was reported to be 31. Therefore, length of stay for FC patients was assumed to be 14 days (45 days minus 31 days). One of the trial publications[21] reported median volume of FFP, RBCs, and platelets transfused for FC- and placebo-treated patients, and zero units of FFP, RBCs, and platelets for FC patients. However, assuming no transfusions for FC is misleading as this same study reported that 55% of patients in the FC group received some type of transfusion. This would lead to an overestimation of the difference in transfusion volume and transfusion costs between FC and placebo patients. Therefore the transfusion volume for FC was adjusted to reflect the difference in transfusion volume reported by Rahe-Myer et al.[21] For example, the authors reported the median volume of FFP to be 0 units and 8 units in the FC and placebo groups, respectively. However, the difference in the point estimate of FFP volume was reported to be 5 units. Therefore the units per patient in the FC group were adjusted to be three units (eight units minus five units). The differences in transfusion volume were reported as statistically significant for FFP ($P < 0.001$), RBCs ($P = 0.007$) and platelets ($P < 0.001$). *P*-values were not reported for differences in mortality, thromboembolic events, or length of stay. However, it was indicated that the difference in mortality was not statistically significant.

Table 13: Data Inputs Used for Prophylactic for Hemorrhage During Cardiac Surgery			
	Fibrinogen Concentrate (n = 29)	**Placebo (n = 32)**	***p*-value**
Age	59	61	
Dose	8 g	n/a	
Mortality	0.03	0.13	NS
Thromboembolic events			
MI	0.034	0.00	NR
Ischemic stroke	0.000	0.031	NR
Hemorrhagic stroke	0.000	0.031	NR
Length of hospital stay	14	12	NR
ICU length of stay	1.9	2.3	NR
Transfusions			
FFP (Units)	3	8	< 0.007
RBCs (Units)	0	2	0.007
Platelets(Units)	2	4	< 0.001

FFP = fresh frozen plasma; ICU = intensive care unit; MI = myocardial infarction; NA = not available; NR = not reported, NS = not significant; RBCs = red blood cells.

Base case results for patients treated for hemorrhage during cardiac surgery are shown in Table 14. The cost of FC used is estimated to be $[redacted]. FC-treated patients were estimated to have $[redacted] less transfusion costs, $[redacted] more in length of stay costs, and $[redacted] less in thromboembolic event-related costs. Total expected costs were estimated to be $2,718 less in FC-treated patients compared with placebo-treated patients. Over the 40-year time horizon of the model, FC-treated patients had 1.19 more QALYs than patients treated with placebo. The higher QALYs for the FC-treated patients reflect both the lower short-term mortality rate and the lower rate of thromboembolic events for FC patients. Since FC patients have both lower expected costs and higher expected QALYs compared with placebo, it would be considered to dominate placebo in terms of cost-effectiveness. Therefore, FC would be considered to be cost-effective regardless of willingness to pay for an additional QALY.

Table 14: Base Case Results: Hemorrhage During Cardiac Surgery – FC vs. Placebo							
	Product	**Transfusion**	**LoS**	**Thrombo**	**Total**	**QALYs**	**$/QALY**
	Costs						
FC	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$21,321	8.80	
Placebo	$0.00	$4,658	$14,173	$5,208	$24,039	7.60	
Incremental (FC-Placebo)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	–$2,718	1.20	FC dominates

FC = fibrinogen concentrate; LoS = length of stay; QALY = quality-adjusted life-year; vs. = versus.

4.5.4 Sensitivity analyses

a) Deterministic sensitivity analysis

Table 15 presents product costs for all comparators of interest assuming a lower cost of FC ($[redacted] per gram) that could be realized with a change in the manufacturing process of the product. These product costs are based upon assumed dosages provided by clinical experts. If the lower FC cost is assumed, FC would have lower product costs than cryoprecipitate for use in the congenital and AFD acute treatment populations and when used as a prophylaxis in the AFD fibrinogen deficiency population. FP remains the cheapest product ($150) in the congenital and AFD acute hemorrhage populations; Tranexamic acid remains the cheapest comparator in the AFD prophylaxis population.

Table 15: Sensitivity Analysis Assuming Lower FC Cost ($ Per Gram): Product Costs Based on Estimated Dosage for Each Product

	Congenital	Acquired	
Blood Product	**Acute Treatment**	**Acute Treatment**	**Prophylaxis**
Fibrinogen concentrate	$4,560	$960	$480
Cryoprecipitate	$4,720	$1,180	$1,180
FFP	$1,047	$1,047	$1,047
FP	$150	$150	$150
Octaplasma	$990	$990	$990
Tranexamic acid	NA	NA	$93

FFP = fresh frozen plasma; FP = frozen plasma; NA = not available.

Table 16 provides cost-effectiveness results for each population assuming a lower cost of FC ($[redacted] per gram instead of $[redacted] per gram). For each population the incremental costs and QALYs of FC relative to its comparator are provided. A different unit cost of FC will affect product costs and total costs but not expected differences in QALYs. In the obstetrical hemorrhage population, the lower cost of FC results in the product cost of FC being $338 less than the cost of cryoprecipitate. Total costs become $187 higher for FC under this scenario. For the trauma-related hemorrhage, lower FC costs result in product costs of $960 and total costs of $6,892 higher for the FC group compared with the no-FC group. No-FC continues to dominate FC from a cost-effectiveness perspective. For the prophylactic population, the lower FC costs result in $480 in product costs for FC and total costs $3,383 lower than for the no-FC group. As with the base case analysis, FC dominates no-FC under this assumption. For the acute cardiac hemorrhage population, product costs for FC become $1,920, and total costs for the FC group become $3,758 less than the placebo group. FC continues to dominate no-FC under this assumption.

Table 16: Sensitivity Analysis: Incremental Costs, QALYS, and Cost per QALY Assuming Lower Price of Fibrinogen Concentrate ($ per gram)							
	Product	**Transfusion**	**LoS**	**Thrombo**	**Total**	**QALYs**	**$/QALY**
Population	**Costs**	**Costs**	**Costs**	**Costs**	**Costs**		
Obstetrical hemorrhage : Lower FC costs	-$338	$[redacted]	$[redacted]	NA	$187	0.00	NA
Base case	$[redacted]	$[redacted]	$[redacted]	NA	$707	0.00	NA
Trauma-related hemorrhage: Lower FC costs	$960	$[redacted]	$[redacted]	$[redacted]	$6,892	–0.64	No-FC dominates
Base case	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$7,412	–0.64	No-FC dominates
Prophylaxis for cardiac surgery: Lower FC costs	$480	$[redacted]	$[redacted]	$[redacted]	–$3,383	0.04	FC dominates
Base case	$[redacted]	$[redacted]	$[redacted]	$[redacted]	–$3,123	0.04	FC dominates
Acute hemorrhage cardiac surgery: Lower FC costs	$1,920	$[redacted]	$[redacted]	$[redacted]	–$3,758	1.20	FC dominates
Base case	$[redacted]	$[redacted]	$[redacted]	$[redacted]	–$2,718	1.20	FC dominates

FC = fibrinogen concentrate; LoS = length of stay; NA = not available; QALY = quality-adjusted life-year.

Table 17 provides cost-effectiveness results if thromboembolic events are excluded from the analysis. Results did not change for the obstetrical hemorrhage population since no events were found for this population. For the trauma-related population, exclusion of thromboembolic events from the model reduced the incremental total cost for FC and reduced the QALY difference, however FC remained dominated by no-FC. For the prophylaxis population, exclusion of thromboembolic events results in QALYs being identical for the FC and no-FC groups. No conclusion on cost-effectiveness can be made. Total costs change from being $3,123 lower for FC in the base case to being $231 more when thromboembolic events are excluded from the model. In the acute cardiac surgery hemorrhage population, exclusion of thromboembolic events changes the total cost of FC from being $[redacted] lower than the placebo group in the base case, to being $[redacted] more. Under this assumption, FC no longer dominates placebo, as there is a trade-off between higher costs and higher QALYs. The incremental cost per QALY for FC in this population becomes $[redacted] when thromboembolic events are excluded from the analysis.

Table 17: Sensitivity Analysis: Incremental Costs, QALYs and Cost per QALY Excluding Thromboembolic Events from the Model

	Product	Transfusion	LoS	Thrombo	Total	QALYs	$/QALY
Population	**Costs**	**Costs**	**Costs**	**Costs**	**Costs**		
Obstetrical hemorrhage: Exclude thrombombolic events	$[redacted]	$[redacted]	$[redacted]	NA	$707	0.00	NA
Base case	$[redacted]	$[redacted]	$[redacted]	NA	$707	0.00	NA
Trauma-related hemorrhage: Exclude thromboembolic events	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$4,706	–0.412	No-FC dominates
Base case	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$7,412	–0.64	No-FC dominates
Prophylaxis for cardiac surgery: Exclude Thromboembolic events	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$231	0.000	NA
Base case	$[redacted]	$[redacted]	$[redacted]	$[redacted]	–$3,123	0.04	FC dominates
Acute hemorrhage cardiac surgery: Exclude thromboembolic events	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$1,117	0.827	$1,350
Base case	$[redacted]	$[redacted]	$[redacted]	$[redacted]	–$2,718	1.20	FC dominates

FC = fibrinogen concentrate; LoS = length of stay; NA = not available; QALY = quality-adjusted life-year.

b) Probabilistic sensitivity analysis

PSAs were conducted for all populations based upon data from comparative studies. Cost-effectiveness acceptability curves (CEACs) were based upon costs and effects generated through 1,000 Monte Carlo simulations. The CEACs show the probability that FC is cost-effective over different values of willingness-to-pay for an additional QALY. Details on findings from the PSA for each population are given below.

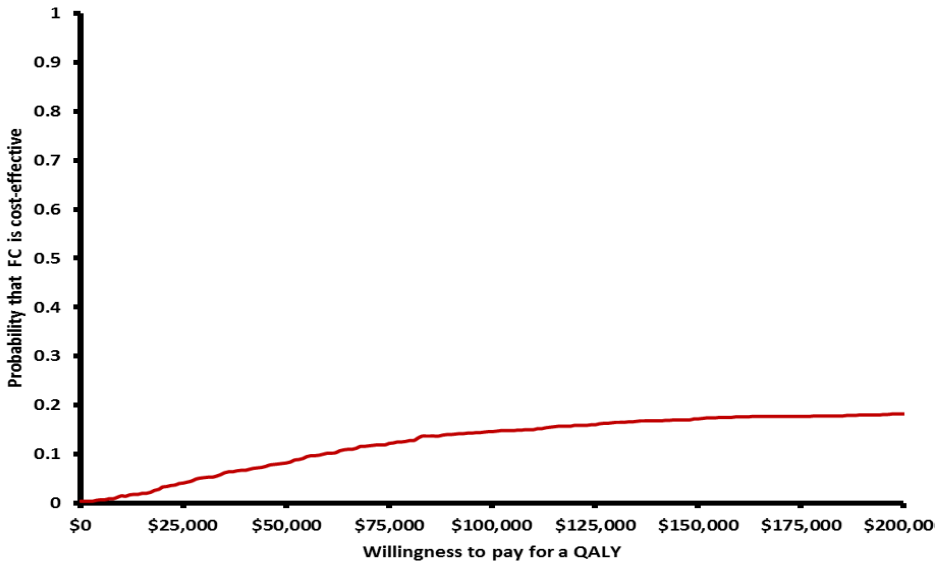
c) Obstetrical hemorrhage

For the obstetrical hemorrhage population, there were no maternal deaths or thromboembolic events reported. Because of this, the model predicted the same expected QALYs for the FC and cryoprecipitate groups. Because there were no data to base uncertainty in differences in mortality or thromboembolic events, there was no variation in incremental QALYs generated in the PSA. Therefore, traditional CEACs could not be generated. However, the probabilistic analysis did find that the probability that treatment with FC in this population would be more expensive than treatment with cryoprecipitate was 0.76.

d) Trauma-related hemorrhage

Figure 2 provides the cost-effectiveness acceptability curve for FC compared to no-FC in patients with trauma-related hemorrhage. For willingness-to-pay (WTP) per QALY thresholds of $25,000, $50,000, $75,000, $100,000, and $150,000, the probability that FC is cost-effective when compared with no-FC is 0.04, 0.08, 0.12, 0.15, and 0.17, respectively. This indicates that the probability that FC is cost-effective is low for WTP values of $100,000 or less in this population.

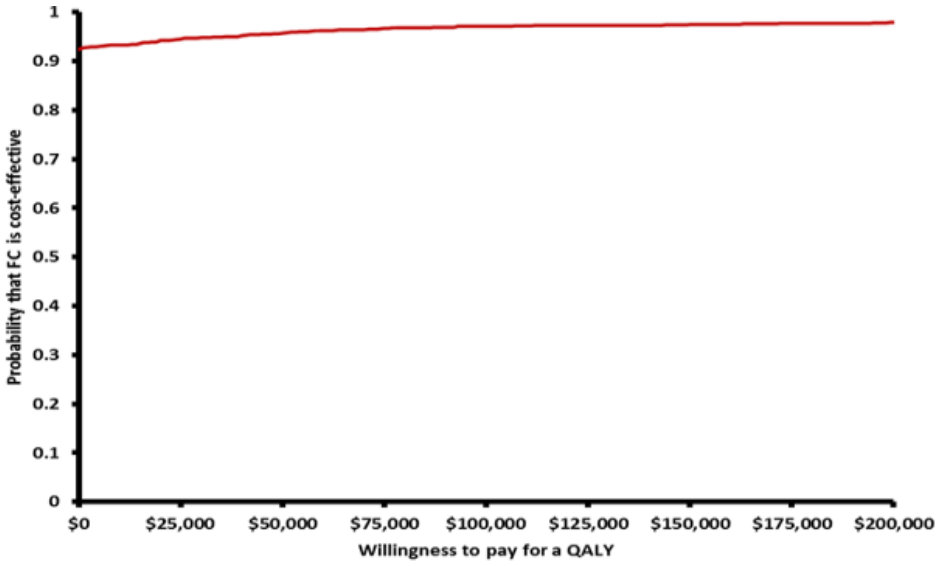
Figure 2: Cost-Effectiveness Acceptability Curve for FC in Trauma-related Hemorrhage



e) Prophylactic for cardiac surgery

The cost-effectiveness acceptability curve for FC treatment compared with no-FC treatment as prophylaxis in cardiac surgery is shown in Figure 3. For WTP per QALY thresholds of $25,000, $50,000, $75,000, $100,000, and $150,000, the probability that FC is cost-effective when compared with no-FC is 0.94, 0.97, 0.97, 0.97, and 0.98, respectively. This indicates that the probability that FC is cost-effective is high for WTP values of $100,000 or less in this population.

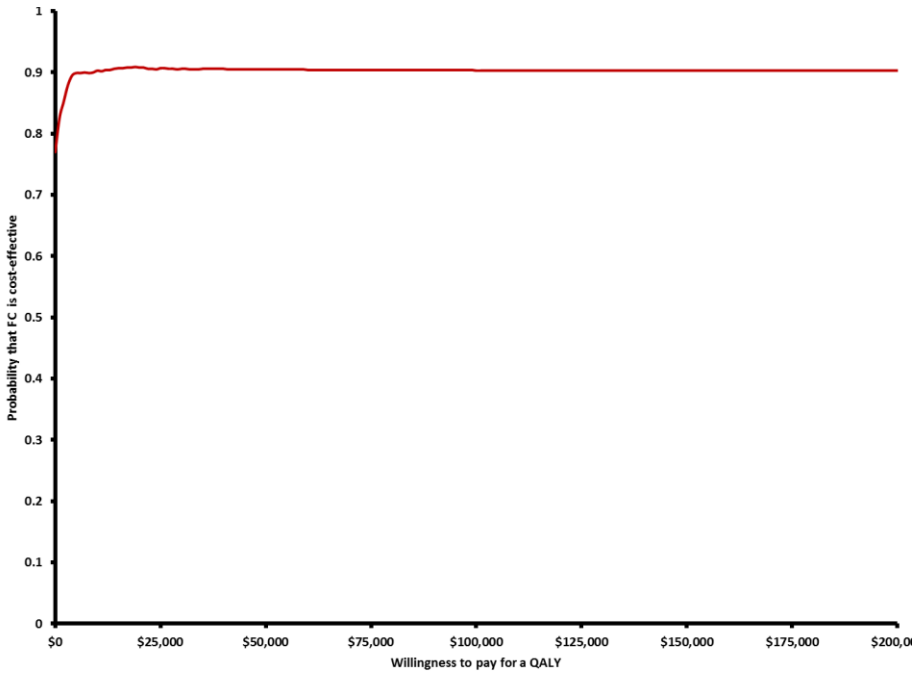
Figure 3: Cost-Effectiveness Acceptability Curve for FC in Prophylactic Cardiac Surgery



f) Hemorrhage during cardiac surgery

The cost-effectiveness acceptability curve for FC treatment compared with no-FC treatment for acute hemorrhage during cardiac surgery is shown in Figure 4. For WTP per QALY thresholds of $25,000, $50,000, $75,000, $100,000, and $150,000, the probability that FC is cost-effective when compared with no-FC is 0.91, 0.91, 0.90, 0.90, and 0.90, respectively. This indicates that the probability that FC is cost-effective is high for WTP values of $100,000 or less in this population.

Figure 4: Cost-Effectiveness Acceptability Curve for FC in Hemorrhage During Cardiac Surgery



5 DISCUSSION

5.1 Summary of Evidence

The main findings of our clinical review are summarized in Table 18. The limited available evidence suggested that very few outcomes were statistically different between the FC and comparator groups. However, some trends were found in the studies, including: (1) a beneficial effect of FC on the amount of blood loss, the number and volume of necessary blood transfusions, as well as mortality and thromboembolic adverse events, when it was compared with no-FC or placebo in patients undergoing cardiac surgeries; (2) lower rate of blood loss and potentially less MI with FC, versus no-FC, in patients undergoing pre-cardiac surgery prophylaxis, (3) a lower incidence of organ failure, and a lower mortality rate in early hours after trauma, when it was compared with no-FC; and (4) no statistically different blood loss or transfusion requirements in postpartum hemorrhage, when it was compared with cryoprecipitate. As shown in Table 18, we found no data on the comparison of FC with cryoprecipitate in cardiac surgery or trauma patients.

5.2 Interpretation of the Results

Economic analyses were conducted based upon data identified in the clinical review. Economic analyses were conducted separately for each population of interest. Since no comparative studies were found for patients with CFD, no economic analyses beyond estimated product costs were conducted. However, data were available for the various AFD populations to conduct further analyses. For the analysis of the obstetrical hemorrhage population, treatment with FC was found

to lead to higher overall costs than treatment with cryoprecipitate ($12,273 versus $11,565). Because no evidence of differences in short-term mortality or thromboembolic events in this patient population was found, incremental cost-effectiveness could not be evaluated. In the analysis of patients with trauma-related hemorrhage, the model predicted FC-treated patients to be both more expensive ($60,471 versus $53,059) and lead to less overall QALYs (9.05 versus 9.69) compared with patients not treated with FC. Therefore, based on this analysis, FC would not be considered cost-effective in this population compared with no-FC. In the analysis of using FC for prophylaxis against bleeding during cardiac surgery, patients treated with FC were found to have lower costs ($1,005 versus $4,128) and generate more QALYs (7.13 versus 7.09) than patients not treated with FC. Similarly, in the analysis of treatment for acute hemorrhage during cardiac surgery, the model predicted patients treated with FC would have lower costs ($21,321 versus $24,039) and higher QALYs (8.80 versus 7.60) than patients treated with placebo. Therefore, in both the prophylaxis and acute bleeding cardiac surgery populations FC would be considered cost-effective compared with no-FC or placebo, respectively. Using a lower cost of FC based on a change in the manufacturing process did not change the conclusions of the analyses. However, running the model without the inclusion of thromboembolic events did change the results in a couple of analyses. Specifically, in the prophylaxis population FC no longer dominates no-FC. Instead, we can only conclude that patients treated with FC would cost more than patients not treated with FC. In the analysis of treatment of acute bleeding during cardiac surgery, FC no longer dominates placebo. Instead, FC is more costly and produces more QALYs compared with placebo-treated patients. The cost per QALY for FC compared with placebo is $1,350 if thromboembolic events are excluded from the model.

Caution should be placed on these findings for a number of reasons. The model was driven by results from studies identified in the clinical review that included treatment with FC as a comparator. However, nearly all of the differences in key model parameters such as length of stay, transfusion volumes, mortality, and thromboembolic event rates were not statistically significant. Additionally, no RCTs were reported for two of the populations evaluated (obstetrical hemorrhage, trauma). Therefore, economic evaluations for these populations had to be based on observational studies. The sample sizes in the RCTs were small. In the RCT providing data for the prophylaxis population,[19] the sample size was 10 patients in the FC group and 10 patients in the no-FC group. In the RCT evaluating patients with acute bleeding during cardiac surgery, 29 patients were in the FC group whereas 32 patients were in the placebo group.[18,20,21]

In only one of the economic evaluations was there an active comparator available for a population of interest: cryoprecipitate in the obstetrical hemorrhage population. In the other populations evaluated, there were no other active comparators. Therefore, conclusions on the cost-effectiveness of FC versus an active comparator such as cryoprecipitate cannot be made in these populations. Furthermore, because no comparative studies were found evaluating individuals with CFD, evaluations in this population were not possible. Viral transmission through blood products was not considered in any of the economic evaluations conducted in this report since no data on viral transmissions were reported in any of the available comparative trials.

Table 18: Summary of the Identified Evidence					
Study Outcomes	**Study Type**	**Study Populations**			
		Acute Hemorrhage During Cardiac Surgery	**Prophylaxis for Cardiac Surgery**	**Trauma-related Hemorrhage**	**Obstetrical Hemorrhage**
Blood loss	RCTs	Statistical reduction, compared with no-FC or placebo	Statistical reduction, compared with no-FC	No data	No data
	Non-RCTs	Statistical increase, compared with no-FC; No statistical difference after adjustment for demographic- and surgery-related variables	No data	No data	No statistical difference, compared with cryoprecipitate
Control of bleeding episodes	RCTs	Statistical improvement, compared with placebo; No statistical difference compared with FFP	No data	No data	No data
	Non-RCTs	Statistical improvement, compared with allogenic blood products	No data	No data	No data
Transfusion requirements	RCTs	Stastically lower, compared with no-FC (2 RCTs) No statistical difference, compared with no-FC (1 RCT)	No data	No data	No data
	Non-RCTs	Statistically lower (in number and volume), compared with no-FC	No data	No data	No statistical difference, compared with cryoprecipitate
Mortality	RCTs	Considerable reduction (3% versus 13%), although not reported to be statistically significant, compared with no-FC	No data	No data	
	Non-RCTs	No statistical difference, compared with no-FC	No deaths reported	Statistically lower, compared with no-FC (in 6-hour follow-up; but not 24-hour and 30-day follow-ups)	No deaths reported

Table 18: Summary of the Identified Evidence					
Study Outcomes	**Study Type**	**Study Populations**			
		Acute Hemorrhage During Cardiac Surgery	**Prophylaxis for Cardiac Surgery**	**Trauma-related Hemorrhage**	**Obstetrical Hemorrhage**
Adverse events	RCTs	Thromboembolic event (1 RCT), 1 case of MI in FC group, and cases of stroke in no-FC group; No statistical difference in other serious AEs, compared with no-FC	No MI in FC group versus 1 MI in no-FC	No data	No data
	Non-RCTs	No statistical difference in thromboembolic and ischemic cardiovascular events, compared with no-FC	No data	Statistically lower rates of organ failure, compared with no-FC No statistical difference in thromboembolic events or sepsis	No data

AE = adverse events; FC = fibrinogen concentrate; FFP = fresh frozen plasma; MI = myocardial infarction; RCTs = randomized controlled trials.

5.3 Strengths and Limitations of the Clinical Review

5.3.1 Strengths

The clinical review provides a comprehensive review of available comparative evidence on clinical effectiveness and safety outcomes of FC, cryoprecipitate, and plasma products in treatment of fibrinogen deficiency disorders. The review also highlights the limitations of the existing evidence by appraising the quality of the included studies.

5.3.2 Limitations

The search was limited to articles that were published in English after January 1, 2008. Therefore, a number of potentially relevant studies written in other languages or those published prior to 2008 may have not been included in our search results. In addition, one reviewer evaluated the eligibility of the identified literature for inclusion and a second reviewer was consulted if needed. Having two independent reviewers could increase the sensitivity of the process for identification of potentially relevant studies.[31] The use of a single reviewer is also suggested to introduce some levels of error and information bias into the data extraction process.[32]

Some of the included studies were limited by their small sample sizes or non-randomized or historical comparators, limitations that might affect the internal validity and generalizability of the study results. Furthermore, there were considerable variations in study populations and measures used to report selected outcomes, which made it difficult to draw a broad and generalizable conclusion.

This review is also limited by the lack of any included studies for CFD. This is mainly because studies were required to have a comparative (head-to-head) randomized or non-randomized design in order to be included in this review. This specification was meant to ensure not only that a control group existed to provide a basis for a comparison of the results, but also that study participants in different comparison groups were recruited from the same population. However, the identified articles on the use of FC in CFD were largely in the form of case reports or case-series in which no comparison groups were available. These studies were excluded from this review, as they did not meet inclusion criteria.

The literature search found no head-to-head studies that would enable FC to be compared with cryoprecipitate in trauma patients or those who undergo major cardiac surgery. One observational study[24] attempted to compare FC with cryoprecipitate in cardiothoracic surgeries, but the reported outcome measure (change in amount of postoperative blood loss) was not compared statistically between the study groups. It was not possible to compare the effects of FC and tranexamic acid in any of the populations of interest due to insufficient data. Tranexamic acid was used by one non-randomized trial,[29] however it was administered in both FC and control groups. In addition, there were insufficient studies to compare clinical outcomes of FC with its comparators in different indications for cardiac surgery (i.e., elective versus urgent surgeries).

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6 CONCLUSIONS AND IMPLICATIONS FOR DECISION- OR POLICY-MAKING

Based on the limited data, the literature review suggests that administration of human FC can reduce blood loss and post-surgical transfusion requirements in patients with massive hemorrhage during major surgeries. None of the included studies showed a statistically significant difference between FC and cryoprecipitate with respect to the above-mentioned outcomes. Economic analyses found FC to be cost-effective in certain populations (pre-cardiac surgery prophylaxis, treating hemorrhage occurring during cardiac surgery) but not in others (treating hemorrhage related to trauma). The lack of comparative studies with active comparators make drawing clear conclusions of the clinical and cost-effectiveness of FC uncertain. Due to the paucity of data and small sample sizes of the majority of the included studies, it is difficult to draw a conclusion on the effect of FC and the candidate comparators on length of hospital stay, mortality, and other treatment-related adverse events. This also applies to effectiveness of FC in patient populations with other indications of hemostatic therapy, such as trauma, postpartum hemorrhage, and prophylactic use of FC.

This review identified no comparative studies reporting on the use of FC in CFD, studies comparing FC with cryoprecipitate in trauma or cardiac surgery, or those comparing FC with antifibrinolytics. Well-designed controlled clinical studies with adequate sample sizes are needed to compare human FC with potential alternatives for fibrinogen replacement therapy, such as cryoprecipitate or plasma in different states of AFD as well as patients with CFD. Therefore, due to lack of comparative evidence, it was not possible to evaluate the effects of FC in CFD.

Given the limitations of the available evidence, additional research is needed to validate these early conclusions.

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APPENDIX 1: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	National Library of Medicine
Databases:	PubMed **Note:** Subject headings have been customized for each database.
Date of Search:	June 13, 2013
Alerts:	None
Study Types:	Systematic reviews; meta-analyses; technology assessments; all other study types.
Limits:	English language Humans (for non-SRs/MAs/HTAs) Publication date 2008 to date of search

SYNTAX GUIDE	
[mh]	Medical Subject Heading
*	Truncation symbol (wildcard) to retrieve plurals or varying endings
[all]	All fields
[Journal]	Journal name
[nm]	Supplementary concept; includes chemical, protocol or disease terms
[pt]	Publication type
[sb]	Subset; method of restricting retrieval by subject, citation status and journal category
[tiab]	Title or abstract
[tw]	Text words; includes all words and numbers in the title, abstract, other abstract, MeSH terms, MeSH Subheadings, Publication Types, Substance Names, Personal Name as Subject

Clinical/Economic Search Strategy	
Line #	**Search Strategy**
#43	Search **#39 OR #40 OR #41** Filters: **English**
#42	Search **#39 OR #40 OR #41**
#41	Search **#37 AND #35**
#40	Search **#37 AND #33**
#39	Search **#38 NOT #34**
#35	Search **systematic[sb] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy*[tw] OR metanaly*[tw] OR metaanaly*[tw] OR met analy*[tw] OR integrative research[tiab] OR integrative review*[tiab] OR integrative overview*[tiab] OR research integration*[tiab] OR research overview*[tiab] OR collaborative review*[tiab] OR collaborative overview*[tiab] OR systematic review*[tiab] OR technology assessment*[tiab] OR technology overview*[tiab] OR technology appraisal*[tiab] OR "Technology Assessment, Biomedical"[mh] OR HTA[tiab] OR HTAs[tiab] OR systematic overview*[tiab] OR methodological overview*[tiab] OR methodologic overview*[tiab] OR methodological review*[tiab] OR methodologic review*[tiab] OR quantitative review*[tiab] OR quantitative overview*[tiab] OR quantitative synthes*[tiab] OR pool analy*[tiab] OR pooled analy*[tiab] OR Cochrane[tiab] OR Medline[tiab] OR Pubmed[tiab] OR Medlars[tiab] OR handsearch*[tiab] OR hand search*[tiab] OR meta-regression*[tiab] OR metaregression*[tiab] OR mega-regression*[tiab] OR data synthes*[tiab] OR data extraction[tiab] OR data abstraction*[tiab] OR mantel haenszel[tiab] OR peto[tiab] OR der-simonian[tiab] OR dersimonian[tiab] OR fixed effect*[tiab] OR latin square*[tiab] OR "Cochrane Database Syst Rev"[Journal:__jrid21711] OR "health technology assessment winchester, england"[Journal] OR "Evid Rep Technol Assess (Full Rep)"[Journal] OR "Evid Rep Technol Assess (Summ)"[Journal] OR "Int J Technol Assess Health Care"[Journal] OR "GMS Health Technol Assess"[Journal] OR "Health Technol Assess (Rockv)"[Journal] OR "Health Technol Assess Rep"[Journal]**
#33	Search **publisher[sb] OR in process[sb] OR pubmednotmedline[sb]**
#37	Search **#26 AND #32** Filters: **Publication date from 2008/01/01 to 2013/12/31**
#34	Search **review[pt] OR newspaper article[pt]**
#38	Search **#26 AND #32** Filters: **Publication date from 2008/01/01 to 2013/12/31; Humans**
#36	Search **#26 AND #32**
#26	Search **#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25**
#32	Search **#27 OR #28 OR #29 OR #30 OR #31**
#31	Search **Haemocomplettan[all] OR Hemocomplettan[all]**
#30	Search **RiaSTAP*[all]**
#29	Search **human* fibrinogen[tiab] OR pasteuri* fibrinogen[tiab] OR plasma* fibrinogen[tiab]**
#28	Search **fibrinogen concentrat*[tiab]**
#27	Search **Fibrinogen[mh]**
#25	Search **consumption coagulopath*[tiab]**
#24	Search **(disseminated intravascular[tiab] OR disseminated intra-vascular[tiab] OR intravascular disseminated[tiab] OR intra-vascular disseminated[tiab]) AND (coagulation*[tiab] OR clott*[tiab])**
#14	Search **liver grafting*[tiab] OR (liver[tiab] AND transplant*[tiab]) OR hepatic transplant*[tiab]**
#15	Search **Ascites[mh]**
#16	Search **ascites[tiab]**

Clinical/Economic Search Strategy	
Line #	**Search Strategy**
#17	Search **Hepatitis[mh]**
#18	Search **hepatitis[tiab] OR hepatitides[tiab]**
#19	Search **Liver Neoplasms[mh]**
#20	Search **(hepatic[tiab] OR hepatocellular[tiab] OR liver[tiab]) AND (cancer*[tiab] OR carcinoma*[tiab] OR neoplasm*[tiab] OR tumour*[tiab] OR tumor*[tiab])**
#21	Search **Shock, Septic[mh]**
#22	Search **endotoxic shock[tiab] OR septic shock[tiab] OR toxic shock[tiab]**
#23	Search **Disseminated Intravascular Coagulation[mh]**
#13	Search **Liver Transplantation[mh]**
#12	Search **bleed*[tiab] OR hemorrhag*[tiab] OR haemorrhag*[tiab]**
#8	Search **hypofibrinogenemi*[tiab] OR hypofibrinogenaemi*[tiab]**
#9	Search **hyperfibrinolysis[tiab]**
#10	Search **(Progressive[tiab] AND familial[tiab] AND (intrahepatic[tiab] OR intra-hepatic[tiab]) AND cholestasis[tiab]) OR "PFIC 2"[tiab] OR PFIC2[tiab] OR BSEP deficiency[tiab] OR Byler syndrome[tiab]**
#11	Search **Hemorrhage[mh]**
#7	Search **hyperfibrinogenemi*[tiab] OR hyperfibrinogenaemi*[tiab]**
#6	Search **dysfibrinogenemi*[tiab] OR dysfibrinogenaemi*[tiab]**
#5	Search **afibrinogenemi*[tiab] OR afibrinogenaemi*[tiab] OR mckusick 20240[tiab]**
#4	Search **"Factor 1" defect*[tiab] OR "Factor 1" defincien*[tiab] OR fibrinogen defect*[tiab] OR fibrinogen deficien*[tiab]**
#3	Search **Plasminogen Activator Inhibitor-1 Deficiency[nm]**
#2	Search **Plasminogen Activator Inhibitor 1/deficiency[mh]**
#1	Search **Afibrinogenemia[mh]**

OTHER DATA BASES	
Cochrane Library Issue 6 of 12 (June 2013) & 2 of 4 (Apr 2013)	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.

Grey Literature

Dates for Search:	**June 13 to 17, 2013**
Keywords:	afibrinogenemia OR afibrinogenaemia OR dysfibrinogenemia OR dysfibrinogenaemia OR hyperfibrinogenemia OR hyperfibrinogenaemia OR hypofibrinogenemia OR hypofibrinogenaemia OR fibrinogen concentrate OR RiaSTAP OR Haemocomplettan OR Hemocomplettan
Limits:	None

Relevant websites from the following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for evidence-based medicine” (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Regulatory Approvals
- Internet Search.

APPENDIX 2: TITLE AND ABSTRACT SCREENING CHECKLIST

	Include	Exclude
1. What is the STUDY POPULATION in this article?	☐ CFD – afibrinogenemia ☐ CFD – hypofibrinogenemia ☐ AFD – Massive hemorrhage due to major surgeries ☐ AFD – Massive hemorrhage due to trauma ☐ AFD – Obstetrical hemorrhage ☐ AFD – Associated liver disorders, e.g., liver transplantation, ascites, hepatitis, hepatic cancer ☐ AFD associated with gastrointestinal bleeding ☐ Hyperfibrinolysis and other forms of increased loss of fibrinogen including hemorrhagic and septic shock, DIC, and microvascular bleeding due to DIC ☐ Catastrophic bleeding thrombolysis, i.e., very serious bleeding associated with the use of thrombolytic agents such as alteplase or streptokinase ☐ Presurgical bleeding prophylaxis	☐ CFD – dysfibrinogenemia ☐ All other populations
2. What is the INTERVENTION?	☐ Human fibrinogen concentrate	☐ No human fibrinogen concentrate as a comparison arm
3. What is the TYPE OF STUDY reported in this article?	☐ Report of a clinical trial (controlled/uncontrolled; randomized/non-randomized) ☐ Report of a prospective or retrospective cohort study ☐ Report of a case-control study (include) ☐ Report of an analytical cross-sectional study (include)	☐ Report of a before-after study (include) ☐ Academic/narrative review, comment, editorial, letter, note, patient handout, study design description (exclude) ☐ Meta-analyses/systematic reviews/HTAs (use for bibliographic search) ☐ All other study designs (exclude)
Selection Decision	☐ **Include**	☐ **Exclude**

AFD = acquired fibrinogen deficiency; CFD = congenital fibrinogen deficiency; DIC = disseminated intravascular coagulation; HTA = health technology assessment.

APPENDIX 3: DOWNS AND BLACK CHECKLIST[4]

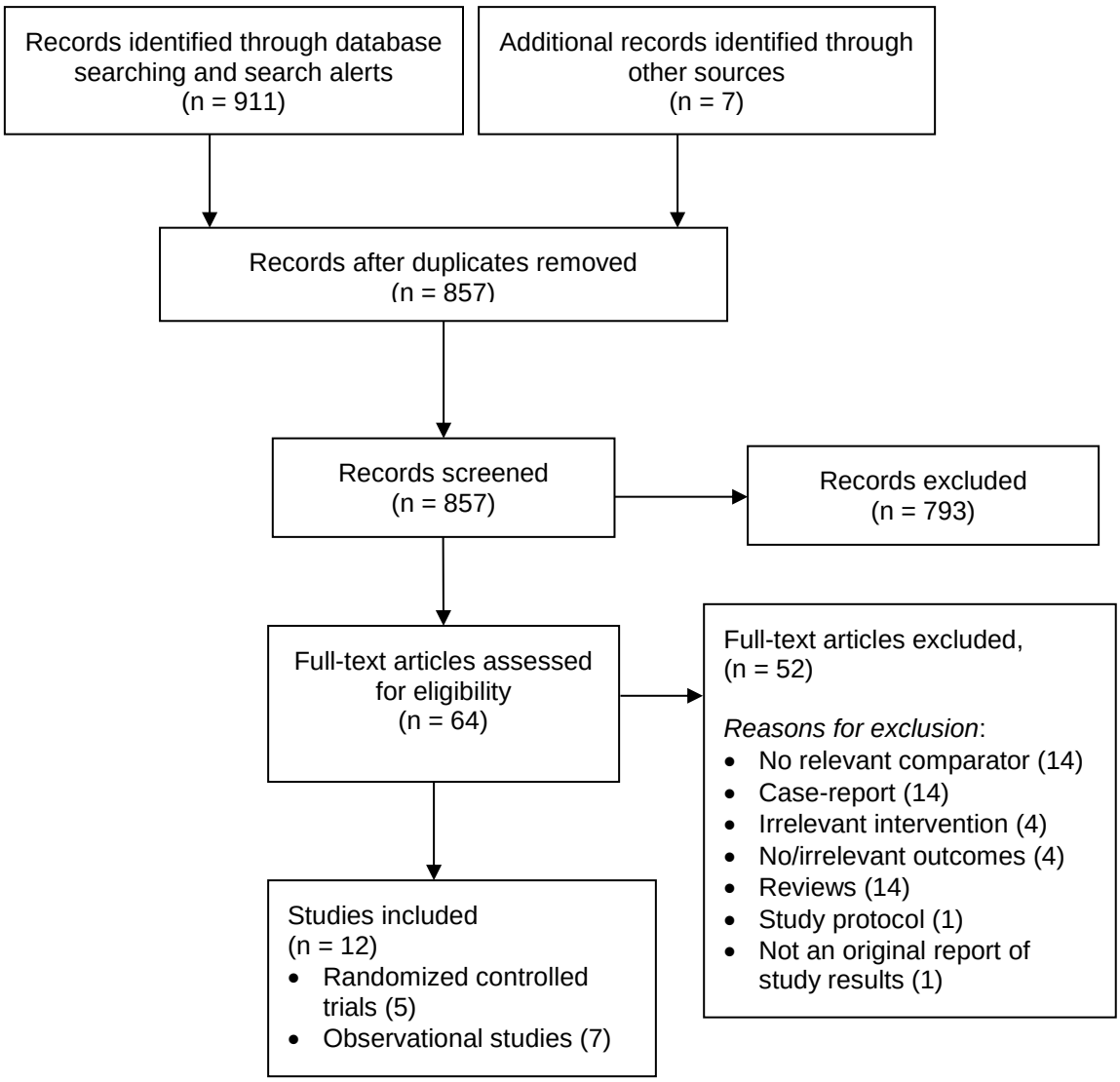
Reviewer: _____ **Date:** _____

Ref ID:_____ **First Author (year):** _____

REPORTING	Yes/No/Partially	Score
Is the objective of the study clear?	Yes = 1, No = 0	
Are the main outcomes clearly described in the Introduction or Methods?	Yes = 1, No = 0	
Are the characteristics of the patients included in the study clearly described?	Yes = 1, No = 0	
Are the interventions clearly described?	Yes = 1, No = 0	
Are the distributions of the principal confounders in each group of subjects clearly described?	Yes = 2, Partially = 1, No = 0	
Are the main findings of the study clearly described?	Yes = 1, No = 0	
Does the study estimate random variability in data for the main outcomes?	Yes = 1, No = 0	
Have all the important adverse events consequential to the intervention been reported?	Yes = 1, No = 0	
Have the characteristics of the patients lost to follow-up been described?	Yes = 1, No = 0	
Have actual probability values been reported for the main outcomes except probability< 0.001?	Yes = 1, No = 0	
EXTERNAL VALIDITY	**Yes/No/Unclear**	**Score**
Were subjects asked to participate in the study representative of the entire population recruited?	Yes = 1, No = 0, Unclear = 0	
Were those subjects who were prepared to participate representative of the recruited population?	Yes = 1, No = 0, Unclear = 0	
Were staff, places, and facilities where patients were treated representative of the treatment most received?	Yes = 1, No = 0, Unclear = 0	
INTERNAL VALIDITY	**Yes/No/Unclear**	**Score**
Was an attempt made to blind study subjects to the intervention?	Yes = 1, No = 0, Unclear = 0	
Was an attempt made to blind those measuring the main outcomes?	Yes = 1, No = 0, Unclear = 0	
If any of the results of the study were based on data dredging, was this made clear?	Yes = 1, No = 0, Unclear = 0	
Was the time period between intervention and outcome the same for intervention and control groups or adjusted for?	Yes = 1, No = 0, Unclear = 0	
Were statistical tests used to assess the main outcomes appropriate?	Yes = 1, No = 0, Unclear = 0	
Was compliance with the interventions reliable?	Yes = 1, No = 0, Unclear = 0	
Were the main outcome measures used accurate? (valid and reliable)	Yes = 1, No = 0, Unclear = 0	

INTERNAL VALIDITY-CONFOUNDING (SELECTION BIAS)	Yes/No/Unclear	Score
Were patients in different intervention groups recruited from the same population?	Yes = 1, No = 0, Unclear = 0	
Were study subjects in different intervention groups recruited over the same period of time?	Yes = 1, No = 0, Unclear = 0	
Were study subjects randomized to intervention groups?	Yes= = 1, No = 0, Unclear = 0	
Was the randomized intervention assignment concealed from patients and staff until recruitment was complete?	Yes = 1, No = 0, Unclear = 0	
Was there adequate adjustment for confounding in the analyses from which main findings were drawn?	Yes = 1, No = 0, Unclear = 0	
Were losses of patients to follow-up taken into account?	Yes = 1, No = 0, Unclear = 0	
POWER	**Size of smallest intervention group Score 0 to 5**	**Score**
Was the study sufficiently powered to detect clinically important effects where probability value for a difference due to chance is < 5%?		

APPENDIX 4: SELECTION OF INCLUDED STUDIES



APPENDIX 5: CHARACTERISTICS OF INCLUDED CLINICAL STUDIES

Table A1: Characteristics of Included Randomized Controlled Trials

Author, Year	Study Design	Country	Study Population			Intervention		Control		Concurrent Treatments	Reported Outcomes
			Condition	N	Eligibility for Treatment	Fibrinogen Concentrate (dose/ frequency)	n1	Type of Product	n2		
Rahe-Meyer et al. 2013[20]	RCT – single-centre, double-blind	Germany	Elective aortic replacement surgery (thoracic and thoracoabdominal)	61	Coagulopathic	FC FC FC	29 29 29	Placebo (0.9% saline) FFP/PLTs (1 cycle) FFP/PLTs (2 cycles)	32 32 32	NR	Mean change in bleeding rate
Rahe-Meyer et al. 2013[21]	Phase 2 RCT– single-centre, double-blind	Germany	Major aortic replacement surgery	61	Clinically relevant bleeding – 5 min bleeding mass of 60 g to 250 g	FC (1 g/50ml water) (med = 8g; range 3g to 14 g])	29	Placebo (50 ml of 0.9% saline)	32	All patients: tranexamic acid (30 mg/kg preoperative and 1 mg/kg during operation), heparin (400 units/kg)	Units of allogeneic blood components (RBC + FFP_ PLT concentrate) during 24 hours, number of units of each blood component (FFP, PLTs), total avoidance of blood products, number of days of hospitalization and ICU (45 days), fibrinogen, Hb, safety (pleural effusion, AF, re-operation due to bleeding, serious AEs leading to death, MI, cerebral hemorrhage, cerebral infarction, operative hemorrhage, viral transmissions)
Lance et al. 2012[22]	RCT – single-centre, blinded	Netherlands	Major elective surgery (cardiovascular, abdominal or orthopedic)	43	Massive bleeding (> 150 mL/hour or > 1.5ml/kg/20 min or > 700 mL at once)	FFP + FC (2 units FFP + 2 g FC	22	FFP (4 units)	21	heparin + protamine	PT, aPTT, Ht, PLTs. fibrinogen, prothrombin, anti-thrombin, Factors VIII, IX, X, safety (pleural effusion, wound infection, septic events, abdominal ischemia)

Table A1: Characteristics of Included Randomized Controlled Trials											
Author, Year	**Study Design**	**Country**	**Study Population**			**Intervention**		**Control**		**Concurrent Treatments**	**Reported Outcomes**
			Condition	**N**	**Eligibility for Treatment**	**Fibrinogen Concentrate (dose/ frequency)**	**n1**	**Type of Product**	**n2**		
Karlsson et al. 2009[19]	RCT – single-centre, double-blind	Sweden	CABG	20	Preoperative fibrinogen < 3.8 g/l	FC (2 g)-prophylactic	10	No-FC	10	NR	PT, aPTT, Hb, creatinine, ASAT, ALAT, fibrinogen, safety (MI, vein graft occlusion) postoperative bleeding, need for blood transfusion, global hemostasis
Fenger-Eriksen et al. 2009[23]	RCT – single-centre, double-blind	Denmark	Elective radical cystectomy	20	30% reduction in hematocrit level from baseline, during surgery	FC (45 mg/kg)	10	Placebo (2.25 ml/kg of 0.9% saline)	10	FFP and PLTs if needed	Maximum clot firmness, platelet function, thrombin generation, blood loss, transfusion requirements, fibrinogen, D-dimer

Table A2: Characteristics of Included Non-randomized Trials or Observational Comparative Studies											
Author, Year	**Study Design**	**Country**	**Study Population**			**Intervention**		**Control**		**Concurrent Treatments**	**Reported Outcomes**
			Condition	**N**	**Eligibility for Inclusion**	**Fibrinogen Concentrate (dose/frequency)**	**n1**	**Type of Product**	**n2**		
Yang et al. 2013[24]	Observational study	UK	Cardiothoracic surgery	84	Patients who had fibrinogen measurements within 12-hour post-operation	FC (46.26 ± 33.64 mg/kg)	8	Cryoprecipitate (4.76 ± 2.9 mL/kg)	76	NR	Postoperative bleeding
Wafaisade et al. 2013[25]	Prospective cohort	Germany	Trauma surgery	588	Administration of at least one RBC unit during ICU admission, relative risk score for TASH > 9	FC	294	No-FC (matched for age, sex, injury severity score, FFP/RBC ratio and prothrombin complex concentration)	294	FFP or RBC if needed Anti-fibrinolytic agents (12%–18%)	Ventilator days, ICU LoS, hospital LoS, thromboembolic events, sepsis, organ failure, time to death, mortality (6 hours, 24 hours, 30-day), overall in hospital mortality
Bilecen et al. 2013[29]	Non-randomized cohort	Netherlands	Complex cardiac surgery	1071	Unsuccessful initial hemostatic management with RBC, PLTs, or FFP, and exclusion of source of bleeding	FC	264	No-FC	811	tranexamic acid	Postoperative blood loss, transfusion (RBC, FFP or PLTs), 30-day mortality, MI, CVA/TIA, renal insufficiency/failure, total infections, prolonged mechanical ventilation (> 24 hours)
Ahmed et al. 2012[30]	Observational study	Ireland	Major obstetric hemorrhage	34	Deliveries with estimated blood loss of 2.5 L or more or transfusion of ≥ 5 units of RBC or treatment of coagulopathy	FC (4 ± 0.8g)	20	Cryoprecipitate (2.21 ± 0.35 pools)	14	NR	Estimated blood loss, Ht, PLTs, fibrinogen transfusions (RBC, Octaplasm PLTs), length of High Dependency Unit (HDU) stay, hospital LoS, medical/surgical interventions

Table A2: Characteristics of Included Non-randomized Trials or Observational Comparative Studies											
Author, Year	**Study Design**	**Country**	**Study Population**			**Intervention**		**Control**		**Concurrent Treatments**	**Reported Outcomes**
			Condition	**N**	**Eligibility for Inclusion**	**Fibrinogen Concentrate (dose/frequency)**	**n1**	**Type of Product**	**n2**		
Solomon et al. 2012[26]	Prospective consecutive cohort	Germany	First time CABG	29	Reduced preoperative platelet function due to long-term aspirin therapy, intraoperative indication of hemostatic therapy	FC (only patients who had ROTEM data) + allogeneic blood products at the discretion of physician	10	Allogeneic blood products (patients with no ROTEM data)	19	Heparin (400 IU/kg) + protamine sulphate	PLT count, PT, aPTT, Hb, maximum cloth firmness, intraoperative and 24-hour post-op transfusion, drainage volume, intubation time, ICU LoS, hospital LoS
Rahe-Meyer et al. 2009[27]	Cohort study	Germany	Excessive bleeding in thoracoabdominal aortic aneurysm surgery	18	5 min bleeding mass of 60 g–250 g	FC (7.8 ± 2.7 g)	6	Allogeneic blood products (retrospective control)	12	NR	intraoperative and 24-hour post-op transfusion of allogeneic blood products (RBC, FFP, PLT concentrate), transfusion avoidance rate, 24-hour postoperative blood loss, ICU time to extubation, ICU LoS, re-exploration for bleeding, renal failure, AF, prolonged ventilator support, major neurologic events, 30-day mortality, hospital LoS, PT, aPTT, Hb, PLTs, fibrinogen
Rahe-Meyer et al. 2009[28]	Cohort study	Germany	Elective aortic valve operation and ascending aorta replacement	57	5 min bleeding mass of 60 g–250 g	FC (5.7 ± 0.7g)	10	PLT + FFP concentrate (retrospective control)	42	NR	Transfusion avoidance rate, 24 -hour postoperative blood ourloss, ICU time to extubation, ICU LoS, re-exploration for bleeding, AF, prolonged ventilator support,

Table A2: Characteristics of Included Non-randomized Trials or Observational Comparative Studies										
Author, Year	**Study Design**	**Country**	**Study Population**			**Intervention**		**Control**		**Concurrent Treatments**	**Reported Outcomes**
			Condition	**N**	**Eligibility for Inclusion**	**Fibrinogen Concentrate (dose/frequency)**	**n1**	**Type of Product**	**n2**		
								PLT + FFP based on algorithm (prospective control)	5		major neurologic events, 30-day mortality, hospital LoS, PT, aPTT, Hb, PLTs, fibrinogen, intraoperative and 24-hour post-op transfusion of allogeneic blood products (RBC, FFP, PLT concentrate, total blood cell concentrate), drainage volume

AE = adverse events; AF = atrial fibrillation; ALAT = alanine amino transferase; aPTT = activated partial thromboplastin time; ASAT = aspartate aminotransferase; CABG = coronary artery bypass grafting; CVA = cardiovascular accident; FC = fibrinogen concentrate; FFP = fresh frozen plasma; g = gram; Hb = hemoglobin; HDU = high dependency unit; Ht = hematocrit; ICU = intensive care unit; IU = international unit; kg = kilogram; LoS = length of stay; MI = myocardial infarction; min = minute; mL = millilitre; NR = not reported; PT = prothrombin time; PLT = platelets; RBC = red blood cells; RCT = randomized controlled trial; ROTEM = rotational thromboelastometry; TASH = trauma-associated severe hemorrhage; TIA = transient ischemic attack.

APPENDIX 6: METHODOLOGICAL QUALITY OF THE INCLUDED STUDIES

Table A3: Summary of Critical Appraisal

Study and Design	Strengths	Limitations
Randomized Controlled Trials		
Rahe-Meyer et al. 2013[20]	• Clearly described objectives, interventions, and study outcomes • Included a representative sample of participants • Randomized study participants to intervention groups • Blinded both the study subjects and evaluators to the intervention • Estimated random variability in data for the study outcomes	• Did not report characteristics of patients lost to follow-up • Did not take into account potential confounding factors in the analysis • Did not report adverse events of the intervention (reported in a different publication of the same study)[21]
Rahe-Meyer et al. 2013[21]	• Clearly described objectives, interventions, and study outcomes • Included a representative sample of participants • Randomized study participants to intervention groups • Blinded both the study subjects and evaluators to the intervention • Reported the distribution of principal confounders in study participants • Estimated random variability in data for the study outcomes • Reported safety outcomes related to the intervention	• Did not report characteristics of patients lost to follow-up • Did not take into account potential confounding factors in the analysis
Lance et al. 2012[22]	• Clearly described objectives, interventions, and study outcomes • Included a representative sample of participants • Randomized study participants to intervention groups • Blinded both the study subjects and evaluators to the intervention • Reported the distribution of principal confounders in study participants • The time period between intervention and the blood samples taken to measure outcome was the same for intervention and control groups • Reported safety outcomes related to the intervention • Estimated random variability in data for the study outcomes	• Did not report characteristics of patients lost to follow-up • Did not take into account potential confounding factors in the analysis • It is not clear if the patients lost to follow-up (if any) were taken into account in the analysis
Karlsson et al. 2009[19]	• Clearly described objectives, interventions, and study outcomes • Included a representative sample of participants • Randomized study participants to intervention groups • Reported the distribution of principal confounders in study participants • The time period between intervention and the blood samples taken to measure outcome was the same for intervention and control groups • Reported safety outcomes related to the intervention • Some of the confounding factors (time) were taken into account in analysis	• It is not clear if the study participants and evaluators were blinded to the intervention • Did not report characteristics of patients lost to follow-up • It is not clear if the patients lost to follow-up (if any) were taken into account in the analysis

Table A3: Summary of Critical Appraisal		
Study and Design	**Strengths**	**Limitations**
Fenger-Eriksen et al. 2009[23]	• Clearly described objectives, interventions, and study outcomes • Included a representative sample of participants • Randomized study participants to intervention groups • Blinded both the study subjects and evaluators to the intervention • Estimated random variability in data for the study outcomes	• It is not clear if the patients lost to follow-up (if any) were taken into account in the analysis • Did not take into account potential confounding factors in the analysis • Did not report adverse events of the intervention
Non-randomized/ Observational Studies		
Yang et al. 2013[24]	• Clearly described objectives, interventions, and study outcomes • Reported the distribution of principal confounders in study participants • Estimated random variability in data for the study outcomes • Attempted to identify recorded adverse events of intervention.	• It is not clear if the included individuals (patients with infusion data available) were representative of eligible population • No randomization and blinding was incorporated in the study design • Did not take into account potential confounding factors in the analysis • It is not clear if the patients lost to follow-up (if any) were taken into account in the analysis
Wafaisade et al. 2013[25]	• Clearly described objectives, interventions, and study outcomes • Intervention and control groups were selected from the same population • Matched the intervention and control groups for potential confounding factors • Reported the distribution of principal confounders in study participants • Estimated random variability in data for the study outcomes • Reported safety outcomes related to the intervention	• It is not clear if the included individuals (patients with infusion data recorded) were representative of eligible population • No randomization and blinding was incorporated in the study design • It is not clear if the patients lost to follow-up (if any) were taken into account in the analysis
Bilecen et al. 2013[29]	• Clearly described objectives, interventions, and study outcomes • Included a representative sample of participants • Reported the distribution of principal confounders in study participants • Estimated random variability in data for the study outcomes • Reported safety outcomes related to the intervention • Included potential confounders in the analysis	• No randomization and blinding was incorporated in the study design • It is not clear if the patients lost to follow-up (if any) were taken into account in the analysis
Ahmed et al. 2012[30]	• Clearly described objectives, interventions, and study outcomes • Included a representative sample of participants • Reported point estimates of principal confounders in study participants • Estimated random variability in data for the study outcomes • Attempted to identify recorded adverse events of intervention.	• No randomization and blinding was incorporated in the study design • Did not take into account potential confounding factors in the analysis • It is not clear if the patients lost to follow-up (if any) were taken into account in the analysis
Solomon et al. 2012[26]	• Clearly described objectives, interventions, and study outcomes • Included a representative sample of participants • Reported the distribution of principal confounders in study participants	• No randomization and blinding was incorporated in the study design • Did not take into account potential confounding factors in the analysis

Table A3: Summary of Critical Appraisal		
Study and Design	**Strengths**	**Limitations**
	• Estimated random variability in data for the study outcomes • Reported safety outcomes related to the intervention	
Rahe-Meyer et al. 2009[27]	• Clearly described objectives, interventions, and study outcomes • Included a representative sample of participants • Reported the distribution of principal confounders in study participants • Estimated random variability in data for the study outcomes	• No randomization and blinding was incorporated in the study design • Intervention and control groups were selected in different time points (historical control group) • Did not take into account potential confounding factors in the analysis • Did not report actual *P*-values

APPENDIX 7: OUTCOMES OF THE INCLUDED STUDIES

Table A4: Randomized Controlled Trials

Author, Year	Sample Size (Int/ Cont)	Blood Loss			Transfusion Requirements			Control of Bleeding Episodes			ICU Stay			Hospital Stay		
		FC	Cont.	*P*-value	FC	Cont.	*P*-value	FC	Cont.	*P*-value	FC	Cont.	*P*-value	FC	Cont.	*P*-value
Randomized Controlled Trials																
Rahe-Meyer et al. 2013[20]		g/5 min [mean change ± SD]			NR			NR			NR			NR		
FC vs. placebo	29/32	–48.3 ± 48.6	0.4 ± 15.1	< 0.001												
FC vs. FFP/PLTs (1 cycle)	29/32	–48.3 ± 48.6 g/5 min	–16.1 ± 26.1	0.003												
FC vs. FFP/PLTs (2 cycles)	29/32	–48.3 ± 48.6 g/5 min	–28.0 ± 46.6 g/5 min	0.11												
Rahe-Meyer et al.2013[21]	29/32	NR			All products unit/24 hour [Median (IQR)] All products			Avoidance of allogeneic blood products			ICU-free time during first 45 days after operation† [Median (IQR)]			hospitalization-free time during first 45 days after operation[a] [Median (IQR)]		
					2 (0 to 8)	13 (8 to 21)	< 0.001	13 (45%)	0 (0%)	< 0.001	43.1 (40.2 to 44.1)	42.7 (41.1 to 44.1)	NR	43.1 (40.2 to 44.1)	42.7 (41.1 to 44.1)	NR
					Packed RBC units/24 hour [Median (IQR)]											
					0 (0 to 3)	2 (2 to 5)	0.007									
					FFP unit/24h [Median (IQR)]											
					0 (0 to 4)	8 (4 to 10)	< 0.001									
					PLTs unit/24 hour [Median (IQR)]											
					0 (0 to 2)	4 (2 to 5)	< 0.001									
Lance et al. 2012[22]	22/21	NR			NR			Satisfactory hemostasis			NR			NR		
								17 (77%)	16 (76%)	0.93						

Table A4: Randomized Controlled Trials																
Author, Year	**Sample Size (Int/ Cont)**	**Blood Loss**			**Transfusion Requirements**			**Control of Bleeding Episodes**			**ICU Stay**			**Hospital Stay**		
		FC	**Cont.**	***P*-value**	**FC**	**Cont.**	***P*-value**	**FC**	**Cont.**	***P*-value**	**FC**	**Cont.**	***P*-value**	**FC**	**Cont.**	***P*-value**
Karlsson et al. 2009[19]	10/10	mL/12 h [mean change ± SD]			All products [Incidence]			NR			NR			NR		
		565 ± 150	830 ± 268ml/12 hours	0.010	1 (10%)	3(30%)	0.29									
Fenger-Eriksen et al. 2009[23]	10/10	NR			RBC [Incidence]			NR			NR			NR		
					2 (20%)	8 (80%)	< 0.05									
					RBC units [Median (range)] during operation											
					2 (0 to 5)	2.5 (0 to 6)	0.91									
					48 h post-operation											
					0 (0 to 3)	1.5 (0 to 2)	< 0.05									

Cont.= control group; FC = fibrinogen concentrate; FFP = fresh frozen plasma; g = gram; ICU = intensive care unit; IQR = interquartile range; Int. = intervention group; min = minutes; mL = millilitre; NR = not reported; PLTs = platelets; RBC = red blood cells; SD = standard deviation; vs. = versus.
Note: Words in brackets indicate the statistical measure used in the study.
[a] These reported median numbers of ICU-free and hospitalization-free days are used to calculate the median length of ICU or hospital stay (to be used in economic evaluation).

Table A5: Non-randomized/Observational Studies																		
Author, Year	**Sample Size (Int./ Cont.)**	**Blood Loss**			**Transfusion Requirements**			**Control of Bleeding Episodes**			**ICU Stay**			**Hospital Stay**			**Other**		
		FC	**Cont.**	***P*-value**	**FC**	**Cont.**	***P*-value**	**FC**	**Cont.**	***P*-value**	**FC**	**Cont.**	***P*-value**	**FC**	**Cont.**	***P*-value**	**FC**	**Cont.**	***P*-value**
Yang et al.2013[24]	8/76	Mean change per infusion (mL/kg/h) –0.95	–1.48	NR Median reduction 30%	50%	NR	NR			NR			NR			NR		
Wafaisade et al. 2013[25]	294/294	NR			RBC units [Mean ± SD] 12.8 ± 14.3	11.3 ± 10.0	0.20 FFP units [Mean ± SD] 10.6 ± 11.4	8.7 ± 8.2	0.07	NR			Days [Mean ± SD] 17.2 ± 17.6	17.3 ± 17.9	0.68	Days [Mean ± SD] 34.6 ± 33.3	32.8 ± 28.4	0.96	Ventilator days [Mean ± SD] 12.2 ± 14.2	11.3 ± 14.7	0.06
Bilecen et al. 2013[29]	264/811	Bleeding (L) During ICU stay [Median (IQR)] 0.67 (0.42,1.08)	0.56 (0.40,0.85)	< 0.01 Crude OR (95% CI)[a] = 1.13 (1.02, 1.25) Adjusted OR (95% CI)[a] = 1.02 (0.91, 1.14)	All products [Incidence] 144 (55%)	351 (43%)	<0.01 RBC [Incidence] 124 (47%) FFP [Incidence] 62 (24%) PLTs[Incidence] 50 (19%) ICU need for transfusion Crude OR (95% CI) = 1.57 (1.19, 2.08) Adjusted OR (95% CI)[b] = 1.14 (0.83, 1.56)	313 (39%) 98 (12%) 81 (10%)	0.02 <0.01 <0.01	NR			NR			NR			> 24 hours on ventilator [Incidence] 52 (20%)	45 (6%)	< 0.01 Crude OR (95% CI) = 4.18 (2.72, 6.40) Adjusted OR (95% CI)[b] = 1.44 (0.83, 2.49)

Table A5: Non-randomized/Observational Studies																		
Author, Year	**Sample Size (Int./ Cont.)**	**Blood Loss**			**Transfusion Requirements**			**Control of Bleeding Episodes**			**ICU Stay**			**Hospital Stay**			**Other**		
		FC	**Cont.**	***P*-value**	**FC**	**Cont.**	***P*-value**	**FC**	**Cont.**	***P*-value**	**FC**	**Cont.**	***P*-value**	**FC**	**Cont.**	***P*-value**	**FC**	**Cont.**	***P*-value**
Ahmed et al. 2012[30]	20/14	Estimated blood loss (L) [Mean ± SEM]			RBC units [Mean ± SEM]			NR			Hours [Mean ± SEM]			Days [Mean ± SEM]			NR		
		3.3 ± 0.5	5.2 ± 1.1	0.10	5.9 0 ± 0.96	7.21 ± 1.23	0.40				33.6 ± 5.44	34.1 ± 4.32	0.95	6.55 ± 0.81	5.21 ± 0.33	0.19			
					Octaplas units [Mean ± SEM]														
					3.15 ± 0.65	4.07 ± 0.74	0.36												
					PLTs pools [Mean ± SEM]														
					1.00 ± 0.30	1.00 ± 0.36	0.99												
Solomon et al. 2012[26]	10/19	NR			All products [Incidence] intra- and 24-hour postoperative			NR			Hours [Median (IQR)]			Days [Median (IQR)]			Ventilator hours [Median (IQR)]		
					4 (40%)	19 (100%)	NR				24 (21,30)	24 (22 50)	NR	9 (8, 11)	9 (7, 10)	NR	13 (9, 17)	12 (9, 16)	NR
					All products units [Median (IQR)]														
					0 (0, 3.8)	6 (5, 8)	0.007												
					RBC units [Median (IQR)]														
					0 (0, 1.8)	3 (3, 4.5)	> 0.05												
					FFP units [Median (IQR)]														
					0 (0, 2)	6 (5, 8)	0.0001												
					PLTs units [Median (IQR)]														
					0 (0, 0)	0 (0, 1.5)	> 0.05												
Rahe-Meyer et al. 2009[27]	6/12	Blood loss after transfusion (g/5 min) [Mean ± SD]			All products units/ 24 hours [Mean]			Avoidance of allogeneic blood products			Hours [Mean ± SD]			Days [Mean ± SD]			Ventilator hours [Mean ± SD]		
		42.0 ± 8.9	NR	-	2.5	26.4	< 0.05	4.6 %	0%	<0.05	37.0±18.9	115.4±60.2	<0.05	14.0±8.4	12.2±5.2	NR	18.5±14.7	42.9±36.3	NR
					RBC units/24 hours [Mean]												> 40 hours on ventilator [Incidence]		
					1.0	4.1	< 0.05												

Table A5: Non-randomized/Observational Studies																			
Author, Year	**Sample Size (Int./ Cont.)**	**Blood Loss**			**Transfusion Requirements**			**Control of Bleeding Episodes**			**ICU Stay**			**Hospital Stay**			**Other**		
		FC	**Cont.**	***P*-value**	**FC**	**Cont.**	***P*-value**	**FC**	**Cont.**	***P*-value**	**FC**	**Cont.**	***P*-value**	**FC**	**Cont.**	***P*-value**	**FC**	**Cont.**	***P*-value**
					FFP units/24 hours [Mean]												1 (17%)	5 (42%)	NR
					1.0	9.1	< 0.05												
					PLTs units/24 hours [Mean]														
					0.5	3.2	< 0.05												
Rahe-Meyer et al. 2009[28]	10/ 5;(42HC)	Blood loss after single transfusion (g/5 min)			All products units/24 hours [Mean ± SD]			Avoidance of allogeneic blood products			Hours [Mean ± SD]			Days [Mean ± SD]			Ventilator hours [Mean ± SD]		
		32.0 ± 18.0	84.0 ± 12.0;	NR	0.7 ± 1.5	8.2 ± 2.3;	< 0.05	8 (80 %)	0 (0%);	< 0.05	20.0±5.0	31.0 ± 21.0;	< 0.05	1.0 ± 2.0	12.0 ± 12.0;	< 0.05	9.0 ± 5.0	12.0 ± 5.0;	NR
			(NR)	-		(8.5 ± 5.3)	< 0.05		(1 (2%))	< 0.05		(36.0 ± 26.0)	< 0.05		(10.0 ± 3.0)	< 0.05		(13.0 ± 12.0)	NR
					RBC units/24 hours [Mean ± SD]												> 40 hours on ventilator [Incidence]		
					0.5 ± 1.1	2.4 ± 1.1;	< 0.05										0 (0%);	0 (0%);	NR
						(2.4 ± 2.5)	< 0.05											0 (0%);	NR
					FFP units/24 hours [Mean ± SD]														
					0.2 ± 0.6	4.2± 1.1;	< 0.05												
						(4.5±2.1)	< 0.05												
					PLTs units/24 hours [Mean ± SD]														
					0.0 ± 0.0	1.6 ± 0.9;	< 0.05												
						(1.6 ± 1.7)	< 0.05												

CI = confidence interval; Cont.= control group; FC = fibrinogen concentrate; FFP= fresh frozen plasma; g- gram; HC = historical control; ICU = intensive care unit; IQR = interquartile range; Int. = intervention group; L = litre; NR = not reported; OR = odds ratio (FC versus control group);PLTs = platelets; RBC = red blood cells; SD = standard deviation; SEM = standard error of mean.
Note: Words in brackets indicate the statistical measures used to describe and compare variables.
[a] Blood loss in ICU based on the ratio of geometric mean.
[b] After adjustment for demographic variables, propensity score for surgery characteristics, propensity score for total blood loss, and transfusion of blood products or coagulation factors.

APPENDIX 8: ADVERSE EVENTS REPORTED IN THE INCLUDED STUDIES

Table A6: Randomized Controlled Trials

Author, Year	Sample Size (Int/Cont	Mortality			Thromboembolic Events			Other Adverse Events		
		FC	Control	*P*-value	FC	Control	*P*-value	FC	Control	*P*-value
Randomized Controlled Trials										
Rahe-Meyer et al. 2013[20]	29/32	NR			NR			NR		
Rahe-Meyer et al. 2013[21]	29/32	SAEs leading to death: 1 (3%)	4 (13%)	RR (95% CI) = 0.3 (0.0, 2.3)	MI: 1 (3%)	0 (0%)	NR	TEAEs (10 day): 24 (83%)	27 (84%)	NR
					Cardiorespiratory arrest: 0 (0%)	0 (0%)	NR	SAEs (45 day): 5 (17%)	5 (16%)	NR
					Cerebral hemorrhage: 0 (0%)	1 (3%)	NR	Viral transmission: 0 (0%)	0 (0%)	NR
					Cerebral infarction: 0 (0%)	1 (3%)	NR	Operative hemorrhage: 0 (0%)	1 (3%)	NR
								Re-operation due to bleeding: 4 (14%)	4 (13%)	RR (95% CI) = 1.1 (0.3, 4.0)
Lance et al. 2012[22]	22/21	NR			NR			Pleural effusion: 1 (4.5%)	1 (4.7%)	NR
								Wound infection 1 (4.5%)	3 (14%)	NR
								Septic complications 2 (9%)	0 (0%)	NR
Karlsson et al. 2009[19]	10/10	NR			MI: 0 (0%)	1 (10%)	NR	NR		
Fenger-Eriksen et al. 2009[23]	10/10	NR			NR			NR		

Cont = control group; CI = confidence interval; FC = fibrinogen concentrate; Int = intervention group; MI = myocardial infarction; NR = not reported; RR = relative risk (FC versus control group); SAEs = serious adverse events; TEAEs = treatment emergent adverse events.

Table A7: Non-randomized/Observational Studies									
Author, Year	**Sample size (Int./Cont.)**	**Mortality**			**Thromboembolic events**			**Other adverse events**		
		FC	**Control**	***P*-value**	**FC**	**Control**	***P*-value**	**FC**	**Control**	***P*-value**
Yang et al. 2013[24]	8/76	NR			NR			NR		
Wafaisade et al. 2013[25]	294/294	6-hour mortality rate [%]			All thromboembolic events [%]			Sepsis [%]		
		10.5	16.7	0.03	6.8%	3.4%	0.06	20.7	17.7	0.35
		24-hour mortality rate [%]						Organ failure [%]		
		13.9	18.4	0.15				73.8	61.9	0.002
		30-day mortality rate [%]						Multiple organ failure [%]		
		27.9	24.8	0.40				61.2	49.9	0.003
		Overall in-hospital mortality rate [%]								
		28.6	25.5	0.40						
Bilecen et al. 2013[29]	264/811	30-day mortality [Incidence]			MI [Incidence]			Renal failure [Incidence]		
		18(7%)	33 (4%)	0.07	14 (5%)	30 (4%)	0.25	13 (5%)	38 (5%)	0.87
		Crude OR (95% CI) = 1.73 (0.95, 3.12)			Crude OR (95% CI) = 1.46 (0.76, 2.79)			Crude OR (95% CI) = 1.0 (0.55, 2.01)		
		Adjusted OR (95% CI)[a] = 0.96 (0.48, 1,92)			Adjusted OR (95% CI)[a] = 1.10 (0.53, 2.27)			Adjusted OR (95% CI)[a] = 0.62 (0.29, 1.32)		
					CVA /TIA			Total infections (Incidence)		
					11(4%)	20 (3%)	0.15	29 (11%)	74 (9%)	0.37
					Crude OR (95% CI) = 1.72 (0.82, 3.64)			Crude OR (95% CI) = 1.23 (0.78, 1.94)		
					Adjusted OR (95% CI)[a] = 1.16 (0.50, 2.72)			Adjusted OR (95% CI)[a] = 1.18 (0.72, 1.95)		
Ahmed et al. 2012[30]	20/14	0 (0%)	0 (0%)	-	NR			NR		
Solomon et al. 2012[26]	10/19	0 (0%)	0 (0%)	-	0 (0%)	1 (5%)	NR	NR		
Rahe-Meyer et al. 2009[27]	6/12	30-day mortality [Incidence]			NR			Re-exploration for bleeding [Incidence]		
		0 (0%)	2 (17%)	NR				0 (0%)	4 (33%)	NR
								Postoperative atrial fibrillation		
								0 (0%)	1 (8%)	NR
								Renal failure		
								0 (0%)	2 (17%)	NR
								Major neurologic events		
								0 (0%)	2 (17%)	NR
Rahe-Meyer et al. 2009[28]	10/ 5;(42HC)	30-day mortality [Incidence]			NR			Re-exploration for bleeding [Incidence]		
		0 (0%)	0 (0%); (0 (0%))	-				0 (0%)	1(20%); 2 (5%)	NR NR
								Postoperative atrial fibrillation		
								1 (10%)	1 (20%); (6 (14%))	NR NR
								Major neurologic events		
								0 (0%)	0 (0%); (0 (0%))	-

CI = confidence interval; Cont. = control group; CVA = cardiovascular accident; FC = fibrinogen concentrate; HC = historical control; Int. = intervention group; MI= myocardial infarction; NR = not reported; OR = odds ratio (FC versus control group); TIA = transient ischemic attack. Note: Words in brackets indicate the statistical measures used to describe and compare variables.

[a] After adjustment for demographic variables, propensity score for surgery characteristics, propensity score for total blood loss, and transfusion of blood products or coagulation factors.