

CSL Behring  
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# Fibrinogen concentrate in elective complex cardiac surgery

## A monocentric trial

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Presents the results from a randomised controlled trial which aimed to determine if fibrinogen concentrate infusion reduces intraoperative blood loss in cardiac surgery patients.

### Background

Excessive bleeding is a common complication in cardiac surgery, and may result in the need for red blood cell (RBC) transfusion. Intraoperative bleeding during cardiac surgery is often treated with coagulation factor concentrates (CFCs). As yet, however, their efficacy has not been conclusively determined.

Since 1980 our knowledge of damage from transfusion has increased. Risks include infection, effects on the immune system, transfusion-related acute lung injury and risks due to the age of transfused blood (Isbister et al. 2011). Healthcare systems need to also be aware of the associated costs. As doctors it is our challenge and duty to reduce preventable damage from blood transfusion.

### Patient blood management

The evidence-based multidisciplinary approach to optimising care of patients who may need transfusion is known as patient blood management (PBM). We know there is considerable variation in perioperative blood transfusion rate. For example, an analysis of 102,470 patients who underwent coronary artery bypass graft surgery at 792 hospitals in the United States found that rates of blood transfusion ranged from 7.8% to 92.8% for red blood cells (Bennett-Guerrero et al. 2010). PBM can also reduce the need for blood transfusions. In cardiac surgery, a study of Jehovah's Witnesses, who refuse blood products, found no difference in morbidity and mortality if patients are evaluated with a multidisciplinary approach to blood management (Moraca et al. 2011).

At Isala Clinics, we have researched patient blood management, including tailor-made transfusion protocols (Bilecen et al. 2014), and the role of point-of-care testing and fibrinogen concentrate (Bilecen et al. 2013). We implemented a specific transfusion protocol for cardiac surgery, and conducted an intervention study to evaluate its effects on transfusion and clinical events (Bilecen et al. 2014). The protocol included giving component therapy and fibrinogen at the end of the schedule. If we measured fibrinogen less than 1g/L we added 2g of extra fibrinogen. If it was more than 1g/L based on the Clauss measurement, we did not give fibrinogen. The cardiac surgery-specific transfusion protocol resulted in fewer patients transfused with RBCs and fresh frozen plasma (FFP) and a lower incidence of myocardial infarction.

### Fibrinogen concentrate therapy

We conducted a cohort study to evaluate the effect of fibrinogen concentrate therapy on postoperative blood loss and transfusion and occurrence of clinical events in complex cardiac surgery; 264/1075 patients received fibrinogen concentrate during surgery (Bilecen et al.

2013). There was no reduction in postoperative blood loss and transfusion (intensive care unit [ICU] blood loss: OR 1.02 (0.91-1.14) and ICU transfusion: OR 1.14 (0.83-1.56) and no increase in risk for adverse clinical events. However, the haemostatic effect may have been attenuated by the low doses and relatively late administration of fibrinogen concentrate therapy.

### Randomised controlled trial

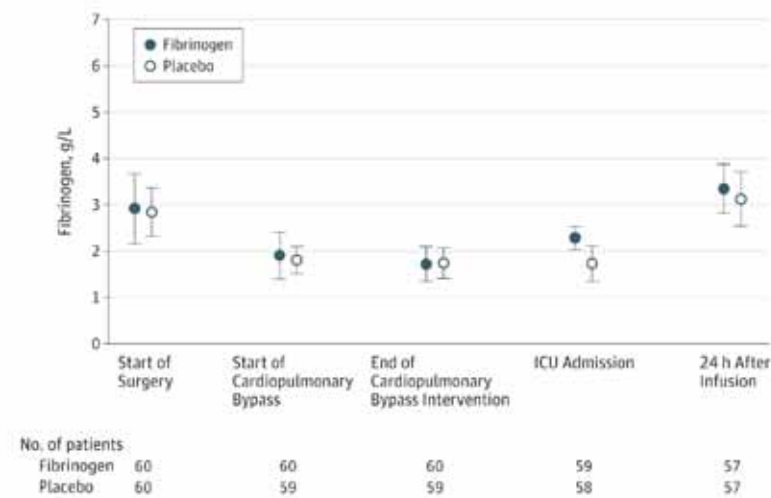
Therefore we initiated a prospective single-centre, randomised, placebo-controlled, double-blind clinical trial to find out if fibrinogen concentrate infusion dosed to achieve a post-infusion plasma fibrinogen level of at least 2.5 g/L in high-risk elective cardiac surgery patients 18 years or over with intraoperative bleeding reduced intraoperative blood loss (Bilecen et al. 2017).

The primary outcome of the study was intraoperative blood loss measured between intervention and closure of the chest when surgery ended. Secondary outcomes included the measured blood loss at 1, 3, 6, 12 and 24 hours after the intervention; the proportion of patients who received transfusion; and number of



**Figure 1.**

IMP investigational medicinal product



**Figure 2.** Fibrinogen concentrate dosing

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**Table 1.** Primary, secondary and exploratory study outcomes

	Median (IQR), mL			P Value
	Fibrinogen (n = 58)	Control (n = 57)	Absolute Difference (95% CI)	
<b>Primary Outcome</b>				
Blood loss between intervention and chest closure	50 [29-100]	70 [33-145]	20 [-13 to 35] <sup>a</sup>	.19
<b>Secondary or Exploratory Outcome</b>				
No. of patients	58	59		
Blood loss in the ICU/time interval starting from admission				
0-1 h	70 [35-130]	90 [46-149]		
>1-3 h	80 [50-156]	110 [40-220]		
>3-6 h	100 [54-169]	110 [60-208]		
>6-12 h	110 [80-160]	125 [83-224]		
>12-24 h	130 [80-180]	160 [90-270]		
Cumulative 24-h blood loss	570 [390-730]	690 [400-1090]	120 [-45 to 355] <sup>a</sup>	.047 <sup>b</sup>

ICU, intensive care unit; IQR, interquartile range. Time point "intervention" is defined as moment of infusion of study medication.

<sup>a</sup> 95% confidence interval of difference in medians is based on a nonparametric bootstrap procedure (10 000 bootstraps with replacement).

<sup>b</sup> P value is based on the constructed mixed-model for repeated measurements.

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**Table 2.** Secondary transfusion outcomes

	Fibrinogen (n = 58)	Control (n = 59)
<b>Patients who received transfusion between intervention and chest closure, No. (%)</b>		
Red blood cells	0	3 (5)
Fresh-frozen plasma	0	1 (2)
Platelets	2 (3)	2 (3)
Any transfusion	2 (3)	4 (7)
<b>Patients transfused between intervention and 24 h, thereafter, No. (%)</b>		
Red blood cells	10 (17)	20 (33)
Fresh-frozen plasma	9 (15)	13 (22)
Platelets	9 (15)	13 (22)
Any transfusion	20 (33)	23 (38)
<b>Transfusion units between intervention and 24 h thereafter, median (IQR)</b>		
Red blood cell transfusion units	0 [0-1]	0 [0-4]
Fresh-frozen plasma transfusion units	0 [0-2]	0 [0-4]
Platelets transfusion units	0 [0-1]	0 [0-1]
Any transfusion units	0 [0-2]	0 [0-8]

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units of RBCs, FFP or platelet concentrate.

The aim was to achieve surgical haemostasis after heparin reversal. It was the surgeons' decision when to start the 5-minute bleeding time. Once patients had bled for 5 minutes they were entered into the treatment algorithm if they were bleeding >60 mL and <250 mL. The intervention was considered to have started on initiation of infusion of the study medication (**Figure 1**) (see p. V).

Over the four years of the trial, over 700 patients had complex cardiac surgery, of which 40% were eligible for the trial. Of the eligible patients, 43% did not agree to participate; 203 patients agreed to participate, of which 73 (36%) experienced no intraoperative bleeding and 10 were excluded for other reasons. We suggest that the high number of patients that experienced no intraoperative bleeding may be due to the Hawthorne effect—performing differently when being observed. This group of patients had very extensive surgical haemostasis before we started with the 5 minutes bleeding time, much longer than usual. The surgeons may have perceived that they were a better surgeon if they were not included in the trial, and also that after closure of the chest the microvascular bleeding was now the problem for the anaesthesiologist.

The patients were randomised to receive either the placebo or the intervention drug in doses between 60ml and 250ml. The fibrinogen doses were calculated based on plasma fibrinogen levels at the end of cardiopulmonary bypass measured using the Clauss method (**Figure 2**).

## Results

### Primary outcome

Among patients with intraoperative bleeding who received infusion of fibrinogen concentrate, compared with placebo, there was no significant difference in blood loss measured from the time of the fibrinogen infusion and chest closure ( $p = 0.19$ ) (**Table 1**).

#### fibrinogen group

(median, 50 mL; IQR, 29-100 mL)

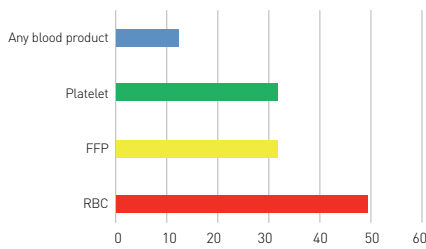
#### control group

(median, 70 mL; IQR, 33-145 mL)

#### absolute difference:

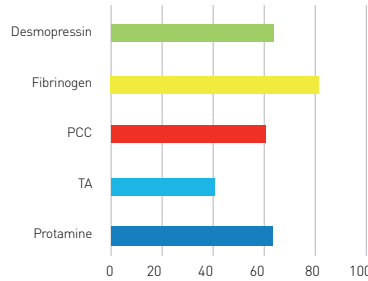
20 mL (95% CI, -13 to 35 mL)

Cumulative 24-hour blood loss was lower in the fibrinogen group compared with placebo ( $p = 0.047$ ).



**Figure 3.** % reduction of transfusion

FFP fresh frozen plasma RBC red blood cells



**Figure 4.** % reduction in procoagulants

PCC prothrombin complex concentrate TA tranexamic acid

**Table 3.** Procoagulants and antifibrinolytics use during surgery and ICU

	Fibrinogen (n = 60)	Control (n = 60)
<b>During surgery, patients receiving, No. (%):</b>		
Tranexamic acid	59 (98%)	60 (100%)
Desmopressin	42 (70%)	41 (68%)
Prothrombin complex concentrate	5 (8%)	2 (3%)
Recombinant factor VIIa	0 (0%)	0 (0%)
<b>During ICU period, patients receiving, No. (%):</b>		
Protamine	3 (5%)	8 (13%)
Tranexamic acid	9 (15%)	15 (25%)
Desmopressin	3 (5%)	8 (13%)
Prothrombin complex concentrate	4 (7%)	10 (17%)
Fibrinogen concentrate	1 (2%)	6 (10%)
Recombinant factor VIIa	0 (0%)	0 (0%)

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**Table 4.** Clinical adverse events within 30 days

	No. of Events <sup>a</sup>	
	Fibrinogen (n = 60)	Control (n = 60)
In-hospital mortality	2	0
Stroke	4	1
Transient ischaemic attack	0	1
Myocardial infarction	3	1
Renal insufficiency or failure	3	2
Thromboembolism	0	0
Allergic reaction	0	0
Infections	3	2
Rethoracotomy (≤5 d)	4	5

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The duration of primary outcome collection was 4.2 minutes (95% CI, 0.4-8.0 minutes) in the fibrinogen group and 8.7 minutes (95% CI, 5.2-12.1 minutes) in the control group.

However, other than these times do suggest these were not the best and fastest surgeons ever. This is why the primary endpoint was different than we expected. We expected that the moment there is a bleeding patient everyone would wait for closure and this would lead to a difference in blood loss in the patient and of course a difference in the intraoperative time factor.

### Secondary outcomes

There were fewer patients in the fibrinogen group and fewer units of blood units used (Table 2). However, the study was not adequately powered to test the secondary outcomes. The percentage of reduction in transfusion is shown in Figure 3.

After surgery, a single patient (2%) in the fibrinogen group and 6 patients (10%) in the control group received additional fibrinogen concentrate. This confounds the effect on overall outcomes.

Procoagulants and antifibrinolytics use is

shown in Table 3. The percentage of reduction is shown in Figure 4.

### Clinical adverse events within 30 days

There were more adverse events in the fibrinogen group (Table 4). Two patients died, and 4 suffered a stroke. One patient in the control group suffered a stroke, and one a transient ischaemic attack. The trial was not designed to evaluate major adverse cardiac events and there was no screening for embolic risk aortic disease.

Almost 50% (9/19) of adverse events occurred in two patients (Table 5) (see p. VIII). Also one stroke occurred in a placebo patient with a fibrinogen level of 0.6g/L.

### Transfusion protocol for cardiac surgery

At Isala Clinics we now use the following transfusion protocol (Figure 5) (see p. VIII). We conduct viscoelastic tests (ROTEM) to guide haemostatic therapies. Maegele and colleagues have provided a useful haemotherapy algorithm (Maegele et al. 2017).

### Conclusion

Fibrinogen is effective after complex cardiac surgery in the bleeding patient. Based on the current trial data, fibrinogen is recommended as a first-line therapy with target plasma level 2.5g/L at the moment there is an idea of microvascular bleeding in these patients. Both visco-elostometry as the conventional Clauss method can be used to determine the level of fibrinogen at the end of bypass surgery and to optimise further treatment.

We have the tools and knowledge now to change transfusion management. But changing transfusion management, as with any change, is a major behavioural process. You need to do this together with your own multidisciplinary group, using a change strategy such as the Kotter model (<https://www.kotterinternational.com/8-steps-process-for-leading-change>). ■

### Conflict of Interest

Arno Nierich is the principal investigator for the fibrinogen concentrate trial at Isala Clinics. CSL Behring sponsored the study and donated the bottles of study medication.

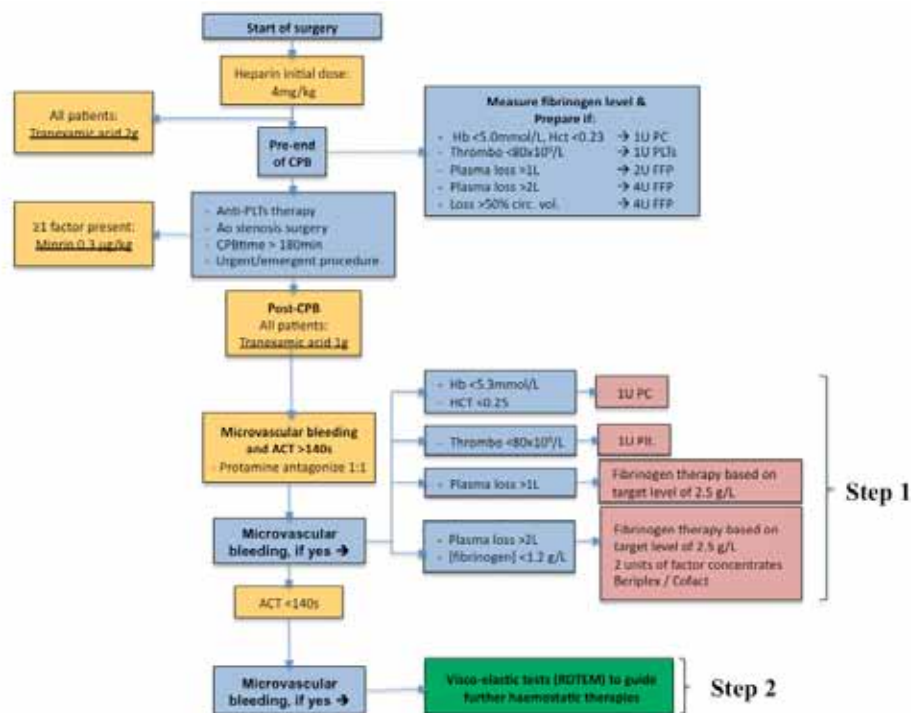
**Table 5.** Data on clinical adverse events, with allocated treatment, infused dose, fibrinogen plasma concentrations and time of event in days after surgery

Participant	Medication	Pre-infusion [fibrinogen g/L] <sup>a</sup>	Infusion dose [g] <sup>b</sup>	Post-infusion [fibrinogen g/L] <sup>c</sup>	Clinical adverse events						
					Mortality	Stroke	TIA	MI	RI	Infections	Rethoractomy
H-012	fibrinogen	1.6	3	2.4	day +10	day +1		day +1	day +2		day 0
H-161	fibrinogen	0.8	6	1.7	day +5	day +1			day +2		day 0
H-047	placebo	0.5	7	0.6		day 0					
H-140	fibrinogen	1.6	4	2.3		day +1				day +30	
H-155	fibrinogen	2.4	0	2.3		day +6					

MI myocardial infarction RI renal insufficiency or failure TIA transient ischemic attack,  
 a Plasma fibrinogen concentration at end-CPB.  
 b Infusion of study medication after removal of cardiopulmonary bypass. For placebo matched number of syringes is infused.  
 c Plasma fibrinogen concentration at ICU admission.  
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## Key Points

- Implement transfusion management with change strategy
- Multidisciplinary group essential
- Point-of-care and lab monitoring:
  - Part of overcoming the 'blind spot' of coagulation management in operating room and intensive care unit
  - Additional tool in fine-tuning bleeding management
  - Measure fibrinogen level by Clauss as first potential bleeding indication
- Fibrinogen is effective after complex cardiac surgery in the bleeding patient: from rescue medication to first-line therapy with target level 2.5 g/L in the bleeding patient



**Figure 5.** Transfusion protocol for cardiac surgery

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## Abbreviations

CFC coagulation factor concentrates  
 FFP fresh frozen plasma  
 ICU intensive care unit  
 PBM patient blood management  
 RBC red blood cells