Supplementary Online Content

Bilecen S, deGroot JAH, Kalkman CJ, et al.. effect of fibrinogen concentrate on intraoperative blood loss among patients with intraoperative bleeding during high-risk cardiac surgery: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2016.21037

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Definitions of Clinical Adverse Events Within 30 Days After Initial Surgery

In-hospital mortality	Death of any cause within 30 days after initial surgery.
Stroke	Within 30 days, new motor or sensory deficit with its origin in the central nervous system or an unexplained coma status lasting longer than 24 hours. Diagnosis by consulting neurologist or confirmed by positive finding on CT or MRI.
TIA	Within 30 days, brief episode of neurological dysfunction resulting from focal temporary cerebral ischemia lasting less than 24 hours, not associated with cerebral infarction. Diagnosis by a consulting neurologist.
Myocardial infarction	Within 30 days, myocardial specific creatine kinase (CKMB) >180 U/L (7.5 times upper reference limit) plus a peak CKMB/CK ratio >10%, or pathological new Q waves or new left bundle branch block on a postoperative electrocardiogram or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium.[1]
Renal injury	Within 30 days, increase in postoperative serum creatinine of at least two times the preoperative value or a decrease in glomerular filtration rate (GFR) of more than 50%.[2]
Renal failure	Within 30 days, increase in postoperative serum creatinine of at least three times the preoperative value and a decrease in GFR of at least 75% or a serum creatinine >354µmol/L associated with an acute increase of serum creatinine of at least 50µmol/l.[2]
Venous thrombosis	Within 30 days, thrombosis in the lower extremity diagnosed with compression ultrasound testing prior to surgery and at day 3 after surgery.
Pulmonary embolism	Within 30 days, pulmonary embolism diagnosed with a spiral CT.
Allergic reaction	Within 30 days, allergic or other systemic reaction to study medication.
Infections	Within 30 days, infection of venectomy site (arm or leg) and sternal infection.
Rethoracotomy	Proportion of subjects that receive a follow-on surgery to correct unacceptable bleeding within 5 days of last suture.

References:

1. Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Eur Heart J.* 2007 Oct;28(20):2525-2538.

2. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care.* 2004 Aug;8(4): R204-212.

eTable 2. Procoagulants and Antifibrinolytics use During Surgery and ICU

	Fibrinogen (n = 60)	**Control (n = 60)**
During surgery, patients receiving, No. (%):		
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%)
During ICU period, patients receiving, No. (%):		
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%)

eTable 3. Data on All Clinical Adverse Events that Occurred During the Study, With Allocated Treatment, Infused Dose, Fibrinogen Plasma Concentrations and Time of Event in Days after Surgery

Participant	Medication	Pre-infusion [fibrinogen g/L][a]	Infusion dose (g)[b]	Post-infusion [fibrinogen g/L][c]	Clinical adverse events						
					Mortality	Stroke	TIA	MI	RI	Infections	Rethoracotomy
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					
H-252	placebo	2.0	2	1.9			day +30				
H-048	fibrinogen	1.5	3	2.1				day +1			
H-065	fibrinogen	2.0	2	2.4				day 0		day +5	day 0
H-022	placebo	1.9	3	2.0				day +1			
H-007	placebo	1.7	3	1.1					day +19		day +1
H-108	placebo	1.9	3	2.2					day +1		
H-112	fibrinogen	1.8	3	2.5					day +5		
H-129	fibrinogen	2.2	1	2.5						day 0	
H-139	placebo	1.5	6	1.2						day +15	
H-244	placebo	2.0	2	2.2						day +17	
H-166	placebo	1.4	4	1.5							day 0
H-239	fibrinogen	1.4	5	1.7							day 0
H-078	placebo	1.6	4	1.6							day 0
H-170	placebo	1.5	4	1.4							day 0
H-107	placebo	1.4	5	1.4							day 0

End-CPB; end-cardiopulmonary bypass, TIA; transient ischemic attack, MI; myocardial infarction, RI; renal insufficiency or failure.

[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.

eAppendix. Sensitivity Analysis Multiple Imputation Procedure

Of the 120 randomized participants, 5 had missing primary outcome results. Of these 5 missed results, 2 were in the Fibrinogen group and 3 in the Control group.

Based on the low incidence of missing outcomes and the (for this particular situation) reasonable assumption of data missing completely at random, the research team determined prior to database lock that a complete case analysis was appropriate for the analysis of the primary endpoint. As a sensitivity analysis to confirm that the missing completely at random assumption indeed adequately accounted for the missing data, the primary analysis was repeated using a multiple imputation approach. Missing data were imputed to generate 10 imputed datasets that had complete outcome data for each of the 120 participants. The imputation was completed using the 'MICE' procedure in R using regression based imputation. Prior to conducting further analyses, the distributional characteristics of the imputed data sets were evaluated descriptively to confirm that they were consistent with the distributions of the raw data.

For the next step of the imputation process, the primary analysis was run for each of the 10 imputation data sets and then standard analytic methods were applied to appropriately account for both the within-imputation data set and between data set variance in generating test statistics and interval estimates of the primary endpoint.

With complete case analysis, there was no significant difference in blood loss measured from the time of the fibrinogen infusion and chest closure between the fibrinogen with an absolute difference of 20 mL (95% CI -13;35). Results of the sensitivity analysis based on multiple imputation of missing data as described above were consistent with those of the primary analysis, resulting in an absolute difference of 20 mL (95% CI -12;35).