

# Fibrinogen Concentrate in Cardiovascular Surgery: A Meta-analysis of Randomized Controlled Trials

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**BACKGROUND:** Postoperative bleeding remains a frequent complication after cardiovascular surgery and may contribute to serious morbidity and mortality. Observational studies have suggested a relationship between low endogenous plasma fibrinogen concentration and increased risk of postoperative blood loss in cardiac surgery. Although the transfusion of fibrinogen concentrate has been increasing, potential benefits and risks associated with perioperative fibrinogen supplementation in cardiovascular surgery are not fully understood.

**METHODS:** PubMed, Cochrane Library, Ovid MEDLINE, Embase, Web of Science, and China National Knowledge Infrastructure were searched on January 15, 2017, with automated updates searched until February 15, 2018, to identify all randomized controlled trials (RCTs) of fibrinogen concentrate, whether for prophylaxis or treatment of bleeding, in adults undergoing cardiovascular surgery. All RCTs comparing fibrinogen infusion versus any other comparator (placebo/standard of care or another active comparator) in adult cardiovascular surgery and reporting at least 1 predefined clinical outcome were included. The random-effects model was used to calculate risk ratios and weighted mean differences (95% confidence interval [CI]) for dichotomous and continuous variables, respectively. Subgroup analyses by fibrinogen dose and by baseline risk for bleeding were preplanned.

**RESULTS:** A total of 8 RCTs of fibrinogen concentrate in adults (n = 597) of mixed risk or high risk undergoing cardiovascular surgery were included. Compared to placebo or inactive control, perioperative fibrinogen concentrate did not significantly impact risk of all-cause mortality (risk ratio, 0.41; 95% CI, 0.12–1.38;  $I^2 = 10\%$ ;  $P = .15$ ). Fibrinogen significantly reduced incidence of allogeneic red blood cell transfusion (risk ratio, 0.64; 95% CI, 0.49–0.83;  $I^2 = 0\%$ ;  $P = .001$ ). No significant differences were found for other clinical outcomes. Subgroup analyses were unremarkable when analyzed according to fibrinogen dose, time of infusion initiation, mean cardiopulmonary bypass time, and rotational thromboelastometry/fibrinogen temogram use (all  $P$  values for subgroup interaction were nonsignificant).

**CONCLUSIONS:** Current evidence remains insufficient to support or refute routine perioperative administration of fibrinogen concentrate in patients undergoing cardiovascular surgery. Fibrinogen concentrate may reduce the need for additional allogeneic blood product transfusion in cardiovascular surgery patients at high risk or with evidence of bleeding. However, no definitive advantage was found for reduction in risk of mortality or other clinically relevant outcomes. The small number of clinical events within existing randomized trials suggests that further well-designed studies of adequate power and duration to measure all-cause mortality, stroke, myocardial infarction, reoperation, and thromboembolic events should be conducted. Future studies should also address cost-effectiveness relative to standard of care. (Anesth Analg 2018;127:612–21)

## KEY POINTS

- **Question:** In high-risk or average-risk patients undergoing cardiovascular surgery, does perioperative infusion of fibrinogen concentrate reduce the risk of adverse outcomes (death, stroke, myocardial infarction, renal failure, and infection), and improve resource-related outcomes (red blood cells transfused, total blood products transfused, length of stay, and cost of care)?
- **Findings:** While infusion of fibrinogen reduced exposure to allogeneic red blood cell transfusion, no other outcomes were reduced, including death, stroke, myocardial infarction, renal failure, infection, total blood products transfused, individual blood product components transfused, or length of stay, when compared to standard of care or inactive control; however, the body of evidence remains underpowered.
- **Meaning:** Current evidence neither supports nor refutes routine use of fibrinogen concentrate infusion in patients undergoing cardiovascular surgery because evidence of positive impact on clinically relevant and resource-related outcomes has not been proven.

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Although improvements in surgical technologies and techniques have resulted in better patient outcomes in recent years, perioperative blood loss remains a frequent complication after cardiac and great vessel surgery, most frequently due to insufficient surgical hemostasis or abnormalities in coagulation after cardiopulmonary bypass (CPB).<sup>1</sup> Excessive bleeding may increase the risk of transfusion, surgical reexploration, organ failure, and death, while also increasing resource usage and costs.<sup>2</sup> Bleeding etiology in cardiac surgery is complex and multifactorial.<sup>3,4</sup> The standard treatment of perioperative cardiac surgery bleeding involves transfusion of allogeneic blood components (red blood cells [RBCs], fresh frozen plasma [FFP], platelet concentrate, or cryoprecipitate). Cardiovascular surgery patients account for over 20% of the global use of blood products worldwide.<sup>5</sup> Because allogeneic blood transfusion may increase the risk of adverse outcomes, and because blood products are costly and limited in supply, perioperative strategies are required to mitigate their use in the cardiovascular surgical setting.<sup>6</sup>

The use of coagulation factor fibrinogen, administered as a concentrated infusion, has recently gained interest as a promising intervention for blood conservation in the cardiovascular surgical setting. Endogenous fibrinogen is a key substrate for blood coagulation and represents >90% of all plasma coagulation factors by weight. Therefore, endogenous plasma fibrinogen concentration levels are the first to drop below critical levels during severe bleeding, whereas other coagulation factors and platelets remain at an acceptable level for a longer time.<sup>5</sup> Observational studies have suggested an association between lower perioperative endogenous fibrinogen levels and higher bleeding risk after cardiac surgery.<sup>7-14</sup> Subsequently, observational studies and clinical trials of fibrinogen concentrate supplementation before cardiovascular surgery demonstrated reduced microvascular bleeding.<sup>1,15-22</sup> These studies spurred interest in the use of fibrinogen concentrate for cardiovascular surgery, and preliminary recommendations have appeared in selected clinical guidelines. In their guidelines for severe perioperative bleeding for all surgical patients (not only cardiovascular surgery), the European Society of Anesthesiology (ESA) recommends that fibrinogen concentrate infusion should be administered to bleeding patients who have hypofibrinogenemia.<sup>23</sup> ESA further recommends that fibrinogen concentrate infusion guided by viscoelastic coagulation monitoring should be used preemptively in complex cardiovascular surgery.

As a procoagulant, fibrinogen theoretically may increase thromboembolic complications. Clinical trials of fibrinogen use during cardiac surgery have been insufficiently powered to provide adequate assessment of efficacy and safety outcomes and should be synthesized through meta-analysis to increase the power to detect potential benefits and risks. Four fibrinogen systematic reviews have been published that can be improved on,<sup>24-27</sup> because they focused on miscellaneous surgeries rather than limiting to cardiovascular

surgery,<sup>24,26,27</sup> combined randomized controlled trials (RCTs) and non-RCTs<sup>26,27</sup> and did not include the most recent randomized trials.

The objective of this systematic review and meta-analysis is to determine whether perioperative (preoperative or intraoperative) supplementation with fibrinogen concentrate in adults undergoing cardiovascular surgery affects risk of mortality, allogeneic RBC transfusion, and other clinically relevant outcomes compared to standard care, placebo, or any other comparator.

## METHODS

The protocol for this systematic review and meta-analysis was preregistered on PROSPERO (CRD42016035235). It was performed according to the recommendations of the *Cochrane Handbook for Systematic reviews of Interventions*<sup>28</sup> and is reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.<sup>29</sup>

## Search for Trials

A systematic search was performed on January 15, 2017, with automated updates until February 15, 2018, for the following databases: PubMed, Cochrane Library, MEDLINE (OvidSP), Embase (OvidSP), Web of Science (Thomson Reuters), and China National Knowledge Infrastructure. The following trial databases were searched for ongoing and unpublished studies: World Health Organization International Clinical Trials Registry Platform (<http://apps.who.int/trialsearch/>), ClinicalTrials.gov (<http://clinicaltrials.gov/>), and Current Controlled Trials (<http://www.controlled-trials.com/>). The original search strategy is attached and was not restricted by date, language, or publication status (Supplemental Digital Content 1, Search Strategy and History, <http://links.lww.com/AA/C426>).

## Inclusion Criteria

RCTs were included if they met the following inclusion criteria: (1) adult patients undergoing initial or redo cardiovascular surgery (including coronary artery bypass grafting [CABG], valve, aortic surgery alone or combined), whether high, intermediate, or low risk for bleeding; (2) randomized to perioperative fibrinogen concentrate infusion (ie, given preoperatively, intraoperatively, and/or postoperatively as prophylaxis or treatment of bleeding) versus standard of care or placebo, or any other comparator; and (3) reporting on  $\geq 1$  clinically relevant outcomes. Studies with patients who underwent robotic surgery were excluded.

## Data Extraction

Data extraction was performed by J.-Y.L. onto a standardized form and was confirmed by one of 2 other authors (J.G., L.U.). Discrepancies were resolved by discussion with coauthors and consensus with the senior author. When possible, we contacted trial authors to verify data uncertainties and to request missing data.

## Outcomes

**Primary Outcome.** The primary outcome of interest was all-cause mortality at study completion. We used the longest

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follow-up data for the primary analysis and preplanned sensitivity analyses to determine if length of follow-up changed the conclusions.

**Secondary Outcomes.** Secondary outcome measures included severe (major) bleeding, incidence of allogeneic RBC and other blood product transfusion, volume of allogeneic blood products transfused (allogeneic RBCs, plasma, platelets, and cryoprecipitate), stroke/cerebrovascular accident, acute myocardial infarction, cardiac failure, atrial fibrillation, respiratory failure, pneumonitis, renal failure, acute kidney injury, renal replacement therapy, surgical reoperation due to bleeding, major immunological and allergic reactions, infection/sepsis, disseminated intravascular coagulation, venous thromboembolic events, deep vein thrombosis, pulmonary embolism, duration of mechanical ventilation (hours), length of stay in the intensive care unit (ICU), length of stay in hospital, and total costs.

### Risk of Bias Assessment

We assessed risk of bias using the Cochrane risk of bias tool.<sup>30</sup> A decision to classify “overall bias” as low, unclear, or high was made by the reviewers using the following definitions:

High: any trial with a high risk of bias listed on  $\geq 3$  domains or any severe methodological concerns that may have affected the study results.

Unclear: any trial with a high risk of bias listed on 2 domains or moderate methodological concerns that may have affected the study results.

Low: any trial with a high risk of bias on none or 1 domain and with no significant methodological concerns that may have affected the study results.

### Statistical Analysis

Statistical analyses were performed using Review Manager (RevMan [computer program], Version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014).<sup>31</sup> Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated for dichotomous outcomes, and mean differences (MDs) with 95% CIs were calculated for continuous outcomes. For results that reached statistical significance (ie, when CIs excluded the point of no effect), the number needed to treat to benefit (NNTB) of 1 patient was calculated using Visual Rx NNT calculator (Population Health Research Institute, London, UK; [www.nntonline.net/visualrx/](http://www.nntonline.net/visualrx/)), imputing a control event rate derived from the aggregate event rate of control (placebo or inactive control) group. Heterogeneity across studies was estimated using the  $I^2$  statistic, where  $I^2 > 50\%$  indicated significant heterogeneity. The random-effects model was used to incorporate heterogeneity across studies and provide conservative estimates.

Results were planned to be analyzed separately for fibrinogen versus inactive control (placebo or standard of care), and fibrinogen versus active control (ie, platelets, other blood components, or other active procoagulant medications and modalities, if tested in the included RCTs). Subgroup analyses were performed for the following factors to explore

whether effect sizes would change: fibrinogen infusion time (preoperatively versus intraoperatively), fibrinogen dose ( $\geq 4$  vs  $< 4$  g), type of surgery (CABG versus aortic versus other), mean CPB time ( $\geq 90$  vs  $< 90$  minutes), and fibrinogen infusion protocol (rotational thromboelastometry/fibrinogen temogram [ROTEM/FIBTEM] guided or other transfusion protocol versus nonprotocol). According to the recommendations for appropriate conduct and interpretation of subgroup analysis,<sup>28</sup> only subgroup analyses showing a statistically significant test for interaction ( $P < .05$ ) across subgroups were considered to be hypothesis-generating results warranting further discussion.

## RESULTS

### Literature Identification

The PRISMA flowchart shows the process of literature screening, study selection, and reasons for exclusion (Figure 1). In total, 8 RCTs<sup>21,22,32–37</sup> including 597 patients were included in the meta-analysis. We also identified 1 ongoing study,<sup>38</sup> and 1 completed unpublished study<sup>39</sup> (Supplemental Digital Content 2, Table, <http://links.lww.com/AA/C427>). We were unable to retrieve data from the investigators of this unpublished study despite several attempts to contact them.

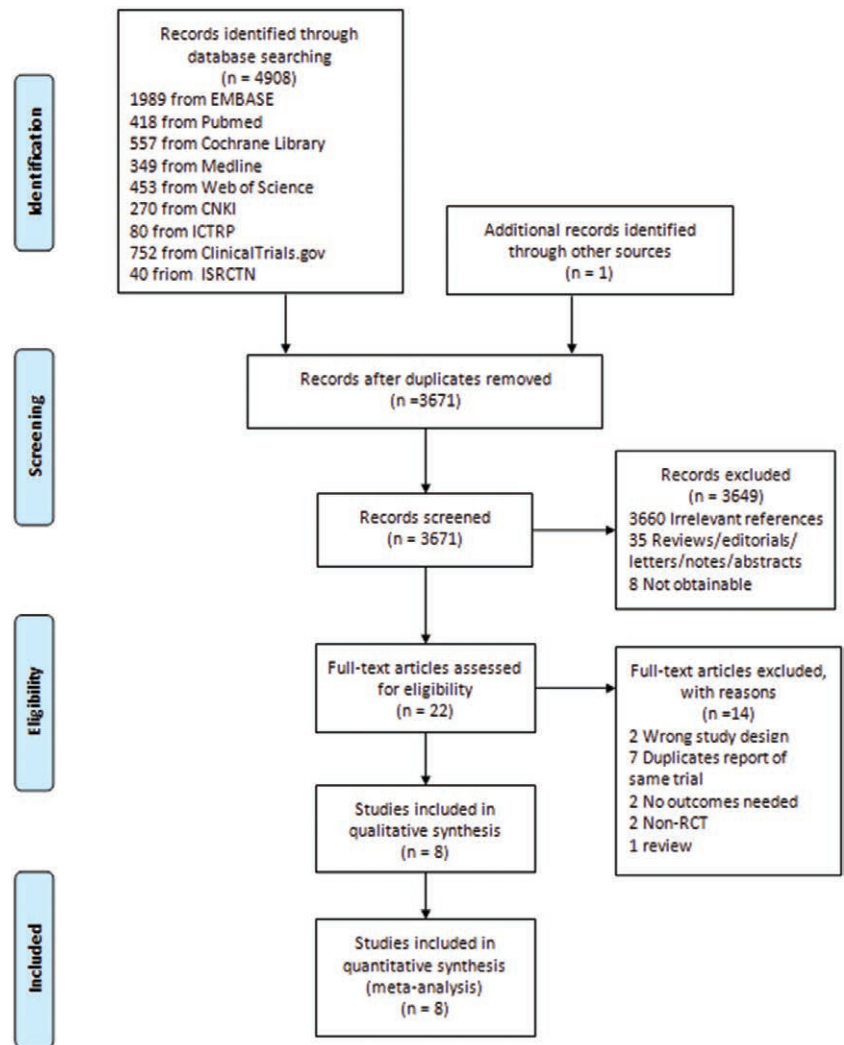
### Study Characteristics

Characteristics of the included trials are summarized in Table 1. The trials were published from 2009 to 2017. Population sizes ranged from 20 to 152. In 3 of 8 included trials, fibrinogen concentrate was infused preoperatively. In the remaining trials, authors infused fibrinogen concentrate after CPB. All trials included only on-pump cardiovascular surgeries. Seven studies compared fibrinogen versus placebo or standard of care, and 1 study compared fibrinogen versus platelet infusion. In general, the studies recruited patients who were planned to undergo cardiac surgery, aortic surgery, or combined procedures involving the heart, valves, and/or aorta. Six studies recruited patients with evidence of active bleeding or who were otherwise at high risk of bleeding due to complex surgery.<sup>21,22,34–37</sup> Two studies included patients with baseline fibrinogen levels  $< 3.8$  g/L with no other high-risk features specified.<sup>32,33</sup> Because the normal range of fibrinogen is typically reported to be 1.5–4.0 g/L, the latter studies were not limited to fibrinogen-deficient patients but were rather ensuring against inclusion of patients with supranormal endogenous fibrinogen levels. None of the studies specifically focused on congenital or acquired bleeding disorders, or recent exposure to antiplatelet agents or oral anticoagulants.

### Risk of Bias Assessment

Overall risk of bias was low in 5 trials,<sup>21,22,32,34,37</sup> unclear in 2 trials,<sup>33,35</sup> and high in 1 trial<sup>36</sup> (Supplemental Digital Content 3, Figure, <http://links.lww.com/AA/C428>). Jeppsson et al<sup>32</sup> had a high risk of bias due to attrition given loss to follow-up and early termination due to low enrollment (55 patients randomized instead of planned 60 patients; 48 patients included in final analysis). Karlsson et al<sup>33</sup> had a high risk of performance bias because anesthetic personnel were not completely blinded, as well as a high risk of funding bias. Rahe-Meyer et al<sup>21,34</sup> and Ranucci et al<sup>22</sup> had a high

**Figure 1.** PRISMA flowchart for studies identification and reasons for exclusion. CNKI indicates China National Knowledge Infrastructure; ICTRP, International Clinical Trials Registry Platform; ISRCTN, International Standard Randomised Controlled Trial Number; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial.



risk of funding bias. Rahe-Meyer et al<sup>34</sup> had baseline imbalance. Sadeghi et al<sup>35</sup> had a high risk of reporting bias due to retrospective trial registration and uncertainty regarding funding source. Tanaka et al<sup>36</sup> had a high risk of selection, detection, attrition, and funding bias.

### Fibrinogen Versus Placebo or Inactive Control

Clinical outcomes for fibrinogen concentrate versus placebo or inactive control are summarized in Table 2 and in Figure 2. Full results are available in Supplemental Digital Content 4, Results, <http://links.lww.com/AA/C429>, including subanalyses when the data were available (ie, when the subgroups were populated by at least 1 study).

### Primary Outcome

In total, 5 trials<sup>21,22,33,34,37</sup> reported on mortality. Because Karlsson et al<sup>33</sup> reported that there were no deaths during the study period, only 4 trials contributed meaningfully to the pooled estimate for relative risk of mortality.<sup>21,22,34,37</sup> In aggregate, these 4 trials showed no difference in risk of death for fibrinogen versus nonactive comparator whether measured at 30–60 days or at longest follow-up (RR, 0.41; 95% CI, 0.12–1.38;  $I^2 = 10\%$ ;  $P = .15$ ). Subgroup analyses according to fibrinogen infusion time (preoperation

versus intraoperation), fibrinogen dose ( $\geq 4$  vs  $< 4$  g), surgery (CABG versus valve versus complex), and mean CPB time ( $\geq 90$  vs  $< 90$  minutes versus not reported) did not find significant differences in effect size across subgroups. While individual subgroups suggested that mortality may be reduced in trials administering mean dose of fibrinogen  $\geq 4$  g, or in studies using ROTEM/FIBTEM-guided fibrinogen protocols, the test for subgroup interaction did not reach significance, suggesting that the effect sizes are statistically similar across subgroups. These results should be considered hypothesis generating only due to the post hoc nature of subgroup analysis and the risk of false positives through multiple testing.

### Secondary Outcomes

**Bleeding and Transfusion.** Fibrinogen significantly reduced the proportion of patients receiving allogeneic RBC transfusion (RR, 0.64; 95% CI, 0.49–0.83;  $I^2 = 0\%$ ;  $P = .0010$ ), which translates to an NNTB of 7 (95% CI, 5–14). Fibrinogen did not significantly reduce the number of patients receiving FFP (RR, 0.60; 95% CI, 0.28–1.29;  $I^2 = 28\%$ ;  $P = .19$ ). Similarly, the number of patients receiving platelet transfusion did not significantly differ between groups (RR, 0.62; 95% CI, 0.29–1.33;  $I^2 = 2\%$ ;  $P = .22$ ). Fibrinogen concentrate did not

**Table 1. Characteristics of Included Studies**

Reference	n	Surgery and Risk Group	CPB Time	Preoperation/ Intraoperation	Dose of Fibrinogen	Comparator	Trial Year	Country	Clinical Trial Registration
Bilecen et al <sup>37</sup>	120	High-risk cardiac (combined CABG valve, multiple valves, or aortic/root) and intraoperative bleeding (blood volume between 60 and 250 mL suctioned from thoracic cavity within 5-min period)	>90 min	Intraoperation (post-CPB)	3.1 g (95% CI, 2.7–3.5 g/L), according to the formula below <sup>a</sup>	Placebo + SOC	2011–2014	Netherlands	NCT01124981
Jeppsson et al <sup>32</sup>	48	CABG, low risk, with preoperative fibrinogen $\leq 3.8$ g/L <sup>b</sup>	<90 min	Preoperation	2 g	Placebo + SOC	2009–2012	Sweden	NCT00968045
Karlsson et al <sup>33</sup>	20	CABG, low risk, with preoperative fibrinogen $\leq 3.8$ g/L <sup>b</sup>	<90 min	Preoperation	2 g	No treatment + SOC	2006	Sweden	Not reported
Rahe-Meyer et al <sup>21</sup>	61	Aortic surgery patients with clinically relevant coagulopathic bleeding, measured by 5-min bleeding mass after CPB removal, protamine administration, and surgical hemostasis	<90 min	Intraoperation (post-CPB)	8 g (IQR, 6–9), according to ROTEM/FIBTEM measures	Placebo + SOC	2008–2010	Germany	NCT00701142
Rahe-Meyer et al <sup>34</sup>	152	Aortic surgery, patients with 5-min bleeding mass of 60–250 g after separation from bypass and surgical hemostasis	Not reported	Intraoperation (post-CPB)	6.29 $\pm$ 1.97 g, according to ROTEM/FIBTEM measures	Placebo + SOC	2012–2014	11 countries	NCT01475669
Ranucci et al <sup>22</sup>	116	Complex cardiac surgery with expected CPB >90 min and age >65 y, nonelective surgery, SCr >1.36 mg/dL, or redo	>90 min	Intraoperation (post-CPB)	4 g (IQR, 3–6), according to ROTEM/FIBTEM measures	Placebo + SOC	2011–2014	Italy	NCT01471730
Sadeghi et al <sup>35</sup>	60	CABG, elective, all-comers (but no redos)	Not reported	Preoperation	1 g	Placebo (albumin)	Not reported	Iran	IRCT201011085140N1
Tanaka et al <sup>36</sup>	20	Valve surgery in patients exceeding visual bleeding scale threshold	>90 min	Intraoperation (post-CPB)	4 g	1 unit of platelets	2011–2013	United States	NCT01283321

All-comers indicates any patient risk groups (otherwise unselected for high risk); high-risk cardiac indicates combined CABG and valve repair or replacement surgery, the replacement of multiple valves, aortic root reconstruction, or reconstruction of the ascending aorta or aortic arch.  
 Abbreviations: CABG, coronary artery bypass grafting; CI, confidence interval; CPB, cardiopulmonary bypass; IQR, interquartile range; ROTEM/FIBTEM, rotational thromboelastometry/fibrinogen temogram; SCr, serum creatinine; SOC, standard of care.  
<sup>a</sup>Formula: (2.5 – [plasma fibrinogen level at the end of cardiopulmonary bypass, g/L])  $\times$  0.07  $\times$  (1–hematocrit on cardiopulmonary bypass)  $\times$  bodyweight (kg) = whole grams fibrinogen concentrate to be dosed.  
<sup>b</sup>Normal reference range for fibrinogen levels is considered to be 1.5–4.0 g/L.

**Table 2. Fibrinogen Versus Placebo or Inactive Control: Summary of Clinical Outcomes**

Discrete Outcomes	n (N)	RR (95% CI)	I <sup>2</sup>	P Value for Overall Effect
Death, longest follow-up	469 (5)	0.41 (0.12–1.38)	10	.15
Death, 1–2 mo	469 (5)	0.41 (0.12–1.38)	10	.15
Death, >5 y	20 (1)	N/A (0 events)	N/A	N/A
Patients transfused RBCs	361 (5)	0.64 (0.49–0.83)	0	.0010
Patients transfused plasma	361 (5)	0.60 (0.28–1.29)	28	.19
Patients transfused platelets	313 (4)	0.62 (0.29–1.33)	2	.22
Patients transfused cryoprecipitate	NR	NR	NR	NR
Patients transfused any blood product	514 (5)	0.79 (0.53–1.18)	79	.25
Severe (major) bleeding events	61 (1)	1.10 (0.30–4.01)	N/A	.88
Reoperation	345 (4)	0.78 (0.34–1.75)	0	.54
Stroke or CVA	449 (4)	0.82 (0.17–4.11)	38	.81
Acute myocardial infarction	317 (4)	3.07 (0.64–14.78)	0	.16
Cardiac failure	61 (1)	0.37 (0.02–8.66)	N/A	.53
Atrial fibrillation	268 (2)	1.04 (0.79–1.38)	0	.78
Respiratory failure or pneumonitis	268 (2)	0.74 (0.21–2.67)	0	.65
AKI or RRT	388 (3)	0.78 (0.36–1.69)	0	0.52
Major immunological or allergic reactions	120 (1)	N/A (zero events)	N/A	N/A
Infection or sepsis	388 (3)	0.89 (0.44–1.81)	0	.75
DIC	0 (0)	NR	NR	NR
VTE (DVT or PE)	388 (3)	2.85 (0.12–68.83)	N/A	.52
Continuous Outcomes	n (N)	WMD (95% CI)	I <sup>2</sup>	P Value for Overall Effect
Total allogeneic blood products transfused, units	398 (5)	–1.87 (–4.68 to 0.94)	89	.19
RBCs transfused, units	574 (7)	–0.51 (–1.26 to 0.24)	85	.18
Plasma transfused, units	514 (6)	–0.85 (–3.31 to 1.41)	97	.46
Platelets transfused, units	514 (6)	–0.88 (–1.79 to 0.04)	95	.06
Cryoprecipitate transfused, units	NR	NR	NR	NR
Duration of mechanical ventilation, h	20 (1)	–1.40 (–3.03 to 0.23)	N/A	.09
ICU length of stay, h	81 (2)	–0.46 (–0.92 to 0.00)	0	.05
Hospital length of stay, d	81 (2)	1.08 (–0.11 to 2.27)	0	.08
Cost	NR	NR	NR	NR

Abbreviations: AKI, acute kidney injury; CI, confidence interval; CVA, cerebrovascular accident; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; ICU, intensive care unit; N/A, not applicable; NR, not reported; PE, pulmonary embolism; RBC, red blood cell; RR, risk ratio; RRT, renal replacement therapy; VTE, venous thromboembolism; WMD, weighted mean difference.

significantly reduce overall exposure to allogeneic blood products (RR, 0.79; 95% CI, 0.53–1.18;  $I^2 = 79\%$ ;  $P = .25$ ). None of the studies reported on cryoprecipitate infusions.

Only 1 trial<sup>21</sup> reported severe bleeding clinical events, and found no difference between fibrinogen concentrate and placebo. Similarly, reoperation for bleeding was not different between groups (RR, 0.78; 95% CI, 0.34–1.75;  $I^2 = 0\%$ ;  $P = .54$ ). No important subgroup effects were found for bleeding-related outcomes.

Fibrinogen did not reduce the total units of allogeneic blood products transfused (MD, –1.87 units; 95% CI, 4.68–0.94;  $I^2 = 89\%$ ;  $P = .19$ ), total units of allogeneic RBC (MD, –0.51 units; 95% CI, 1.26–0.24;  $I^2 = 85\%$ ;  $P = .18$ ), total units of FFP (MD, –0.85 units; 95% CI, 3.31–1.41;  $I^2 = 95\%$ ;  $P = .46$ ), and total units of platelets transfused (MD, –0.88; 95% CI, 1.79–0.04;  $I^2 = 95\%$ ;  $P = .06$ ).

**Other Clinical Outcomes.** No differences were found between fibrinogen and inactive comparator for stroke (RR, 0.82; 95% CI, 0.17–4.11;  $I^2 = 38\%$ ;  $P = .81$ ), myocardial infarction (RR, 3.07; 95% CI, 0.64–14.78;  $I^2 = 0\%$ ;  $P = .16$ ), atrial fibrillation (RR, 1.04; 95% CI, 0.79–1.38;  $I^2 = 0\%$ ;  $P = .78$ ), respiratory failure or pneumonitis (RR, 0.74; 95% CI, 0.21–2.67;  $I^2 = 0\%$ ;  $P = .65$ ), or renal failure (RR, 0.78; 95% CI, 0.36–1.69;  $I^2 = 0\%$ ;  $P = .52$ ).

Only 1 study reported outcomes related to immune reactions after blood product exposure and found no incidents of allergic reactions.<sup>37</sup> Similarly, no significant difference

was found for infections, and for venous thromboembolic events. None of the trials reported on disseminated intravascular coagulation.

### Resource-Related Outcomes

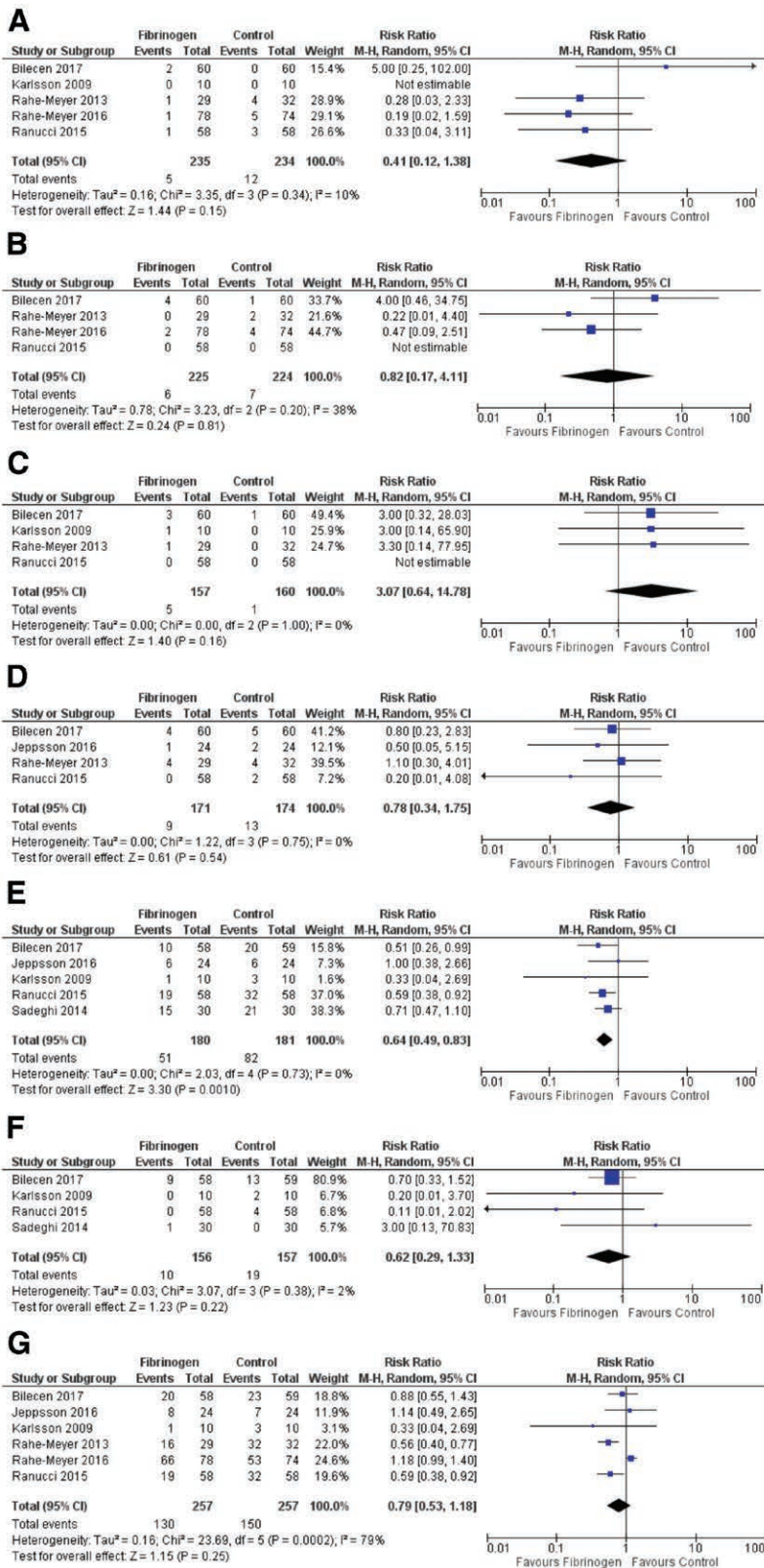
Differences for length of ICU stay (MD, –0.46 days; 95% CI, 0.92–0.00 days;  $I^2 = 0\%$ ;  $P = .05$ ) and hospital stay (MD, 1.08 days; 95% CI, 0.11–2.27;  $I^2 = 0\%$ ;  $P = .08$ ) did not reach significance. Only 1 trial<sup>36</sup> reported on costs of hemostatic components per case, and none of the trials provided data on overall hospital costs per case.

### Fibrinogen Versus Platelet

Only 1 trial<sup>36</sup> provided data for fibrinogen versus active comparator (platelet transfusion), with no clear differences in outcomes (Table 3).

## DISCUSSION

In this meta-analysis of randomized trials of perioperative administration of fibrinogen concentrate versus inactive control in patients undergoing cardiovascular surgery, no significant reduction was found for all-cause mortality or other clinically relevant outcomes such as stroke, myocardial infarction, organ dysfunction, reoperation for bleeding, transfusion-related reactions, and infections. While fibrinogen significantly decreased the number of patients receiving allogeneic RBCs, this did not result in differences in any other clinically relevant or resource-related outcomes.



**Figure 2.** Forest plots for prophylactic fibrinogen versus placebo or inactive control for all-cause mortality at 1–2 mo (A); stroke (B); acute myocardial infarction (C); reoperation for bleeding (D); patients transfused with RBCs (E); patients transfused with PLTs (F); and patients transfused with any additional blood products (G). CI indicates confidence interval; M-H, Mantel-Haenszel odds ratio; PLT, platelets; RBC, red blood cell.

The NNTB for reduction in risk of RBC transfusion was 7 (95% CI, 5–14), with CIs indicating some uncertainty of the true magnitude of effect. Whether the effect of fibrinogen on reduction in patient exposure to allogeneic RBCs is worthy of the net costs and risks when compared to other

available alternatives to achieve the same end remains unclear because only 1 small randomized trial included in this meta-analysis directly compared fibrinogen with an active control (platelet transfusion), and was underpowered to show differences in outcomes. An ongoing study of 220

**Table 3. Fibrinogen Versus Platelet Infusion: Summary of Clinical Outcomes**

<b>Discrete Outcomes</b>	<b>n (N)</b>	<b>RR (95% CI)</b>	<b>I<sup>2</sup> (95% CI)</b>	<b>P Value for Overall Effect</b>
Death, 30-d follow-up	20 (1)	N/A	N/A	N/A
Death, longest follow-up	20 (1)	N/A	N/A	N/A
No. severe (major) bleeding events	NR	NR	NR	NR
Patients transfused RBCs	NR	NR	NR	NR
Patients transfused plasma	20 (1)	0.60 (0.19–1.86)	N/A	0.38
Patients transfused platelets	20 (1)	0.43 (0.21–0.88)	N/A	0.02
Patients transfused cryoprecipitate	20 (1)	0.75 (0.22–2.52)	N/A	0.64
Patients transfused any blood product	NR	NR	NR	NR
Reoperation	20 (1)	0.50 (0.05–4.67)	N/A	0.54
VTE (DVT or PE)	20 (1)	N/A	N/A	N/A
Acute myocardial infarction	20 (1)	0.33 (0.02–7.32)	N/A	0.49
Stoke or CVA	NR	NR	NR	NR
DIC	NR	NR	NR	NR
Major immunological or allergic reactions	NR	NR	NR	NR
Infection or sepsis	NR	NR	NR	NR
Respiratory failure or pneumonitis	20 (1)	0.60 (0.19–1.86)	N/A	0.38
Cardiac failure	NR	NR	NR	NR
Atrial fibrillation	NR	NR	NR	NR
AKI or RRT	NR	NR	NR	NR
<b>Continuous Outcomes</b>	<b>n (N)</b>	<b>WMD (95% CI)</b>	<b>I<sup>2</sup></b>	<b>P Value for Overall Effect</b>
Total allogeneic blood products transfused, unit	NR	NR	NR	NR
RBCs transfused, unit	NR	NR	NR	NR
Plasma transfused, unit	NR	NR	NR	NR
Platelet transfused, unit	NR	NR	NR	NR
Cryoprecipitate transfused, units	NR	NR	NR	NR
Length of stay in hospital, d	20 (1)	0.20 (–2.64 to 3.04)	N/A	0.89
Length of stay in ICU, h	20 (1)	–1.18 (–3.06 to 0.69)	N/A	0.22
Duration of mechanical ventilation, h	NR	NR	NR	NR
Cost	NR	NR	NR	NR

Abbreviations: AKI, acute kidney injury; CI, confidence interval; CVA, cerebrovascular accident; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; ICU, intensive care unit; N/A, not applicable; NR, not reported; PE, pulmonary embolism; RBC, red blood cell; RR, risk ratio; RRT, renal replacement therapy; VTE, venous thromboembolism; WMD, weighted mean difference.

patients randomized to fibrinogen versus tranexamic acid may provide more information regarding clinically relevant comparative outcomes after completion (NCT01623531).

Costs and resource-related outcomes were poorly reported in all of the studies, and did not provide supporting evidence to suggest that fibrinogen concentrate will offset total resource usage and costs. None of the studies reported overall hospital cost per patient. One trial<sup>33</sup> reported the cost of fibrinogen dose as 450 Euros, and another trial<sup>36</sup> reported 1 g of fibrinogen to cost 233 Euros. However, it is important to note that the median costs of hemostatic components per case do not represent overall hospital costs, and furthermore, they do not indicate relative cost-effectiveness versus alternatives. While the impact of fibrinogen versus inactive control reached borderline significance for ICU length of stay in this meta-analysis, this was based on only a few trials and should not constitute definitive proof of impact on ICU stay because many RCTs failed to report on this outcome. Future studies should address net costs per net health benefit to inform cost-effectiveness with all costs incurred and cost offsets included.

Although this meta-analysis represents the best available evidence to date from existing randomized trials, even after synthesis of all available data, the current evidence base remains underpowered to provide definitive conclusions. In total, the 8 existing randomized trials have included only 597 adult cardiovascular surgery patients. For the outcome of mortality, there were only 17 events (5 deaths in the fibrinogen group and 12 deaths in the inactive control group) in total across all randomized trials, which is insufficient to definitively form conclusions on whether or not

relevant differences exist. While subgroup analysis suggested that high-dose fibrinogen ( $\geq 4$  g) or use of FIBTEM/ROTEM-guided administration may be associated with reduced risk of death compared with inactive control, we recognize that subgroup analyses are prone to false positives and overstated results, especially when 1 positive result is drawn from a multitude of subgroup analyses performed. Because this significant result is drawn from a large number of exploratory subgroup analyses in our meta-analysis, and because the test for interaction across subgroups did not reach significance, we encourage extreme caution in interpreting the results of the subgroup analyses. At this time, it would be premature to conclude that higher doses of fibrinogen and/or FIBTEM/ROTEM-guided administration will reduce the risk of death. Prospective randomized studies of sufficient size to detect differences in mortality across different doses and across FIBTEM/ROTEM protocols will be needed to provide definitive answers.

Another word of caution relates to the fact that the existing body of randomized trials has inherent risk of bias that may jeopardize the overall integrity of the conclusions, as shown by our risk of bias assessment. Only 1 included trial<sup>32</sup> was clearly independent of industry sponsorship. Missing data due to patient attrition due to loss to follow-up, early termination, and/or incomplete reporting of outcomes occurred within a number of randomized trials. Some of the trials lacked adequate blinding to sufficiently protect against biased outcomes assessment. There is an existing completed randomized trial that remains unpublished<sup>39</sup> (Supplemental Digital Content 2, Table, <http://links.lww.com>).

com/AA/C427). Given the fragility of each of the findings in this analysis, conclusions could change with the addition of another published RCT. If this RCT remains unpublished due to lack of incentive to publish “negative” findings, the results of this meta-analysis may be positively biased without the available totality of negative evidence.

This meta-analysis improves on existing published meta-analyses with the inclusion of more recent trials, and through our focus only on cardiovascular surgery. Other meta-analyses and systematic reviews have a number of limitations because they combined studies of surgical and nonsurgical patients, or evaluated miscellaneous surgical studies rather than focusing on cardiovascular surgery, or combined randomized with observational data.<sup>24–27</sup> Additional strengths of our meta-analysis include protocol preregistration, and compliance with PRISMA guidelines and Cochrane Collaboration methodology.

Further limitations of the existing trials, beyond those related to inadequate power and risk of bias discussed above, include the heterogeneity of patient risk groups included. While 2 small studies in this meta-analysis focused on low-risk patients,<sup>22,37</sup> the majority enrolled patients with evidence of bleeding or with otherwise high risk of bleeding due to surgical complexity. However, the definition for “evidence of bleeding” or “high-risk surgery” was not homogeneous across these studies. Furthermore, protocols for administering fibrinogen in response to patient bleeding were heterogeneous. Another limitation relates to the absence of data on potential interaction of fibrinogen with heparin, protamine, or other antithrombotics and antifibrinolytics and impact on long-term clinically relevant outcomes such as graft patency and risk of stroke or other thromboembolic events.

Current guidelines on the use of fibrinogen concentrate are varied. Guidelines from ESA and American Society of Anesthesiologists recommend fibrinogen for the treatment of actively bleeding perioperative patients in their guidelines for surgical patients in general (not specifically for cardiovascular surgery). The American Society of Anesthesiologists Task Force on Perioperative Blood Management suggests that fibrinogen concentrate should “be considered in patients with excessive bleeding [Category A2-B evidence].”<sup>40</sup> ESA recommends “treatment of hypofibrinogenemia in bleeding patients” (1C Recommendation), where hypofibrinogenemia is defined as fibrinogen concentration of <1.5–2 g/L.<sup>23</sup> Our meta-analysis does not negate these recommendations for surgery in general, which are based on additional evidence from combined surgical and nonsurgical studies of bleeding patients beyond the setting of prophylaxis in cardiovascular surgery.<sup>24</sup> Specifically for cardiovascular surgery, ESA further recommends that fibrinogen concentrate infusion guided by viscoelastic coagulation monitoring should be used preemptively in complex cardiovascular surgery (1B Recommendation).<sup>23</sup> Previous ESA guidelines had recommended prophylactic preoperative fibrinogen concentrate infusion in patients with fibrinogen concentration <3.8 g/L in complex cardiovascular surgery.<sup>41</sup> Because our meta-analysis shows that the effect of fibrinogen concentrate is modest at best (NNTB of 7 for RBC transfusion) even in the setting of evidence of ongoing bleeding, with no changes in clinically relevant outcomes, a policy of routine prophylaxis for all patients remains premature. Routine fibrinogen

concentrate for prophylaxis should remain as a focus of further research rather than considered definitively proven for routine clinical practice.

In conclusion, current evidence remains insufficient to support or refute routine perioperative administration of fibrinogen concentrate in patients undergoing cardiovascular surgery. Fibrinogen concentrate may reduce the need for additional allogeneic blood product transfusion in cardiovascular surgery patients at high risk or with evidence of bleeding. However, no definitive advantage was found for reduction in risk of mortality or other clinically relevant outcomes. High-powered randomized trials of clinically relevant impacts are needed before definitive recommendations for or against routine perioperative fibrinogen concentrate infusion in the setting of cardiovascular surgery can be made. Further research should establish the optimal dosing, administration schedule, monitoring requirements, and cost-effectiveness of fibrinogen concentrate relative to standard of care. ■

## DISCLOSURES

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