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Use of Prothrombin Complex Concentrates and Fibrinogen Concentrates in the Perioperative Setting: A Systematic Review

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ABSTRACT

The use of prothrombin complex concentrates (PCCs) and fibrinogen concentrates (FIBCs) to achieve hemostasis in the perioperative setting as alternatives to allogeneic blood products remains controversial. To examine the efficacy and safety of PCCs and FIBCs, we conducted a systematic review—in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement—to compare the use of these transfusion alternatives in bleeding surgical patients. We performed a literature search of English articles published between July 1997 and July 2012 in MEDLINE via PubMed, The Cochrane Library, and CINAHL. Five randomized trials and 15 nonrandomized studies with a comparator group were included in the final review. Studies were sorted into 1 of the following 3 clinical settings: cardiac surgery, non–cardiac surgery, and reversal of warfarin anticoagulation. Risk of bias was assessed using the Cochrane risk of bias tool. With the exception of 2 randomized controlled trials, the existing body of literature on the use of PCCs and FIBCs in the perioperative setting was assessed to have a high degree of methodological bias. Overall, prospective studies in the cardiac surgery grouping suggested that patients receiving FIBC and/or PCCs required less allogeneic blood transfusion and had less chest tube drainage. In studies of warfarin reversal, PCCs more rapidly corrected the International Normalized Ratio compared to plasma; however, in the setting of intracranial hemorrhage, functional outcomes were poor regardless of the reversal strategy. With regards to safety outcomes, reporting was not uniform and raises concerns of underreporting. Adequately powered, methodologically sound trials would be required for more definitive conclusions to be drawn about the efficacy of PCCs and FIBC over conventional blood components for the treatment of perioperative coagulopathy in bleeding patients.

Contents

"Conflict of Interest" statement: This study was performed without external funding.

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PLASMA AND CRYOPRECIPITATE (CRYO) transfusions have both infectious and noninfectious risks. Whereas most infectious risks are on the order of 1 in 1,000,000, the noninfectious risks—in particular, transfusion-associated circulatory overload and allergic transfusion reactions—are orders of magnitude more common, ranging from 1 in 100 to 1 in 10,000 [1].

Recent systematic reviews have called into question the efficacy of prophylactic plasma transfusions [2,3]. Administering fresh frozen plasma (FFP) in patients with minimally elevated International Normalized Ratio (INR) values has been shown to be ineffective in producing meaningful corrections [4,5]. Commonly recommended doses vary between 10 and 30 mL/kg [6,7]. At these therapeutic doses, a 70-kg patient might receive between 700 and 2100 mL of plasma. In the right clinical setting, these volumes place patients at risk for transfusion-associated circulatory overload and other adverse outcomes [8].

As alternatives have emerged, CRYO is now no longer the agent of choice for patients with congenital factor deficiencies. For example, recombinant factor VIII has replaced CRYO in the treatment of hemophilia A. Perhaps the most clinically important remaining use of CRYO is replenishing fibrinogen in patients who develop acquired hypofibrinogenemia intraoperatively. However, despite its widespread use, a recent review published in this Journal [9] concluded that there are insufficient data to guide the appropriate use of CRYO in the perioperative setting.

Prothrombin complex concentrates (PCCs) contain components of the prothrombinase complex—factors II, VII, IX, and X—prepared as a lyophilized powder for reconstitution with small volumes of (ie, 10 - 20 mL of Sterile Water for Injection). Different formulations contain varying amounts of proteins C and S, but PCCs are mainly distinguished by their factor VII content. Four-factor concentrates contain clinically significant levels of factor VII; in contrast, 3-factor concentrates have little to none. Examples of 3-factor concentrates include Bebulin (Baxter, Westlake Village, California), Profilnine SD (Grifols Biologicals, Inc, Los Angeles, California), Prothrombinex HT/VF (CSL Limited, Broadmeadows Victoria, Australia) and Cofact (Sanquin, Amsterdam, the Netherlands). Examples of 4-factor concentrates include Beriplex (CSL Behring, Marburg, Germany), Prothromplex (Immuno, Vienna, Austria), Octaplex (Octapharma, Vienna, Austria), and PPSB-HT (Nihon Pharmaceuticals, Tokyo, Japan). Four-factor concentrates are widely available in several European countries but are not yet available in the US market.

PCCs and fibrinogen concentrates (FIBCs) are used as off-label alternatives to FFP and CRYO to treat acquired coagulopathy in bleeding medical and surgical patients. These concentrates allow for high doses of clotting factors to be administered—unlike therapeutic plasma transfusions—with minimal concerns about volume overload. Because immunoglobulins and other antigenic proteins are removed, these products are ABO neutral and less likely to cause allergic transfusion reactions compared to blood products.

To examine the efficacy and safety of PCCs and FIBCs, we conducted a systematic review of studies comparing these transfusion alternatives to allogeneic blood transfusion (ABT) in the perioperative setting. Both randomized controlled trials and nonrandomized studies were included for appraisal; however, nonrandomized studies were required to have a comparator group.

Methods

Protocol Registration and Eligibility Criteria

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement for guidance throughout the entire process of writing this systematic review and registered a protocol online in advance (PROSPERO 2012:CRD42012002599). The PICOS (Population, Intervention, Comparison, Outcomes, Study Design) approach was used to define the criteria for inclusion (Table 1). Any disagreements between review authors (DL and MT) in the process of study selection and appraisal were resolved by discussion.

Search Strategy and Information Sources

We conducted a systematic literature search of English articles published between July 1997 and July 2012 in MEDLINE via PubMed,

Table 1
Inclusion criteria using the PICOS approach

Population	Adults bleeding due to warfarin anticoagulation and/or acquired states of coagulopathy in the perioperative setting. Studies of adults with congenital bleeding disorders were excluded.	
Intervention	Use of PCCs and/or FIBCs to treat acquired coagulopathy in the perioperative setting and/or to reverse warfarin anticoagulation	
Comparator	FFP, CRYO, vitamin K, crystalloid, colloid, or no intervention	
Outcomes	Efficacy	• Hematologic parameters, such as INR and MCF • Clinical outcomes, such as chest tube drainage and hematoma expansion • Need for ABT
	Safety	• Thromboembolic events • Other adverse events related to the allocated intervention
Study design	Randomized controlled trials and nonrandomized studies with a comparator group	

International normalized ratio (INR), maximum clot firmness (MCF), allogeneic blood transfusion (ABT).

Table 2
Criteria for high risk of bias using the Cochrane risk of bias tool

Randomization generation	Describes nonrandom sequence generation, such as odd or even. Nonrandomized studies have a high risk of selection bias that is inherent to the design.
Allocation concealment	Participants and/or investigators could possibly foresee assignment to treatment arms.
Blinding to intervention(s)	Outcomes potentially influenced by knowing the allocated intervention ahead of time.
Incomplete outcome data	The reasons or numbers of missing data are not addressed or not balanced across intervention groups. For randomized studies, a modified ITT population was used to analyze treatment efficacy.
Selective outcomes reporting	Reports efficacy outcomes clearly specified in the methods section
Potential conflict(s) of interest	Funding source or authors receive fees or honoraria from the manufacturer of hemostatic therapies used in the study.

Intention to treat (ITT).

The Cochrane Library, and CINAHL (Table A1 in Appendix A). Additional studies were identified by manually searching the reference lists of eligible studies.

Study Selection

Two reviewers (DL and MT) independently screened the titles and abstracts of retrieved records for potential inclusion and then together performed a full text review of the remaining records to exclude studies that did not fulfill the eligibility criteria.

Data Items and Extraction

Two reviewers (DL and MT) extracted the data independently and then together checked for completeness and accuracy. Data extracted included references, funding, details of study design, patient population, primary and comparator intervention(s), and efficacy and safety outcomes. Efficacy outcomes included hematologic parameters and clinical outcomes. Safety outcomes included thromboembolic events and other reported adverse events related to the allocated therapeutic interventions.

Risk of Bias Assessment

Two reviewers (DL and MT) independently assessed the risk of bias using the Cochrane risk of bias tool. In particular, we critically appraised each study by assessing the method of randomization, allocation concealment, whether blinding to intervention was likely to influence efficacy and safety outcomes, whether incomplete outcomes data were addressed, selective outcomes reporting, and potential conflict(s) of interest. The criteria used to assess for high risk of bias are summarized in Table 2.

Results

Study Selection and Characteristics

The study selection process is depicted in a PRISMA flow diagram (Fig. 1). Most of the identified records were easily excluded based on relevance by reviewing the title or abstract alone. After this initial screening, records that potentially fulfilled the FIBC (n = 35) and PCC (n = 62) inclusion criteria were selected for full text review. Nine articles from FIBC search and 13 articles from the PCC search were eligible for inclusion. After removing 2 duplicate records, 5 randomized trials and 15 nonrandomized studies with a comparator group were included in our final review. Studies were sorted into 1 of the following 3 clinical settings in Table 3: cardiac surgery, non–cardiac surgery, and reversal of warfarin anticoagulation. Study characteristics are summarized using the PICOS format in Tables 4A, 4B, and 4C.

Cardiac Surgery

Overall, we identified 6 prospective [10–15] and 2 retrospective [16,17] studies in the cardiac surgery grouping. Of the 6 prospective studies, 3 were randomized and 3 were nonrandomized. All 8 were single-center studies. Two of the randomized trials assessed the clinical efficacy and safety of FIBC given preoperatively in elective coronary artery bypass graft (CABG) surgery [10] and perioperatively in elective cardiovascular and other major surgery [11]. A third randomized trial assessed the perioperative use of PCC in reversing warfarin anticoagulation and reducing ABT requirements in nonelective cardiac surgery [12].

Non–Cardiac Surgery

We identified 1 randomized trial and 3 retrospective studies in the non–cardiac surgery grouping. Fenger-Eriksen and colleagues (2009) [18] was a double-blinded randomized trial conducted at a single institution that compared the efficacy of FIBC in reducing perioperative ABT requirement and reversing acquired coagulopathy—as measured by maximum clot firmness (MCF)—induced by hydroxyethyl starch (HES) compared to isotonic sodium chloride solution in elective radical cystectomy for localized bladder cancer. Of the 3 retrospective studies, 2 used data from trauma registries [19,20], whereas the third was a single-center study [21].

Reversal of Warfarin Anticoagulation

We identified 1 randomized trial [22], 3 prospective studies with historical comparison groups [23–25], and 4 retrospective studies

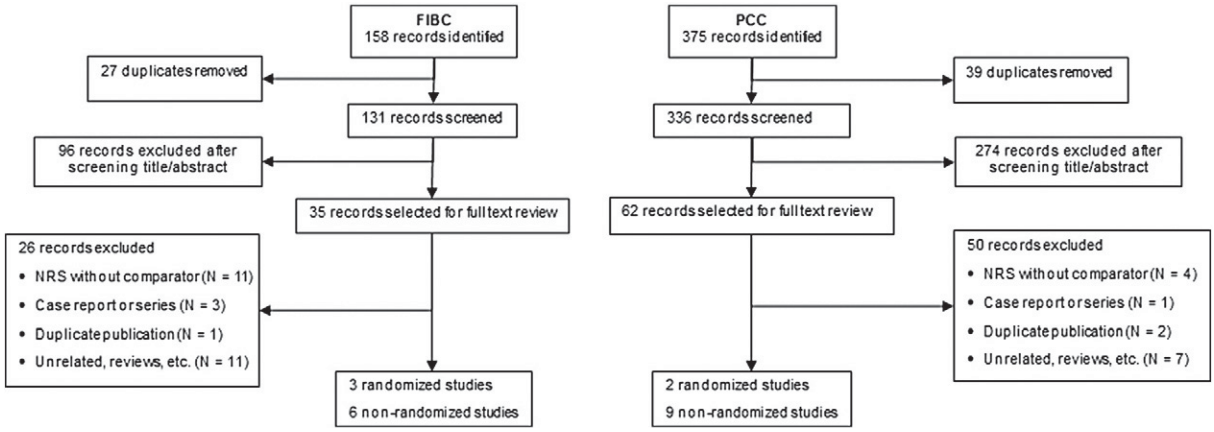

Fig. 1. PRISMA flow diagram depicting the study selection process.

Table 3
Three clinical groupings: cardiac surgery, non–cardiac surgery, and reversal of warfarin anticoagulation

Grouping	Study type	Study type	Study
Cardiac surgery (n = 8) (Tables 4A, 5A)	Prospective (n = 6)	Randomized (n = 3)	[10] Preoperative prophylactic fixed dosing of FIBC in elective CABG
			[11] Perioperative fixed dosing of FIBC in major elective surgery
			[12] Perioperative weight-based dosing of 4-factor PCC for warfarin reversal in on-pump surgery
		Nonrandomized (n = 3)	[13] Intraoperative TEM-guided dosing of FIBC and/or ABT protocol in AV-AA surgery
			[14] Intraoperative TEM-guided dosing of FIBC and/or ABT protocol in TAAA surgery
			[15] Intraoperative TEM-guided dosing of FIBC in elective CABG
	Retrospective (n = 2)		[16] Postoperative discretionary (ie, no protocol) dosing of PCC and/or FFP in cardiac surgery
			[17] Intraoperative TEM-guided dosing of FIBC and PCC in elective CABG
Non–cardiac surgery (n = 4) (Tables 4B, 5B)	Prospective (n = 1)	Randomized	[18] Intraoperative weight-based dosing of FIBC after deliberate hemodilution in bladder surgery
	Retrospective (n = 3)		[19] Fixed dosing FIBC in major bleeding or consumptive coagulopathy
			[20] FIBC vs CRYO in acquired hypofibrinogenemia
			[21] Comparison of responses to FIBC or CRYO in acquired hypofibrinogenemia
Warfarin reversal (n = 8) (Tables 4C, 5C)	Prospective (n = 4)	Randomized (n = 1)	[22] Weight-based dosing of 3-factor PCC in traumatic intracranial bleed
		Nonrandomized (n = 3)	[23] Weight-based dosing of 3-factor PCC in spontaneous intracerebral bleed
			[24] Protocol-driven dosing of 4-factor PCC in intracranial bleed due to blunt trauma
			[25] Weight-based dosing of 3-factor PCC in patients with supratherapeutic INR ± clinical evidence of bleeding
	Retrospective (n = 4)		[26] Discretionary (ie, no protocol) dosing of 4-factor PCC in spontaneous intracerebral bleed
			[27] Discretionary (ie, no protocol) dosing of 4-factor PCC in spontaneous intracerebral bleed
			[28] Weight-based dosing of 3-factor PCC in traumatic or spontaneous intracerebral bleed
			[29] Weight-based dosing of 3-factor PCC in trauma admission or neurosurgery patients

Aortic valve and ascending aorta (AV-AA), thoracoabdominal aortic aneurysm (TAAA).

[26–29] of PCC for warfarin reversal. Six studies [22–24,26–28] specifically assessed the efficacy of PCC in traumatic or spontaneous intracranial hemorrhage, whereas 2 studies [25,29] focused on reversal of supratherapeutic INR. Boulis and colleagues [22] was an open-label randomized trial conducted at a single institution that compared the time and rate of warfarin reversal in patients with traumatic intracranial bleeding who were treated with 3-factor PCCs or FFP. Both study arms received subcutaneous vitamin K.

Cochrane Risk of Bias Assessment

The risk of bias tool assessment was applied across all studies; and the results are graphically presented in Figures 2A, 2B, and 2C. With the exception of randomized controlled trials by Karlsson and colleagues [10] and Fenger-Eriksen and colleagues [18], most studies were assessed to have a high degree of methodological bias (Table A2 in Appendix A).

Efficacy and Safety Outcomes in Cardiac Surgery

Five prospective studies in this clinical grouping demonstrated reductions in ABT requirements [10,12–15], of which 4 showed reduction in 24-hour chest tube drainage [10,13–15] compared to the comparator arm (Table 5A). The study by Karlsson and colleagues [10] was assessed to have the lowest overall risk of methodological bias overall; the study reports that a prophylactic 2-g dose of FIBC given preoperatively in patients undergoing elective CABG surgery reduces chest tube drainage postoperatively ($P < .01$). Although an improved Δ MCF was noted in the study by Lance and colleagues [11], this difference did not translate to a reduction in ABT utilization. Overall, thrombotic events were similar in both the intervention group and the comparator arm, with an overall low incidence rate [10–15].

Two retrospective studies were also appraised. Arnekain and colleagues [16] reported that PCC monotherapy when compared to PCC-FFP combination therapy and FFP monotherapy was the most effective in reducing postoperative chest tube drainage. Gorlinger and colleagues [17] found that a thromboelastometry (TEM)-driven hemostasis protocol in cardiac surgery when compared to an antecedent "no-protocol" period reduced ABT needs. The most significant reduction was in FFP use (1.1% vs 19.4%, $P < .001$); in addition, composite thromboembolic events were lower (1.77% vs 3.19%, $P < .05$).

Efficacy and Safety Outcomes in Non–Cardiac Surgery

The only prospective trial in this clinical grouping [18] randomized patients undergoing radical cystectomy to weight-based dosing of FIBC compared to saline control following deliberate hemodilution with HES (Table 5B). Outcomes demonstrated an overall greater improvement in Δ MCF in the intervention arm; however, there were no differences in intraoperative red cell use between groups, and safety outcomes were not reported. Nevertheless, the study was assessed to have the lowest overall risk of methodological bias in this group.

Two of the retrospective studies in this group [19,20] compared TEM-guided dosing of FIBC and 4-factor PCC against trauma registry data constituting prevailing clinician practice for patients fulfilling detailed inclusion and exclusion criteria. Patients with major head trauma were excluded from both studies as well as

Table 4A
Study characteristics of FIBCs and/or PCCs in cardiac surgery

Reference	Funding	Design	Population	Intervention	Comparator	Outcomes
Karlsson et al (2009) [10]	CSL Behring, Swedish Heart & Lung Foundation, internal funding	Single center Randomized Double blinded Modified ITT	Elective CABG with preop fibrinogen level ≤3.8 g/L without surgical source of bleeding	Preop prophylactic 2 g FIBC (n = 10)	No preop hemostatic therapy (n = 10)	• Postop chest tube drain in first 12 h • Postop ABT needs • Postop graft patency by CT angiography • Safety reported as clinical adverse events
Lance et al (2012) [11]	CSL Behring	Single center Randomized Single blinded Modified	Major elective surgery (OR time >120 min) with major intraop or postop bleeding	2 U FFP + fixed dose 2 g of FIBC then standard ABT protocol if hemostasis not achieved (n = 22)	4 U FFP then standard ABT protocol (n = 21)	• Δ in MCF • # of patients who achieved hemostasis • Safety reported but not prespecified
Demeyere et al (2010) [12]	Sanquin/CAF-DCF	Single center Randomized Open label Modified ITT	Urgent on-CPB cardiac surgery with INR 2.1 to 7.8 due to warfarin anticoagulation	Weight-based 4-factor PCC (PPSB-SD, Cofact) with target INR 1.5. 50% given before CPB; 50% after heparin reversal; no vitamin K (n = 20)	2U FFP before CPB; 2U FFP after heparin reversal; no vitamin K (n = 20)	• # of patients achieve INR ≤1.5 • Time needed to achieve INR ≤1.5 • # of patients needing additional hemostasis • Periop ABT needs • Safety reported but not prespecified
Rahe-Meyer et al (2009) [13]	CSL Behring	Single center Nonrandomized Compared a prospective cohort with a historical	Elective AV-AA with diffuse microvascular bleeding (by weighed swabs) after weaning from CPB	Group C (n = 10) received TEM-guided dosing of FIBC with MCF target 22 mm followed by 2-step ABT protocol (platelets + FFP)	Group A (n = 42) received ABT off protocol. Group B (n = 5) received 2-step ABT protocol only	• ABT needs in 24 h • Postop chest tube drain in 24 h • Safety reported but not prespecified
Rahe-Meyer et al (2009) [14]	CSL Behring	Single center Nonrandomized Compared 2 prospective cohorts with a historical	Elective TAAA with high level of bleeding post-CPB by weighed swabs (prospective) or by visual estimation (historical)	TEM-guided dosing of FIBC to achieve MCF 22 mm followed by ABT protocol (platelets + FFP) (n = 6)	Historical cohort receiving ABT protocol only (n = 12)	• Periop ABT needs • % patients not needing any periop ABT • Postop chest tube drain in 24 h • Safety reported but not prespecified
Solomon et al (2012) [15]	CSL Behring	Single center Nonrandomized Compared 2 prospective cohorts	Elective CABG with preop platelet dysfunction who developed diffuse nonsurgical bleeding after heparin reversal	If TEM was used then TEM-guided dosing of FIBC (n = 10)	If TEM is not available, ABT off protocol (platelets + FFP) (n = 19)	• Periop ABT needs • Postop chest tube drain in 24 h • Safety reported but not prespecified
Arnekian et al (2012) [16]	Internal funding	Single center Nonrandomized Compared 3 historical cohorts	Cardiac surgery on CPB with active postop bleeding treated with PCC and/or FFP. Dosing was not standardized.	Group I received 4-factor PCC only (Octaplex, Octapharma) (n = 24). Group III received both PCC and FFP (n = 27)	Group II received only FFP (n = 26)	• Postop chest tube drain • % need reexploration • Periop ABT needs • Safety reported as postop complications
Gorlinger et al (2011) [17]	Fees and/or honoraria from CSL Behring, internal funding	Single center Nonrandomized Compared 2 historical cohorts	Cardiac surgery on CPB with diffuse bleeding after heparin reversal	Post-2009 TEM-guided dosing of FIBC + PCC. Use of ABT (platelets only) was 3rd line. No FFP or CRYO transfused. (n = 2147)	Pre-2004 ABT protocol (FFP + platelets). Use of FIBC was 3rd line (n = 1718)	• Periop ABT needs • Periop PCC and FIBC needs • Safety reported as VTE, arterial embolism, stroke, graft occlusion by "postop coronary angiography

Computed tomography (CT), operating room (OR).
All FIBCs used in the above studies were Haemocomplettan (CSL Behring); Gorlinger et al. (2011) used two 4-factor PCCs: Beriplex (CSL Behring) or Octaplex (Octapharma).

registry patients resuscitated with FIBC and PCC. Two thromboembolic complications occurred in the intervention group of one study [19], both in association with traumatically injured vessels at the site of thrombosis; safety outcomes were not reported in the latter study [20].

In the final retrospective study, fibrinogen increments for FIBC and CRYO were compared for medical and surgical patients with acquired hypofibrinogenemia [21]. The mean increment in fibrinogen was greater when equivalent doses of FIBC were administered compared to CRYO. The authors attributed this to variability of fibrinogen concentration between cryoprecipitate pools. Safety was not reported.

Efficacy and Safety Outcomes in Reversal of Warfarin Anticoagulation

One randomized controlled study was reported in this clinical grouping [22] that demonstrated shorter time to INR reversal with PCC, FFP, and subcutaneous vitamin K compared to those who did not receive PCC (2.95 ± 0.46 vs 8.9 ± 1.51 hours, $P < .01$) (Table 5C). Whereas no complications were observed in the PCC arm, 5 of the 8 patients in the comparator arm developed complications of fluid overload: 1 case of myocardial infarction, 3 cases of oxygen desaturation (one of whom requiring endotracheal intubation and mechanical ventilation), 2 cases of supraventricular tachycardia, and another case of renal insufficiency from congestive heart failure.

Three prospective studies compared reversal outcomes to retrospective groups [23–25]. In the 2 focusing on intracranial bleeding [23,24], data supported a more rapid and durable INR correction with PCC-based warfarin reversal protocol. Kalina and colleagues [24] reported that 3 patients who received PCC developed deep vein thrombosis (DVT), but no one in the study received Novo-Seven (Novo Nordisk, Inc, Princeton, NJ) - M. Kalina, personal communication.

In the study excluding intracranial hemorrhage in its prospective arm but including it in its historical comparator arm, Holland and colleagues concluded that 3-factor PCC inadequately reverses

Table 4B
Study characteristics of FIBCs and/or PCCs in non–cardiac surgery

Reference	Funding	Design	Population	Intervention	Comparator	Outcomes
Fenger-Eriksen et al (2009) [18]	CSL Behring, University Foundation, private foundation	Single center Randomized Double blinded Modified ITT	Elective radical cystectomy for localized bladder CA with severe intraop blood loss	30% hemodilution with HES then FIBC 45 mg/kg (n = 11)	30% hemodilution with HES then equal volume of isotonic saline 2.25 mL/kg (n = 10)	• Δ in MCF • Periop ABT needs • Safety not reported
Nienaber et al (2011) [19]	Fees, grants, or honoraria from CSL Behring	Trauma registries Nonrandomized Compared 2 retrospective cohorts	Severe bleeding from blunt trauma with coagulopathy upon arrival to ER	TEM-guided or non–TEM-guided FIBC and 4-factor PCC without FFP (Austria-ITB registry n = 18)	Primarily 1 to 1 ratio of RBC to FFP protocol. No FIBC or PCC given. (Germany-DGU registry n = 18)	• Periop ABT needs • Safety reported but not prespecified
Schochl et al (2011) [20]	Fees and/or honoraria from CSL Behring and TEM	Single center (FIBC-PCC) Trauma registry (ABT only) Nonrandomized Compared 2 retrospective cohorts	Major trauma treated with TEM-guided FIBC ≥1 g and PCC ≥500 U Comparator population includes severely injured ICU patients given at least 2 U of FFP	Fixed dose FIBC 2 to 4 g followed by TEM-guided PCC 1000 to 1500 U, then MCF-guided platelet transfusion (n = 80)	Off protocol ABT. Must not have received FIBC or PCC (n = 601)	• Periop ABT needs • FIBC, PCC needs • Safety not reported
Theodoulou et al (2012) [21]	No reported conflict of interest	Single center Nonrandomized Compared 2 retrospective cohorts	Surgical and nonsurgical patients with major bleeding or consumptive coagulopathy	2 to 4 g of FIBC (n = 36)	2 bags of cryoprecipitate equivalent to 10 donor pools (n = 64)	• Δ in fibrinogen • Safety not reported

All FIBCs used in the above studies were Haemocomplettan (CSL Behring), except that Nienaber and colleagues used Beriplex (CSL Behring). Nienaber and colleagues used 2 formulations of 4-factor PCCs: Prothromplex P (Baxter) or Beriplex (CSL Behring). Schochl and colleagues used FIBC and PCC manufactured by CSL Behring (Haemocomplettan and Beriplex).

warfarin anticoagulation [25]. Potentially important confounders include the degree of coagulopathy (mean baseline INR of 9 for the PCC arm and 9.4 for the historical cohort) and the timeframe for follow-up INR testing (mean of 11 hours in the PCC arm compared to 21 hours in the historical cohort).

The retrospective studies comparing PCC to matched historical controls [26–29] demonstrated reduced subsequent intracerebral hematoma expansion [26,27]—albeit without major improvements in function—as well as quicker achievement of INR target [27–29]. Safety outcomes were not reported in 2 studies [26,27]. The remaining 2 studies report similar incidence of venous thrombotic events (VTEs) [28,29]. Venous thromboembolic events included 1 case of pulmonary embolism (PE) and 1 case of DVT in the PCC group (occurring on days 8 and 11, respectively; neither patient was receiving VTE prophylaxis) and 1 case of possible stroke in the rVIIa group (which occurred on day 4) [28]. Chapman and colleagues [29] reported 2 DVT cases in the PCC arm (subclavian PICC-line associated and right common femoral DVT in patient with a history of protein S deficiency who sustained a traumatic femur fracture) and 1 DVT case in the comparator cohort (bilateral internal jugular vein DVT with collaterals discovered on day 10 suggestive of chronic venoocclusive disease).

Discussion

In this systematic review, we used the PICOS approach to define the study question and to clarify the eligibility criteria. The strength of our review lies in our specification that all included studies must have a comparator group. This strict criterion resulted in the exclusion of the majority of published articles returned by the search strategy. An additional strength is the rigorous risk of bias assessment based on the Cochrane risk of bias tool. Compared to studies that used PCC to reverse warfarin anticoagulation, FIBC studies more commonly involved conflicts of interest and industry funding. With these latter studies, the sample size in the prospective arms was generally small (mean, 12; range, 6-22); and the historical comparator cohorts were not well matched to the intervention arm groups. Therefore, with the exception of randomized controlled trials by Karlsson and colleagues (2009) [10] and Fenger-Eriksen and colleagues (2009) [18], most studies were assessed to have a high degree of methodological bias.

Prospective studies involving FIBC and/or PCC in cardiac surgery were limited by small sample size and potential conflicts of interest. Favorable design elements include randomization [10–12], use of an objective method (ie, weighing sponges) to estimate mediastinal bleeding [13,14], and an intraoperative transfusion protocol using point-of-care coagulation parameters [13–15]. Overall, these studies demonstrated a reduction in ABT and chest tube drainage and improved hemostatic laboratory parameters.

It is important to stress that although Demeyere and colleagues [12] reported equivalent mean postintervention INR values at the 1-hour post–cardiopulmonary bypass (CPB) point and equivalent 24-hour chest tube drainage between groups, the comparator FFP arm required considerably more therapeutic measures to reach these targets. All patients (20 of 20) in the plasma arm, compared to only 6 of 20 in the PCC arm, required additional therapies because of failure to achieve INR target or continued bleeding following initial plasma transfusion. Specifically, the FFP arm required 19.4 L additional plasma over the 8 L (400 mL × 20 patients) initially intended as well as additional PCC infusions.

The conclusion in Arnekian and colleagues [16] that low-dose PCC significantly reduced postoperative bleeding in CPB is flawed because of important differences in baseline characteristics. The progressive increase in postoperative bleeding and mortality noted across groups was accompanied by parallel reductions in body mass index (BMI) and increases in the proportion of female patients, preoperative use of clopidogrel, CPB duration, and degree of hemodilution, all of which are important risk factors for bleeding and ABT in cardiac surgery. A similar discrepancy was notable in the retrospective comparator group in Rahe-Meyer and colleagues [14], with longer CPB duration, lower BMI, and a greater proportion of women compared to the intervention group.

An important point to make about MCF as an end point is that it is a laboratory outcome, rather than a clinical outcome. In addition, standard nephelometric and Clauss-method measurement platforms are less sensitive to HES-induced coagulation defects, whereas TEM is able to detect this specific disturbance [30]. For example, in a study by Urwyler and colleagues [31], specimens drawn from patients during major surgery were tested in parallel using standard Clauss methodology and TEM. All patients received crystalloids; 89% of

Table 4C
Study characteristics of PCCs in reversal of warfarin anticoagulation

	Reference	Funding	Design	Population	Intervention	Comparator	Outcomes
4-Factor PCC	Kalina et al (2008) [24]	No reported conflict of interested	Single center Nonrandomized Compared a prospective cohort with a historical	CT confirmed intracranial bleed due to blunt trauma on preinjury warfarin with INR >1.5	Postprotocol weight-based PCC (Proplex, Baxter) dosing + FFP + IV vitamin K 5 mg (n = 46)	Preprotocol using discretionary PCC + FFP + IV vitamin K (n = 65)	• % achieve INR ≤1.5 • Time to INR ≤1.5 • Time to OR • Safety reported but not prespecified
	Kuwashiro et al (2011) [27]	Japan Ministry of Health, Lab, and Welfare	Single center Nonrandomized Compared 2 retrospective cohorts	CT confirmed spontaneous intracerebral bleed on preinjury warfarin without INR cutoffs. Excluded infarct, tumor, vascular anomaly	PCC (Nichiyaku, Nihon Pharmaceutical) dosing at discretion of treating physician without target INR (n = 22)	No PCC given. Some received discretionary FFP + vitamin K without target INR (n = 28)	• INR trend over time • % HE on repeat CT • Function mRS • Safety not reported
	Huttner et al (2006) [26]	Not disclosed	Single center Nonrandomized Compared 3 retrospective cohorts	CT confirmed spontaneous intracerebral bleed on preinjury warfarin with INR >1.5 within 12 h of symptoms onset	PCC (Beriplex, CSL Behring) ± FFP or vitamin K (n = 31)	FFP ± vitamin K (n = 18) Vitamin K only (n = 6)	• HE >33% on repeat CT at 24 h • Function mRS • Safety not reported
3-Factcor PCC	Boulis et al (1999)* [22]	No reported conflict of interest	Single center Randomized Modified ITT Open label	CT confirmed traumatic intracranial bleed on preinjury warfarin with PT >17 s.	PCC (Konyne, Bayer) dosing based on weight and target factor level 50%; SQ vitamin K 10 mg + FFP (n = 8)	SQ vitamin K 10 mg + FFP (n = 13)	• Time to INR reversal • Rate of INR correction • Safety reported but not prespecified
	Cartmill et al (2000) [23]	Not disclosed	Single center Nonrandomized Compared a prospective cohort with a historical	Spontaneous intracerebral bleed on preinjury warfarin without INR cutoffs	PCC 50 U/kg (Factor IXa, Bio Products Lab) + IV vitamin K 10 mg (n = 6)	FFP 4 U + IV vitamin K 10 mg (n = 6)	• Pre, postinfusion INR • Time to INR reversal • Safety not reported
	Chapman et al (2011) [29]	No reported conflict of interest	Single center Nonrandomized Compared 2 retrospective cohorts	Trauma admission and/or neurosurgery consult on preinjury warfarin with INR >1.5 who were treated with vitamin K, FFP, and/or PCC	PCC 20 U/kg (Profilnine, Grifols) + discretionary FFP + vitamin K. Repeated until target INR ≤1.5 (n = 13)	Discretionary FFP + vitamin K (n = 18)	• Time to INR correction ≤1.5 • Safety reported as thromboembolic events
	Holland et al (2009) [25]	Heart and Stroke Foundation of Ontario	Single center Nonrandomized Compared a prospective cohort with a historical	Preinjury warfarin with INR >5 ± clinical evidence of bleeding Prospective cohort excluded intracranial bleed; historical included intracranial bleed	PCC (Profilnine, Grifols Biological) low dose 25 U/kg or high dose 50 U/kg with supplemental FFP (n = 40)	FFP + vitamin K (n = 42)	• % reversed to INR <3 • Safety reported but not prespecified
	Pinner et al (2010) [28]	No reported conflict of interest	Single center Nonrandomized Compares 2 retrospective cohorts	Traumatic or spontaneous intracranial bleed on preinjury warfarin with INR >1.3 treated with PCC or rVIIa	PCC weight-based dosing (Bebulin VH, Baxter Healthcare Corp) (n = 9)	rVIIa weight-based dosing (NovoNordisk) (n = 15)	• % correct to INR ≤1.3 • % HE on repeat CT • Safety reported as thrombogenic events

Intravenous (IV), hematoma expansion (HE), subcutaneous (SQ).
Boulis et al. (1999) included 2 nonrandomized cohorts that were not mentioned in the methodology: a retrospective preprotocol cohort (n = 6) and a prospective postprotocol cohort (n = 6).

patients received HES during surgery. Interestingly, if transfusion decisions had been based upon Clauss-method fibrinogen results, FIBC would be given to none of the 36 patients. However, if transfusion decisions had been based upon TEM guidance, 36% of patients would have received FIBC. This point is critical because it bespeaks the influence of methodology on transfusion practice and because nearly all of the non–warfarin reversal studies reviewed used some aspect of TEM in their treatment algorithms.

The importance of methodology is again underscored when interpreting the positive findings in the randomized controlled trial by Fenger-Eriksen and colleagues [18] that compared the effects of FIBC and saline control on MCF (a primary end point) following deliberate hemodilution with HES. Outcomes demonstrated an overall greater improvement in Δ MCF in the intervention arm; however, there were no differences in intraoperative red cell use between groups.

Huttner et al [26] and Kuwashiro et al [27] evaluated intracerebral hematoma growth in a retrospective fashion. In both studies, PCC use was associated with a reduction in hematoma growth but differed in their assessment of functional outcomes. This is likely the result of differences in definition: Huttner et al defined a poor outcome as a modified Rankin Scale (mRS) score of 4 to 6, whereas

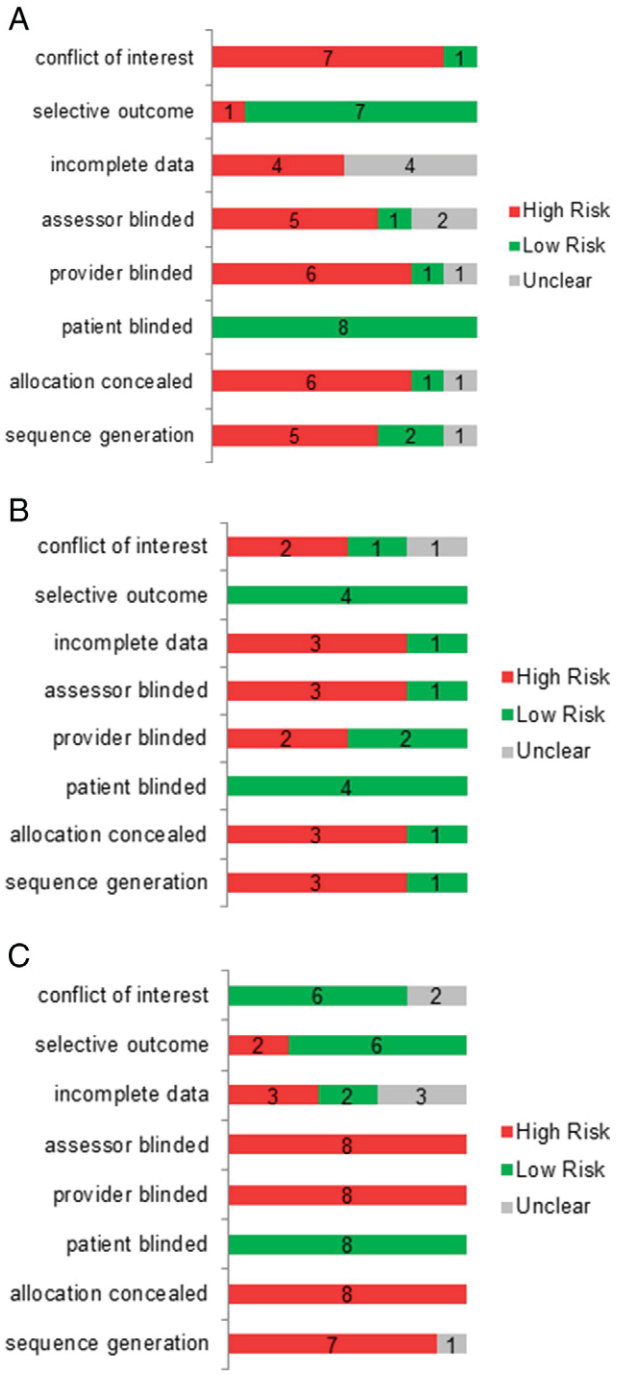

Fig. 2. A, Risk of bias of included studies for cardiac surgery. B, Risk of bias of included studies for non–cardiac surgery. C, Risk of bias of included studies for reversal of warfarin anticoagulation.

Kuwashiro et al defined it as 3 to 6. Although Kuwashiro et al reported better clinical outcomes ($P = .45$) among PCC-treated patients, it is not clear if the differences in functional outcome between groups were clinically meaningful.

Boulis et al [22] reported a major clinically significant safety issue in the FFP arm: importantly, the volume of FFP required for correction with PCC was 399 ± 271 mL compared to 2712 ± 346 mL in the FFP-only arm, leading to significant complications of volume overload in 5 of 8 patients.

Holland and colleagues [25] concluded that 3-factor PCCs do not adequately lower supratherapeutic INR; however, the authors' conclusions may be confounded by multiple factors. Although patients in both arms received vitamin K initially, the routes of administration were noticeably different. Oral, subcutaneous, and intravenous routes were used in 63%, 29%, and 8% of the PCC arm compared to 30%, 61%, and 5% in the FFP arm. Furthermore, subsequent INR measurements were drawn a mean of 11 hours in the PCC arm and 21 hours in the FFP group. A target INR less than 3 at 24 hours was the definition for adequate INR reversal; this target was successfully achieved in 55% of the PCC arm at 11 hours and in about 60% of the FFP arm at 21 hours. It is unclear whether the degree of INR reversal at 11 hours in the PCC arm was due to the initially administered vitamin K or to the PCC infusion. Regardless, based on the 11-hour INR measurement, the PCC arm received FFP; and subsequent INR measurement drawn within 3 hours achieved a success rate of 90%. Finally, the success rate of INR reversal at 21 hours in the FFP arm was equally suboptimal (62%), and this may reflect the preference for subcutaneous administration of vitamin K.

In a randomized controlled study of vitamin K monotherapy for warfarin reversal [32], patients with baseline INR ranging from 6 to 10 (similar to the study of Holland et al) demonstrated a 50% reduction by 12 hours and correction to INR less than 3 at 24 hours regardless of oral or intravenous route and without FFP or PCC administration. Furthermore, in a pharmacokinetic study of FFP (~12 mL/kg) administered to warfarin-treated participants [33], the effect of plasma on both factor VII levels and PT measurements peaked at 15 minutes and persisted only for 8 hours. Warfarin rebound effect occurred in all participants by 12 hours and required oral vitamin K for definitive correction.

An alternate interpretation is that the partial INR correction in the PCC arm at 11 hours could be due to either PCC administration or vitamin K administration, that further correction 3 hours after FFP in the PCC group was likely all due to the FFP intervention (and that warfarin rebound effect occurred in at least some of these patients thereafter), and that the suboptimal INR correction (only 60% of patients with INR <3 at 21 hours) in the FFP arm was in large part likely the result of the suboptimal route of administration (subcutaneous) used in the majority (60%) of these patients. Therefore, an important consideration during warfarin reversal is the route of administration of vitamin K. The preferred routes of administration are intravenous and oral, with the oral route demonstrating a somewhat delayed initial onset of effect compared to intravenous but similar responses by 24 hours [32]. A recent expert review [34] advised against the use of subcutaneous vitamin K because of its unpredictable and suboptimal effect.

Conclusion

Preferred primary end points are patient-related clinical outcomes, such as perioperative ABT needs, postoperative chest tube drainage, and level of functioning as measured by mRS. Less meaningful end points are laboratory parameters, such as Δ in fibrinogen, MCF, or INR, as these represent surrogate markers of clinical efficacy. Safety outcomes are difficult to estimate especially in prospective trials because of the relatively low incidence of intervention-related adverse events.

For studies involving FIBC alone or combined with PCC, the existing body of literature on the use of PCCs and FIBCs in the perioperative setting was assessed to have a high degree of methodological bias. The majority of studies using FIBC based their decision-making upon TEM results, which may be more sensitive to fibrinogen defects or deficits than Clauss-based methods and therefore may significantly influence transfusion decision.

Prospective studies, primarily in the cardiac surgery setting, appear to support a reduction in allogeneic exposures and more rapid achievement of laboratory-based hemostatic targets but were

Table 5A
Efficacy and safety outcomes for FIBCs and/or PCCs in cardiac surgery

Reference	Efficacy outcome			Safety outcome
Karlsson et al (2009) [10]	FIBC arm (n = 10)	No FIBC arm (n = 10)		1 patient in FIBC arm had subclinical PE; 1 patient in comparator arm had periop MI
	Postop chest tube drain in 12 h = 565 ± 150 mL**	830 ± 268 mL		
	Postop ABT needs = 1 of 10 patients required RBC	3 of 10		
	LIMA-LAD patency by CT angiography = 100%	100%		
	Vein graft patency by CT angiography = 16 of 17 (94%)	20 of 20 (100%)		
Lance et al (2012) [11]	FIBC arm (n = 22)	No FIBC arm (n = 21)		In FIBC arm, 1 had wound infection, 2 had septic complications, and 1 developed abdominal ischemia requiring surgical revision. In comparator arm, 3 had wound infections with 1 DVT.
	Mean MCF before FIBC = 32.2 (SD 12.4)	40 (SD 13.6)		
	Mean MCF after FIBC = 39.9 (SD 14.7)	43.4 (SD 11.1)		
	Mean Δ in MCF prepost FIBC = 7.7 *	3.4		
	17 of 22 patients achieved hemostasis	16 of 21		
Demeyere et al (2010) [12]	PCC arm (n = 20)	No PCC arm (n = 20)		3 in PCC arm experienced 4 serious adverse events unrelated to PCC (low cardiac output, left hemisyndrome, air embolism, permanent disability)
	# of patients (%) with INR ≤1.5			
	After 15 min on CPB = 7 of 16 (43.8%)**	0 of 15 (0%)		
	After 60 min on CPB = 6 of 15 (40%)	4 of 15 (26.7%)		
	6 of 20 (30%) needed additional PCC**	20 of 20 (100%) needed additional FFP ± PCC		
	Periop ABT needs = 16 patients received 33 U RBC	19 patients received 50 U PRBC		
Rahe-Meyer et al (2009) [13]	FIBC arm + ABT protocol (n = 10)	ABT protocol only (n = 5)	Off protocol (n = 42)	No immediate neurologic and cardiorespiratory complications were observed in FIBC arm or ABT protocol only arm
	Mean 24-h RBC needs = 0.5 U (SD 1.1)*	2.4 (1.1)	2.4 (2.5)	
	Mean 24-h FFP needs = 0.2 U (SD 0.6)*	4.2 (1.1)	4.5 (2.1)	
	Mean 24-h platelet needs = 0.7 U (SD 1.5)*	1.6 (0.9)	1.6 (1.7)	
	Mean 24-h postop chest tube drain = 366 mL (SD 199)*	716 (219)	793 (560)	
Rahe-Meyer et al (2009) [14]	FIBC arm (n = 6)	No FIBC arm (n = 12)		Postoperative thrombotic complications similar between groups
	Periop ABT (mean # U) = RBC 1.0*, FFP 1.0*, PC 0.5*	RBC 4.1, FFP 9.1, PC 3.2		
	# of patients not needing any periop ABT = 4 of 6 (66%)*	0 (0%)		
	Mean 24-h postop chest tube drain = 449 mL*	1093		
Solomon et al (2012) [15]	FIBC arm (n = 10)	No FIBC arm (n = 19)		No treatment-related complications were observed
	Periop ABT needs = 4 patients (40%)**	19 (100%)		
	Periop RBC (median # U) = 0 (IQR 0 to 1.8)	2 (1.5 to 3)		
	Periop FFP (median # U) = 0 (IQR 0 to 2)****	3 (3 to 4.5)		
	Periop platelets (median # U) = 0 (IQR 0 to 0)	0 (0 to 1.5)		
	Median 24-h postop chest drain = 775 mL (412, 937)	580 (375, 925)		
Arnekian et al (2012) [16]	PCC arm (n = 24)	FFP arm (n = 26)	PCC-FFP arm (n = 27)	The only thromboembolic event occurred in FFP arm with 1 patient having cerebral infarction
	Chest tube drain at 1 h = 224 ± 131 mL*	339 ± 296 mL	434 ± 398 mL	
	Chest tube drain at 24 h = 475 ± 398 mL **	667 ± 244 mL	970 ± 1122 mL	
	Reexploration = 4% **	8% **	37%	
	ABT needs = RBC 0 U (0–1)**	0 (0 to 2)	2 (0 to 3)	
Gorlinger et al (2011) [17]	Post-2009 FIBC + PCC (n = 2147)	Pre-2004 ABT only (n = 1718)		Pre-2004 vs post-2009 composite thromboembolic events 46/1441 (3.19%) vs 28/1582 (1.77%)*
	% with any ABT needs = 42.2%****	52.5%		
	% with ABT needs = RBC 40.4%****, FFP 1.1%****, PC 13%***	RBC 49.7%, FFP 19.4%, PC 10.1%		
	% with FIBC or PCC needs = FIBC 10.01%****, PCC 8.9%****	FIBC 3.73%, PCC 4.42%		

Red cell concentrate (RBC), left internal mammary artery (LIMA), left anterior descending (LAD), myocardial infarction (MI), standard deviation (SD), interquartile range (IQR).
* $P < .05$ compared between groups; for Arnekian et al (2012) compared to PCC-FFP arm.
** $P < .01$ compared between groups; for Arnekian et al (2012) compared to PCC-FFP arm.
*** $P < .005$ compared between groups.
**** $P < .001$ compared between groups.

underpowered to support firm conclusions about the risk-benefit ratio of FIBC and PCC. Instead, these studies may be thought of as feasibility studies or initial new drug studies to support future randomized, controlled, adequately powered studies.

Large retrospective studies comparing preprotocol to postprotocol implementation of concentrate-based resuscitation in the perioperative setting support a reduction in ABT, predominantly because such protocols exchange PCC and/or CRYO for FFP. Another consideration is that these studies represent a comparison of practice between single centers in which a culture of blood conservation has already been established against registry data that are representative of the wide variation in transfusion practice in various regions.

The assessment of safety outcomes was not uniform and raises concerns of underreporting. Adverse events that did occur, however, could also be attributed to underlying patient-specific factors (underlying inherited thrombophilia) or clinical circumstances (eg,. lack of pharmacologic DVT prophylaxis). The largest study reviewed by Gorlinger and colleagues [17] demonstrated no increase in mortality or thromboembolic outcomes despite an increase in use of FIBC and PCC during the postimplementation period.

In terms of warfarin reversal, PCCs more rapidly corrected INR than plasma. In the setting of intracranial hemorrhage, functional outcomes were poor regardless of reversal strategy. Efficacy of INR reversal should take into account the baseline INR, the pharmacokinetic aspects of the reversal strategy (onset and duration of effect), and the potential for INR rebound when short-acting strategies are implemented. Definitive warfarin reversal requires the utilization of vitamin K, preferably via the intravenous or oral route.

Adequately powered, methodologically sound trials would be required for more definitive conclusions to be drawn about the efficacy of PCCs and FIBC over conventional blood components for the treatment of perioperative coagulopathy in bleeding patients. Such studies would require stratification of important differences in bleeding based upon the population and surgical setting being studied for example, body surface area, preoperative anemia, and female sex in the setting of cardiac surgery. They would additionally be enhanced by attempts to objectively measure surgical and postoperative blood loss and ABT between groups. Transfusion protocols would be applied to both groups and would be driven by both clinical outcomes and point-of-care laboratory measurements.

Table 5B
Efficacy and safety outcomes for FIBCs and/or PCCs in non–cardiac surgery

Reference	Efficacy outcome		Safety outcome
Fenger-Eriksen et al (2009) [18]	FIBC arm (n = 11)	Placebo arm (n = 10)	Safety not reported
	Δ in MCF is higher (no numeric value)*	Lower (no numeric value)	
	Intraop RBC needs = 2 U (0 to 5)	2.5 (0 to 6)	
	48-h postop RBC needs = 0 U (0 to 2)*	1.5 (0 to 2)	
Nienaber (2011) [19]	FIBC + PCC arm (n = 18)	ABT only arm (n = 18)	In FIBC + PCC arm, 1 case of thrombosis within soleus muscle with subsequent paradoxical embolization. Another case of bilateral media infarct in presence of carotid artery dissection
	Median RBC needs within 6 h = 1 U (IQR 0 to 3)***	7.5 (4 to 12)	
	Median RBC needs after 24 h = 3 U (IQR 0 to 5)***	12.5 (8 to 20)	
	Median Platelet needs after 24 h = 0 U***	2 (1 to 3)	
	Median FIBC given within 6 h = 4 g (IQR 2 to 4)	N/A	
	Median FIBC given after 24 h = 4 g (IQR 2 to 4)	N/A	
	Median PCC given within 6 h = 1200 IU (IQR 1000 to 1200)	N/A	
	Median PCC given after 24 h = 1200 IU (IQR 800 to 1200)	N/A	
	N/A	Median FFP needs within 6 h = 6 U (4 to 12)	
	N/A	Median FFP needs after 24 h = 10 U (7 to 22)	
Schochl et al (2011) [20]	FIBC + PCC (n = 80)	ABT off protocol (n = 601)	Safety not reported
	Complete avoidance of RBC = 29% ****	3%	
	Total RBC = ranging from 1 to 28 U	1 to 64 U	
	% of patient given platelets = 9%****	44% (data only available for 371 of 601)	
	Median FIBC given in ER-OR = 6 g (IQR 3 to 9)	N/A	
	Median PCC given in ER-OR = 1200 IU (IQR 0 to 2400)	N/A	
	Median FIBC given postop = 6 g (IQR 3 to 10)	N/A	
	Median PCC given postop = 1200 IU (IQR 0 to 2400)	N/A	
	N/A	Median FFP in ER-OR = 6 U (IQR 4 to 10)	
	N/A	Median FFP in postop = 3 U (IQR 0 to 6)	
Theodoulou (2012) [21]	FIBC arm (n = 36)	CRYO arm (n = 64)	Safety not reported
	Median Δ in fibrinogen = 0.44 g/L	0.26 g/L	

International units (IU), not applicable (N/A), emergency room (ER), operating room (OR).
* $P < .05$ compared between groups.
** $P < .01$ compared between groups.
*** $P < .005$ compared between groups.
**** $P < .0001$ compared between groups.

Table 5C
Efficacy and safety outcomes for PCCs in reversal of warfarin anticoagulation

	Reference	Efficacy outcome			Safety outcome
4-Factor PCC	Kalina et al (2008) [24]	Postprotocol (n = 46)	Preprotocol (n = 65)		3 developed DVT in postprotocol arm
		% patients given PCC = 54.3%*	35.4%		
		Time to INR ≤1.5 = 331.3 ± 279.9 min*	737.8 ± 692		
		% achieve INR ≤1.5 = 73.2%*	50.9%		
		Time to OR = 222.6 ± 186.3 min*	351.3 ± 399.7 min		
	Kuwashiro et al (2011) [27]	PCC arm (n = 22)	No PCC arm (n = 28)		Safety not reported
		INR trend at 0 h = 2.29, 2 h = 1.17***, 24 h = 1.14***	0 h = 2.24, 2 h = 1.85, 24 h = 1.52		
		HE at any INR = 18%; INR >2 = 16%*	Any INR = 43%; INR >2 = 56%		
		Poor outcome by mRS at any INR = 45%; INR >2 = 16%*	Any INR = 71%; INR >2 = 78%		
	Huttner et al (2006) [26]	PCC arm (n = 31)	FFP arm (n = 18)	Vitamin K arm (n = 6)	Safety not reported
		HE >33% at 24 h = 19.3%**	33.3%	50%	
		Poor outcome by mRS = 78%	78%	83%	
3-Factor PCC	Boulis et al (1999) [22]	PCC arm (n = 8)	No PCC arm (n = 13)		In the comparator arm, 5 patients developed complications of fluid overload
		Time to INR reversal = 2.95 ± 0.46 h **	8.9 ± 1.51 h		
		Rate of INR correction = 0.63 ± 0.18/h **	0.18 ± 0.03/h		
	Cartmill et al (2000) [23]	PCC arm (n = 6)	No PCC arm (n = 6)		Safety not reported
		Mean pre-PCC INR = 4.86 (2.5 to 10)	5.32 (2.4 to 10)		
		Mean post-PCC INR = 1.32 (1.09 to 1.49)	2.3 (1.3 to 2.3)		
		Mean time to INR reversal = 41 min (30 to 60)	115 min (60 to 180)		

Table 5C (*continued*)

	Reference	Efficacy outcome		Safety outcome
	Chapman et al (2011) [29]	PCC arm (n = 13) Time to INR ≤1.5 = 16:59 h *	No PCC arm (n = 18) 30:03 h	In PCC arm, 2 cases of DVT (central line, protein S deficiency). In comparator arm, 1 chronic DVT
	Holland et al (2009) [25]		PCC arm (n = 40) No PCC arm (n = 42)	
		No reported adverse transfusion effects	Low dose (n = 23) reversed INR <3 in 55% at 11 h And in 89% ** 3 h after extra units of FFP given High dose (n = 17) reversed INR <3 in 43% at 11 h	% reversed INR <3 = 62% at 21 h
	And in 93% ** 3 h after extra units of FFP given			
HE on repeat CT = 11% (1/9)	Pinner et al (2010) [28]	PCC arm (n = 9) INR ≤1.3 at 6 h = 50% (3/6) 20% (3/15)	rVIIa arm (n = 15) 93% (14/15)	PCC arm = 1 PE, 1 DVT rFVIIa arm = 1 possible stroke

* $P < .05$ compared between groups.
** $P < .01$ compared between groups.
*** $P < .001$ compared between groups.

Appendix A

Table A1
Electronic search strategy in MEDLINE via PubMed

FIBC	PCC
1. fibrinogen concentrate* Filters: Publication date from 1997/07/03 to 2012/07/03; English	1. prothrombin complex concentrate* 2. hemophilia 3. #1 NOT #2 Filters: Publication date from 1997/07/03 to 20120/07/03; English

Cardiac Surgery

No study completely fulfilled the 8 predefined criteria for low risk of bias (Fig. 2A); however, the study by Karlsson et al [10] fulfilled 6 of the 8 criteria for low risk of bias but was high risk of bias for analyzing the results not with intention to treat and receiving financial support from CSL Behring. Two other randomized trials were at high risk of bias or provided inadequate information regarding methods of randomization, allocation concealment, and blinding [11,12]. Three nonrandomized studies had differences in clinically important baseline characteristics between the study arms that potentially confound the observed study effect [13,15,16]. For example, in the study by Arnekian et al (2012), women had lower BMI and so were at an increased risk of ABT requirement during CPB. No study prospectively compared FIBC with cryoprecipitate, the most directly comparable allogeneic blood component therapy. Instead, 7 of 8 studies compared FIBC to FFP alone or protocol-based ABT guideline; and 1 study compared preoperative FIBC to no hemostatic therapy [10]. Lastly, 7 of 8 studies reported financial support from CSL Behring, except for Arnekian et al [16].

Non–Cardiac Surgery

No study completely fulfilled the 8 predefined criteria for low risk of bias (Fig. 2B); however, the study by Fenger-Eriksen et al [18] fulfilled 6 of the 8 criteria for low risk of bias but was at high risk of bias for analyzing the results not with intention to treat and receiving financial support from CSL Behring. Differences in transfusion protocol [19], differences in clinically important baseline characteristics [20], and variability in the timing of fibrinogen measurement [21] between study arms potentially confound the observed study effects. Of note, only Theodoulou et al [21] directly compared FIBC with cryoprecipitate, albeit retrospectively.

Reversal of Warfarin Anticoagulation

No study completely fulfilled the 8 predefined criteria for low risk of bias. The only randomized trial in this clinical grouping was at high risk of bias for lack of allocation concealment, for unblinded providers and assessors, and for analyzing results not with intention to treat [22]. Variability in the timing of INR measurement makes the therapeutic effect of FFP, PCC, and vitamin K on warfarin reversal difficult to interpret [23,24,25,29]. Differences in clinically important baseline characteristics—baseline INR, proportion of traumatic bleeding—between study arms potentially confound the observed study effect in Pinner et al [28]. Hemostatic therapy was discretionary in all 4 retrospective studies; dosing was not guided by an institutional transfusion protocol [26,27,28,29].

Table A2
Risk of bias assessment of individual studies by clinical grouping

Reference	Sequence generation	Allocation concealment	Patients blinded	Provider blinded	Assessor blinded	Incomplete data	Selective outcomes reporting	Potential conflict(s) of interest	Reviewers' comments
Karlsson et al (2009) [10]	L	L	L	L	L	H	L	H	It is unclear how many patients were excluded based on prespecified exclusion criteria for surgical bleeding. Results were not analyzed with intention to treat Authors do not discuss if any data were missing. Study financially supported by CSL Behring.
Lance et al (2012) [11]	?	H	L	H	?	H	L	H	Randomization process not clearly described. Study population included patients across 3 major surgical subspecialties (cardiac, abdominal, and spinal column). Fibrinogen content in 4 U FFP is not comparable to 2 g of FIBC. Nine of 52 patients were excluded not based on prespecified criteria. ROTEM data missing in 11 patients. It is unclear if MCF is FIBTEM channel. Authors do not report ABT needs after intervention.
Demeyere et al (2010) [12]	L	?	L	?	?	H	L	H	Vitamin K was not used in the study. Some patients in FFP arm received more than the prespecified dose, and some even received PCC. Primary outcome was not analyzed with intention to treat. Study financially supported by SANQUIN for CAF-DCF.
Rahe-Meyer et al (2009) [13]	H	H	L	H	H	H	H	H	Authors do not clearly prespecify in their methods which groups are to be compared. Prospective portion of the study was powered to detect 30% change in MCF values. Comparator arm did not use cryoprecipitate.
Rahe-Meyer et al (2009) [14]	H	H	L	H	H	H	L	H	Comparator arm had more women (42% vs 17%) with lower BMI (23.9 vs 26.6); both are risk factors for increased ABT requirements during CPB. Authors report consecutive enrollment, but intraoperative use of RBC is clearly different between groups (FIBC arm, 1.3 U; ABT arm, 8.3 U); multiple units of plasma poor RBC induces greater dilutional coagulopathy. Comparator arm did not use cryoprecipitate. Group A had more missing data.
Solomon et al (2012) [15]	H	H	L	H	H	?	L	H	No objective criteria for diffuse bleeding. Possible selection bias as availability of ROTEM determined study arm. Comparator arm did not use cryoprecipitate. Authors do not address if any data were missing.
Arnekian et al (2012) [16]	H	H	L	H	H	?	L	L	Group III (PCC + FFP arm) had the highest SAPS II score, the lowest BMI, and the longest on-pump time, and were subject to the highest degree of hemodilution than the other 2 study groups. These may be confounding factors that explain the overall highest chest tube drainage volume and rates of reexploration for bleeding. Active bleeding is not objectively predefined. Postop ABT was not standardized. Postop fibrinogen was not measured.
Gorlinger et al (2011) [17]	H	H	L	H	H	?	L	H	POC algorithm is so complex that it is difficult to tease out the relative contributions of individual factor concentrates to reductions in ABT requirements. Authors do not address if any data were missing.
Fenger-Eriksen et al (2009) [18]	L	L	L	L	L	H	L	H	Not all patients who underwent radical cystectomy were randomized; 6 patients were excluded not based on prespecified criteria (2 protocol deviation due to excessive bleeding). After randomization, allocation concealment was kept until data collection complete. Study powered to detect 10% change in MCF; unfortunately, no numeric results for MCF provided. Comparator arm did not use cryoprecipitate; further dilutional coagulopathy induced by giving equal volume of isotonic sodium chloride solution. Authors do not report postinfusion MCF parameter.

Table A2 (*continued*)

Reference	Sequence generation	Allocation concealment	Patients blinded	Provider blinded	Assessor blinded	Incomplete data	Selective outcomes reporting	Potential conflict(s) of interest	Reviewers' comments
Nienaber et al (2011) [19]	H	H	L	H	H	L	L	H	Imbalance in number of eligible patients derived from Austria-ITB trauma registry (N = 72) compared to 2147 in TR-DGU trauma registry. Austria-ITB patients were transfused according to single-center transfusion protocol, whereas TR-DGU reflects transfusion practices across multiple centers.
Schochl et al (2011) [20]	H	H	L	H	H	H	L	?	It is unclear if fibrinogen dosing was TEM guided. Marked differences between important baseline characteristics; for example, FFP arm was more hemodynamically stable but with more head-chest traumas; FIBC-PCC arm sustained more severe abdominal injuries. Missing data (ie, fibrinogen data not available for comparator group) may influence observed effect size of intervention.
Theodoulou et al (2012) [21]	H	H	L	H	H	H	L	L	Only study comparing FIBC with cryoprecipitate. Baseline demographics from study arms are not provided. It is unclear if FIBC was infused pre-, intra-, or postoperatively. Authors do not report the dose of FIBC administered. There was a wide range of time (0.5-24 h) when fibrinogen level was rechecked after FIBC infusion. No statistical analysis performed to compare observed differences between groups.
Boulis et al (1999) [22]	?	H	L	H	H	H	L	L	Random sequence generation not described. 21 patients who met inclusion criteria were randomized; however, 8 were excluded from analysis because of withdrawal of care and/or missing blood draw. Thus, results were not based on ITT analysis. For PCC arm only, INR was checked immediately before and after PCC dose; thus, a faster rate of INR correction observed in this group may be confounded.
Cartmill et al (2000) [23]	H	H	L	H	H	L	H	?	Pilot study with small sample size (6 vs 6). 4 U FFP is not equivalent comparison to PCC 50 U/kg. *Correction time* was defined as time from start of hemostatic treatment to time laboratory results reported; FFP takes much longer to infuse. INR at 48 h no longer reflects effect of PCC and FFP but vitamin K.
Chapman et al (2011) [29]	H	H	L	H	H	L	L	L	Decisions about hemostatic therapy were entirely discretionary, not algorithm guided. Thus, PCC arm appears to be sicker with higher injury severity score (17.8 vs 9.1) and with greater need for surgical intervention (7 vs 2). Furthermore, follow-up INR check was not standardized; and this may confound time to INR correction because sicker patients were likely to have more frequent INR checks especially before surgery.
Holland et al (2009) [25]	H	H	L	H	H	?	L	L	Prospective PCC study arm excluded ICH patients because the author's intention was to reverse INR to a safer range. INR was rechecked at variable times; and thus, INR may not necessarily reflect the intervention received. For example, for low-dose PCC group, mean time to INR check for was 11.7 h (median, 6.9 h) with range 2.5 to 40 h. ~12 h post-PCC is toward end of PCC effect and beginning of vitamin K effect. Authors do not address if any data were missing.
Huttner et al (2006) [26]	H	H	L	H	H	?	L	?	Hemostatic therapy was entirely discretionary, not guided by standard algorithm. It is unclear what doses of PCC, FFP, or vitamin K were given. Authors report results derived from unspecified post hoc analysis of data. Authors do not address if any data were missing.
Kalina et al (2008) [24]	H	H	L	H	H	H	L	L	Adherence to PCC protocol was not mandatory. Patients who did receive PCC on protocol had INR rechecked in 4 h; thus, a quicker time to INR reversal may be confounded simply by virtue of being on protocol.

(*continued on next page*)

Table A2 (*continued*)

Reference	Sequence generation	Allocation concealment	Patients blinded	Provider blinded	Assessor blinded	Incomplete data	Selective outcomes reporting	Potential conflict(s) of interest	Reviewers' comments
Kuwashiro et al (2011) [27]	H	H	L	H	H	?	H	L	Hemostatic therapy was entirely discretionary, not guided by standard algorithm. Authors focused reporting on patients with INR >2 without prespecifying this subgroup analysis in the methods section. Authors do not address if any data were missing.
Pinner et al (2010) [28]	H	H	L	H	H	H	L	L	Baseline INR statistically different between rFVIIa arm (5.6; 1.6-10) compared with PCC arm (2.6; 1.3-3.4). More patients in rFVIIa arm (10 of 15) had traumatic bleeds compared to PCC arm (3 of 9). There was no standard dosing protocol for either factor concentrate. No. of missing INR data may be confounded: in PCC, 3 of 9 had missing 6-h postinfusion INR level; in rFVIIa, 1 of 15 had missing INR level at 6 h.

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