3-Factor versus 4-Factor Prothrombin Complex Concentrates for the Reversal of Vitamin K Antagonist-Associated Coagulopathy: A Systematic Review and Meta-analysis

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Abstract

Long-term anticoagulation is used worldwide to prevent or treat thrombotic events. Anticoagulant therapy using vitamin K antagonists (VKAs) is well established; however, anticoagulants carry an increased risk of potentially life-threatening bleeding. In cases of bleeding or need for surgery, patients require careful management, balancing the need for rapid anticoagulant reversal with risk of thromboembolic events. Prothrombin complex concentrates (PCCs) replenish clotting factors and reverse VKA-associated coagulopathy. Two forms of PCC, 3-factor (3F-PCC) and 4-factor (4F-PCC), are available. Using PRISMA methodology, we systematically reviewed whether 4F-PCC is superior to 3F-PCC for the reversal of VKA-associated coagulopathy. Of the 392 articles identified, 48 full texts were reviewed, with 11 articles identified using criteria based on the PICOS format. Data were captured from 1,155 patients: 3F-PCC, $n = 651$; 4F-PCC, $n = 504$. ROBINS-I was used to assess bias. Nine studies showed international normalized ratio (INR) normalization to a predefined goal, ranging from ≤ 1.5 to ≤ 1.3, following PCC treatment. Meta-analysis of the data showed that 4F-PCC was favorable compared with 3F-PCC overall (odds ratio [OR]: 3.50; 95% confidence interval [CI]: 1.88–6.52, $p < 0.0001$) and for patients with a goal INR of ≤ 1.5 or ≤ 1.3 (OR: 3.45; 95% CI: 1.42–8.39, $p = 0.006$; OR: 3.25; 95% CI: 1.30–8.13, $p = 0.01$, respectively). However, heterogeneity was substantial ($I^2 = 62\%$, $I^2 = 70\%$, $I^2 = 64\%$). Neither a significant difference in mortality (OR: 0.72; 95% CI: 0.42–1.24, $p = 0.23$) nor in thromboembolisms was reported. These data suggest that 4F-PCC is better suited than 3F-PCC for the treatment of patients with VKA-associated coagulopathy, but further work is required for a definitive recommendation.

Keywords
► anticoagulants
► coagulopathy
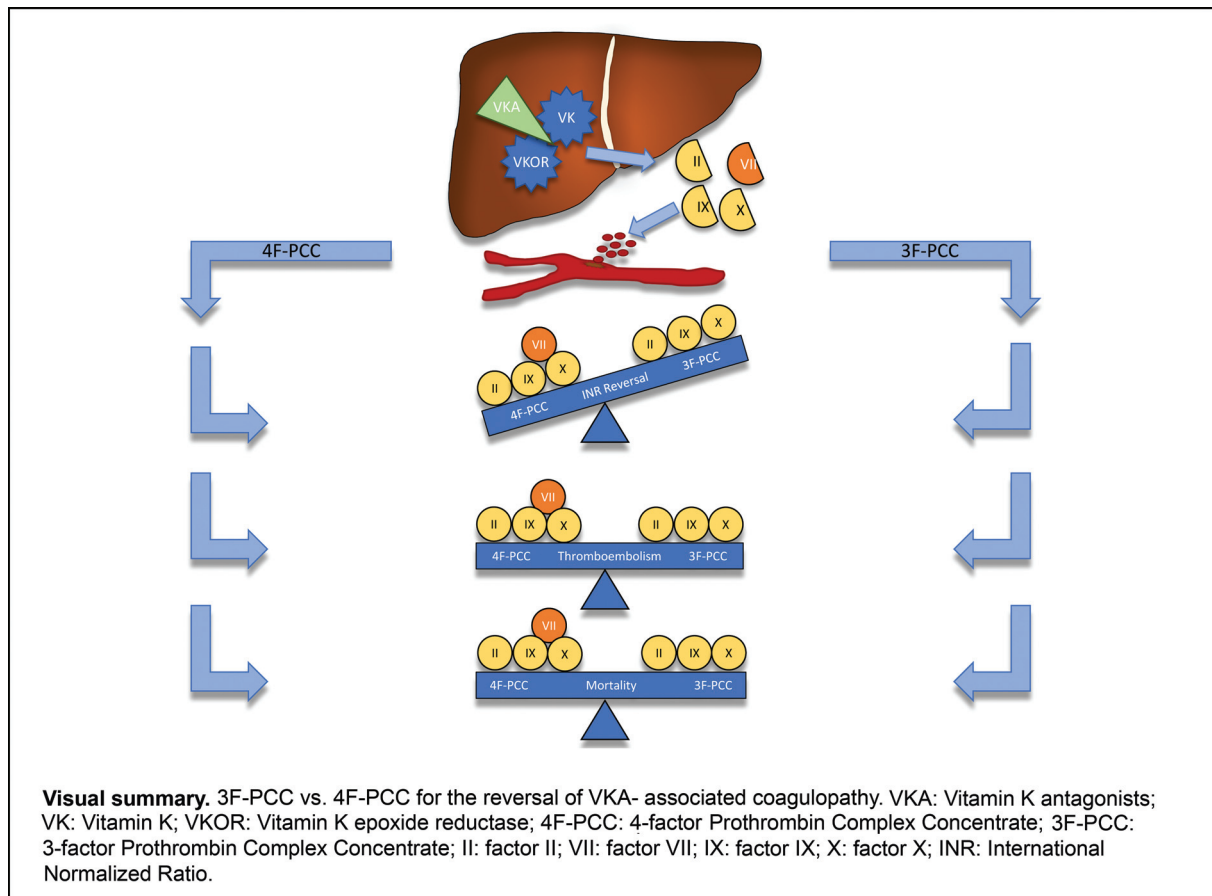► prothrombin complex concentrates
► vitamin K antagonists

Visual summary. 3F-PCC vs. 4F-PCC for the reversal of VKA- associated coagulopathy. VKA: Vitamin K antagonists; VK: Vitamin K; VKOR: Vitamin K epoxide reductase; 4F-PCC: 4-factor Prothrombin Complex Concentrate; 3F-PCC: 3-factor Prothrombin Complex Concentrate; II: factor II; VII: factor VII; IX: factor IX; X: factor X; INR: International Normalized Ratio.

Introduction

Long-term anticoagulation is used worldwide to treat thrombotic events such as deep vein thrombosis and to prevent embolisms such as stroke from atrial fibrillation.[1] Most patients take oral anticoagulants that either directly inhibit coagulation factors (direct oral anticoagulants [DOACs]) or that inhibit the formation of vitamin K-dependent coagulation factors II, VII, IX, and X (vitamin K antagonists [VKAs]).[2] Although the use of newer DOACs is increasing, VKAs are often preferred based on comorbidities, the reason for anticoagulation and availability.[1]

By its very nature, all treatments with anticoagulants are associated with an increased risk of bleeding, with the risk of major bleeding for VKA therapy reported to be around 4 to 7% per patient-year.[3–6] Bleeding in patients with coagulopathy is potentially life-threatening and can lead to severe disability. In cases of planned interventions, VKA medication can be paused or vitamin K can be substituted as clinically needed. However, some conditions such as life-threatening bleeding or need for immediate surgery may require reversal of VKA therapy while at the same time balancing the risks of thromboembolic events.[1] While direct antagonists for DOAC are available, rapid reversal of coagulopathy associated with VKA relies on substitution of the affected clotting factors. In practice, this can be achieved using fresh frozen plasma (FFP) or prothrombin complex concentrates (PCCs).[7]

PCCs are plasma-derived mixtures of clotting factors II, VII, IX, and X in varying concentrations. Dosage is typically defined by the amount of factor IX in International Units (IU). Depending on the amount of factor VII, PCC can be categorized as either 3-factor PCC (3F-PCC) or 4-factor PCC (4F-PCC).[8] ►Table 1 shows the composition of different products.

A systematic review by Chai-Adisaksopha et al analyzing the data of 2,114 patients in 13 studies has already demonstrated PCC to be superior to FFP for the reversal of VKA-associated coagulopathy.[9] Pathophysiological considerations suggest 4F-PCC to be more effective in comparison to 3F-PCC for the reversal of VKA-associated coagulopathy and some consensus guidelines recommend its preferred use.[10,11] However, at present, there are only limited empirical data to support this practice.

In this systematic review and meta-analysis, we investigated whether 4F-PCC is superior to 3F-PCC for the reversal of VKA-associated coagulopathy.

Methods

Search Strategy

The search strategy was constructed following recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline.[12] A search of five electronic databases (Medline, Cochrane Library, Web of Science, ClinicalTrials.gov, and EU Clinical Trials Register) from inception to February 18, 2022 was

Table 1 Concentration (in international units) of coagulation factors per 500 unit PCC, 3-factor (3F), and 4-factor (4F)

	Factor II	Factor VII	Factor IX	Factor X	Protein C	Protein S	Heparin (IU/IU FIX)	Antithrombin
Bebulin[11] (3F, discontinued in 2018)	500	< 25	500	500			<0.15	
Profiline SD (3F)[43]	≤750	≤ 175	500	≤500			0	
Beriplex (4F)[44]	400–960	200–500	400–620	440–1,200	300–900	240–760	0.2–0.5	5–15
Octaplex (4F)[42]	280–760	180–480	500	360–600	260–620	240–640	0.2–0.5	0
Cofact (4F)[42]	280–700	140–400	500	280–700	22–780	20–160	0	<0.6 IU/mL

Abbreviations: FIX, factor IX; IU, international units.

conducted. Search terms were ""PCC" AND "vitamin K"" and ""PCC" AND "3-factor" AND "4-factor"" and no language restrictions were applied. Furthermore, the references of papers included in full-text screening were searched for other studies eligible for inclusion.

The inclusion criteria were constructed around the PICOS tool from the Cochrane Handbook for Systematic Reviews of Interventions.[13] Studies were included if patients with VKA-associated coagulopathy (P) were treated with either 4F-PCC (Intervention, I) or 3F-PCC (Control, C). Outcomes (O) were reversal of anticoagulation measured using international normalized ratio (INR), mortality, thromboembolisms (TEs), and transfusion of further blood products. All study types (S) were included. Two reviewers (D.P. and F.R.) screened titles and abstracts. Cases of doubt about inclusion of full-text screened papers were resolved by discussion with a third reviewer (O.G.).

Study quality was evaluated by two reviewers (O.G. and D.P.) using the ROBINS-I assessment tool (Risk Of Bias In Non-randomized Studies of Interventions).[14] Because of the small number of studies meeting inclusion criteria, a formal assessment of the risk of publication bias was not performed.

Statistical Analysis

For dichotomous outcomes including both-armed zero-event studies, risk difference (RD) with 95% confidence intervals (CIs) was chosen as an effect measure. For all other dichotomous outcomes, the inverse-variance-weighted odds ratio (OR) with 95% CI was determined. For continuous outcomes, mean difference with 95% CI was calculated.

Heterogeneity between pooled studies was evaluated using the I^2 statistic.[15] Heterogeneity was considered as low when I^2 was ≤35%, moderate when I^2 was 36 to 60%, and substantial when I^2 was >60%.

A random-effects model was used for all analyses. If only a median value was reported, the mean and standard deviation (SD) were calculated using the formulas described by Hozo et al and Wan et al.[16,17] If only mean difference without SD was reported, SD was calculated via the p-value and sample size, as suggested in the Cochrane Handbook.[13] Results were considered statistically significant if the p-value was ≤0.05. Results were rounded to the second decimal place. Statistical analysis was conducted using Review Manager 5.4 and statistical software R 3.6.3 including the pwr package.

Results

Studies and Patients

In total, 425 articles were identified through the electronic search strategy. Review of references and expert recommendations identified a further 27 articles. After the removal of duplicates, 392 articles were screened by title and abstract. Overall, 48 articles were retained for full-text review. Of these, a total of 11 studies met the inclusion criteria, all of which were retrospective cohort studies.[18–28] Three of these studies either compared PCC with other treatments (Wanek et al), or were for more than one indication (Mangram et al, Mohan et al), and only reported data on the comparison of 3F-PCC versus 4F-PCC for the reversal of VKA-associated coagulopathy in subgroup analyses.[24,26,28] The study selection process is presented in ►**Fig. 1**. In total, the data of 1,155 patients were included: 651 in the 3F-PCC group, and 504 in the 4F-PCC group. Characteristics of the included studies are summarized in ►**Table 2**.

Risk of Bias

The detailed risk of bias (RoB) assessment is presented in ►**Table 3**. All studies had at least one serious RoB due to
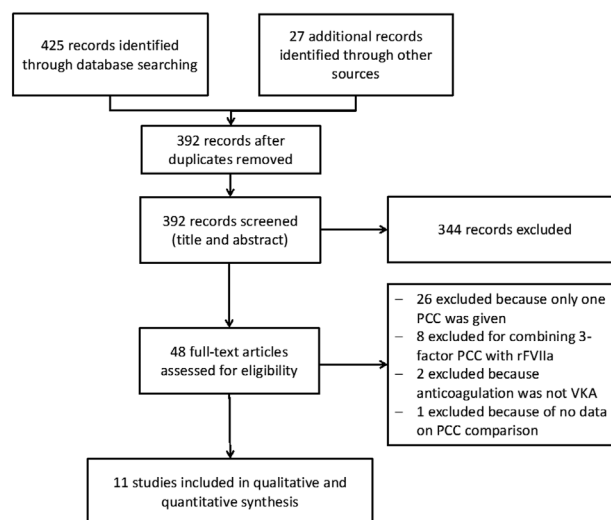

Fig. 1 Flow chart describing the study selection process. PCC, prothrombin complex concentrate; rFVIIa, activated recombinant factor VII; VKA, vitamin K antagonist.

Table 2 Characteristics of included studies

	Number of patients	PCC used	Indication for reversal of anticoagulation	Intervention groups	PCC dose (units/kg)	Baseline INR	Time to repeat INR	Recruiting centers	Study period	Outcomes included in synthesis
Voils et al, 2015	165	Profiline vs. Kcentra	Intracranial hemorrhage (60%) Gastrointestinal hemorrhage (10.30%) Other (29.70%)	3F-PCC vs. 4F-PCC	3F-PCC: 28 (25–31)[a] 4F-PCC: 27 (24–31)[a]	3F-PCC: 2.5 (2.0–3.2)[a] 4F-PCC: 2.4 (2.0–4.2)[a]	All measurements within 30 minutes	Single center (United States)	12/2011–7/2014	Thromboembolisms In-hospital mortality Goal INR ≤ 1.5 Mean change in INR
Al-Majzoub et al, 2016	53	Profiline Kcentra	Intracranial hemorrhage (73.58%) Gastrointestinal hemorrhage (16.98%) Other hemorrhage (9.43%)	3F-PCC vs. 4F-PCC	3F-PCC: 25.5 (4.3)[b] 4F-PCC: 27.9 (6.9)[b]	3F-PCC: 2.3 (0.6)[b] 4F-PCC: 3 (1.5)[b]	3F-PCC: 5 h (7.4 h)[b] 4F-PCC: 3.7 h (4 h)[b]	Brigham and Women's Hospital, Boston (United States)	3F- PCC: 8/2012–1/2013 4F-PCC: 8/2013–1/2014	Thromboembolisms In-hospital mortality Goal INR ≤ 1.3 Mean change in INR Mean post-PCC INR
Jones et al, 2016	148	Bebulin vs. Kcentra	Intracranial hemorrhage (81.08%) Gastrointestinal hemorrhage (8.78%) Other (10.14%)	3F-PCC vs. 4F-PCC	3F-PCC: 30.6 (28.2–32.3)[a] 4F-PCC: 26.3 (24.7–34.3)[a]	3F-PCC: 2.6 (2.2–3.5)[a] 4F-PCC: 3.0 (2.2–4.6)[a]	3F-PCC: 48.59 minutes (31.00–91.00 minutes)[a] 4F-PCC: 23.40 minutes (15.33–90.00 minutes)[a]	3F-PCC: Methodist University Hospital Memphis (United States) 4F-PCC: University of Florida Health, University of Kentucky Health-Care, Temple University Hospital (United States)	Date of discharge: 01.01.2012–15.04.2015	Thromboembolisms In-hospital mortality Goal INR ≤ 1.4 Mean post-PCC INR
Mangram et al, 2016	61 (plus 3 treated with rivaroxaban, 1 in 3F-, 2 in 4F-group)	Bebulin vs. Kcentra	Trauma patients (100%)	3F-PCC vs. 4F-PCC for reversal of VKA or rivaroxaban	3F-PCC: 29 (9)[b], 2nd dose for 9 (all 9 treated with VKA, 20%) 4F-PCC: 26 (6)[b] Dosing for entire cohort including patients treated with rivaroxaban	(Including patients treated with rivaroxaban) 3F-PCC: 3.1 (2.3)[b] 4F-PCC: 3.4 (3.7)[b]	(Including patients treated with rivaroxaban) 3F-PCC: 3 h (0.6–16.5 h) 4F-PCC: 4.2 h (0.6–18.9 h) (not specified whether median with IQR or range)	1 level-I trauma center, 1 level-III trauma center (United States)	1/2010–10/2014	Goal INR ≤ 1.4
DeAngelo et al, 2018	89	Profiline vs. Kcentra	Surgery (47.19%) Intracranial hemorrhage (34.83%) Other bleeding locations (17.98%)	3F-PCC vs. 4F-PCC	3F-PCC: 25 (23–27)[a], 2nd dose for 10 (17.54%): 24 (12–28)[a] 4F-PCC: 23 (20–27)[a] 2nd dose for 5 (15.63%): 10 (10–10)[a]	3F-PCC: 2.6 (2.2–3.7)[a] 4F-PCC: 2.6 (2.0–3.4)[a]	Number of patients with repeat INR within 6 hours: 3F-PCC: 50/57 4F-PCC: 31/32	2 tertiary care centers affiliated with the University of Arizona (United States)	2/2014–8/2015 (change from 3F- PCC to 4F-PCC in early 2015)	Thromboembolisms In-hospital mortality Goal INR ≤ 1.5
Fischer et al, 2018	103	Profiline vs. Kcentra	Intracranial hemorrhage (100%)	3F-PCC vs. 4F-PCC	3F-PCC: 26 (20–41)[a], 2nd dose for 5 (12.5%) 4F-PCC: 25 (23–29)[a], 2nd dose for 3 (4.76%)	3F-PCC: 2.8 (2.3–3.7)[a] 4F-PCC: 2.6 (2.2–3.1)[a]	n/a	Intermountain Health Care (System of 22 hospitals, United States)	01.10.2013–31.08.2015 (Switch to 4F-PCC in 2014)	Thromboembolisms In-hospital mortality Mean post-PCC INR
Kuroski and Young, 2017	137 (6 in each group without follow-up INR)	Bebulin vs. Kcentra	Intracranial hemorrhage (74.45%) Gastrointestinal	3F-PCC vs. 4F-PCC	3F-PCC: 28.9 (22.5–40.1)[c] 4F-PCC: 25 (12–50)[c]	3F-PCC: 3.15 (1.6–19)[c] 4F-PCC: 3.1 (2–19)[c]	Only reported for those with repeat INR within 8 hours: 3F-PCC: 191 minutes	Allegheny General Hospital, Pittsburgh (United States)	3F- PCC: 01.01.2013–31.05.2014 4F-PCC:	Thromboembolisms In-hospital mortality Goal INR ≤ 1.5

(Continued)

Table 2 (Continued)

	Number of patients	PCC used	Indication for reversal of anticoagulation	Intervention groups	PCC dose (units/kg)	Baseline INR	Time to repeat INR	Recruiting centers	Study period	Outcomes included in synthesis
			hemorrhage (4.38%) Surgery (2.19%) Other (18.98%)			(laboratory maximum: 19)	(195 minutes)[b] 4F-PCC: 169 minutes (230 minutes)[b]		01.06.2014–15.09.2015	Goal INR ≤ 1.3 Mean post-PCC INR
Mohan et al, 2018	128	Bebulin vs. Kcentra	Intracranial hemorrhage (35.16%) Gastrointestinal hemorrhage (25.78%) Other (39.06%)	3F-PCC vs. 4F-PCC for elevated INR[d]	3F-PCC: 40.99 (18.00)[b] 4F-PCC: 32.22 (11.07)[b]	3F-PCC: 4.64 (2.88)[b] 4F-PCC: 4.54 (3.45)[b]	Reported for entire cohort: 3 h (median)	1 public and 1 private hospital (United States)	01.01.2012–01.07.2015	Thromboembolisms Mean change in INR Mean post-PCC INR
Holt et al, 2018	134	n/a	Intracranial hemorrhage (52.99%) Gastrointestinal hemorrhage (14.18%) Other bleeding locations (32.84%)	3F-PCC vs. 4F-PCC	3F-PCC: 24.6 (9.3)[b], 2nd dose for 3 patients 4F-PCC: 36.3 (12.8)[b]	3F-PCC: 3.61 (2.3)[b] 4F-PCC: 6.87 (2.3)[b] (values as described in text, SD different in Table of Study data)	3F-PCC: 3.8h (0.12 h)[b] 4F-PCC: 3.3h (0.10 h)[b]	5 hospitals (United States)	5/2011–9/2014	Thromboembolisms In-hospital mortality Goal INR ≤ 1.5 Goal INR ≤ 1.3 Mean post-PCC INR
Wanek et al, 2019	57	Profiline vs. Kcentra	Heart transplantation (100%)	PCC vs. historical control without PCC[d]	3F-PCC: 19.2 (6.4)[b], 2nd dose for 34 patients, further doses for 12 patients 4F-PCC: 14.2 (5.4)[b], 2nd dose for 2 patients	Reported only for entire cohort: 2.44 (0.57)[b]	n/a	Single center (United States)	7/2013–12/2016 (4F-PCC starting in 12/2015)	Thromboembolisms Goal INR ≤ 1.5
Margraf et al, 2020	80	Profiline vs. Kcentra	Intracranial hemorrhage (62.5%) Gastrointestinal hemorrhage (15%) Other bleeding locations (22.5%)	3F-PCC vs. 4F-PCC	3F-PCC: 21.5 (20.4–25.9)[a] 4F-PCC: 29.3 (25.9–37.3)[a] (only patients receiving 20–50 units/kg included)	3F-PCC: 2.8 (2.1–4.1)[a] 4F-PCC: 3.7 (2.6–4.9)[a]	3F-PCC: 215 minutes (133.0–326.0 minutes)[a] 4F-PCC: 296 minutes (241.0–483.0 minutes)[a]	North Memorial Medical Center, Robbinsdale (United States)	29.08.2007–30.06.2014	Thromboembolisms In-hospital mortality Goal INR ≤ 1.5 Mean change in INR Mean post-PCC INR

Abbreviations: INR, international normalized ratio; PCC, prothrombin complex concentrate; VKA, vitamin K antagonist.
[a]Median with IQR (interquartile range).
[b]Mean, SD (standard deviation).
[c]Median with range.
[d]3F-PCC versus 4F-PCC for VKA reversal in subgroup analysis.

Table 3 Risk of bias (RoB) assessment

	Voils 2015	Al-Majzoub 2016	Jones 2016	Mangram 2016	DeAngelo 2018	Fischer 2018	Kuroski 2017	Mohan 2018	Wanek 2019	Holt 2018	Margraf 2020
Bias due to confounding	++	++	++	++	++	++	++	+++	++	++	++
Bias in selection of participants	−	−	−	−	−	−	−	−	−	−	−
Bias due to classification of interventions	−	−	−	−	−	−	−	−	−	−	−
Bias due to deviation from intended interventions	+	+	+	+	+	+	+	++	+	+	+
Bias in measurements of outcome	−	−	−	−	−	−	−	−	−	−	−
Bias due to missing data	−	−	+	−	+	−	−	−	−	−	−
Bias in selection of the reported result	+	+	+	+	+	+	+	+	+	+	+

Note: "−": low RoB, "+": moderate RoB, "++": serious RoB, "+++": critical RoB.

confounding by transfusion of FFP and other blood products. Two studies, Wanek et al and Mohan et al, did not specify how many patients in each PCC subgroup received FFP.[26,28] In the study by Wanek et al, 94.74% of all patients received FFP with the possible difference between groups being considered to pose a serious RoB, while the RoB due to confounding for the study by Mohan et al was considered to pose a critical risk as 21.88% of all patients received FFP.[26,28] Mangram et al reported information about co-administration of blood products for the entire cohort, including patients treated with rivaroxaban.[24] However, as 13.04% of patients in the 3F-PCC group received a mean of 0.4 units of FFP and no patients in the 4F-PCC group received FFP before measuring INR, the risk of confounding was considered serious but not critical.[24] None of the studies followed a preregistered protocol concerning the selection of reported results. Three studies, DeAngelo et al, Jones et al, and Holt et al, showed moderate RoB due to missing patient data.[19,21,22] The RoB assessment was the same for all outcomes.

International Normalized Ratio Reversal

Nine studies reported on the number of patients in whom the predefined goal INR was reached. Seven studies reported INR at either first control (after PCC therapy) or within a predetermined timespan after administration of PCC. Four studies reported on the change from pre- to post-PCC INR.

The predefined goal INR was not identical in all studies, ranging from ≤ 1.5 to ≤ 1.3. Jones et al reported on a goal INR of ≤ 1.4, while Mangram et al reported on a goal INR of < 1.5. The data from these studies were pooled as the observed difference between INR values was considered clinically irrelevant by the authors.[22,24]

Kuroski and Young provided data for the goal INR of ≤ 1.5 for all included patients and for the goal INR of ≤ 1.3 for a subgroup excluding five patients from the 4F-PCC and four patients from the 3F-PCC group whose follow-up INR was not measured within 8 hours of PCC administration.[23] Holt et al reported a goal INR of ≤ 1.3 for all patients and a goal INR of ≤ 1.5 for a subgroup excluding four patients from the 4F-PCC group whose weight at admission was not recorded.[21]

►**Fig. 2(A,B)** shows the number of patients to reach the goal INR in each of the studies. 4F-PCC was shown to be favorable in comparison with 3F-PCC for patients with a goal INR ranging from ≤ 1.5 to ≤ 1.3. A statistically significant difference between patients receiving 4F-PCC and 3F-PCC overall (►**Fig. 2A**; OR: 3.50; 95% CI: 1.88–6.52, $p < 0.0001$) and for patients with a goal INR of ≤ 1.5 and ≤ 1.3 was observed (►**Fig. 2B**; OR: 3.45; 95% CI: 1.42–8.39, $p = 0.006$ and OR: 3.25; 95% CI: 1.30–8.13, $p = 0.01$, respectively). This difference was not statistically significant for the subgroup of patients with a goal of INR ≤ 1.4 (OR: 2.30; 95% CI: 0.94–5.65, $p = 0.07$). Heterogeneity overall and in the INR ≤ 1.5 and INR ≤ 1.3 subgroups was substantial ($I^2 = 62\%$, $I^2 = 70\%$, and $I^2 = 64\%$, respectively). A sensitivity analysis, excluding the data from the study by Wanek et al due to unclear co-medication with FFP,[28] was performed. The sensitivity analysis showed no relevant difference in outcome in the INR ≤ 1.5 subgroup.

Fig. 2 (A) Number of patients reaching goal INR; studies in order of descending ratio of 3F-PCC group patients/4F-PCC group patients who received FFP (prior to control INR if reported). Inclusion of data for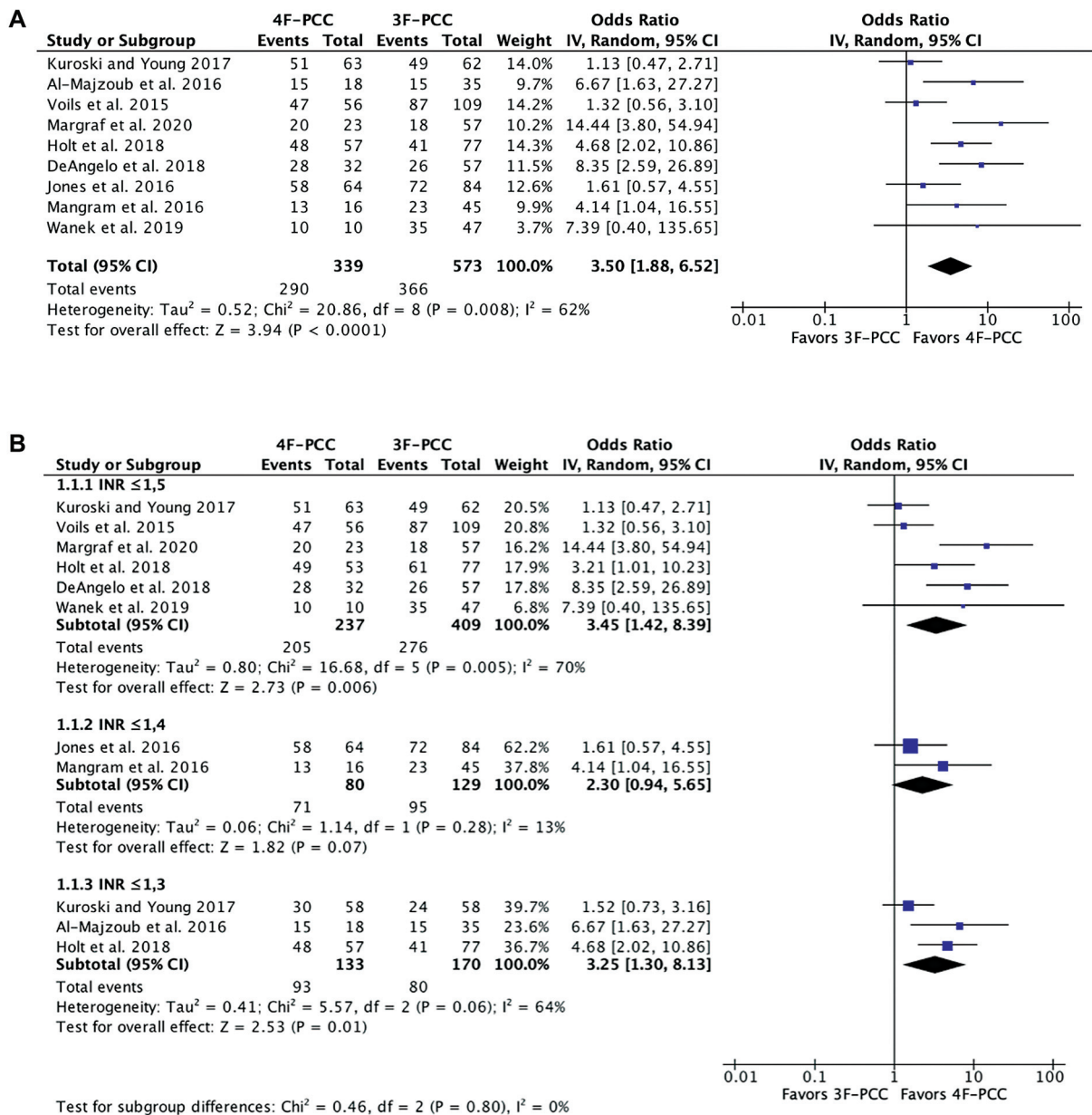 primary goal INR from studies reporting on more than one goal INR. (B) Number of patients reaching goal INR; studies in order of descending ratio of 3F-PCC group patients/4F-PCC group patients who received FFP (prior to control INR if reported). Inclusion of subgroup data from studies reporting on more than one goal INR. CI, confidence interval; FFP, fresh frozen plasma; INR, international normalized ratio; PCC, prothrombin complex concentrate.

Further to this, four studies reported mean change in INR (►**Fig. 3**). These studies showed a statistically significant pooled mean difference of 0.86 (95% CI: 0.43–1.28, $p < 0.0001$) favoring 4F-PCC over 3F-PCC.

Additionally, seven studies reported the INR after PCC administration: INR after administration of 4F-PCC was −0.21 (95% CI: −0.31, −0.11, $p < 0.0001$) lower compared with the 3F-PCC group. Heterogeneity between studies was substantial ($I^2 = 87\%$), but six out of the seven studies reporting on mean post-PCC INR reached statistical significance (►**Fig. 4**).

Mortality

All studies reported in-hospital mortality. However, the study by Mangram et al included patients on treatment with rivaroxaban and did not report mortality for the subgroup of patients treated with VKA. In that study, the mortality of the entire cohort was 4.35% (3F-PCC) and 11.11% (4F-PCC).[24] The studies by Wanek et al and Mohan et al reported mortality only for the entire PCC group.[26,28] The pooled data from the remaining eight studies showed no statistically significant difference between patients treated with 4F-PCC (OR: 0.72; 95% CI: 0.42–1.24, $p = 0.23$; ►**Fig. 5**).

Study or Subgroup	4F–PCC Mean	SD	Total	3F–PCC Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Al–Majzoub et al. 2016	1.8	1.5	18	0.9	0.5	35	35.3%	0.90 [0.19, 1.61]
Voils et al. 2015 (1)	2.2	3.44	56	1.4	3.1	109	15.6%	0.80 [−0.27, 1.87]
Margraf et al. 2020 (2)	2.27	1.66	23	1.23	1.06	57	33.4%	1.04 [0.31, 1.77]
Mohan et al. 2017	3.23	3.48	96	2.8	2.33	32	15.8%	0.43 [−0.64, 1.50]
Total (95% CI)			**193**			**233**	**100.0%**	**0.86 [0.43, 1.28]**

Heterogeneity: Tau² = 0.00; Chi² = 0.88, df = 3 (P = 0.83); I² = 0%
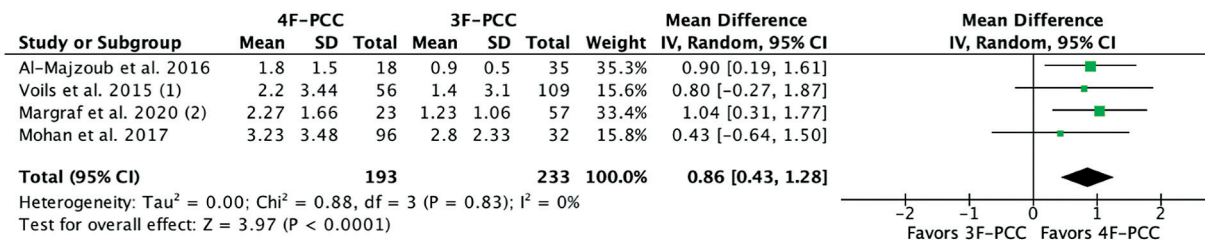Test for overall effect: Z = 3.97 (P < 0.0001)

Fig. 3 Mean change in INR (absolute value); studies in order of descending ratio of 3F-PCC group patients/4F-PCC group patients who received FFP (prior to control INR if reported). (1) SD calculated using *p*-value; (2) mean and SD calculated from median and IQR. CI, confidence interval; FFP, fresh frozen plasma; INR, international normalized ratio; IQR, interquartile range; PCC, prothrombin complex concentrate; SD, standard deviation.
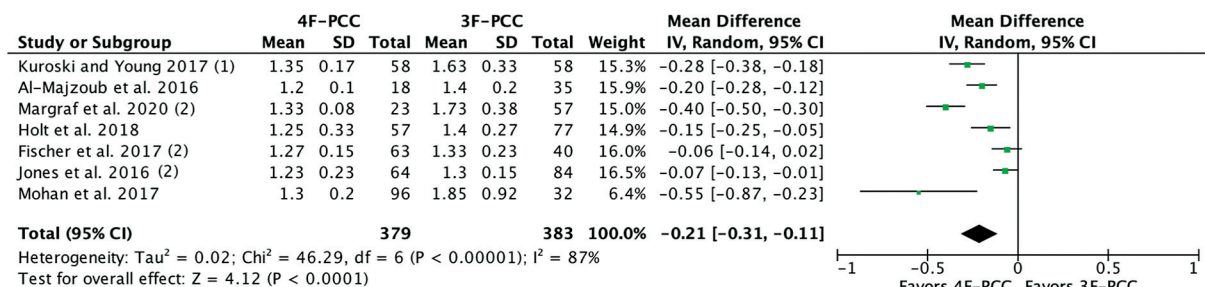
Study or Subgroup	4F–PCC Mean	SD	Total	3F–PCC Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kuroski and Young 2017 (1)	1.35	0.17	58	1.63	0.33	58	15.3%	−0.28 [−0.38, −0.18]
Al–Majzoub et al. 2016	1.2	0.1	18	1.4	0.2	35	15.9%	−0.20 [−0.28, −0.12]
Margraf et al. 2020 (2)	1.33	0.08	23	1.73	0.38	57	15.0%	−0.40 [−0.50, −0.30]
Holt et al. 2018	1.25	0.33	57	1.4	0.27	77	14.9%	−0.15 [−0.25, −0.05]
Fischer et al. 2017 (2)	1.27	0.15	63	1.33	0.23	40	16.0%	−0.06 [−0.14, 0.02]
Jones et al. 2016 (2)	1.23	0.23	64	1.3	0.15	84	16.5%	−0.07 [−0.13, −0.01]
Mohan et al. 2017	1.3	0.2	96	1.85	0.92	32	6.4%	−0.55 [−0.87, −0.23]
Total (95% CI)			**379**			**383**	**100.0%**	**−0.21 [−0.31, −0.11]**

Heterogeneity: Tau² = 0.02; Chi² = 46.29, df = 6 (P < 0.00001); I² = 87%
Test for overall effect: Z = 4.12 (P < 0.0001)

Fig. 4 Mean post-PCC INR; studies in order of descending ratio of 3F-PCC group patients/4F-PCC group patients who received FFP (prior to control INR if reported). (1) Mean and SD calculated from median and range; (2) mean and SD calculated from median and IQR. CI, confidence interval; FFP, fresh frozen plasma; INR, international normalized ratio; IQR, interquartile range; PCC, prothrombin complex concentrate; SD, standard deviation.
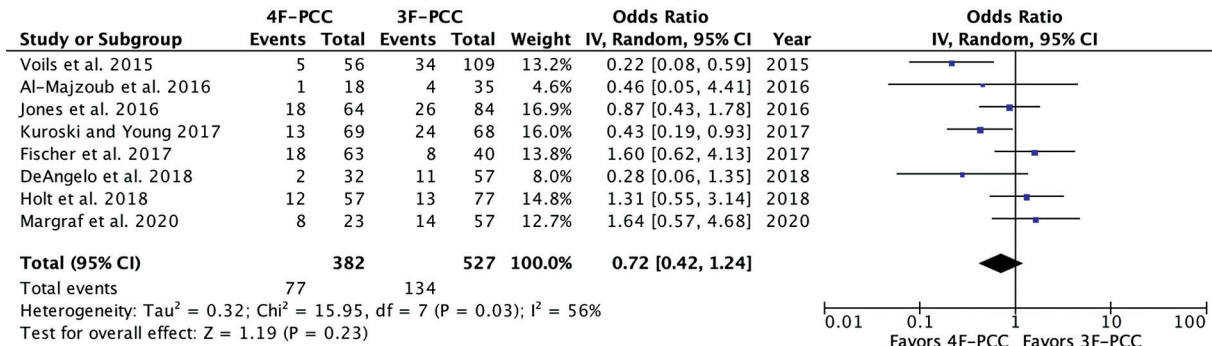
Study or Subgroup	4F–PCC Events	Total	3F–PCC Events	Total	Weight	Odds Ratio IV, Random, 95% CI	Year
Voils et al. 2015	5	56	34	109	13.2%	0.22 [0.08, 0.59]	2015
Al–Majzoub et al. 2016	1	18	4	35	4.6%	0.46 [0.05, 4.41]	2016
Jones et al. 2016	18	64	26	84	16.9%	0.87 [0.43, 1.78]	2016
Kuroski and Young 2017	13	69	24	68	16.0%	0.43 [0.19, 0.93]	2017
Fischer et al. 2017	18	63	8	40	13.8%	1.60 [0.62, 4.13]	2017
DeAngelo et al. 2018	2	32	11	57	8.0%	0.28 [0.06, 1.35]	2018
Holt et al. 2018	12	57	13	77	14.8%	1.31 [0.55, 3.14]	2018
Margraf et al. 2020	8	23	14	57	12.7%	1.64 [0.57, 4.68]	2020
Total (95% CI)		**382**		**527**	**100.0%**	**0.72 [0.42, 1.24]**	
Total events	77		134				

Heterogeneity: Tau² = 0.32; Chi² = 15.95, df = 7 (P = 0.03); I² = 56%
Test for overall effect: Z = 1.19 (P = 0.23)

Fig. 5 Mortality. CI, confidence interval; PCC, prothrombin complex concentrate.

Thromboembolisms

All 11 studies reported the number of TEs. The study by Mangram et al reported data for the entire cohort, with seven events in the 3F-PCC group and zero in the 4F-PCC group (15.22 vs. 0%, *p* = 0.177).[24] Pooled data from the remaining 10 studies did not show a statistically significant RD between groups (RD: 0.01; 95% CI: −0.01, 0.03, *p* = 0.30; ►**Fig. 6**). Furthermore, none of these studies individually reached statistical significance.

Transfusion of Blood Products

►**Table 4** summarizes the co-administration of blood products and other hemostatic agents. The number of patients receiving FFP varied between studies and groups, with some centers adopting local protocols recommending the co-administration of FFP, while in other centers the decision was left to the physicians.[18,23,27] Wanek et al, Mohan et al and Mangram et al reported transfusion of blood products for the entire cohort and not by subgroup.[24,26,28] In only one study, Jones et al, did patients in the 4F-PCC group receive more FFP than in the control group.[22] There were no data on the indication regarding the transfusion of packed red blood cells, platelets, or cryoprecipitate, or on the use of antifibrinolytics or activated recombinant factor VII. Apart from one study in which all patients received vitamin K, and another study that did not report on its administration, all others reported at least slightly higher rates of treatment with vitamin K in the 4F-PCC groups. DeAngelo et al also reported on the use of desmopressin for two patients who were also taking antiplatelet medication.[19]
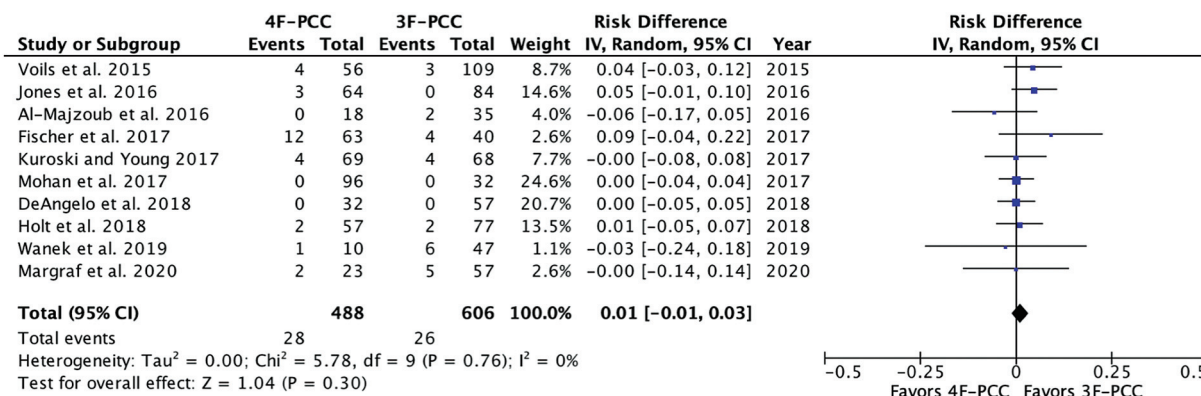
Fig. 6 Thromboembolisms. CI, confidence interval; PCC, prothrombin complex concentrate.

Discussion

In this systematic review and meta-analysis, we present evidence that 4F-PCC is more effective for the rapid reversal of VKA-associated coagulopathy in comparison with 3F-PCC. This is demonstrable in terms of normalizing INR, while the risk of TE remains unaffected. There was no statistically significant reduction in mortality. Patients receiving 3F-PCC received more FFP in comparison with those receiving 4F-PCC. This is the first systematic review of studies directly comparing 3F-PCC with 4F-PCC for the reversal of VKA-associated coagulopathy on effectiveness and safety. All included studies reported not only laboratory findings but also clinical outcomes such as mortality and occurrence of TE.

A systematic review by Voils and Baird investigated whether 4F-PCC was superior to 3F-PCC.[29] That review included data from studies evaluating the effect of either 3F-PCC or 4F-PCC, but with no direct comparison of 3F-PCC versus 4F-PCC at the same study center. The authors found 4F-PCC to cause a more consistent decrease in INR, and repeated INR measurements were reported within a clearly defined timespan in most of the included studies.[29] In the present analysis, varying time intervals between administration of PCC and repeat INR may have influenced the results due to differing half-lives of coagulation factors.[7] However, clinical outcomes such as mortality and TE were not reported in the review performed by Voils and Baird, thus limiting the possibility for practical application of the results.[29]

The studies included in this review utilized INR as a marker to assess reversal of anticoagulation. 4F-PCC was shown to be favorable overall and for patients with a goal INR of ≤1.5 and ≤1.3 (►**Fig. 2a, b**) in comparison with 3F-PCC. However, INR variability is an important consideration when interpreting these results.[30–32] Not all authors reported when repeat INR measurements were taken and, due to the short half-life of factor VII, a late measure of INR could underestimate the initial effect of higher concentrations of factor VII in 4F-PCC. Conversely, an early measurement may show adequate but not lasting reversal of anticoagulation when using 3F-PCC.[30–32]

Another important consideration is that there is no consensus regarding the ideal threshold of INR to prevent bleeding progression. In the studies presented herein, the goal INR value ranged from ≤1.5 to ≤1.3. INR as a standardized prothrombin time (PT) ratio can also be unevenly influenced by substituted factors: factor IX has no relevant influence on PT, and whether factor II, VII, or X has the greatest influence on INR is not definitively proven.[30–32] Measuring the concentration of individual factors may be a more precise measure; however, these tests are not as readily available and may have a longer turnaround time. Moreover, recommendations on reversal goals based on individual factors would lack empirical basis. Furthermore, despite efforts to standardize results of PT through the introduction of INR, results from different laboratories do not always correlate well, further complicating the interpretation of results and limiting their practical value.[33,34]

TE rates remained consistent in patients treated with 4F-PCC versus those treated with 3F-PCC. Similar rates of TE suggest that 4F-PCC is no more thrombogenic than 3F-PCC. None of the studies reported a systematic screening for TE in all patients; therefore, it is likely that the true rate of TE is higher than those reported. Indeed, the pooled incidence of TE for each group (4.29% for 3F-PCC, 5.74% for 4F-PCC) was slightly lower than reported in studies on single PCC products (6.77–10% for 3F-PCC,[35,36] 6.81–7.77% for 4F-PCC[37,38]). However, as no studies reported a systematic screening for TE it is reasonable to expect similar rates of under-detection in both groups.

The studies analyzed in this review also showed that treatment with 4F-PCC was not associated with a statistically significant reduction in mortality (►**Fig. 5**). This finding is not surprising, as a normalization of the INR has not been shown to correlate with a reduction in mortality, which is also explained by the innumerable confounders influencing mortality.[39,40] Also, the difference in resulting INR following 4F-PCC versus 3F-PCC treatment was too small (►**Fig. 4**), to show a clinical impact.

Besides the heterogeneity of studies, especially the serious RoB due to confounding caused by co-medication could bias our results in either direction. Without prospective studies controlling for co-medication, the effect of this bias cannot be estimated exactly. As there was no difference in thromboembolic complications between the 3F-PCC and 4F-

Table 4 Use of blood products and other hemostatic agents

	FFP[a]	Vitamin K[a]	Recombinant factor VIIa[a]	Cryoprecipitate[a]	Platelets[a]	pRBC[a]	Others[a]
Voils et al, 2015	3F-PCC: 80.73% (median 2 units)[b] 4F-PCC: 25% (median 2 units)	3F-PCC: 91.74% 4F-PCC: 94.64%					
Al-Majzoub et al, 2016 (within 24h of PCC administration)	3F-PCC: 60% (3.66 units, SD 3.8) (2–3 units recommended by dosing protocol) 4F-PCC: 16.67% (1.7 units, SD 0.6)	3F-PCC: 77.14% 4F-PCC: 94.44%			3F-PCC: 45.71% (1.6 bags, SD 1) 4F-PCC: 33.33% (0.65 bags, SD 1.5)	3F-PCC: 25.71% (0.57 units, SD 1.2) 4F-PCC: 27.78% (0.6 units, SD 1.2)	
Jones et al, 2016	3F-PCC: 5.95% during hospital stay, 0 prior to repeat INR (median 2 units) 4F-PCC: 53.13%, 21.88% prior to repeat INR (median 2 units)	3F-PCC: 90.48% 4F-PCC: 92.19%					
Mangram et al, 2016[c]	3F-PCC: 13.04% prior to PCC administration (mean 0.4 units, SD 1.2) 4F-PCC: 0 prior to PCC administration	3F-PCC: 45.65% 4F-PCC: 66.67%			3F-PCC: n/a (mean 0.1 units, SD 0.4) 4F-PCC: n/a (mean 0.3 units, SD 0.7)	3F-PCC: n/a (mean 0.4 units, SD 0.8) 4F-PCC: n/a (mean 0.8 units, SD 1.7)	
DeAngelo et al, 2018	3F-PCC: 31.58% (median: 612 mL, IQR 542–1136 mL) 4F-PCC: 28.13% (median: 670 mL, IQR 546–918 mL)	3F-PCC: 28.07% 4F-PCC: 65.63%[d]		3F-PCC: 5.26% (median: 229 mL, IQR 225–864 mL) 4F-PCC: 12.5% (median: 255 mL, IQR 149–578 mL)	3F-PCC: 15.79% (median: 296 mL, IQR 233–875 mL) 4F-PCC: 28.13% (median: 817 mL, IQR 500–1,056 mL)	3F-PCC: 36.84% (median: 1039 mL, IQR 625–1,433 mL) 4F-PCC: 46.88% (median: 625 mL, IQR 320–1705 mL)	Aminocaproic acid: 3F-PCC: 10.53% 4F-PCC: 21.88% Desmopressin: 3F-PCC: 1.75% 4F-PCC: 3.13%
Fischer et al, 2018	3F-PCC: 52.5% 4F-PCC: 26.98%	3F-PCC: 90% 4F-PCC: 98.41%					
Kuroski and Young, 2017	3F-PCC: 60.29% during hospital stay (median 3 units (range 1–15)[e], 47.06% prior to repeat INR 4F-PCC: 28.99% during hospital stay (median 2 units, range 2–10), 7.25% prior to repeat INR	3F-PCC: 94.12% 4F-PCC: 98.55%	3F-PCC: 2.94% 4F-PCC: 0			3F-PCC: 25% (median 3 units, range 1–26 units) 4F-PCC: 18.84% (median 2 units, range 1–5)	
Mohan et al, 2018[c] (within 6h before or after PCC administration)	21.88% (mean 2.32 units)	100%			14.84% (mean 1.74 units)	23.44% (mean 2.10 units)	
Holt et al, 2018	3F-PCC: 51.95% 4F-PCC: 17.54%	3F-PCC: 90.91% 4F-PCC: 96.49%	3F-PCC: 0 4F-PCC: 1.75%				

(Continued)

Table 4 (Continued)

	FFP[a]	Vitamin K[a]	Recombinant factor VIIa[a]	Cryoprecipitate[a]	Platelets[a]	pRBC[a]	Others[a]
Wanek et al, 2019[c]	94.74% (median 6 units, IQR 4–8)	98.25%		73.68% (median 2 units, IQR 2–4)	100% (median 2 units, IQR 1–3)	87.72% (median 7 units, IQR 4–11)	Aminocaproic acid: 56.14%
Margraf et al, 2020	3F-PCC: 59.65% (range 1–12 units) during hospital stay, 26.32% prior to repeat INR (range 1–4 units) 4F-PCC: 30.43% (range 1–6 units) during hospital stay, 8.70% prior to repeat INR (range 1–2 units)	3F-PCC: 85.96% 4F-PCC: 95.65%	Exclusion criteria			3F-PCC: 36.84% (range 1–12 units) 4F-PCC: 30.43% (range 1–4 units)	

Abbreviations: FFP, fresh frozen plasma; IQR, interquartile range; pRBC, packed red blood cells; SD, standard deviation.
[a]Percentage of patients receiving product, dose if reported.
[b]2 units recommended by dosing protocol.
[c]Only reported for entire cohort.
[d]Prompt to administer vitamin K concurrently introduced in computer system with switch to 4F-PCC.
[e]2 units recommended by dosing protocol if INR ≥ 4.

PCC groups, the additional procoagulative activity of 4F-PCC does not influence the occurrence of TE.

We cannot determine the probability of a type II error within the analysis. However, we can use our data to calculate a sample size for possible future studies comparing 4F-PCC and 3F-PCC toward mortality differences. Based on the mortality rates in both groups in our data, Cohen's h effect size for the difference between them is 0.13.[41] This is a very small effect size, warranting the question whether this would be a clinically relevant effect to investigate. In fact, based on this effect size, the sample size needed for a significance level of 0.05 and a power of 0.80 would be $n = 1,984$. However, because of the high relevance of the outcome to individual patients, it might still be useful to conduct further studies even if we expect only a statistically small effect.

Noteworthy was the heterogeneity of co-medication that patients received. All but one study with comparative data reported that patients receiving 3F-PCC were given more FFP in comparison with those receiving 4F-PCC, possibly indicating that 3F-PCC requires supplementation to adequately reverse VKA-associated coagulopathy.[22] Further, before the availability of 4F-PCC in the United States, physicians tended to transfuse FFP plus 3F-PCC to mimic the content of 4F-PCC and to increase factor VIIa levels.

However, the number of patients receiving blood products varied extensively between studies and groups, making interpretation of the data difficult. For instance, the administration of FFP varied from study to study, with several centers co-administering FFP alongside PCC as per local guidelines, while at other centers the decision was left to the physician.[18,23,27] Of the nine studies reporting the dose of FFP, seven reported a mean or median dose of less than 4 units.[18,19,22–24,26,27] The amount of factor VII in FFP may vary and therefore the effect of FFP in addition to 3F-PCC is hard to predict; however, taking into consideration that when PT is prolonged by 1% the recommended dose of FFP is 1 mL/kg, it is unlikely that this dose affected our findings.[42]

Vitamin K may also be administered to facilitate the reversal of VKA-associated coagulopathy. The rate of vitamin K administration, while above 90% in both groups for most centers, was also seen to vary from study to study, while factor VII was only administered in three patients in two studies.[21,23]

In the event that the goal INR was not reached and anticoagulation reversal was deemed inadequate, few authors reported on whether repeat doses of PCC were given or how patients were treated, further hampering interpretation of the data across studies.[19–21,24,28] This might indicate that increased awareness of the physiology and pathophysiology of coagulation and anticoagulation and the relevant treatments is necessary in clinical practice.

Limitations

Limitations of this review include the lack of randomized prospective studies and that every eligible study was conducted in the United States. However, the literature search and

screening strategy did not exclude randomized prospective studies or studies from outside the United States.

The substantial heterogeneity of study outcomes may at least in part be due to this lack of randomized prospective studies and poses a serious limitation in itself.

Another limitation was that some centers switched from 3F-PCC to 4F-PCC as the new standard for the reversal of VKA-associated coagulopathy.[18–20,23,28] It is unclear whether any other changes to guidelines or general treatment options might have influenced patient outcomes.

The only authors commenting on such a change were DeAngelo et al, who noted that a reminder to administer vitamin K when ordering PCC was introduced to the electronic ordering system used at the study centers. As such, the difference in percentage of patients who received vitamin K was highest in this study.[19] Of note, the patients from the 4F-PCC group were significantly more likely to reach the goal INR of ≤ 1.5 (OR: 8.35; 95% CI: 2.59–26.89; ►Fig. 2b), a difference which exceeded the pooled OR of the subgroup (►Fig. 2b). Overall, fewer patients (from both groups) received vitamin K at these centers. Apart from two studies which did not provide comparative data on vitamin K administration, all others reported slightly higher rates of vitamin K use in the 4F-PCC groups (►Table 4). Whether this was coincidence or caused by procedural changes, as described by DeAngelo et al, is unclear. However, a clear switch from one product to another eliminates the RoB by physicians choosing one treatment option over another for certain patients based on the assumed superiority of one. It is also noteworthy that none of the studies included patients treated after 2016, so even the centers that compared PCC products during the same treatment period might by now have switched due to the availability of 4F-PCC and its recommendation in consensus guidelines.

Finally, the mean or median doses of PCC were different for the two groups, with seven studies reporting a difference of more than 10% for the first dose of PCC, five with higher doses of 3F-PCC,[22–24,26,28] and two with higher doses of 4F-PCC.[21,25] However, the patients from the 3F-PCC group reported on by Wanek et al (highest relative difference for higher doses of 3F-PCC) and Mohan et al (highest total difference for higher doses of 3F-PCC) tended to more often fail to reach the goal INR (►Fig. 2a) or have lower post-PCC INR (►Fig. 4), respectively, than those from studies with more even doses.[26,28]

Conclusion

The results of our meta-analysis show a statistically significant better INR normalization with 4F-PCC without any difference in thromboembolic complications. Our data support current recommendations and consensus guidelines[10,11] to use 4F-PCC for VKA reversal. Further research is needed to define a consensus regarding the ideal, individualized degree of INR normalization required to achieve adequate reversal of anticoagulation to prevent bleeding progression. Besides, systematic screening for adverse effects and documentation of clinical indicators of in vivo coagulation (i.e., bleeding cessation, blood loss during surgery) in future studies will help to generate results more applicable to real-world clinical settings.

What is known about this topic?

- Bleeding in patients undergoing anticoagulant therapy can be life-threatening.
- Although use of newer direct oral anticoagulants (DOACs) is increasing, vitamin K antagonists (VKAs) are still widely used. Prothrombin complex concentrates (PCCs) can be used to reverse coagulopathy associated with VKA therapy.
- PCC contains the vitamin K-dependent coagulation factors and is available in two forms, i.e., 3-factor (3F-PCC) or 4-factor (4F-PCC); only 4F-PCC contains a significant amount of factor VII.

What does this paper add?

- 4F-PCC is better suited for rapid reversal of VKA-associated coagulopathy in comparison with 3F-PCC.
- International normalized ratio normalization achieved via 4F-PCC treatment does not increase the risk of thromboembolism in comparison with 3F-PCC.

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