Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists

A meta-analysis

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Summary

Prothrombin complex concentrates (PCCs) are recommended as the treatment of choice in warfarin-related coagulopathy. However, the risk of thromboembolic complications associated with their use is not well defined. We performed a meta-analysis to estimate the rate of thromboembolic complications in patients receiving vitamin K antagonists (VKAs) treated with PCCs for bleeding or before urgent surgery. Medline and Embase databases were searched. Two reviewers performed study selection and extracted data independently. Studies providing data on incidence of thromboembolic complications in VKA-treated patients were eligible for the study. Weighted mean proportion of the rate of thromboembolic complications and the mortality rate were calculated. Twenty-seven studies (1,032 patients) were included. Seven studies used 3-factor, and 20 4-factor PCCs. Twelve patients had a thromboembolic complication (weighted mean 1.4%; 95% CI 0.8–2.1), of which two were fatal. The incidence of thromboembolic events was 1.8% (95% CI 1.0–3.0) in patients treated with 4-factor PCCs, and 0.7% (95% CI 0.0–2.4) in patients treated with 3-factor PCCs. Total mortality rate was 10.6% (95% CI 5.9–16.6). In conclusion, our results suggest there is a low but quantifiable risk of thromboembolism in VKA-treated patients receiving PCCs for anticoagulation reversal. These findings should be confirmed in randomised, controlled trials.

Keywords

Prothrombin complex concentrates, PCC, coumarins, thromboembolic complications, haemorrhage

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Introduction

Prothrombin complex concentrates (PCCs) are coagulation factor products with pro-haemostatic activity prepared from pooled plasma. All PCCs contain factors II (prothrombin), IX, and X with variable amounts of factor VII, as well as natural anticoagulant proteins C and S (1, 2). These products provide a rapid and effective method for correcting clotting factor deficiency, particularly in patients treated with vitamin K antagonists (VKAs) (3). Initial success was reported in 1976 followed by numerous case reports confirming their efficacy (3). PCCs represent one of the treatments available to reverse the anticoagulant activity of VKAs (4), which may be achieved with both three- and four-factor PCCs. Activated PCCs are used specifically in haemophilic patients or in non-haemophilic patients with acquired inhibitors to factors VII, XI, and XII.

There are approximately around 30 million prescriptions of warfarin in the United States (US) annually (6). It is estimated that 3% to 7% per year of VKA-treated patients require rapid reversal annually because of major bleeding or the need for urgent surgery or other invasive procedures (7). Fresh frozen plasma (FFP) is the most widely used coagulation factor replacement product in North America for VKA reversal (7–9). However, FFP is not optimal for immediate correction of VKA-associated coagulopathy because it may transmit infectious agents, it causes allergic reactions and volume overload, it rarely completely corrects the International Normalised Ratio (INR) and unless a supply of thawed plasma is kept on hand, and its administration is delayed as it requires thawing and slow administration (10).

Unlike FFP, PCCs are stored as lyophilized powders, and are not blood-group specific. In addition, PCCs contain a high clotting factor concentration which can be administered quickly in small volumes. As a result of these advantages, PCCs are thought to correct VKA-related coagulopathy more rapidly than FFP (7). Several international guidelines support PCCs as the treatment of choice for reversal of the anticoagulant effect of VKAs (11). The safety profile of PCCs is still unclear. The aim of this systematic review and meta-analysis of the literature is to estimate the risk of throm-

boembolic complications in patients treated with PCCs for a VKA-associated bleeding event or before an urgent invasive procedure.

Materials and methods

Study identification

We attempted to identify all published studies that reported on the use of PCCs in patients treated with VKAs using the MEDLINE (1966 to June 2010, Week 2) and EMBASE (1980 to June 2010, Week 2) electronic databases. The search strategy was developed without any language restriction, and used the subject headings and text words presented in the Appendix. We supplemented our search by reviewing abstracts books from the Congress of the International Society on Thrombosis and Haemostasis (ISTH) (2003–2009) and by manually reviewing the reference lists of all retrieved articles.

Study selection

Two reviewers (CM and MGP) performed study selection independently, with disagreements resolved through discussion and by the opinion of a third reviewer (FD), if necessary. Studies were considered potentially eligible for this systematic review if they met the following criteria:

i) PCCs were used for the rapid reversal of anticoagulation because a major bleeding event or because of the need for surgery or invasive procedure; and ii) the number of thromboembolic events was reported. Studies using activated prothrombin complex concentrates were excluded from selection, given their specific indication in haemophilic patients with inhibitors or in non-haemophiliac patients with acquired inhibitors to factors VIII, XI, and XII (5). The following thromboembolic events were considered: deep-vein thrombosis or pulmonary embolism, myocardial infarction or acute coronary syndrome, ischaemic stroke, transient ischaemic attack or arterial thrombosis of a limb. To avoid bias which is more likely in smaller studies (12), only studies including at least five patients were included. When multiple papers on a single study had been published, the latest publication was used. Data from the earlier publications was included if necessary.

To assess study selection agreement between reviewers, we used the kappa (k) statistic, which measures agreement beyond chance (13).

Study validity assessment

Two unmasked investigators independently completed the assessment of study validity (FD, CM). Because the use of quality scoring systems or quality scales in observational studies is controversial (14), the internal validity of each study was evaluated considering whether the study was prospective or retrospective and whether the patients were enrolled consecutively or not. Studies were considered of high quality when they were prospective and the enrolment was consecutive. Otherwise, studies were considered of low quality. The presence of non-governmental funding was also noted.

Data extraction

The following data were extracted: study characteristics (year of publication, study type); patient characteristics (mean or median age, gender); indication for anticoagulation reversal; type, dose and route of administration of PCC; number of thromboembolic complication including the case fatality rate and total mortality; and episodes of viral transmission.

If the required data could not be located in the published report, we attempted to obtain the necessary information by contacting the corresponding author.

Statistical analysis

Weighted mean proportion of the risk of thromboembolic events and mortality were calculated using the random effect model (15). A random effects model was chosen because we assumed that studies would be heterogeneous with respect to included patients and outcomes. Since patients included in the analysis had a high risk of developing thromboembolic events, and some of these events occurred many days after PCCs administration, not all thromboembolic events could be attributed with certainty to the use of PCCs. Thus, we planned to include all the thromboembolic events registered in the follow-up period of each study, in agreement with the cautious attitude shown by all the authors of the original studies. Subgroup analyses were performed considering different types of PCCs and separately considering the treatment of patients with major bleeding events or patients requiring urgent surgery or invasive procedure. Statistical heterogeneity was evaluated using the I^2 statistic (16). Analysis was performed with StatsDirect software (Version 2.7; StatsDirect Ltd, UK).

Results

A total of 3,890 citations (1448 MEDLINE, 2456 EMBASE) were identified by our systematic search strategy (see Appendix). Of these, 175 studies were duplicates. After screening of the title and abstract using the predefined inclusion and exclusion criteria, 59 studies were retrieved for more detailed evaluation. Eighteen articles were excluded because they did not contain original data, as well as nine papers did not report clinical outcomes. Clinical out-

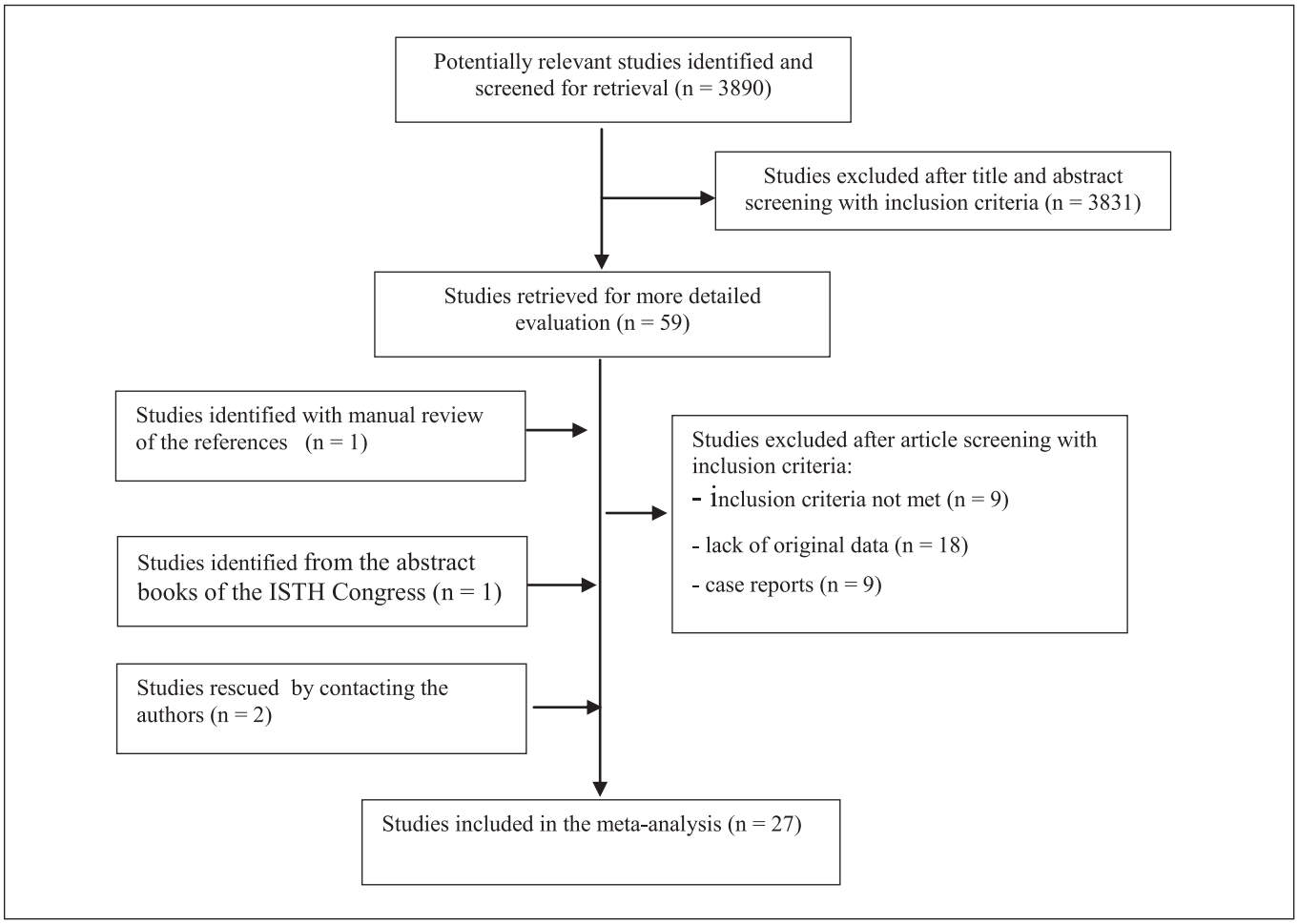

Figure 1: Studies selection progression. n = number.

comes were obtained for two papers by contacting the authors. Nine case reports were excluded . One study was identified through manual review of references, and one abstract was identified from the ISTH Congress. Thus, 27 studies were included in our systematic review (17–43). Study identification and selection are summarised in ▶Figure 1. Inter-observer agreement for selection was substantial (k = 0.94). Baseline characteristics of the included studies are summarised in ▶Table 1. Studies ranged in size from six to 261 patients for a total of 1,032 patients. A total of 631 patients (N=26 studies) (17–42) were treated with PCCs because of a major bleeding event, while 319 patients (N=14 studies) (18–23, 24, 27, 30, 32, 33, 39, 40, 43) because of emergency surgery. Fifteen studies were prospective (17, 20, 22, 23, 26–28, 31–33, 36, 37, 41–43), and among them, four studies enrolled patients consecutively (N=140 patients) (22, 23, 26, 42), achieving the criteria for high quality studies.

Eight prospective studies were sponsored by a commercial entity (17, 22, 23, 26, 28, 32, 33, 43).

All patients included in the studies received treatment with PCCs. The amount of each coagulation factor varied slightly among different PCCs preparations, and some contained the natural anticoagulant proteins C and S (and heparin). Details of all PCC preparations are reported in the legend of ▶Table 1. All PCCs contained coagulation factors II, IX, X at high concentration, while factor VII was present at high concentration only in four-factor PCCs. Three-factor PCCs were defined by either the complete lack of factor VII or its presence in very low concentration. Seven studies (192 patients) used three-factor PCCs (17, 25, 31, 34–36, 40), 18 studies used four-factor PCCs (18–20, 22–24, 26–30, 32, 33, 38, 40–43), and two studies used three-factor PCCs together with factor VII and were thus considered with the four-factor PCCs in subgroup analyses (840 patients) (21, 38). The total dose and the mean infusion time of PCCs treatment varied widely among the studies and are described in ▶Table 1. In most studies (N=24) PCCs were administered at a weight-adjusted dose, while a fixed dose was used in only two studies (one of them compared two treatment regimens). Baseline or target INR, or both, were taken into account to select the dose of PCCs in 12 studies. Five studies based the dose on perceived bleeding severity. Concomitant vitamin K was administered in 20 studies, and FFP was administered in six studies.

The follow-up periods ranged from seven days to six months, although the duration of follow-up was not clearly reported for many studies.

Table 1: Baseline characteristics of the studies.

Author	Study type/ Sponsor	Selected population	Total N° of pts treated (age, M/F ratio)	PCCs and concomitant treatment	Follow-up	Death	Thrombotic events	Viral transmission
Imberti 2007	Prospective, multicentre Sponsor: Baxter (Italy)	OAT reversal (INR ≥2) for ICH	92 74 y (34–92) M/F: 50/42	Protromplex* (PCC-3F) Dose according to BW and baseline INR: INR=2–3.9, 35–39 IU; 4–6, 40–45 IU; >6, 46–50 IU (35–50 IU/kg) All pts received vit. K 10 mg; 1 pt received also FFP	90 days	18	0	0
Bruce 2008	Retrospective Sponsor: CSL Behring (Germany)	OAT reversal for ICH (7 pts) or surgery (1 pt)	8 68.5 y (41–82) -	Beriplex P/N 500° (PCC-4F) Dose according to BW and baseline INR (500–4,000 IU) FFP, PLTs, cryoprecipitate	-	2	0	-
Yasaka 2005	Retrospective Sponsor: none	OAT reversal (INR between 5–1.9) for bleeding (39 pts) or surgery (3 pts)	42 70 y (24–90) M/F: 28/14	PPSB-HT Nichiyaku^ (PCC-4F) Dose: 200 IU in 6 pts, 500 IU in 30 pts, 1,000 IU in 3 pts, 1,500 IU in 3 pts. Pts treated with 200 IU has been given a second infusion of 300 IU Vit. K 10 mg (20 pts), 20 mg (11 pts)	-	1	0	-
Van Aart 2006	Prospective, randomised, controlled, comparative Sponsor: none	OAT reversal (INR > 2.2) for bleeding (37 pts) or surgery (56 pts)	93 Group A: 75 y M/F: 26/21 Group B: 71.1 y M/F: 17/29	Cofact² (PCC-4F) Dose: – Group A: fixed dose of 500 IU (47 pts) – Group B: dose individualised on BW, baseline and target INR (600–2,000 IU) (46 pts) Dose were repeated if target INR not achieved All pts: Vit. K 10 mg	-	0	2 non-fatal strokes in pts treated for bleeding control	-
Nitu 1998	Retrospective Sponsor: none	OAT reversal (INR > 6 in 15/18) for bleeding (16 pts) or surgery (2 pts)	18 77 y (53–92) M/F : 11/7	Factor 9A+ factor VII concentrate# (PCC-3F+FVII à PCC-4F) Dose: 12–50 IU/kg based on severity of bleeding and target INR 1 pt received a second infusion of factor 9A and 1 pt only factor 9A 3 pts were given vit. K 2.5 mg iv	-	0	0	-
Riess 2006	Prospective, multicetre, consecutive pts Sponsor: Octapharma (Austria)	OAT reversal for bleeding (3 pts) or surgery (57 pts)	60 70 y (24–93) M/F : 33/27	Octaplex† (PCC-4F) Dose: individualised on BW, baseline and target and INR (mean dose 3,000 IU, range 900–8,000 IU) Vit K in 24 pts, only 1 immediately before Octaplex	-	3	1 fatal PE in a pt treated for bleeding control	1/54 pts (1.9%) had positive PCR for parvovirus B19
Preston 2002	Prospective, consecutive pts Sponsor: Aventis (UK)	OAT reversal for bleeding (37 pts) or surgery (5 pts)	42 70 y (26–83) M/F: 26/42	Beriplex P/N 250°° (PCC-4F), Dose calculated on BW and baseline INR: 2–3.9, 25 IU/kg; 4–6, 35 IU/kg; >6, 50 IU/kg All pts: Vit. K 2–5 mg	7 days	8	1 fatal stroke in a pt undergoing surgery for emergency leg amputation	

Table 1: Continued

Author	Study type/ Sponsor	Selected population	Total N° of pts treated (age, M/F ratio)	PCCs and concomitant treatment	Follow-up	Death	Thrombotic events	Viral transmission
Schick 2009	Retrospective, comparative Sponsor: CSL Behring (Germany)	OAT reversal for bleeding 2 pts were receiving concomitant LMWH	12 66.1 ± 1.8 y M/F: 28/10	Beriplex P/N 500° (PCC-4F) Dose calculated on BW, baseline and target INR (median dose 2,000 IU) 7 pts received vit. K iv	-	-	0	0 (follow-up only up to discharge)
Safaoui 2009	Retrospective Sponsor: nd	OAT reversal for ICH	28 78.2 y (55–94) M/F: 14/14	FIX complex containing factor II, IX, X, low levels of factor VII, no heparin, low levels of activated clotting factors (PCC-3F) Dose: - Vit. K was administered to 23/28 pts, FFP to 27/28 pts	weeks	10	0	0
Lubetsky 2003	Prospective, multicentre, consecutive pts Sponsor: Octapharma (Austria)	OAT reversal for bleeding (10 pts) or surgery (10 pts)	20 72.5 y (43–83) M/F: 11/9	Octaplex†† (PCC-4F) Dose individualised on BW and clinical judgement (25–50 IU/kg) Vit. K 1–5 mg was administered in 7/20 pts	4–8 weeks	2	0	3 (2) pts sero-positive for Parvovirus B-19
Evans 2001	Prospective Sponsor: none	OAT reversal (INR>8) for bleeding	10 73 y (39–88) M/F: 2/8	Beriplex P/N 500° (PCC-4F) Dose individualised on BW (30 UI/kg) All pts received vit. K 5 mg	-	0	0	-
Pabinger-Fasching 2008	Prospective, multicetre Sponsor: CSL Behring	OAT reversal for bleeding (17 pts) or surgery (26 pts) 17 pts were taken phenprocoumon	43 70 y (22–85) M/F: 21/22	Beriplex P/N 500° (PCC-4F), Dose according to BW and baseline INR (25–50 UI/kg, INR: 2–3.9 or >6) Most of pts received also vit. K iv or po	-	3	1 fatal PE and 1 non-fatal event in pts treated for bleeding control	0 viral transmission (3 months follow-up)
Junagade 2007	Retrospective Sponsor: nd	OAT reversal (INR > 2) for bleeding	21 - -	Beriplex P/N (PCC-4F) Dose according to baseline INR (500–1500IU) or BW (50IU/kg) 3 pts received also FPP	-	-	0	-
Lankiewic 2006	Retrospective Sponsor: nd	OAT reversal (INR > 2) for bleeding (54 pts) or surgery (2 pts)	56 75.5 y (26–92) -	Proplex-T[??] (PCC-4F) Dose according to BW (25–50 UI/kg), baseline INR and severity of bleeding All pts received also oral vit. K; 50% of pts received FFP	-	21/58	3 non-fatal events in pts treated for bleeding control	-
Cartmill 2000	Prospective Sponsor: nd	OAT reversal for ICH	6 69 y (45–77) M/F: 3/3	Factor IXa-BPL[x] (PCC-3F) Dose individualised on BW (50 IU//kg) Vit K 10 mg iv to all pts	-	1	0	-
Lorenz 2007	Prospective, multicetre Sponsor: CSL Behring	OAT (phenprocoumon) reversal for bleeding (1 pt) or surgery (7 pts)	8 75.1 ± 9.9 y M/F: 2/6	Beriplex P/N 500° (PCC-4F) Dose according to BW (mean 57 UI/kg) and risk of bleeding 2 pts received a second infusion of PCCs 1 pt with ICH received vit. K 5 pts undergoing surgery received 1,000 IU AT, and 2 of them also heparin	-	0	0	0 viral contamination

Table 1: Continued

Author	Study type/ Sponsor	Selected population	Total N° of pts treated (age, M/F ratio)	PCCs and concomitant treatment	Follow-up	Death	Thrombotic events	Viral transmission
Lavenne-Pardonge 2006	Prospective, multicenter Sponsor: none	OAT reversal for bleeding (6 pts) or surgery (8 pts)	14 78 y (33–91) M/F: 9/5	PPSB-SD (Solvent Detergent)[xxx] (PCC-4F) Dose calculated according to BW, baseline and target INR (< 2 for moderate bleeding and abdominal surgery, < 1.5 for severe bleeding and cardio-vascular surgery) (mean 1,574 UI)	-	0	0	-
Siddiq 2008	Retrospective Sponsor: nd	OAT reversal (mean INR at presentation 2.44 ± 1.48) for ICH	10 67.2±18.51 y M/F : 5/5	Profilnine-SD[xx] (PCC-3F) Dose individualised on BW and baseline INR (25 UI/kg for INR<4, and 50 UI/kg for INR>4)	-	0	0	-
Fredriksson 1992	Retrospective, comparative Sponsor: none	OAT reversal (INR > 2) for ICH	10 71.9 ± 6.0 M/F: 9/1	Preconativ[?] (PCC-3F) Dose individualised according to BW, taking into account baseline PT (average of 25.8 IU/kg)	-	2	0	-
Boulis 1999	Prospective, randomised, controlled, comparative Sponsor: none	OAT reversal (PT > 17) for ICH	8 - -	FIXCC[???] (PCC-3F) Dose calculated according to BW, baseline and target INR (range 2,000–5,000 IU)	-	2	0	-
Kalina 2008	Prospective, comparative Sponsor: nd	OAT reversal (INR >1.5) for ICH for blunt trauma	46 77.4 ± 13.2 M/F: 26/20	Proplex T[??] (PCC-4F) Dose according to BW and per cent desired increase in clotting factor levels Vit. K 5 mg iv and FFP (not specified number of pts)	-	11	2 fatal DVT and 1 non-fatal DVT	-
Makris 1997	Retrospective, comparative Sponsor: nd	OAT reversal for bleeding	29 (21–88) -	Used 2 PCCs: – 9A (BPL, UK, PCC-3F) + factor VII (equivalent to PCC-4F, 13 pts) – Prothromplex T (PCC-4F, 16 pts) Dose individualised for BW (25–50 IU/kg) All pts received vit. K 1–5 mg iv	-	0	0	-
Tiraferri 2004	- Sponsor: nd	OAT reversal for bleeding (31 pts) or surgery (7 pts)	38 - -	Protromplex TIM 3 (PCC-3F) Dose individualised for BW and baseline INR: 2–3.9, 27–30 IU/kg; 4–6, 35–37 IU/kg; >6, 43–45 IU/kg All pts were given vit. K 10 mg	-	3	0	-
Carvalho 2007	- Sponsor: nd	OAT reversal for bleeding (136 pts) or surgery (125 pts)	261 66.7 (20–96) M/F (123/138)	Octaplex (PCC-4F) Dose individualised on BW and baseline INR: INR <5, 15 IU/kg; >5, 30 IU/kg Vit. K in serious events (not better defined)	-	-	0	-

Table 1: Continued

Author	Study type/ Sponsor	Selected population	Total N° of pts treated (age, M/F ratio)	PCCs and concomitant treatment	Follow-up	Death	Thrombotic events	Viral transmission
Sharples 2003	Prospective, multicenter Sponsor: nd	OAT reversal for bleeding	19 72 (35–95) M/F (9/10)	Beriplex P/N (PCC-4F) Dose individualised for BW (30 IU/kg) All pts received vit. K 5 mg iv	-	-	0	-
Vigué 2006	Prospective, consecutive Sponsor: nd	OAT reversal for ICH	18 71 ± 10 -	Kaskadil** (PCC-4F) Dose individualised for BW (20 IU/kg) All pts received vit. K 5 mg po	6 months	4	0	-
Demeyere 2010	Prospective, randomised, comparative Sponsor: CAF-DCF – Sanguin	OAT reversal for surgery	20 69.6 ± 9 M/F (10/10)	PPSB-SD[xxx] (PCC-4F) Dose individualised for BW, initial and target INR	-	0	0	-

nd: not decleared; pts: patients; y: years; ICH: intracerebral haemorrhage; FFP: fresh frozen plasma; BW: body weight; PE: pulmonary embolism; DVT: deep-vein thrombosis; AMI: acute myocardial infarction; iv: intra-venous; po: per os; *Protromplex (Baxter, Italy): factor II (35.5 IU/ml), factor IX (31.8 IU/ml), factor X (28.6 IU/ml). °Beriplex P/N 500 (CSL Behring, Germany): factor II (400–960 IU), factor VII (200–500 IU), factor IX (400–620 IU), factor X (440–1200 IU), protein C (300–900 IU), protein S (260–520 IU), antithrombin (4–30 IU), heparin (8–40 IU). °°Beriplex P/N 250 (Aventis UK): factor II (320 IU), factor VII (170 IU), factor IX (250 IU), factor X (380 IU), protein C (300 IU). ^PPSB-HT Nichiyaku (Nihon Pharmaceutical, Japan): factor II, VII, IX, X (500 IU) and protein C (380 IU). [?]Cofact: factor II (≥15 IU/ml), factor VII (≥5 IU/ml), factor IX (≥20 IU/ml), factor X (≥15 IU/ml), antithrombin (≤0.6 IU/mL). [?]Preconativ (Kabi): factor II (50 IU/ml), factor IX (60 IU/ml), factor X (50 IU/ml). †Octaplex (Octapharma, Austria): factor II (11–38 IU), factor VII (9–24 IU), factor IX (20–31 IU), factor X (18–30 IU), protein C (7–31 IU), protein S (7–32 IU), and heparin (0.2–0.5 IU). ††Octaplex (Octapharma, Austria): factor II, VII, X, protein C and S (10–40 IU/ml), factor IX (20–31 IU/ml), and heparin (0.2–0.5 IU/IU). [??]Proplex-T (Baxter, USA): factor II (50 IU), factor VII (400 IU), factor IX (100 IU), factor X (50 IU). [x]Factor IXa-BPL (Bio Products Laboratory: factor II, factor IX, factor X. [xx]Profilnine-SD (Grifols Biologicals, USA): factor II (150 IU), factor IX (100 IU), factor X (100 IU) (very low level of factor VII [35 IU]). [xxx]PPSB-SD (Solvent Detergent) (CAF-DCF (cvba)): factor II (≥15 IU/ml), factor VII (≥5 IU/ml), factor IX (≥20 IU/ml), factor X (≥15 IU/ml). [#]Factor 9A+ factor VII concentrate (Blood Products Laboratory (BPL), UK): factor II, IX, X, and VII, heparin and other plasma proteins. [???]FIXCC: factor II (38 IU/ml), factor VII (4 IU/ml), factor IX (25 IU/ml), factor X (38 IU/ml). [@] Prothrombinex HT: factor II (500 IU), factor IX (500 IU), factor X (500 IU), AT III (25 IU), heparin (192 IU), <500 mg plasma proteins (very low levels of factor VII and V). **Kaskadil (Laboratoire Français du Fractionnement et des Biotechnologies, Courtaboeuf, France): factor II (37 IU/ml), factor IX (25 IU/ml), factor X (40 IU/ml), factor VII (10 IU/ml), and heparin (5 IU/ml).

Twelve patients had a thromboembolic complication after PCC administration (weighted mean 1.4%; 95% confidence interval [CI] 0.8–2.1 %). All events occurred within a few days (1–4 days) of PCC administration. There was no heterogeneity among the studies for this endpoint ($I^2 = 0\%$). Of the thromboembolic events, three were fatal (25%). Events included: two non-fatal and one fatal stroke; two fatal pulmonary emboli; three deep-vein thrombi; and four non-fatal thromboembolic events not better defined.

In total, 91 patients died during follow-up for a mean mortality rate of 10.6% (95% CI 5.9–16.6 %). Despite the cause of mortality was not available for all the patients, only few deaths can be attributed to thromboembolic complications.

The incidence of thromboembolic events was 1.9%; (95% CI 1.0–3.1 %) in patients treated for bleeding and 0.8% (95% CI 0.1–2.0 %) in patients treated before urgent surgery or invasive procedures. The incidence of thromboembolic events was 1.8% (95% CI 1.0–3.0%) in patients treated with four-factor PCCs, and 0.7% (95% CI 0.0–2.4%) in patients treated with three-factor PCCs.

The four high-quality studies (enrolling 140 patients) were included in a sensitivity analysis; in this group, there were two thromboembolic events (mean incidence 2.3% [95% CI 0.5–5.4%]).

Seven studies (257 patients) provided data on viral transmission after PCC administration; four episodes of positivity for parvovirus B19 were reported for a mean incidence of 1.9% (95% CI 0.3–4.9%).

The rate of complications is summarised in ▶Table 2.

Discussion

Our systematic review of the literature found PCC therapy to be associated with a low but quantifiable risk of thromboembolic complications. The findings of a low thromboembolic risk have been further supported by the results of our subgroup analyses separately evaluating treatment with three- or four-factors PCCs and by different indications for PCC therapy. The risk of viral transmission, although evaluated in few studies only, appeared similarly low. Mortality rate was substantial, and consistent with published case-fatality rates for VKA-associated major bleeding

Table 2: Rate of complications.

	Rate (95% CI)
TE events	1.4% (0.8–2.1)
Death for all causes	10.6% (5.9–16.6)
TE events in pts treated for bleeding	1.9% (1.0–3.1)
TE events in pts treated before urgent surgery or invasive procedures	0.8% (0.1–2.0)
TE events in pts treated with 4-factor PCCs	1.8% (1.0–3.0)
TE events in pts treated with 3-factor PCCs	0.7% (0.0–2.4)
TE events in high quality studies	2.3% (0.5–5.4)
Viral transmission after PCC administration	1.9% (0.3–4.9)

TE, thromboembolic, pts: patients, PCCs: prothrombin concentrates.

(44). We are unable to conclude what impact, if any, PCCs had on death rates. Potential benefits of PCCs use in reducing bleeding related mortality should be weighted against the risk of fatal thromboembolic complications associated with the use of these compounds.

The number of individuals who receive coumarin therapy for the prevention and treatment of thromboembolic diseases has dramatically increased in recent years and there are around 30 million prescriptions of warfarin in the US annually (6). VKAs provide beneficial anticoagulant effects, but also increase the risk of severe and potentially fatal bleeding events (44). The effects of anticoagulants are monitored with the INR; an INR above the target range of 2.0–3.0 independently predicts major bleeding (45). Despite regular monitoring of anticoagulant treatment, only 50 to 60% of patients are within the therapeutic range at any one time and INR values above the therapeutic range are frequent (45). Patients on VKAs have been reported to experience 16.5 haemorrhagic events per 100 treatment-years (46), with a major haemorrhage risk of approximately 1% per year. Current guidelines recommend the use of FFP, PCCs, or recombinant factor VIIa supplemented with intravenous vitamin K for the management of major bleeding in VKA-treated patients (45).

However, PCCs seem to be more effective in rapidly reversing warfarin-related coagulopathy than FFP (5), and the small-volume PCCs preparations can be administered within minutes without the need for matching the blood group or thawing the product, as is the case with FFP. The recommended volume of FFP for an average adult weighing 70 kg is 1,050 ml, and transfusion of such large volumes of FFP may lead to fluid overload (47). Moreover, unlike the majority of FFP preparations, PCCs are prepared using viral inactivation methods (4).

Low-dose rFVIIa also seems to be effective and rapid in bleeding control, but the use of this therapy has been shown to be associated with an increased frequency of arterial events in patients with acute cerebral haemorrhage (48). Also, treatment with high doses of rFVIIa significantly increased the risk of arterial but not venous thromboembolic events, especially among the elderly (49). Thus, the use of PCCs may offer a number of advantages in terms of both efficacy and safety as compared to the use of the alternative agents.

The recommended dose of PCCs is up to 50 IU kg^{-1} (50), and is calculated according to the concentration of factor IX present in the concentrate. However, some studies have shown that lower doses can also be efficacious in restoring normal INR levels (4). Thus, the optimal dose of PCCs required to correct warfarin or other coumarins associated coagulopathy and to stop bleeding is still unknown. Data are needed on the relative contribution of individual clotting factors to haemostasis and other outcomes.

Our systematic review has potential limitations. First, since there are no randomized controlled trials that compared different therapeutic strategies in this setting, the efficacy or safety of PCCs therapy in comparison with FFP or rFVIIa could not be evaluated. Second, our meta-analysis was restricted to retrospective and prospective cohort studies only, and the application of formal meta-analytic methods to observational studies is controversial, since bias implicit in the study design may misrepresent the strength of associations within the data (50). However, to avoid misleading results, we decided to exclude case reports and case series with less than five patients. Lastly, studies included in our meta-analysis have different size, different follow-up intervals, and different inclusion and exclusion criteria; thus, combining results across studies may be inappropriate. However, the heterogeneity among the studies was generally low. Furthermore, we pooled results using a random-effects model, an approach which accounts for some of the variance between studies.

In conclusion, our results suggest that in patients on VKAs treatment who are experiencing major bleeding or who require rapid reversal of the INR for an urgent procedure, the administration of PCCs is associated with a low but quantifiable risk of thromboembolic complications. Ongoing randomised trials comparing PCCs to FFP for the emergent reversal of warfarin (51) may provide definitive conclusions on the efficacy or safety of PCCs therapy in comparison with other current therapies.

What is known about this topic?

- Prothrombin complex concentrates (PCCs) are recommended as the treatment of choice in vitamin K antagonist (VKA)-related coagulopathy.
- While the efficacy of PCCs is well established, the risk of thromboembolic complications associated with their use is not well defined, since the knowledge on the safety profile of PCCs is based on small studies.

What does this paper add?

- This is the first systematic review and meta-analysis of the literature evaluating the risk of thromboembolic complications in patients treated with PCCs for a VKA-associated bleeding event or before an urgent invasive procedure.
- Our results suggest that the administration of PCCs is associated with a low but quantifiable risk of thromboembolic complications.

Database: Ovid MEDLINE (1950 to February Week 4, 2010)

Search strategy:

1: Blood Component Transfusion/ (2210)
2: Coagulants/ (887)
3: Plasma/ (11662)
4: Prothrombin/tu (167)
5: Factor X/tu (69)
6: Factor IX/tu (703)
7: Factor VII/tu (633)
8: Factor VIIa/ (2650)
9: Warfarin/ (11209)
10: Anticoagulants/ (41438)
11: Phenprocoumon/ (663)
12: Acenocoumarol/ (908)
13: 9 or 10 or 11 or 12 (47339)
14: Blood Coagulation Factors/ (10739)
15: 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 14 (27666)
16: 13 and 15 (1448)
17: from 16 keep 1–500 (500)

Conflict of interest

E. M. Hylek was in the executive steering committee for the ARISTOTLE trial of apixaban vs. warfarin in atrial fibrillation. She has served on the advisory board for Bristol-Myers Squibb, Daichi Sankyo, Johnson & Johnson, Merck and Pfizer. None of the other authors declare any conflict of interest.

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