**Prothrombin complex concentrates are superior to fresh frozen plasma for emergency reversal of vitamin K antagonists: a meta-analysis in 2606 subjects**

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# **ABSTRACT**

**Background**: Urgent reversal of vitamin K antagonists (VKA) is required for major bleeding or urgent surgery by intravenous vitamin K with either prothrombin complex concentrates (PCC) or fresh frozen plasma (FFP). However, there is lack of consensus regarding the superiority of either reversal agent. We sought to compare the performance of PCC and FFP in urgent reversal of VKA.

**Methods:** A meta-analysis was conducted up to November 2018. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using a random effects model.

**Results:** Seventeen studies comprising 2606 participants met inclusion criteria. Compared with FFP treatment, PCC treatment led to reduction in 90day all-cause mortality (OR=0.60, 95%CI=0.40-0.90, p=0.01), better reversal of INR (OR=7.36, 95%CI=4.18-12.98; p<0.00001) and lower risk of at least one treatment-related adverse event (OR=0.45, 95%CI=0.26-0.80, p=0.006). Among patients with VKA-associated intracranial haemorrhage, PCC treatment led to reduction in 90day all-cause mortality (OR=0.58, 95%CI=0.35-0.94, p=0.03) and better reversal of INR (OR=6.52, 95% CI=1.66-25.59, p=0.007). There were no differences between these two agents in thrombogenicity, requirement for and quantity of red blood cell transfusions, all adverse events, fluid overload or disability on discharge or at 90days.

**Conclusions:** As an agent for urgent reversal of VKA, PCC outperforms FFP in 90day all-cause mortality including those with VKA-related intracranial haemorrhage, INR reversal and treatment-related adverse events.

**KEY POINTS**

Urgent reversal of vitamin K antagonists (VKA) is required for major bleeding or urgent surgery by intravenous vitamin K with either prothrombin complex concentrates (PCC) or fresh frozen plasma (FFP).

There is lack of consensus regarding the superiority of either reversal agent.

Using a meta-analysis strategy, we report PCC outperforms FFP in 90day all-cause mortality including those with VKA-related intracranial haemorrhage, INR reversal and treatment-related adverse events.

# **INTRODUCTION**

Vitamin K antagonists (VKAs) are anticoagulant drugs used for the treatment and prevention of multiple thrombotic conditions. Whilst they have been proven to cause a significant decrease in the rate of mortality in patients with previous thromboembolic events, they are associated with an increased risk of spontaneous bleeding events and prolonged bleeding, with some studies reporting the relative risk for fatal bleeding as high as 4.8 compared with no treatment [1,2]. Warfarin is still the most commonly prescribed VKA.

Urgent reversal of VKAs may be required in the case of major haemorrhage, prior to surgery or warfarin overtreatment. The direct antidote vitamin K can take up to four hours to take effect [3]. The two most commonly used rapidly acting reversal agents alongside vitamin K are prothrombin complex concentrates (PCC) and fresh frozen plasma (FFP). PCCs require concurrent vitamin K administration based on studies and labelling for VKA reversal [4]. Both PCC and FFP work by replacing vitamin K dependent coagulation factors, which PCC has in a more concentrated dose than FFP [5]. However, there is a lack of consensus on which should be the preferred agent, with PCC becoming more widely used in Europe, while FFP is still routinely used in the US [6,7].

Two previous meta-analyses comparing PCC to FFP reached conflicting conclusions, with Chai-Adisaksopha *et al* [8] suggesting PCC resulted in a decrease in all-cause mortality while Johansen *et al* [9] suggesting no differences. However, both of these studies included treatment groups where patients were given both PCC and FFP together, making their findings difficult to interpret [10]. Since the publication of these studies, new data comparing PCC against FFP have been published.

We undertook a meta-analysis in order to compare the performance of PCC and FFP in urgent reversal of VKAs in patients with active haemorrhage and those who required urgent reversal for surgery. To the best of our knowledge, this is the largest meta-analysis of this kind and the only study to perform a sub-analysis comparing PCC versus FFP specifically in VKA-associated intracranial haemorrhage (ICH).

# **METHODS**

**Search criteria**

The methodology followed guidelines from the Cochrane and PRISMA recommendations on conducting a meta-analysis [11,12]. We performed literature search of MEDLINE and Google Scholar up to November 2018 using the key terms: prothrombin complex, PCC, Beriplex, Kaskadil, Octaplex, PPSB, Kcentra, Confidex, fresh frozen plasma, FFP. No language or data filters were applied. The Boolean operator ‘OR’ was used to combine search terms. Relevant studies were hand searched within their references.

**Selection criteria**

*Inclusion criteria*: Studies comparing PCC against FFP as separate treatment methods for the urgent reversal of vitamin K antagonists in patients 18 years-old or over, with at least one of the relevant study outcomes. In multiple publications of the same study, the largest and most updated study was selected. Both randomised control trials (RCTs) and observational studies (prospective/retrospective) were included in order to maximise the power of our analysis.

*Exclusion criteria*: Studies which included patients who were initially treated both with PCC and FFP, younger than 18 years by the end analysis, discrepancies in supplementary treatment between the PCC and FFP groups and coagulopathy that may have been caused by mechanisms other than VKAs. Letters to the editor and abstracts were excluded.

**Outcome measures**

The primary outcome for the comparative analysis was 90day all-cause mortality. If the study lasted less than 90 days, then the final mortality rates were used. Studies recording ‘In-hospital mortality’ without dates or time-limits were not used. Secondary outcomes included reversal of international normalised ratio (INR), thromboembolic events, adverse events, treatment related adverse events, requirement for red blood cells (RBCs) and the quantity of RBCs (units) transfusions. In subgroup analysis of VKA reversal for ICH, disability at discharge or at 90days was also included as secondary outcome.

**Definition of outcome measures**

The definition of outcome measures was by study authors which may vary between studies. Adequate INR reversal was described as patients who achieved INR target of <2.5 as set by authors of studies included in our present meta-analysis. Thromboembolic events (TEE) included deep vein thromboses (DVT), pulmonary embolisms (PE), myocardial infarcts (MI) and ischaemic strokes. All types of adverse events and treatment-related adverse events were defined by study authors. Patients receiving RBC transfusions were those who had received at least 1 unit of RBCs. Fluid overload events included pulmonary oedema and pleural effusion. Disability following VKA reversal for an ICH was assessed by modified Rankin Scale (mRS): patients with mRS score of 0-3 were considered to have no disability to moderate disability, 4-5 to have moderately-severe to severe disability and 6 to have died.

**Statistical Analysis**

Meta-analysis was performed using Review Manager v5.3. Odds ratio (OR) and 95% confidence intervals (CI) were calculated using a random effects model. Statistical significance threshold was accepted as *p* <0.05. Inter-study heterogeneity was assessed by I2 test with a value of >50% being considered substantial heterogeneity. Funnel plots were generated to assess publication bias. Specific analyses was undertaken on 90-day all-cause mortality, INR reversal, thrombogenicity, RBC transfusion and their quantities, adverse events, and subgroup analyses of VKA associated ICH and mortality, disability on discharge. Risk of bias was assessed using Cochrane Collaboration’s tool [13].

# **RESULTS**

The initial literature search yielded 17343 publications. After the application of selection criteria, full text analysis left 17 articles with dichotomous, discrete and relevant data (**Figure 1**). Characteristics of studies are described in **Supplementary Table 1A-C**.

**90day all-cause mortality**

A total of 1,988 patients in all nine studies were analysed [14-22]. Three studies were prospective and six were retrospective. The rates of 90day all-cause mortality were significantly lower among patients who were treated with PCC (299/1138, 26.27%) than with those of patients who were treated with FFP (258/850, 30.35%): OR = 0.60, 95%CI = 0.40-0.90, p = 0.01 (**Figure 2**). There was no inter-study heterogeneity (I2 = 42%, p = 0.09) or publication bias.

**INR reversal**

Ten studies comprising 1007 patients were analysed [15-17,20,23-28]. The rates of achieving adequate INR reversal were greater by patients who received PCC (314/459 patients, 68.41%) than those by patients who received FFP (184/548 patients, 31.51%): OR = 7.36, 95% CI = 4.18-12.98, p <0.00001 (**Figure 3**). There was evidence of heterogeneity (I2 = 56%, p = 0.01), which arose from multiple studies, but no publication bias.

**Thrombogenicity**

Seven studies comprising 916 patients were analysed [15-18,20,22,29]. The rates of at least one thromboembolic event were similar in patients treated with PCC (26/457, 5.69%) to those treated with FFP (23/459, 5.01%): OR = 1.12; 95% CI = 0.60-2.08, p = 0.72) (**Supplementary Fig 1**). There was no heterogeneity (I2 = 0%, p = 0.50) or publication bias.

**Patients requiring RBC transfusions**

Five studies comprising 529 patients were analysed [15,17,20,22,30]. The rates of at least one RBC transfusion was similar in patients treated with PCC (93/257, 36.19%) to those treated with FFP (104/272, 38.24%): OR = 0.81, 95% CI = 0.44-1.48, p = 0.49 (**Supplementary Fig 2**). There was no heterogeneity (I2 = 37%, p = 0.18) or publication bias.

**Quantity of RBC transfusions**

Three studies comprising 702 patients were analysed [15,18,20]. There were no differences in the quantity of RBCs (units) prescribed for patients treated with PCC and those treated with FFP: mean difference = -0.57, 95%CI: -1.73, 0.60, p = 0.34 (**Supplementary Fig 3**). There was evidence of inter-study heterogeneity (I2 = 97%, p <0.00001) or publication bias.

**All types of adverse events**

There were six studies comprising 833 patients studied [15-18,20,30]. The rate of patients having at least one adverse event was similar in patients treated with PCC (157/419 patients, 37.5%) to those treated with FFP (179/414 patients, 43.2%): OR = 0.78, 95% CI: 0.55-1.11, p = 0.17 (**Supplementary Fig 4**). There was no evidence of heterogeneity (I2 = 16%, p = 0.31) or publication bias.

**Treatment related adverse events**

Three studies comprising 429 patients were analysed [15,17,20]. The rate of patients having at least one treatment related adverse event as determined by the study practitioners was significantly less in patients treated with PCC (21/207 patients, 10.1%) than patients treated with FFP (45/222 patients, 20.3%): OR = 0.45, 95% CI: 0.26-0.80, p = 0.006 (**Figure 4**). No evidence of inter-study heterogeneity (I2 = 0%, p = 0.89) or publication bias was observed.

**Fluid overload events**

There were five studies comprising 806 patients included [15,17,18,20,29]. The rate of patients having at least one fluid overload event in patients treated with PCC (13/400 patients, 3.25%) was not significantly different to that in patients treated with FFP (34/406 patients, 8.37%): OR = 0.45, 95% CI = 0.20-1.03, p = 0.06 (**Supplementary Fig 5**). There was no evidence of inter-study heterogeneity (I2 = 24%, p = 0.26) or publication bias.

**Subgroup analysis: 90day all-cause mortality in patients with VKA-associated ICH**

Five studies comprising 1226 patients were analysed [14,16,17,19,21]. Two studies were prospective and three were retrospective. The risk of 90day all-cause mortality in patients with VKA-associated ICH was lower for those who were treated with PCC (271/752, 36.04%) than with those of patients who were treated with FFP (220/474, 46.41%): OR = 0.58, 95% CI = 0.35-0.94, p = 0.03 (**Figure 5**). No evidence of inter-study heterogeneity (I2 = 40%, p = 0.16) or publication bias was observed.

**Subgroup analysis: INR reversal in patients with VKA-associated ICH**

Four studies comprising 223 patients were included [16,17,23,28]. The rates for achieving adequate INR reversal were higher in patients who were treated with PCC (66/80 patients, 82.50%) than in those who were treated with FFP (86/143 patients, 60.14%): OR = 6.52, 95% CI = 1.66-25.59, p = 0.05 (**Figure 6**). There was no evidence of inter-study heterogeneity (I2 = 54% p = 0.09) or publication bias.

The corresponding funnel plots for **Figures 2-6** are presented **Supplementary Fig 7**.

**Subgroup analysis: Disability on discharge**

There were only three studies comprising 108 patients available for analysis [16,17,31]. The rates of those without or with moderate disability on discharge were similar in patients who received PCC treatment (22/53 patients, 41.5%) and in patients who received FFP treatment (13/55 patients. 23.6%): OR = 2.58, 95% CI = 0.65 – 10.26, p = 0.18 (**Supplementary Fig 6**). We found no evidence of inter-study heterogeneity (I2 = 53% p = 0.12) or publication bias.

**90day all-cause mortality using only RCTs**

Analysis of RCT data without observational studies (**Supplementary Fig 8**) could only include 3 studies with just over 200 participants and ~20 events. This considerably reduces the power of our study and the reliability of our conclusion.

**Risk of bias**

**Figure 7** shows risk of bias assessments for the 17 studies in the present meta-analysis. Random sequence allocation was considered high risk in all retrospective or observational studies as patients were allocated due to centre guidelines, date based guidelines or physician judgement. Allocation concealment was low in all RCTs due to blinding but the level of allocation concealment was often undetermined in all retrospective or observational studies. Blinding of participants and personnel was not possible due to differences in treatment regimes, including volume and administration time. Studies with only pre-decided serious adverse events or death was considered more objective and as such, lower risk.

# **DISCUSSION**

This meta-analysis of 17 studies, examining 2606 patients, is the largest to date for comparing the performance of PCC and FFP in urgent reversal of VKA in patients with haemorrhage or undergoing urgent surgery. Our work demonstrates PCC treatment outperforms FFP treatment for 90day all-cause mortality, including in patients with ICH, achieving adequate INR reversal and treatment-related adverse events. These two agents did not differ in the rates TEE, requirement for and quantity of RBC transfusions, all adverse events, fluid overload events or disability on discharge. There are a number of factors that may explain superiority of PCC over FFP including its greater concentration of vitamin-K factors, faster reversal of INR, smaller fluid volume administered and its property in viral inactivation. These favourable factors make PCC the most suitable treatment option in emergency situations such acute haemorrhage or urgent surgery.

Similar to FFP, PCC directly delivers the coagulation factors that are depleted by VKA, but in a more concentrated dose than in FFP [5]. While FFP ultimately reverses coagulopathy, unlike PCC, it does not solely restore the depleted vitamin K dependant coagulation factors.

Administration methods of the two agents tend to vary considerable. FFP, often requires thawing beforehand, is normally given with the addition of between 750 and 1500 ml of fluid over a period between 30 minutes and 4 hours [32]. The relatively large volume required together with additional proteins within FFP limited amount it can be administered; this reduces its ability to replete the missing coagulation factors and decreased effectiveness. Goldstein *et al* showed a 20% decrease in achieving adequate INR reversal for every 30 minutes of FFP treatment delay within the first 24 hours [33]. Conversely, PCC is usually given over a shorter period of 15 minutes [32].

Benefit and risk profile of treatment with PCC or FFP must be considered and the balance between procoagulant and anticoagulant effects is important to avoid thromboembolic events. Thrombotic risk with PCC administration*, i.e.* thrombin potential, may be a drawback of this agent. However, we found no differences in patients experiencing at least one TEE between treatment groups were observed. It appears that the risk of TEE exaggerated by 4.5-fold in patients with a prior history of DVT or PE who received PCC for warfarin-associated ICH [34].

Our subgroup analysis of reversal of VKA in patients with ICH revealed that PCC treatment also outperformed FFP treatment for 90day all-cause mortality outcome as well as for achieving adequate INR reversal. This discrepancy is possibly due to the faster response time of PCC compared with FFP (as described above). ICH expansion is associated with increased mortality [35] therefore this adverse condition should be minimised as much as possible. Steiner *et al* have reported that PCC treatment was associated with less haematoma expansion at 3 hours and 24 hours than FFP in patients with ICH [16] while Huttner *et al* reported no differences in haematoma expansion between these two agents for INR reversal within 2 hours, indicating that the faster and more efficacious PCC in INR reversal may be the contributing factor for reducing mortality [36]. However, we found PCC treatment did not better FFP in disability on discharge, possibly due to the small sample size or survivor effects. The volumes of fluid administered to patients with acute ICH are also relevant; infusing over 3000 ml of fluid increases the risk of decompensated heart failure, especially in those with underlying heart disease. Elevated systolic blood pressure may also lead to haematoma expansion and there is evidence that lowering blood pressure reduces haematoma expansion [37].

As with all meta-analysis, there are several limitations to be noted. Heterogeneity was detected within both the analyses comparing proportion of patients to achieve INR reversal between the treatment groups. Meta-analyses are susceptible to publication bias, although we found little evidence in our study, as indicated by funnel plots. There was variability in treatment within the PCC or FFP cohorts between the studies, making direct comparison by the two agents challenging. No selection criteria determined either the type of PCC that should be used (e.g. brand types, 3-F vs. 4-F) or the dosage amount for either PCC or FFP. Similarly, time for adequate INR reversal varied between studies, which may have skewed the results since PCC reverses INR faster than FFP, thus studies with shorter time allowed to target INR would show a greater favour towards PCC. The present study included both observational and RCTs to increase power of prediction due to paucity of published data from RCTs. As a result, bias may have been introduced from findings based on observational studies, although double-blind RCT would not be possible since methods of administration of FFP and PCC would be apparent to prescribers. This may explain, in part, conflicting results between previous studies on these two agents. Further, there were variable definitions of successful reversal of INR and short-term mortality. We chose the 90-day cut-off in this meta-analysis as the majority of papers defined outcome with this timescale [38]. Thus, we believe this timeframe is suitable for covering most deaths associated with PCC and FFP as most studies show that the majority of patients died within 48 hours of receiving FFP and 5 days of receiving PCC [16]. Finally, we did not asses the timeframe in which treatment was given. This was determined by the individual clinical teams of each patient and was too variable to assess or was not reported at all. Clearly, timing of intervention could affect our patient outcomes. However, as such timing was highly variable and it was left to individual clinicians to administer according to their own protocol, our study represents a real-world pragmatic scenario which could be argued makes our overall conclusions more realistic.

In conclusion, as an agent for urgent reversal of VKA, PCC outperforms FFP in 90day all-cause mortality including those with VKA-related intracranial haemorrhage, INR reversal and treatment-related adverse events.

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**Contributor and guarantor information:** PS and PB created the study concept and analysis design. RH performed the data collection and wrote the first draft, analysed, interpreted the data. TSH further edited the draft. PS, PB, NM and IL edited and TSH revised the manuscript. All authors checked, interpreted results and approved the final version.

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# **LEGENDS**

**Figure 1.** PRISMA study flow diagram showing the application of the selection criteria.

**Figure 2.** Forest plot of 90day all-cause mortality in all VKA reversal trials comparing PCC against FFP.

**Figure 3.** Forest plot of patients achieving adequate INR reversal in all VKA reversal trials comparing PCC against FFP.

**Figure 4.** Forest plot comparing proportion of patients having at least one treatment related adverse event in all VKA reversal trials comparing PCC against FFP.

**Figure 5.** Forest plot comparing 90 day all-cause mortality in all VKA reversal trials for the treatment of ICH for PCC against FFP.

**Figure 6.** Forest plot comparing the proportion of patients who achieved the INR target in all VKA reversal trials for the treatment of ICH for PCC against FFP.

**Figure 7.** Risk of bias assessments for studies of PCC and FFP in emergency VKA reversal.

**SUPPLEMENTARY MATERIAL**

**Supplementary Figure 1.** Forest plot of patients suffering at least one thromboembolic events in all VKA reversal trials comparing PCC against FFP.

**Supplementary Figure 2.** Forest plot of patients requiring at least one RBC transfusion in all VKA reversal trials comparing PCC against FFP.

**Supplementary Figure 3.** Mean difference in units of RBCs transfused in all VKA reversal trials comparing PCC to FFP.

**Supplementary Figure 4.** Forest plot of patients having at least one adverse event in all VKA reversal trials comparing PCC against FFP

**Supplementary Figure 5.** Forest plot comparing proportion of patients who had at least one fluid overload event in all VKA reversal trials comparing PCC against FFP.

**Supplementary Figure 6.** A forest plot comparing mRS outcome (0-3) at 90 days or discharge in all VKA reversal trials for the treatment of ICH for PCC against FFP.

**Supplementary Figure 7**. Funnel plots A-E for **Figures 2-6** respectively**.**

**Supplementary Figure 8**. Forest plot of 90day all-cause mortality using only RCTs.