



## ORIGINAL CONTRIBUTION

# Safety of a Four-factor Prothrombin Complex Concentrate Versus Plasma for Vitamin K Antagonist Reversal: An Integrated Analysis of Two Phase IIIb Clinical Trials

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## Abstract

**Objectives:** Clinicians often need to rapidly reverse vitamin K antagonists (VKAs) in the setting of major hemorrhage or urgent need for surgery. Little is known about the safety profile of the traditional reversal agent, plasma, or the newly approved agent, four-factor prothrombin complex concentrate (4F-PCC), in a randomized setting. This is an integrated analysis of safety data from two clinical trials that evaluated 4F-PCC versus plasma for the treatment of patients requiring rapid VKA reversal for acute major bleeding or prior to an urgent surgical/invasive procedure.

**Methods:** This descriptive analysis comprised adverse event (AE) data from two phase IIIb, randomized, controlled trials. The bleeding and surgical studies were performed across 36 and 33 sites, respectively, in nine countries, with the integrated analysis comprising 388 patients (4F-PCC,  $n = 191$ ; plasma,  $n = 197$ ) aged  $\geq 18$  years, who required VKA reversal due to major bleeding or prior to an urgent surgical/invasive procedure. Patients received either 4F-PCC, containing nonactivated factors II, VII, IX, and X and proteins C and S (Beriplex/Kcentra, CSL Behring) or plasma, both dosed according to baseline international normalized ratio and body weight. Patients were also to receive vitamin K1. AEs and serious AEs (SAEs) were assessed up to days 10 and 45, respectively.

**Results:** The proportion of patients with AEs (4F-PCC, 115/191 [60.2%]; plasma, 124/197 [62.9%]) and SAEs (4F-PCC, 54/191 [28.3%]; plasma, 49/197 [24.9%]) was similar between groups. The proportion of patients with thromboembolic events was also similar between groups (4F-PCC, 14/191 [7.3%]; plasma, 14/197 [7.1%]). There were 13 (6.8%) deaths in the 4F-PCC group and 13 (6.6%) in the plasma group. Fluid overload events occurred in more patients in the plasma group than the 4F-PCC group (25 [12.7%] and 9 [4.7%], respectively).

**Conclusions:** These safety data represent the largest controlled assessment of a 4F-PCC to date. For patients requiring urgent VKA reversal, 4F-PCC had a safety profile similar to that of plasma (AEs, SAEs, thromboembolic events, and deaths), but was associated with fewer fluid overload events.

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In the United States, clinicians prescribe the vitamin K antagonist (VKA) warfarin to 3.4 million patients each year for the treatment and prophylaxis of various prothrombotic conditions.<sup>1</sup> Although effective for this indication, its use is often associated with adverse drug-related events; data collected between 2007 and 2009 implicate warfarin as the medication associated with the largest number of adverse drug events requiring emergency treatment in patients over 65 years of age.<sup>2</sup> These events most commonly manifest as acute bleeding<sup>3</sup> and result in an estimated 33,000 hospitalizations per year.<sup>2</sup>

Patients receiving VKAs often require rapid anticoagulation reversal when they present with major bleeding or require urgent surgical or invasive procedures. Treatment options include vitamin K (oral or intravenous [IV]) concomitant with plasma or prothrombin complex concentrates (PCCs).<sup>4</sup> PCCs are lyophilized concentrates of vitamin K-dependent coagulation factors (F) either activated or nonactivated.<sup>5</sup> Many treatment guidelines recommend the use of nonactivated PCCs rather than plasma for rapid VKA reversal in case of major bleeding or prior to urgent surgery or other invasive procedure.<sup>6–9</sup> Currently, plasma is the most commonly used agent for VKA reversal in many countries, particularly in those where PCCs are not licensed for use.

Recently, two phase IIIb clinical trials were conducted to evaluate the efficacy and safety of a nonactivated four-factor prothrombin complex concentrate (4F-PCC) versus plasma for urgent VKA reversal.<sup>10,11</sup> The patients enrolled in the two studies had similar baseline characteristics, comorbidities, and reasons for receiving VKA therapy and thus may be considered to have been at similar risk of AEs when anticoagulation was reversed. The similarity of the two studies in terms of patient populations, treatment regimens and safety outcomes affords the opportunity to pool safety data. Compared with the single studies, this provides a larger data set with which to assess the safety profile of the two interventions and allows a wider evaluation of the full safety data set, including rare events such as thromboembolic events, fluid overload events, viral transmission, and deaths. Here, we present the first full analysis of the integrated safety data from the two randomized, controlled trials comparing 4F-PCC and plasma for urgent VKA reversal. Patient-level data on thromboembolic events and an in-depth analysis of fluid overload events have been published previously;<sup>14,15</sup> the present analyses aim to assess the overall safety profile of this 4F-PCC versus plasma, including deaths, viral transmission, and all other adverse events (AEs), when used in this setting.

## METHODS

### Study Design

This integrated analysis comprised AE data from two prospective, randomized, open-label, active-controlled, noninferiority, multicenter phase IIIb trials.<sup>10,11</sup> These trials investigated the use of a nonactivated 4F-PCC, containing FII, FVII, FIX, and FX and proteins C and S (Beriplex/Kcentra, CSL Behring, Marburg, Germany),

versus plasma in VKA-treated patients who required urgent anticoagulation reversal due to acute major bleeding (NCT00708435) or prior to an urgent surgical/invasive procedure (NCT00803101). Patients were randomized (1:1) to receive either 4F-PCC or plasma.

The primary endpoint of both studies was effective hemostasis in patients receiving 4F-PCC or plasma for rapid VKA reversal. The coprimary endpoint of both studies was rapid international normalization ratio (INR) reduction (INR  $\leq$  1.3 at 0.5 hours after the end of infusion). One of the secondary objectives of each of the studies was to compare the safety profile and tolerability of 4F-PCC and plasma. Further details of the study designs have been described previously.<sup>10,11</sup>

### Study Setting and Population

The acute bleeding and surgical studies were performed across 36 and 33 sites, respectively, in the United States, Europe, Russia, Belarus, and Lebanon. Both studies were sponsored by CSL Behring and registered at www.clinicaltrials.gov. They were approved by the independent ethics committees and institutional review boards of the participating centers and conducted in accordance with local ethics regulations. Informed consent was obtained from patients prior to participation in the trials.

Patients in the study populations of both clinical trials were  $\geq$  18 years of age, had received VKAs, had either presented with acute bleeding or required urgent surgery or other invasive procedure within 24 hours, and had an INR  $\geq$  2 during the 3 hours prior to the start of study treatment.<sup>10,11</sup> Acute major bleeding was based on International Society on Thrombosis and Haemostasis (ISTH) criteria and defined as one of the following: life-threatening or potentially life-threatening bleeding according to the treating physician, acute bleeding associated with a fall in hemoglobin  $\geq$  2 g/dL, or bleeding requiring blood product transfusion.<sup>10</sup> Exclusion criteria have been described previously.<sup>10,11</sup>

### Study Protocol

On Day 1, patients received an IV infusion of 4F-PCC or plasma, dosed according to baseline INR and body weight as shown in Table S1 (see Data Supplement S1, available as supporting information in the online version of this paper). All patients were also to receive vitamin K, which was administered according to American College of Chest Physicians guidelines (2008)<sup>12</sup> or local practice if different (2–10 mg). Vitamin K administration was not standardized in the protocol due to variations in local practice and guidelines.

### Funding/Support and Role of Sponsor

The two studies analyzed within this article were sponsored by CSL Behring. A steering committee of academic medical experts and representatives of the sponsor oversaw the design and conduct of the studies. The sponsor participated in the selection of the board members. The sponsor was responsible for data collection, management, and analysis of the data in each study according to a predefined statistical analysis plan. Preparation and review of the manuscript as well as decision to submit the manuscript for publication was

performed by a publication steering committee that included academic medical experts and representatives of the sponsor. Medical writing assistance was funded by the sponsor.

### Data Analysis

**Safety Analysis.** Adverse events. AEs defined as symptoms that developed or worsened following exposure to the study product, were coded using the Medical Dictionary for Regulatory Activities (MedDRA version 12.0). Further details of the AE definition can be found in the Supplementary Methods in Data Supplement S1. AEs were categorized as either “serious” or “nonserious.” We used the standard definition of serious AEs (SAEs) (Supplementary Methods, Data Supplement S1). Study investigators reported AEs up to day 10 (visit window days 7–11) and SAEs up to day 45 (visit window days 43–51). AEs were identified as possible thromboembolic events using the following standardized MedDRA queries (SMQs): embolic and thromboembolic events, arterial; embolic and thromboembolic events, venous; and embolic and thromboembolic events, vessel type unspecified and mixed arterial and venous. Data on fluid overload and similar cardiac events were collected utilizing the following SMQs: fluid overload, pulmonary edema, cardiac failure congestive, cardiac failure, and cardiac failure chronic.

**Safety Assessments.** The study investigators recorded AEs and SAE as described and assessed the relationship of these events to study treatment. AEs with a missing relationship to treatment were considered related. SAEs of interest (thromboembolic SAEs, late bleeding event SAEs, and deaths) were referred to a blinded safety adjudication board (SAB) for case confirmation and assessment of relatedness to study treatment. An independent data and safety monitoring board (DSMB) was responsible for evaluating safety and could also refer SAEs of interest to the SAB.

The methodology for AE/thromboembolic event identification, assessment, and adjudication in the studies was based on the predefined SMQ coding as defined in the statistical analysis plan (SAP) and the process for data review defined in the DSMB charter. Thromboembolic event counts in this paper reflect the prospective methodology noted. The FDA conducted an independent adjudication of thromboembolic events as part of their review for U.S. licensure of the 4F-PCC, resulting in a difference between the reported number of thromboembolic events in the published study results<sup>10,11</sup> and the package insert for the 4F-PCC in the United States.<sup>13</sup>

**Virus Safety.** We evaluated virus markers for hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV)-1/HIV-2, and parvovirus B19 (B19V) using enzyme immunoassay and polymerase chain reaction (PCR). The presence of each virus was determined before infusion of study product and at day 10 (B19V only), day 45 (HAV, HBV, HCV, and HIV-1/-2 only), and day 90 (HCV and HIV-1/-2 only).

**Integrated Analysis.** We used information from the two study databases to generate a report for all variables of interest for this integrated safety analysis. Patients were evaluated for safety if they received any portion of the study treatment and were analyzed “as treated.”

**Statistical Analysis.** We did not power the two trials to support a comparison of safety between treatment groups. Therefore, we treated testing of data as descriptive and reported all differences using ranges and confidence intervals (CIs). The CI for the risk difference was determined by the Newcombe-Wilson method using the correction for continuity.

## RESULTS

### Demographics and Treatment

A total of 388 patients were included in the pooled safety population; 191 received 4F-PCC and 197 received plasma (Data Supplement S1, Figure S1). The median (range) dose of 4F-PCC was 25 (15.5–50.5) IU/kg, administered in a volume of 90 (48–230) mL, which was infused over 17 (7–288) minutes. For plasma, the median (range) dose was 10 (3.9–17.7) mL/kg, representing a volume of 800 (353–1525) mL, which was infused in 120 (22–928) minutes. The demographics and baseline characteristics of the safety population were similar between treatment groups (Table 1).

### Integrated Safety Analysis

A summary of the integrated safety data from the two treatment groups is shown in Figure 1.

**Deaths.** Up to day 45 of the studies, 13 deaths occurred in each treatment group (difference between groups = 0.2% [95% CI = –5.3 to 5.8]). Causes of death are shown in Table 2. In each treatment group, no deaths were considered treatment related by the investigator. The SAB considered one death in each group to be possibly related to treatment (sudden death [day 7] in the 4F-PCC group and acute myocardial infarction [onset on day 4, death on day 8] in the plasma group). Deaths typically occurred at later time points in the 4F-PCC group than in the plasma group (Figure 2).

**AEs of Interest.** Thromboembolic Events. Possible thromboembolic events were reported in 14 patients in each treatment group (difference between groups = 0.2% [95% CI = –5.5 to 6.0]). Events considered by the site primary investigators to be treatment related were observed in eight of 191 (4.2%) patients in the 4F-PCC group and five of 197 (2.5%) patients in the plasma group (difference between groups = 1.7% [95% CI = –2.6 to 6.1]).

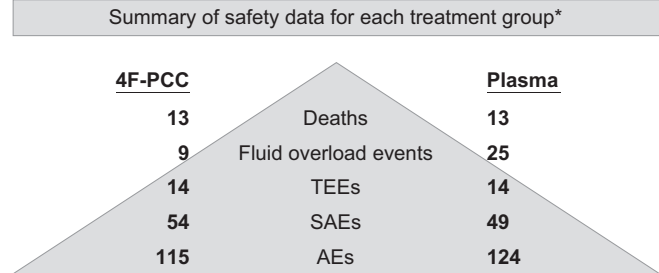
The FDA review of thromboembolic events identified 13 patients in the 4F-PCC group and 14 patients in the plasma group with possible events; this included confirmed thromboembolic events as well as deaths of unknown causes. Of these, 10 of 191 (5.2%) patients in the 4F-PCC group and eight of 197 (4.1%) patients in the plasma group had thromboembolic events that were considered treatment related.

**Table 1**  
Demographic and Baseline Characteristics (Safety Population)

Parameter	Analysis Pool (N = 388)	
	4F-PCC (n = 191)	Plasma (n = 197)
Sex, n (%)		
Female	87 (45.5)	89 (45.2)
Male	104 (54.5)	108 (54.8)
Age (y), mean (±SD)	69.8 (±13.5)	68.8 (±13.3)
Age group (y), n (%)		
<65	66 (34.6)	71 (36.0)
≥65 to <75	49 (25.7)	48 (24.4)
≥75	76 (39.8)	78 (39.6)
Race, n (%)		
White	179 (93.7)	175 (88.8)
Nonwhite	12 (6.3)	22 (11.2)
BMI (kg/m <sup>2</sup> ), mean (±SD)*	28.0 (±8.6)	27.9 (±7.1)
Region, n (%)		
United States	116 (60.7)	118 (59.9)
Rest of world	75 (39.3)	79 (40.1)
Preinfusion INR, n (%)		
<2	3 (1.6)	2 (1.0)
≥2 to <4	118 (61.8)	124 (62.9)
≥4 to ≤6	34 (17.8)	33 (16.8)
>6	35 (18.3)	37 (18.8)
Missing	1 (0.5)	1 (0.5)
Reason for VKA therapy, n (%)		
Arrhythmia	103 (53.9)	89 (45.2)
Thromboembolic event	30 (15.7)	41 (20.8)
Vascular disease	27 (14.1)	33 (16.8)
Artificial heart valve or joint	27 (14.1)	27 (13.7)
Other	4 (2.1)	7 (3.6)
Medical history (most frequently listed terms), n (%)		
Hypertension	161 (84.3)	162 (82.2)
Atrial fibrillation	117 (61.3)	111 (56.3)
Coronary artery disease	65 (34.0)	59 (29.9)
Anemia	61 (31.9)	55 (27.9)
Cardiac failure congestive	50 (26.2)	54 (27.4)
VKA reversal due to acute major bleeding	n = 103	n = 109
Type of acute bleed, n (%)		
Gastrointestinal/other nonvisible	63 (61.2)	64 (58.7)
Visible	18 (17.5)	25 (22.9)
Intracranial hemorrhage	12 (11.7)	12 (11.0)
Musculoskeletal	10 (9.7)	8 (7.3)
VKA reversal prior to urgent surgery	n = 88	n = 88
Type of surgery/invasive procedure, n (%)		
Other surgical	50 (56.8)	49 (55.7)
Major orthopedic	20 (22.7)	18 (20.5)
Invasive procedure	14 (15.9)	17 (19.3)
Cardiothoracic	3 (3.4)	3 (3.4)
Cranial neurosurgical	1 (1.1)	1 (1.1)

4F-PCC = four-factor prothrombin complex concentrate; BMI = body mass index; INR = international normalized ratio; VKA = vitamin K antagonist.  
\*BMI data only available for 183 patients in 4F-PCC group and 196 patients in the plasma group.

Serious possible thromboembolic events occurred in eight of 191 (4.2%) patients in the 4F-PCC group and 10 of 197 (5.1%) patients in the plasma group and were reviewed by the blinded SAB (difference between groups = -0.9% [95% CI = -5.8 to 4.0]). The SAB adjudicated that four patients in the 4F-PCC group (2.1% of 4F-PCC-treated patients) and six patients in the plasma group (3.0% of plasma-treated patients) had serious



**Figure 1.** Summary of safety data. \*Data represent the number of patients in each group experiencing each AE/outcome. 4F-PCC = four-factor prothrombin complex concentrate; AE = adverse event; SAE = serious adverse event; TEE = thromboembolic event.

thromboembolic events that were treatment related (difference between groups = -1.0% [95% CI = -5.0 to 3.0]). Further details on the thromboembolic events that occurred in the studies are published separately.<sup>14</sup>

**Fluid Overload and Similar Cardiac Events.** Fluid overload and similar cardiac events were reported in 25 of 197 (12.7%) patients in the plasma group, compared with nine of 191 (4.7%) in the 4F-PCC group (difference between groups = -8.0% [95% CI = -14.1 to -2.0]). Some patients experienced > 1 event; there were 29 events in 25 patients in the plasma group and 11 events in nine patients in the 4F-PCC group. (Subsequent to the publication of the efficacy analysis of the acute bleeding study, an additional fluid overload event was reported in the 4F-PCC treatment group. This additional event was omitted from the fluid overload count in the bleeding study efficacy manuscript<sup>10</sup> due to a coding error; however, it appeared in the AE count and is included in the integrated analysis of fluid overload events reported here.) Investigators did not consider any fluid overload or similar cardiac events related to 4F-PCC treatment, whereas 14 events in the plasma group were considered treatment related (difference between groups = -7.1% [95% CI = -11.9 to -3.2]). Further details on the fluid overload events that occurred in the studies are published separately.<sup>15</sup>

**Virus Safety Results**

In patients treated with 4F-PCC, no viral transmission was confirmed. In the plasma group, two patients each had a single AE suggestive of viral transmission. For one patient, PCR testing for B19V changed from negative before infusion to positive by day 10 of the study. The patient did not have any other associated AEs, and follow-up testing was not performed. The other patient with test results suggestive of viral transmission had a positive HCV nucleic acid test result at day 45; however, transaminases, antibody, and nucleic acid test results were found to be negative upon follow-up testing.

**Overall AEs.** Overall, the proportion of patients with one or more AE was similar between treatment groups; these were reported in 115 of 191 (60.2%) and 124 of 197 (62.9%) patients in the 4F-PCC group and plasma group, respectively (Table 3). The most common AEs

Table 2  
Listings of Deaths up to Day 45 (Pooled Safety Population)

Patient	Day	Age at Study Entry (y)	Cause of Death (Investigator Term)	SAB Causality	Abbreviated Patient Narrative and SAB Review
<i>4F-PCC</i>					
K1	3	82	Increased size of ICH	Not related	<ul style="list-style-type: none"> <li>• Patient entered the study with ICH and was diagnosed with an increased size of ICH on day 1 of the study</li> <li>• The patient died 2 days later</li> </ul>
K2	5	75	Gradual worsening of cardiogenic heart failure	Not related	<ul style="list-style-type: none"> <li>• On day 5 of the study, following administration of plasma and activated factor VII, the patient, who had significant cardiac history, experienced “gradual worsening of cardiogenic heart failure”</li> <li>• There was no evidence of a thromboembolic event</li> <li>• The SAB assessed the cause of death to be due to ICH and cardiomyopathy</li> </ul>
K3	6	78	GI hemorrhage	Not related	<ul style="list-style-type: none"> <li>• The cause of death was unclear; severe anemia in an elderly man with cardiac disease could be primary/ contributing factor</li> </ul>
K4	7	68	Intestinal obstruction*	Not related	<ul style="list-style-type: none"> <li>• The cause of death was posthemorrhagic anemia due to postprocedure rupture of lumbar vein to the IVC</li> <li>• IVC rupture led to renal failure, multiorgan failure and death</li> <li>• None of these events, or death, were related to treatment according to the SAB</li> </ul>
K5	7	56	Sudden death	Possibly related	<ul style="list-style-type: none"> <li>• The patient died at home and the cause of death is unknown</li> <li>• Possible etiologies include PE, CVA, MI, rebleeding, or sepsis</li> <li>• The patient had multiple medical problems, including a history of iliofemoral DVT, which increases the risk of a TEE</li> <li>• Due to a compatible time course and the unknown cause of death, the SAB assessed the event as possibly related to study product administration</li> </ul>
K6	26	66	Sepsis	Not related	<ul style="list-style-type: none"> <li>• On day 4 of the study, the patient developed sepsis</li> <li>• The death may be explained by the patient’s many risk factors for infection and multiple comorbidities</li> </ul>
K7	26	66	Worsening advanced-stage lung cancer	Not related	<ul style="list-style-type: none"> <li>• Worsening of advanced-stage lung cancer was diagnosed on the day of product administration</li> <li>• The patient was discharged after 6 days and died on day 26</li> </ul>
K8	29	71	Acute renal failure	Not related	<ul style="list-style-type: none"> <li>• The patient developed acute renal failure on day 25 of the study</li> <li>• The patient was placed on comfort care and died 4 days later</li> <li>• Cause of death was acute or chronic renal failure with underlying liver disease</li> <li>• Due to the lack of temporal relationship and the patient’s medical history (end-stage liver disease, chronic renal insufficiency), the SAB considered the death not related to study product administration</li> </ul>
K9	30	84	Pancreatic cancer	Not related	<ul style="list-style-type: none"> <li>• The death was due to pancreatic cancer; this was diagnosed 1 day after product administration but the onset clearly preceded study entry</li> </ul>
K10	31	54	Cardiopulmonary arrest	Not related	<ul style="list-style-type: none"> <li>• The SAB assessed the exact cause of death as unknown</li> <li>• Possible causes include pneumonia, acute aspiration, PE, arrhythmia, MI, or CNS event</li> </ul>
K11	33	79	Respiratory failure	Not related	<ul style="list-style-type: none"> <li>• The SAB considered the cause of death to be secondary to the underlying conditions, respiratory disease (COPD) and congestive heart failure</li> </ul>
K12	34	73	Stage IV lung cancer	Not related	<ul style="list-style-type: none"> <li>• The cause of death was secondary to metastatic lung cancer</li> </ul>

(Continued)

Table 2 (continued)

Patient	Day	Age at Study Entry (y)	Cause of Death (Investigator Term)	SAB Causality	Abbreviated Patient Narrative and SAB Review
K13	38	88	MI	Not related	<ul style="list-style-type: none"> <li>The patient died at home and the exact cause of death was unknown</li> <li>Possible causes of death include recurrent GI bleeding, aortic stenosis, sudden cardiac death, recurrent hypoglycemia, and CVA</li> <li>As the death occurred 37 days after treatment, and there was no evidence of a TEE, the SAB considered the death unrelated to study treatment</li> </ul>
<i>Plasma</i> P1	4	89	Systemic infection	Not related	<ul style="list-style-type: none"> <li>The cause of death was likely secondary to systemic infection, which occurred 3 days after study product administration</li> </ul>
P2	6	74	Cardiorespiratory arrest	Not related	<ul style="list-style-type: none"> <li>On day 3, the patient developed bronchopneumonia</li> <li>The patient's condition worsened; sepsis and respiratory failure were diagnosed on day 5. This led to a cardiac arrest on day 6</li> <li>The cause of death was likely secondary to bronchopneumonia and underlying COPD and was considered not related to treatment</li> </ul>
P3	7	85	Worsening metastatic lung cancer	Not related	<ul style="list-style-type: none"> <li>The SAB agreed with the assessment of cause of death as being metastatic lung carcinoma</li> </ul>
P4	7	80	Progression of hemorrhagic anemia	Not related	<ul style="list-style-type: none"> <li>The cause of death was attributed to respiratory insufficiency due to hypoxemia and anemia, with an underlying cause of GI bleed</li> </ul>
P5	8	61	Acute MI	Possibly related	<ul style="list-style-type: none"> <li>On day 4, the patient had a MI</li> <li>Stenosis of the coronary artery was carried out and the stent was placed successfully</li> <li>The patient had further complications including ventricular fibrillation and cardiogenic shock</li> <li>A coronary angiogram on day 6 indicated a new occlusion of the right coronary artery, and coronary bypass surgery was performed</li> <li>On day 7, the patient went into ventricular tachycardic rhythm</li> <li>The patient did not respond to attempts to increase blood pressure and died on day 8</li> <li>The SAB adjudicated that the TEEs (coronary artery occlusions) and death were possibly related to study product administration</li> </ul>
P6	13	85	Worsening congestive heart failure	Not related	<ul style="list-style-type: none"> <li>Three days after study product administration, the patient experienced worsening of congestive heart failure</li> <li>The patient was placed on comfort care and died on day 13</li> <li>Due to the lack of temporal relationship, the SAB considered the death not related to treatment</li> </ul>
P7	14	80	Septic shock	Not related	<ul style="list-style-type: none"> <li>The cause of death was likely secondary to septic shock with underlying pneumonia</li> </ul>
P8	16	92	Pulmonary embolism	Not related	<ul style="list-style-type: none"> <li>There was no evidence or symptoms of pulmonary embolism; the SAB considered that the cause of death was likely to be profound anemia resulting in congestive heart failure in an already compromised cardiac patient</li> </ul>
P9	17	72	Death (unknown cause)	Not related	<ul style="list-style-type: none"> <li>No clinical symptoms of thrombosis were reported</li> <li>During initial hospitalization, the patient developed bradycardia and cardiac arrest</li> <li>The patient did not respond to life support treatment</li> <li>The death appeared to be secondary to sepsis with underlying ventilator-associated pneumonia</li> </ul>
P10	17	68	Cardiac arrest†	Not related	
P11	22	71	Septic shock	Not related	<ul style="list-style-type: none"> <li>The patient presented with an intra-abdominal infection and pneumonia</li> <li>A complicated hospital course progressed to septic shock</li> </ul>
P12	24	72	Worsening hepatic failure	Not related	<ul style="list-style-type: none"> <li>The death was secondary to liver failure, which occurred 22 days after study product administration</li> </ul>

(Continued)

Table 2 (continued)

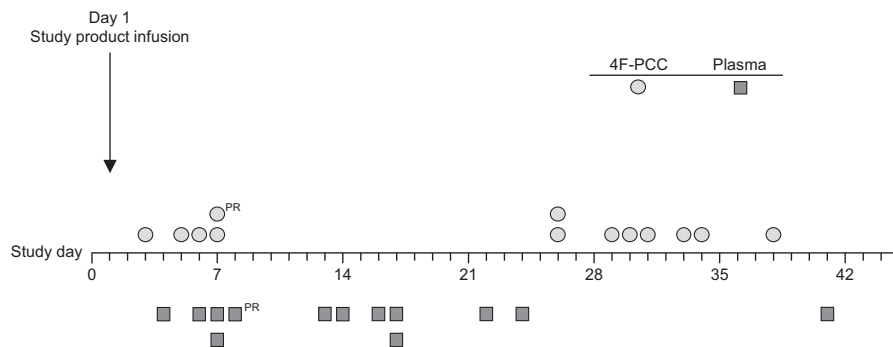
Patient	Day	Age at Study Entry (y)	Cause of Death (Investigator Term)	SAB Causality	Abbreviated Patient Narrative and SAB Review
P13	41	62	Tumor hemorrhage	Not related	<ul style="list-style-type: none"> <li>On day 39, the patient presented with brain metastasis accompanied by hemorrhage, which resulted in cerebral swelling and coma</li> <li>The course of events was consistent with progression of an underlying disease</li> <li>Neither the time course nor the hemorrhagic event was consistent with study product causality</li> <li>The SAB assessed the cause of death to be breast cancer metastatic to the brain</li> </ul>

The FDA assessed all deaths with unknown causes as TEEs, which differed from the study investigators/SAB, resulting in a difference in the numbers of TEEs reported in the published study results<sup>10,11</sup> and the package insert for the 4F-PCC in the United States.<sup>13</sup> In the package insert, tabulation of TEEs included three patients in the 4F-PCC group who died of unknown causes on days 7, 31, and 38 (K5, K10, and K13) and one patient in the plasma group who died of unknown causes on day 18 (P9); patients K5, K10, and P9 were included in the TEE count by the FDA, but not included in the TEE count as assessed using the predefined SMQs.

COPD = chronic obstructive pulmonary disease; CNS = central nervous system; CVA = cerebrovascular accident; DVT = deep vein thrombosis; GI = gastrointestinal; ICH = intracranial hemorrhage; IVC = inferior vena cava; MI = myocardial infarction; PE = pulmonary embolism; SAB = safety adjudication board; SMQs = standardized MedDRA queries; TEE = thromboembolic event.

\*SAB assessed cause of death to be postprocedure rupture of inferior vena cava.

†SAB assessed cause of death to be ventilator-associated pneumonia.



**Figure 2.** Timeline of deaths that occurred in the two studies. In the 4F-PCC group, most of the deaths (8/13; 61.5%) occurred on or after day 26; in the plasma group, all except one of the deaths occurred before day 26. 4F-PCC = four-factor prothrombin complex concentrate; PR = possibly related.

reported up to day 10 in the 4F-PCC group were constipation (15 patients; 7.9%), headache (14 patients; 7.3%), peripheral edema (12 patients; 6.3%), and hypotension (12 patients; 6.3%). In the plasma group, the most common AEs were hypokalemia (14 patients; 7.1%), peripheral edema (13 patients; 6.6%), anemia (12 patients; 6.1%), and constipation (12 patients; 6.1%) (Data Supplement S1, Table S2).

Investigators did not consider most of the AEs related to study product administration; the proportion of patients with AEs judged by the investigator to be at least possibly related to treatment was 9.4% (18/191) and 19.3% (38/197) in the 4F-PCC and plasma groups, respectively (Table 3). There were no patients in the 4F-PCC group who discontinued treatment due to an AE, whereas three of 197 (1.5%) patients discontinued treatment for this reason in the plasma group (fluid overload, transfusion reaction, and hyperthermia).

The frequency of SAEs, including those related to treatment, was similar between groups (Table 3). SAEs

were reported for 54 of 191 (28.3%) patients in the 4F-PCC group and 49 of 197 (24.9%) patients in the plasma group. Six SAEs that were considered at least possibly treatment related were reported in five patients in the 4F-PCC group (ischemic stroke [*n* = 2], deep vein thrombosis [*n* = 2], thrombosis [*n* = 1], and venous insufficiency [*n* = 1]; Data Supplement S1, Table S3). Seven patients in the plasma group experienced treatment-related SAEs (myocardial ischemia [*n* = 2], fluid overload [*n* = 1], embolic cerebral infarction [*n* = 1], acute pulmonary edema [*n* = 1], respiratory failure [*n* = 1], and deep vein thrombosis [*n* = 1]).

**DISCUSSION**

This analysis illustrates the safety profile of a 4F-PCC compared with plasma for urgent VKA reversal and represents the largest full safety assessment of any PCC to date to use randomized controlled clinical trial data. Overall, the incidence of AEs, SAEs, thromboembolic

Table 3  
Overview of AEs (Pooled Safety Population)

AE (MedDRA Preferred Term)	Number (%) of Patients		
	4F-PCC ( <i>n</i> = 191)	Plasma ( <i>n</i> = 197)	Difference Between Groups (95% CI),* 4F-PCC – plasma
Any AE†	115 (60.2)	124 (62.9)	–2.7 (–12.7 to 7.2)
Treatment-related AE‡	18 (9.4)	38 (19.3)	–9.9 (–17.2 to –2.5)
AE leading to treatment discontinuation	0	3 (1.5)	–1.5 (–4.7 to 1.2)
SAE§	54 (28.3)	49 (24.9)	3.4 (–5.7 to 12.5)
Treatment-related SAE	5 (2.6)	7 (3.6)	–0.9 (–5.2 to 3.3)

4F-PCC = four-factor prothrombin complex concentrate; AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities Version 12.0; SAE = serious adverse event.  
 \*Difference in proportion of events (expressed as a percentage), proportion in 4F-PCC group – proportion in plasma group.  
 †AEs were reported to day 11.  
 ‡Treatment-related AEs were defined as events whose relationship to study treatment was related, probably related, or possibly related in the opinion of the investigator. AEs with missing relationships were considered related to treatment.  
 §SAEs were reported to day 51.

events, and deaths was similar in patients receiving either 4F-PCC or plasma. Fewer fluid overload events occurred in the 4F-PCC group than the plasma group. No AEs associated with viral transmission were reported in the 4F-PCC group, whereas one patient in the plasma group may have been exposed to B19V. The majority of the deaths were considered not related to treatment and were generally reflective of the age and underlying comorbidities of the study population.

Efficacy analyses have been reported previously;<sup>10,11</sup> in summary, the 4F-PCC was noninferior to plasma for effective hemostasis and superior for rapid INR reversal in cases of major bleeding<sup>10</sup> and superior for both outcomes in patients requiring urgent surgical intervention.<sup>11</sup> An integrated efficacy analysis of rapid INR reversal would simply strengthen the superiority demonstrated in both studies, but a combined clinical hemostatic efficacy analysis is problematic as the hemostatic efficacy scales were necessarily different in the disparate clinical settings of major hemorrhage versus need for urgent surgery. Therefore, the hemostatic efficacy results cannot be readily combined. However, taking these efficacy data together with the safety findings reported in the present analysis and the advantages of 4F-PCC in terms of the smaller volume administered and shorter time of infusion,<sup>10,11</sup> we suggest that 4F-PCC is an effective alternative to plasma for rapid VKA reversal.

All VKA reversal strategies may be associated with AEs. Generally, patients receiving VKAs have underlying comorbidities, and those requiring emergency reversal can be moderately or critically ill at the time of treatment. Therefore, it can be difficult to determine whether AEs occur due to a patient's underlying comorbidity, the acute medical condition for which they are being treated, or the reversal strategy used.

#### Safety Profile of 4F-PCCs: Results in Context With Previous Studies

Available data on the safety profile of 4F-PCCs for VKA reversal are generally from small study populations,<sup>16–19</sup> or from large pharmacovigilance studies,<sup>20</sup> which are based on voluntary reporting to regulatory bodies and

tend to underestimate the incidence of AEs. The majority of these studies do not have a comparison group. As such, there are few data available with which to place our study into context with the current literature. In the only other randomized trial of VKA (warfarin, acenocoumarol, or phenprocoumon) reversal, Demeyere et al.<sup>16</sup> compared the efficacy of a 4F-PCC (Cofact, Sanquin, Amsterdam, the Netherlands) and plasma in 40 patients undergoing cardiopulmonary bypass surgery. In this study, seven of 20 (35.0%) and nine of 20 (45.0%) patients reported AEs in the 4F-PCC and plasma groups, respectively. These proportions are slightly lower than those reported in the present study, which could be explained by the smaller study population size or the different dosing schedule used (patients received half the calculated 4F-PCC dose prior to surgery and the other half after surgery). No thromboembolic events were reported in either treatment group.<sup>16</sup>

The overall incidence of SAEs in our study is higher than that reported by a retrospective study of patient records to determine the AE frequency in patients treated with plasma (*n* = 149) or a 4F-PCC (*n* = 165) for emergency VKA reversal.<sup>21</sup> However, a direct comparison between these results and our study is difficult owing to differences in study design, including the 4F-PCC product and dose used, inclusion/exclusion criteria, and the shorter follow-up period (7 days). The study reported a significantly higher incidence of SAEs in patients who received plasma compared with those who received 4F-PCC (19.5% vs. 9.7%, *p* = 0.0164). After adjusting for medical history and reason for treatment, the increased incidence of SAEs in the plasma group remained significant (relative risk = 1.85, 95% CI = 1.03 to 3.31, *p* = 0.0384).

#### AEs of Interest When Reversing VKAs

Although the association of PCCs with thromboembolic events has historically been a concern, small prospective studies investigating the use of PCCs have reported a low incidence of these events (0%–4.6%).<sup>17–19,22</sup> Two comprehensive reviews evaluating the safety and thrombogenicity of PCCs concluded that patients treated with PCCs for VKA reversal have a low risk of



thromboembolic events;<sup>23,24</sup> the meta-analysis conducted by Dentali et al.<sup>24</sup> estimated the incidence of these events as 1.8% (95% CI = 1.0 to 3.0) in patients treated with 4F-PCCs. A pharmacovigilance study of safety data on the 4F-PCC used in this study, collected from February 1996 to March 2012, also reported a low incidence of thromboembolic complications (approximately one event per 31,000 infusions).<sup>20</sup> In the present study, thromboembolic events occurred with similar frequencies in the 4F-PCC and plasma treatment groups. Thromboembolism may occur in this patient population due to underlying predisposing risk factors, the acute medical condition for which they are being treated, their acute care hospitalization or, finally, either a delay in reinitiating or the complete withdrawal of anticoagulation therapy, rather than the treatment option used for VKA reversal.<sup>25,26</sup>

Observational data, including the Serious Hazards of Transfusion (SHOT) hemovigilance reporting scheme, have shown that plasma use is associated with fluid overload events.<sup>27–29</sup> A lower incidence of fluid overload and related cardiac events would be expected in patients treated with 4F-PCC versus plasma because 4F-PCCs are administered in smaller volumes. In the studies reported here, median infusion volumes were almost nine times larger for plasma than for 4F-PCC. Our data are the first from randomized controlled studies to indicate an increased frequency of fluid overload events in patients treated with plasma compared with those treated with 4F-PCC. Three patients in the plasma group discontinued treatment owing to AEs, one of which was fluid overload, whereas no patients discontinued treatment for this reason in the 4F-PCC group. However, since the infusion duration for 4F-PCC is shorter than for plasma (<20 minutes vs. hours),<sup>10</sup> there is more opportunity to discontinue plasma before the end of infusion compared with 4F-PCC.

Plasma may still have a role in rapid VKA reversal in younger patients (who typically have better cardiac reserve) or in patients with hemorrhagic shock who are in need of volume resuscitation. While the cost per unit of plasma is lower than that for PCCs, the cost-effectiveness of PCCs versus plasma is currently unclear. Plasma administration is associated with the development of several complications, such as fluid overload, which may lead to increased duration of hospitalization and treatment costs.<sup>30</sup>

The manufacturing process of PCCs involves a series of viral inactivation and elimination steps, which results in a minimal risk of viral transmission. In the present analysis, and in a pharmacovigilance study of the same 4F-PCC used in this analysis,<sup>20</sup> there was no evidence of confirmed viral transmission in patients treated with 4F-PCC.

### Relevance to Clinical Practice

Although many guidelines recommend 4F-PCC rather than plasma for urgent VKA reversal,<sup>6–9</sup> there is little comparative evidence about the safety of these products available in the literature. These safety data represent the largest randomized controlled assessment of a 4F-PCC in comparison with plasma in patients

receiving VKAs who require urgent replacement of vitamin K–dependent clotting factors. The study showed that this 4F-PCC has a similar safety profile to that of plasma, but may be associated with fewer fluid overload events.

### LIMITATIONS

Our study has a number of strengths and limitations. The analyses presented here use data from the two largest, prospective, randomized controlled trials of VKA reversal. However, neither of the trials were powered to demonstrate significant differences between the treatment groups for safety outcomes. Although there may be pathophysiologic differences between preoperative patients and bleeding patients, pooling the data from the two studies allows further investigation of rare events such as thromboembolic events, fluid overload events, and deaths and provides an overall assessment of 4F-PCC safety in patients requiring VKA reversal in two settings. Another limitation was that the clinicians and study investigators could not be blinded to study treatment allocation due to differences in the administration of 4F-PCC and plasma. However, a blinded SAB assessed deaths and serious thromboembolic events for relatedness to treatment.

### CONCLUSIONS

Overall, the results demonstrate that four-factor prothrombin complex concentrate has a similar safety profile to plasma for patients who require urgent vitamin K antagonist reversal; incidences of adverse events, serious adverse events, thromboembolic events, and deaths were similar between treatment groups, but four-factor prothrombin complex concentrate may be associated with fewer fluid overload events than plasma.

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### Supporting Information

The following supporting information is available in the online version of this paper:

**Data Supplement S1.** Supplemental material.