Coagulation Factor Plasma Levels Following Administration of a 4-Factor Prothrombin Complex Concentrate for Rapid Vitamin K Antagonist Reversal in Japanese Patients ☆

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A B S T R A C T

Background: Four-factor prothrombin complex concentrates (4F-PCCs) have been approved for urgent vitamin K antagonist reversal in Western countries for many years. Ethnicity and genetic variations between populations may influence the pharmacokinetic profile of 4F-PCC treatments.
Objective: To report plasma levels of vitamin K-dependent coagulation factors and proteins C and S in Japanese patients following administration of a 4F-PCC approved recently in Japan.
Methods: This was a subanalysis of a prospective, open-label, Phase IIIb study in Japanese patients requiring rapid vitamin K antagonist reversal owing to major bleeding (n = 6) or need for urgent surgery (n = 5). International normalized ratio and plasma levels of factors II, VII, IX, and X, and proteins C and S were measured before PCC infusion and at specific time points for the next 24 hours. Adverse events and serious adverse events were recorded up to Day 14 and 45, respectively.
Results: Rapid increases in plasma concentrations 30 minutes following 4F-PCC infusion were seen for all factors and proteins C and S, with median concentrations compared with baseline increasing by ≥100% and 70% in the bleeding and surgical groups, respectively. A concurrent decrease in international normalized ratio was observed. Plasma levels for each factor and protein remained within physiologic levels throughout the assessment period. No relationship between thromboembolic events and elevated plasma levels was identified.
Conclusions: Administration of 4F-PCC in Japanese patients receiving vitamin K antagonist anticoagulation therapy resulted in rapid and sustained increases in plasma levels and was well tolerated, indicating that this treatment is effective for the urgent reversal of vitamin K antagonist therapy in this population.

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Introduction

Vitamin K antagonists (VKAs) are frequently prescribed for the prevention and treatment of thromboembolic events (TEEs). Bleeding events are a known risk of anticoagulation therapy—annually, approximately 1% to 7% of VKA-treated patients in Western countries[1,2] and 6.6% of VKA-treated Japanese patients experience major bleeding.[3] In cases of major bleeding or need for urgent surgery, these patients require rapid VKA reversal.

Nonactivated 4-factor prothrombin complex concentrates (4F-PCCs) have long been approved and recommended in Europe for urgent VKA reversal[4–6]; and based on results from 2 large, multinational randomized controlled trials (RCTs) (primarily US and European sites) evaluating 4F-PCC use for urgent VKA reversal in patients with acute major bleeding[7] or needing urgent surgical intervention,[8] a 4F-PCC (Kcentra; CSL Behring, Marburg, Germany) was also approved in the United States. During March 2017, the same 4F-PCC was approved in Japan based on this global clinical program and the results of a Phase IIIb study in Japanese patients.[9]

Pharmacokinetic (PK) analyses in specific ethnicities are an important consideration for the licensing of new medicines[10] because ethnicity and genetic variability may influence the PK profile of a medicine and also individual response to therapies. In particular, PK profiles are known to differ between global and Japanese populations and studies have demonstrated that in some cases lower doses administered in Japanese populations lead to similar drug exposure, efficacy, and safety profiles as seen in global populations.[11–13] Furthermore, current guidelines for patients with nonvalvular atrial fibrilliation taking VKAs recommend different therapeutic international normalized ratio (INR) ranges in different regions, with US guidelines recommending an INR of 2.0 to 3.0 for all patients,[14] and Japanese guidelines recommending an INR of 2.0 to 3.0 for patients younger than age 70 years but 1.6 to 2.6 in those aged 70 years or older.[15]

This short report discusses the effect of 4F-PCC infusion on the plasma levels of the vitamin K-dependent coagulation factors and proteins C and S in VKA-anticoagulated Japanese patients requiring rapid reversal of anticoagulation before an urgent surgical/invasive procedure or due to acute major bleeding.

Methods

This was a subanalysis of a prospective, open-label, single-arm Phase IIIb study (ClinicalTrials.gov identifier: NCT02281201) conducted in Japan (November 2014–March 2016). Written informed consent was obtained from all patients (or their legally authorized representatives). The study was sponsored by CSL Behring, approved by the independent ethics committees of the participating centers, and performed in accordance with local ethical and legal requirements; written informed consent was obtained from all patients (or legally authorized representatives).

The methods of the study, including study design, treatment allocation, and inclusion/exclusion criteria, have been described in detail elsewhere.[9] Briefly, VKA-treated Japanese patients presenting with an INR ≥ 2.0 and requiring rapid anticoagulation reversal for either an acute major bleeding event (bleeding group) or before an urgent surgical/invasive procedure (surgical group) were enrolled. Patients received 4F-PCC (Beriplex; CSL Behring, Marburg, Germany); also marketed as Kcentra, dosed according to baseline INR and bodyweight (INR between ≥ 2.0 and < 4.0, 25 IU/kg, INR between ≥ 4.0 and ≤ 6.0, 35 IU/kg, and INR > 6.0, 50 IU/kg), and concomitant vitamin K was administered according to local practice.

The plasma activity levels of factors II, VII, IX, X, and proteins C and S were measured at the same points in time as the multinational RCTs by Goldstein et al[8] and Sarode et al,[7] namely, within 3 hours before the start of 4F-PCC infusion and 0.5, 1, 3, 6, 12, and 24 hours following the end of infusion. Blood collection and sample preparation was performed at each site according to their specified standards. In brief, 4.5 mL blood was drawn into a sodium citrate tube, inverted gently 3 to 4 times and centrifuged for 15 minutes at 4000 to 5000 rpm. The plasma was transferred into a 3.6 mL transfer tube and centrifuged again for 15 minutes at 4000 to 5000 rpm. Plasma samples (1 mL) were then extracted, transported to the central laboratory, and stored at –70 °C until analysis, where they were thawed in a water bath at 37 °C. Analysis of the coagulation factors was performed using 1-stage clotting assays with commercially available reagents (Thromborel S and Pathromtin SL) purchased from Siemens Healthineers, Erlangen, Germany. Determination of protein C and S was performed with Berichrom Protein C and Innovance Protein S assays (Siemens Healthineers). All assays were processed on a BCS device (Siemens Healthineers) calibrated against standard human plasma.

Factor levels (activity) were summarized by descriptive statistics, as described previously.[9] C_{max} was observed as maximum plasma level and AUC_{last} was area under the curve from the beginning of infusion to the last measurable plasma level using the actual sampling times. All values were baseline corrected. The classical and incremental in vivo recovery (IVR) were determined for each coagulation factor and for proteins C and S. Classical IVR (%) was calculated as follows: $100 \times$ (actual increase) / (expected increase). Incremental IVR (IU/dL) / (IU/kg) was calculated as follows: (IU/dL activity rise in plasma) / (IU/kg body weight infused). All data analysis was performed using SAS version 9.3 (SAS Institute Inc, Cary, North Carolina).

Adverse events (AEs) and serious AEs were recorded up to Day 14 and Day 45, respectively.

Results

Patients

In total, 11 patients were enrolled in the study: 6 in the bleeding group and 5 in the surgical group; all patients completed the study (Fig. 1). The 11 patients enrolled are the same patients previously described: median (range) age was 87 years (53–92 years) and 78 years (61–91 years) in the bleeding and surgical groups, respectively, whereas the median (range) INR at baseline was 4.76 (2.26–10.56) and 3.13 (2.11–5.82), respectively.[9] Both groups had a median weight of 60 kg (bleeding group range = 46–73 kg and surgical group range = 31–70 kg).[9]

The median (range) dose of 4F-PCC administered was 2250 IU (1150–3650 IU) in the bleeding group and 1500 IU (1085–1750 IU) in the surgical group. A dose of 25 IU/kg and 50 IU/kg was administered in 3 patients each in the bleeding group, and 4 patients received a dose of 25 IU/kg and 1 received a dose of 50 IU/kg in the surgical group. Nine patients received intravenous vitamin K (range = 10–20 mg) within 24 hours of 4F-PCC infusion and 2 patients, both in the bleeding group, were not administered any vitamin K. Further details of patient characteristics and dosing are described elsewhere.[9]

INR reduction and hemostatic efficacy

Efficacy results have been presented in full elsewhere.[9] Briefly, 30 minutes after infusion end, INR reduction to ≤ 1.3 was achieved in 83% and 80% of patients in the bleeding and surgical groups, respectively. This achievement of target INR was maintained over 24 hours in both the bleeding and surgical groups (Fig. 2). Effective hemostasis (as evaluated by the treating physician using predefined rating criteria [excellent or good, and very good or satisfactory in the bleeding and surgical groups, respectively]) was achieved in 60% and 100% of evaluable patients in the bleeding and surgical groups, respectively.[9]

Coagulation factor and protein C and S plasma levels

Following 4F-PCC infusion, rapid increases in plasma concentrations of all vitamin K-dependent coagulation factors, and proteins C and S were seen in both groups. Compared with baseline, the median concentrations of all coagulation factors and proteins C and S, were increased at 30 minutes after the end of the 4F-PCC infusion by at least 100% and 70% in the bleeding and surgical groups, respectively. Median values 30 minutes after infusion end and the numerical change from baseline are shown in Table 1. This increase was consistent irrespective of an individual's baseline INR across both groups, and median plasma levels were within normal reference ranges 30 minutes after infusion end in both groups for factors II, IX, and X, and proteins C and S (Table 1). An increase in median factor VII levels was seen in both groups but neither group reached normal reference ranges 30 minutes after infusion

Table 1
Median plasma levels and pharmacokinetic profile of coagulation factors and protein C and S.*

	Normal range, % normal	Bleeding group					Surgical group				
		Baseline, % normal	30 min after infusion end, % normal	Change from baseline, % normal	AUC$_{last}$	C$_{max}$	Baseline, % normal	30 min after infusion end, % normal	Change from baseline, % normal	AUC$_{last}$	C$_{max}$
Factor II	70–120	20.2 (0.0 to 34.9)	87.2 (54.7 to 108.3)	62.0 (29.7 to 108.3)	1168.9 (783.3 to 2164.4)	68.5 (45.2 to 110.8)	32.5 (18.3 to 39.5)	71.1 (56.0–114.1)	38.6 (32.9–74.6)	879.4 (420.0 to 1700.8)	40.0 (32.9 to 81.3)
Factor VII	70–120	16.2 (8.4 to 39.0)	51.9 (38.9 to 84.2)	31.8 (−0.1 to 75.4)	895.6 (498.6 to 1826.6)	54.0 (36.5 to 89.3)	28.2 (9.0 to 41.9)	44.8 (24.8–87.8)	21.7 (15.8–45.9)	937.7 (246.8 to 1402.8)	43.0 (18.0 to 64.8)
Factor IX	70–120	31.1 (9.9 to 49.0)	79.2 (49.7 to 92.7)	41.9 (7.8 to 82.8)	861.0 (173.0 to 2254.5)	53.7 (34.1 to 118.7)	50.5 (24.2 to 63.9)	78.2 (42.2 to 104.4)	30.5 (14.3 to 49.0)	929.6 (146.0 to 1716.3)	54.0 (15.8 to 109.4)
Factor X	70–120	10.0 (5.6 to 22.0)	103.4 (55.8 to 138.2)	88.4 (44.2 to 132.6)	1656.1 (1130.4 to 2467.0)	93.9 (61.4 to 132.6)	21.3 (8.0 to 24.9)	76.9 (58.9 to 129.1)	55.6 (50.9 to 104.2)	1485.0 (821.7 to 2266.8)	69.2 (50.9 to 104.2)
Protein C	70–140	38.4 (23.5 to 52.5)	116.0 (68.4–139.0)	77.5 (19.0 to 110.1)	1278.8 (863.9 to 2223.0)	86.6 (56.9 to 110.1)	44.2 (19.6 to 55.6)	99.3 (59.7 to 144.2)	43.7 (40.1 to 94.9)	940.2 (381.4 to 1920.6)	43.7 (40.1 to 96.6)
Protein S	60–139	37.1 (21.8 to 46.5)	91.6 (45.9 to 110.7)	54.7 (9.6 to 75.7)	829.6 (539.7 to 1473.3)	66.2 (37.3 to 86.6)	39.4 (23.2 to 54.5)	77.8 (62.6 to 109.2)	34.8 (32.3 to 69.8)	657.3 (344.9 to 1310.6)	34.8 (32.3 to 75.4)

* Data are presented as median (minimum–maximum). Change from baseline was calculated based on the individual patient change and not the median values.

end (Table 1). The AUC and C$_{max}$ for each coagulation factor and protein are also shown in Table 1.

Following the initial rapid increase, median plasma levels of all coagulation factors and proteins C and S remained elevated from baseline, and within physiologic levels, for at least 24 hours postinfusion in both the bleeding and surgical groups (Fig. 2).

Two patients in the bleeding group did not receive concomitant vitamin K. Overall, lower levels of coagulation factors and proteins C and S were observed in these patients at 12 and 24 hours after 4F-PCC administration compared with patients who received vitamin K. One of these patients maintained an INR ≤ 1.3 at 12 hours, although the other patient had a 12-hour INR of 2.68.

Plasma activity levels of a coagulation factor exceeded the upper limit of normal (ULN) in 3 patients. In 1 patient in the bleeding group, plasma levels of factor X were above the ULN 30 minutes after infusion; this patient did not experience any AEs. In the surgical group, 2 patients had plasma levels above the ULN. One patient had increases of factors II, VII, and X, and protein C at several points in time; this patient was diagnosed with a left atrial appendage thrombus 3 days after receiving 4F-PCC. The second patient had a level of factor VII exceeding the normal range 24 hours after infusion end; this patient did not experience any TEEs or serious AEs.

Overall, administration of 4F-PCC in VKA-treated patients experiencing acute bleeding or needing urgent surgery rapidly raised vitamin K-dependent coagulation factors without producing sustained supraphysiologic levels.

In vivo recovery and response of coagulation factors and proteins C and S

The median classical IVR ranged from 44.6% to 102.2% in the bleeding group and 54.1% to 130.7% in the surgical group, whereas the median incremental IVR (response) varied from 1.136 to 2.2554 in the bleeding group and 0.868 to 2.262 in the surgical group (Table 2). In line with the change from baseline at 30 minutes, factor VII had the lowest median classical and incremental IVR in both groups, whereas the highest were seen with factor X.

Safety profile

4F-PCC infusion was well tolerated in both groups with no patients discontinuing treatment or withdrawing from the study owing to an AE.[9] Two patients in the surgical group experienced a TEE (left atrial appendage thrombosis on Day 3 in 1 patient and splenic infarction on Day 2 in the other). Both events were classed by investigators as related to 4F-PCC use and of mild severity, and further follow-up was not deemed necessary. No relationship between TEEs and elevated plasma levels of any individual coagulation factor was identified in this study.

Discussion

As expected, the baseline levels of coagulation factors were lower in the bleeding group than the surgical group, which is consistent with the higher baseline INR seen in the bleeding group. Administration of 4F-PCC resulted in rapid and sustained increases in the plasma levels of coagulation factors and proteins C and S, without exceeding normal reference levels in the majority of patients. The slower increase in factor VII levels in comparison with the other coagulation factors is likely a result of the lower content of factor VII in 4F-PCC, with endogenous production stimulated by vitamin K responsible for the continued increase after 8 hours. Furthermore, factor VII binds with tissue factor at the start of the coagulation cascade,[16] and this earlier consumption of this factor compared with the other coagulation factors may explain the more
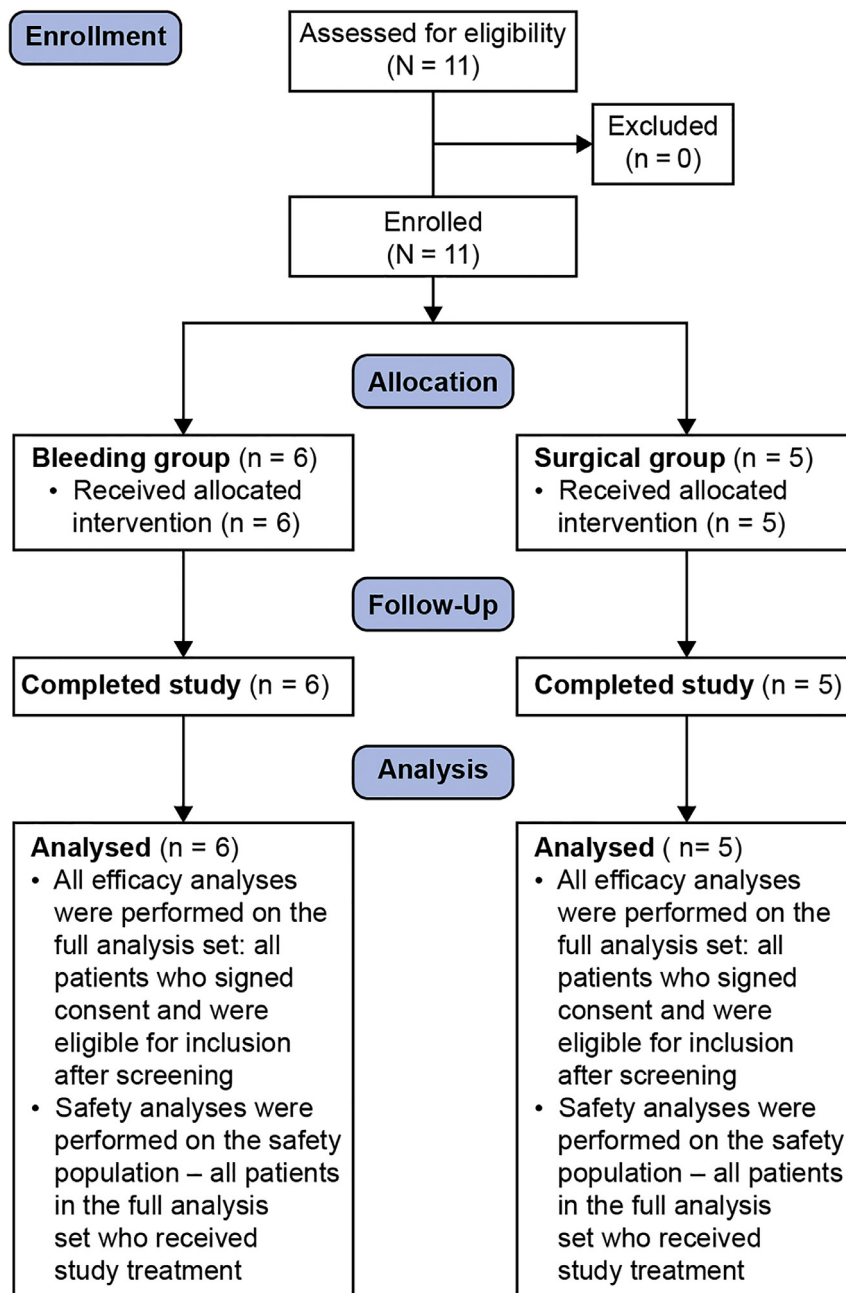
Fig. 1. Consolidated standards of reporting trials diagram.

gradual increase in plasma levels seen with factor VII. Overall, the increases in factor levels correlated well with the rapid reduction in patients' INR and achievement of hemostasis following 4F-PCC infusion.[9]

These results are consistent with those seen in the 2 large, multinational RCTs that evaluated 4F-PCC use for urgent VKA reversal in patients with acute major bleeding[7] or before an urgent surgical/invasive procedure.[8] As with the results presented here, 4F-PCC administration resulted in a rapid increase from baseline in plasma levels of the coagulation factors and proteins C and S, which remained elevated over the following 24 hours.[7,8]

Concomitant vitamin K administration with PCC is important to avoid patients experiencing an increase in INR after 12 hours, as highlighted by the reduced coagulation factor and proteins C and S plasma levels and elevated 12-hour INR seen in those patients who did not receive vitamin K.

No specific tolerability concerns were identified in this Japanese population, with a safety profile consistent to that seen in the large, multinational RCTs.[7,8] Of note, no relationship between coagulation factor levels and risk of TEE development was identified in this study. This finding was also shown in an integrated analysis of the 2 multinational RCTs, which demonstrated no notable difference between median factor levels in patients with or without TEEs, and concluded that the levels of coagulation factors may not have a major role in determining the occurrence of TEEs.[17] Inherent risk factors and delayed reanticoagulation may be more important contributors to TEE risk; reversing anticoagulation restores the underlying thrombotic risk that required anticoagulation in the first place; therefore, restarting anticoagulation should be restarted whenever possible as soon as the risk of thrombosis outweighs the risk of further bleeding.
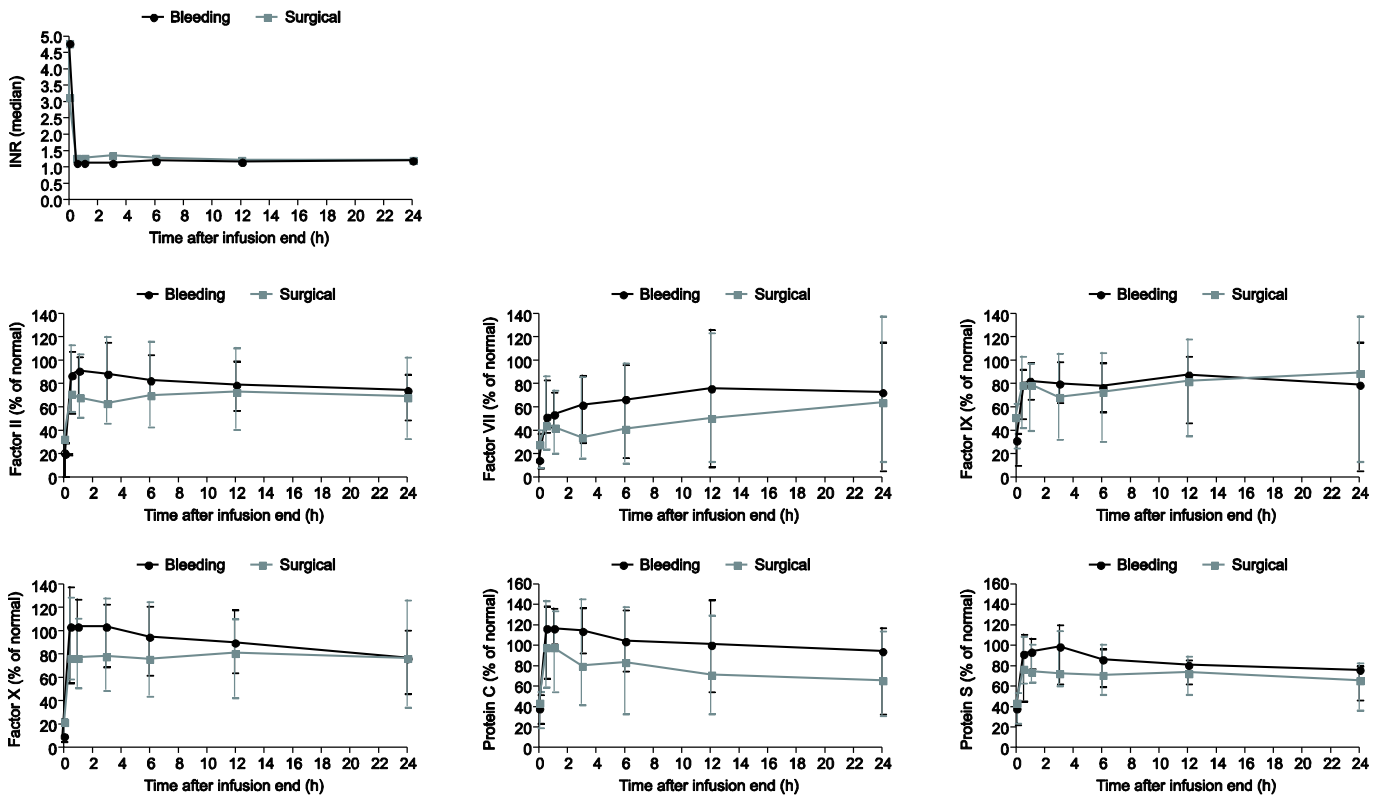
Fig. 2. International normalized ratio (INR) values and plasma levels of coagulation factors and proteins C and S over 24 hours. Data are presented as median for INR and median (range) for plasma levels.

Table 2
Classical and incremental in vivo response (IVR).*

	Bleeding group		Surgical group	
	Classical IVR[†]	Incremental IVR[‡]	Classical IVR[†]	Incremental IVR[‡]
Factor II	80.7 (63.6–121.1)	1.961 (1.501–2.308)	85.6 (48.0–124.7)	1.554 (0.940–2.963)
Factor VII	44.6 (31.1–84.3)	1.136 (0.735–11.508)	54.1 (23.0–78.7)	0.868 (0.451–1.823)
Factor IX	60.5 (42.6–92.6)	1.478 (1.004–1.976)	67.1 (26.0–83.8)	1.220 (1.454–4.138)
Factor X	102.2 (91.2–148.2)	2.554 (2.102–3.100)	130.7 (74.2–159.9)	2.262 (1.454–4.138)
Protein C	90.7 (81.8–123.1)	2.1199 (1.899–2.556)	105.5 (58.5–139.3)	1.759 (1.146–3.769)
Protein S	65.7 (60.3–84.6)	1.503 (1.452–1.808)	84.3 (47.1–102.5)	1.4010 (0.923–2.772)

* Data are presented as median (minimum–maximum).
† Classical IVR (%) = $100 \times$ (actual increase)/(expected increase).
‡ Incremental IVR [(IU/dL)/(IU/kg)] = (IU/dL activity rise in plasma)/(IU/kg body weight infused).

Limitations of this study include the small number of patients enrolled and the lack of a comparator group and as such these results should be interpreted with caution.

Conclusions

4F-PCC infusion resulted in rapid increases in coagulation factor levels in patients requiring urgent VKA reversal, without reaching supraphysiologic levels and were in line with the decrease seen in INR within 30 minutes after the end of infusion. These results are consistent with the results seen in the pivotal multinational RCTs[7,8] and indicate that the 4F-PCC dosing regimen used in Europe and the United States is appropriate in Japanese patients. 4F-PCC has a favorable safety profile and is an effective therapeutic option for urgent reversal of VKA therapy in Japanese patients presenting with major bleeding or requiring urgent surgery.

Conflicts of Interest

The study was sponsored by CSL Behring. The study drug and all PK analyses undertaken as part of the study protocol were

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.curtheres.2018.08.001.

References

1. Schulman S, Beyth RJ, Kearon C, et al. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133:257S–298S.
2. Lip GY, Andreotti F, Fauchier L, et al. Bleeding risk assessment and management in atrial fibrillation patients: a position document from the European Heart Rhythm Association, endorsed by the European Society of Cardiology Working Group on Thrombosis. *Europace*. 2011;13:723–746.
3. Yamaguchi T. Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with nonvalvular atrial fibrillation: a multicenter, prospective, randomized trial. Japanese Nonvalvular Atrial Fibrillation-Embolism Secondary Prevention Cooperative Study Group. *Stroke*. 2000;31:817–821.
4. Rossaint R, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. *Crit Care*. 2016;20:100.
5. Keeling D, Baglin T, Tait C, et al. Guidelines on oral anticoagulation with warfarin - fourth edition. *Br J Haematol*. 2011;154:311–324.
6. Kozek-Langenecker SA, Ahmed AB, Afshari A, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: First update 2016. *Eur J Anaesthesiol*. 2017;34:332–395.
7. Sarode R, Milling Jr TJ, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. *Circulation*. 2013;128:1234–1243.
8. Goldstein JN, Refaai MA, Milling Jr TJ, et al. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial. *Lancet*. 2015;385:2077–2087.
9. Kushimoto S, Fukuoka T, Kimura A, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate for rapid vitamin K antagonist reversal in Japanese patients presenting with major bleeding or requiring urgent surgical or invasive procedures: a prospective, open-label, single-arm phase 3b study. *Int J Hematol*. 2017;106:777–786.
10. International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Ethnic Factors in the Acceptability of Foreign Clinical Data. E5(R1). Available from: http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html.
11. Nakagawara J, Minematsu K, Okada Y, et al. Thrombolysis with 0.6 mg/kg intravenous alteplase for acute ischemic stroke in routine clinical practice: the Japan post-Marketing Alteplase Registration Study (J-MARS). *Stroke*. 2010;41:1984–1989.
12. Tanigawa T, Kaneko M, Hashizume K, et al. Model-based dose selection for phase III rivaroxaban study in Japanese patients with non-valvular atrial fibrillation. *Drug Metab Pharmacokinet*. 2013;28:59–70.
13. Kawaguchi T, Komori A, Seike M, et al. Efficacy and safety of eltrombopag in Japanese patients with chronic liver disease and thrombocytopenia: a randomized, open-label, phase II study. *J Gastroenterol*. 2012;47:1342–1351.
14. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e152S–e184S.
15. Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS 2013). *Circulation Journal*. 2014;78:1997–2021.
16. Monroe DM, Hoffman M. What does it take to make the perfect clot? *Arterioscler Thromb Vasc Biol*. 2006;26:41–48.
17. Milling Jr TJ, Refaai MA, Goldstein JN, et al. Thromboembolic Events After Vitamin K Antagonist Reversal With 4-Factor Prothrombin Complex Concentrate: Exploratory Analyses of Two Randomized, Plasma-Controlled Studies. *Ann Emerg Med*. 2016;67:96–105 e5.