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ORIGINAL ARTICLE

# 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

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**Abstract** Rapid vitamin K antagonist (VKA) reversal is required in patients experiencing major bleeding or requiring urgent surgery. Four-factor prothrombin complex concentrate (4F-PCC; Beriplex®/Kcentra®) was shown in two large randomized controlled, international phase 3b trials to be an effective alternative to plasma for urgent VKA reversal. In the present prospective, open-label, single-arm phase 3b trial, we evaluate the efficacy and safety of 4F-PCC in Japanese patients. Eleven patients [international normalized ratio (INR) ≥2] requiring rapid VKA reversal owing to major bleeding ($n = 6$) or before urgent surgical/invasive procedures ($n = 5$) were administered 4F-PCC dosed based on INR and weight. INR reduction (≤1.3 0.5 h postinfusion; primary endpoint) was achieved in 81.8% of patients (major bleeding, 83.3%; surgical/invasive procedures, 80.0%). Effective hemostasis (main secondary endpoint) was met in 60.0% (major bleeding) and 100% (surgical/invasive procedure) of evaluable patients. Adverse events (AEs) and serious AEs were reported in 90.9 and 45.5% of patients, respectively. Two AEs were considered treatment-related; thromboembolic events rated mild and not clinically relevant by investigators. There were no deaths, fluid overload events, or viral transmission cases. Consistent with the previous results, 4F-PCC may be an effective and well-tolerated treatment for rapid VKA reversal in Japanese patients experiencing major bleeding or requiring urgent surgical/invasive procedures.

**Keywords** Anticoagulant · Hemorrhage · Prothrombin complex concentrate · Surgery · Vitamin K antagonist

## Introduction

Vitamin K antagonists (VKAs), such as warfarin, are among the most commonly prescribed anticoagulants in Japan [1], as in Western countries [2]. These agents are used for treating and preventing thrombosis in conditions such as atrial fibrillation. In Japan and Western countries, the prevalence of these conditions has been shown to increase as the population ages [3–5], which may in turn lead to increased anticoagulant use.

Anticoagulant use carries a risk of bleeding. Annually, major bleeding occurs in approximately 1–5% of VKA-treated patients in Western countries [6, 7]; the proportion is slightly higher in Japanese patients (~5–7%) [8, 9]. Of particular concern is intracranial hemorrhage (ICH), which has a higher incidence in Asian populations than other ethnicities [10–12].

Patients receiving VKAs presenting with major bleeding, or requiring emergency surgical/invasive procedures, often need urgent VKA reversal. While interruption of VKA treatment and administration of vitamin K are routine

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interventions that increase vitamin K-dependent coagulation factor levels, international normalized ratio (INR) correction may take more than 24 h, and the response to vitamin K is slow and unpredictable [13]. Treatment options for urgent VKA reversal include administration of plasma or prothrombin complex concentrates (PCCs), concomitant with vitamin K [14, 15]. Though plasma is still used for this purpose, disadvantages include time delays due to blood typing and thawing, large infusion volumes, long infusion times, and risk of complications (fluid overload, transfusion-related acute lung injury, and pathogen transmission) [14].

PCCs are virally inactivated concentrates of activated or non-activated vitamin K-dependent coagulation factors, referred to as three-factor (3F)-PCCs (containing factors II, IX, and X) or four-factor (4F)-PCCs (also containing clinically relevant quantities of factor VII) [14]. PCCs can be administered more rapidly and in smaller volumes than plasma, and are generally the preferred option for urgent VKA reversal; reflected in European and US treatment guidelines [15, 16]. The Japanese Circulation Society Joint Working Group issued "Guidelines for management of anticoagulant and antiplatelet therapy in cardiovascular disease" [17], which recommend plasma or PCCs for patients who require urgent VKA reversal. The Japanese Stroke Society recommends use of PCCs over plasma [18]; however, no non-activated 4F-PCC is licensed in Japan for VKA reversal in patients presenting with major bleeding or requiring urgent surgical/invasive procedures. Data from medical record review studies in Japanese populations suggest that these agents may be effective for this purpose [19–21].

Two multinational, phase 3b randomized controlled trials (RCTs) investigating the use of a 4F-PCC versus plasma for urgent VKA reversal in patients presenting with acute major bleeding or requiring an urgent surgical/invasive procedure were conducted at 36 and 33 sites, respectively, mainly across the USA and Europe; no Japanese patients were included [22, 23]. Based on results from these studies, the 4F-PCC used was licensed in the USA for urgent VKA reversal [24] (this product had been approved in Europe for this indication since 1996). The present study was conducted to evaluate the efficacy and safety of 4F-PCC for rapid VKA reversal in Japanese patients with major bleeding or before urgent surgical/invasive procedures.

## Materials and methods

### Study design

This prospective, open-label, single-arm phase 3b trial (NCT02281201) was conducted between November 2014 and March 2016 at 7 centers in Japan. 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).

### Patients

Japanese patients (≥20 years) receiving VKA therapy, with an elevated INR (≥2.0 within 3 h before study treatment initiation) and requiring urgent VKA reversal for either an acute major bleeding event (bleeding group) or before an urgent (within 24 h) surgical/invasive procedure (surgical group) were eligible for enrollment. Consistent with the International Society on Thrombosis and Haemostasis definition [25], acute major bleeding was defined as one of the following: life-threatening or potentially life-threatening; acute bleeding associated with a fall in hemoglobin ≥2 g/dL; and bleeding requiring blood product transfusion. Exclusion criteria are listed in Supplementary Table 1.

### Treatment

On day 1, patients received 4F-PCC (Beriplex®/Kcentra®, CSL Behring, Marburg, Germany) dosed according to baseline INR and bodyweight, with patients receiving 25, 35, or 50 IU/kg for a baseline INR of ≥2 to <4, ≥4 to ≤6, or >6, respectively. For patients weighing over 100 kg, the dose calculation was based on 100 kg bodyweight, ensuring that the maximum dose would not exceed 2500, 3500 or 5000 IU of factor IX for patients with a baseline INR of ≥2 to <4, ≥4 to ≤6, or >6, respectively. 4F-PCC was administered as a single intravenous dose, with a maximum infusion speed of 3 IU/kg/min. Patients were to receive concomitant vitamin K according to local clinical practice. Total volume and infusion time of study treatment were recorded.

### Outcomes

The primary endpoint was INR reduction to ≤1.3 at 0.5 h after study treatment infusion end, regardless of baseline INR, which was assessed within 3 h before the start of infusion. The target INR of ≤1.3 was chosen for alignment with the two previously conducted multinational RCTs [22, 23].

The main secondary endpoint was hemostatic efficacy, which was assessed by the treating physician based on prespecified criteria using the descriptive terms 'excellent', 'good', or 'poor/none' in the bleeding group and 'very good', 'satisfactory', 'questionable', or 'none' in the surgical group (Table 1). These were further categorized to give a binary endpoint of 'effective' (excellent or good, and very good or satisfactory in the bleeding and surgical groups, respectively) or 'non-effective' (poor/none in the bleeding group; questionable or none in the surgical group). Bleeding

**Table 1** Hemostatic efficacy definitions

| Definition | | | |
|---|---|---|---|
| Major bleeding | | | |
| | Excellent (effective) | Good (effective) | Poor/none (non-effective) |
| Visible bleeding | Cessation of bleeding ≤1 h after end of infusion and no additional coagulation intervention required | Cessation of bleeding between >1 and ≤4 h after end of infusion and no additional coagulation intervention required | Cessation of bleeding >4 h after end of infusion and/or additional coagulation intervention required (e.g., plasma, whole blood cell pack or coagulation products) |
| Non-visible bleeding | Muscular/skeletal: Pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding ≤1 h after the end of infusion, and the condition had not deteriorated during the 24-h period<br>ICH: ≤20% increase in hematoma volume compared to baseline on repeat CT scan performed at the 3- and 24-h time point<br>Other: ≤10% decrease in both Hb/Hct at 24 h compared to baseline (initial correction of decrease in Hb with PRBCs, with a transfusion trigger of Hb ≤8 ± 1 g/dL)<br>All types: no additional plasma, blood products and/or coagulation factor products required | Muscular/skeletal: Pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding between >1 and ≤4 h after the end of infusion; and the condition had not deteriorated during the 24-h period<br>ICH: >20%, but ≤35% increase in hematoma volume compared to baseline on repeat CT scan performed at the 24-h time point<br>Other: >10 to ≤20% decrease in both Hb/Hct at 24 h compared to baseline (initial correction of decrease in Hb with PRBCs, with a transfusion trigger of a Hb ≤8 ± 1 g/dL)<br>All types: ≤2 additional plasma, blood products and/or coagulation factor products required | Muscular/skeletal: No improvement by 4 h after the end of infusion and/or the condition had deteriorated during the 24-h period<br>ICH: >35% increase in hematoma volume compared to baseline on repeat CT scan performed at the 24-h time point<br>Other: >20% decrease in both Hb/Hct at 24 h compared to baseline (initial correction of decrease in Hb with PRBCs, with a transfusion trigger of a Hb ≤8 ± 1 g/dL)<br>All types: >2 additional plasma, blood products and/or coagulation factor products required |

| Surgery | | | | |
|---|---|---|---|---|
| Rating | Very good (effective) | Satisfactory (effective) | Questionable (non-effective) | None (non-effective) |
| | Hemostasis during surgical or invasive procedure clinically not significantly different from normal hemostasis[a] | Mildly abnormal hemostasis[b] during surgical or invasive procedure in terms of quantity and/or quality—slight oozing | Moderately abnormal hemostasis[c] during surgical or invasive procedure—controllable bleeding | Severely abnormal hemostasis[c] during surgical or invasive procedure in terms of quantity and quality—severe hemorrhage difficult to control |

[a] Defined as achieving hemostasis comparable to that expected after a similar procedure in a non-coagulopathy patient

[b] Defined as somewhat increased bleeding compared to that expected after a similar procedure in a non-coagulopathy patient in terms of quantity and/or quality (e.g., slight oozing or prolonged time to hemostasis)

[c] Defined as moderately to substantially increased bleeding compared to that expected after a similar procedure in a non-coagulopathy patient in terms of quantity and/or quality (e.g., moderate-to-severe hemorrhage that is difficult to control)

*CT* computed tomography, *Hb/Hct* hemoglobin/hematocrit, *ICH* intracranial hemorrhage, *PRBC* packed red blood cell

patients were assessed over a 24-h period from start of infusion and surgical patients from start of infusion to the end of procedure.

Other efficacy outcomes included: INR and plasma levels of factors II, VII, IX, X, and proteins C and S measured preinfusion and at 0.5, 1, 3, 6, 12, and 24 h postinfusion end; blood product use over 24 h post 4F-PCC infusion start; neurological outcome assessed by modified Rankin Scale at day 45 (patients with ICH only); and predicted versus actual blood loss for each procedure (surgical group only).

Adverse events (AEs) and serious AEs (SAEs) were recorded up to day 14 (visit window day 12–16) and day 45 (visit window day 43–47), respectively.

### Statistical analysis

In the absence of factor-replacement therapy, INR was not expected to decrease within the scheduled sampling period (0.5 h postinfusion end); given the robust effect of 4F-PCC in the previous studies and the predictable recoveries of coagulation factor products, a sample size of ten patients (≥5 patients in both the bleeding and surgical groups) was expected to be sufficient to evaluate the efficacy of 4F-PCC in Japanese patients.

All efficacy analyses were performed on the full analysis set (FAS)—all patients who signed consent and were eligible for inclusion after screening. The analysis plan specified that if the INR 0.5 h after infusion was missing, the INR at 1 h would be used for the primary efficacy analysis. Safety analyses were performed on the safety population—all patients in the FAS who received study treatment.

Data were analyzed using SAS version 9.3. Efficacy and safety data were analyzed descriptively for all patients and independently for the bleeding and surgical groups. Summary statistics included mean, standard deviation (SD), median and range for interval data, and frequency and percentage distribution for discrete data.

## Results

### Demographics and treatment

Eleven patients were enrolled: six in the bleeding group and five in the surgical group. All patients received a dose of 4F-PCC and completed the study. Table 2 shows patient demographics and baseline characteristics. Details of bleeding events experienced and types of procedures undertaken are listed in Table 3. Details of 4F-PCC infusions and vitamin K therapy are shown in Table 3. In the bleeding group, three patients received a dose of 25 IU/kg and 3 a dose of 50 IU/kg. In the surgical group, four patients received a dose of 25 IU/kg and 1 received a dose of 35 IU/kg. The median (range) dose of 4F-PCC was 2250 (1150–3650) IU, in the bleeding group, administered in a median volume of 90 (46–146) mL, and infused over a median of 14 (8–23) min. In the surgical group, a median (range) dose of 1500 (1085–1750) IU was administered in a median volume of 60 (43–70) mL over a median of 15 (10–30) min. Planned and actual doses of 4F-PCC were consistent in all patients. Two patients in the bleeding group did not receive vitamin K during the study. All other patients received intravenous

**Table 2** Patient demographics and baseline characteristics (FAS)

| | Treatment group | | Overall ($N = 11$) |
|---|---|---|---|
| | Bleeding ($N = 6$) | Surgical ($N = 5$) | |
| Age, years | | | |
| Median (range) | 87 (53–92) | 78 (61–91) | 84 (53–92) |
| Sex, *n* (%) | | | |
| Male | 4 (67) | 3 (60) | 7 (64) |
| Weight, kg | | | |
| Median (range) | 60.0 (46.1–72.5) | 60.0 (31.0–69.5) | 60.0 (31.0–72.5) |
| Baseline INR | | | |
| Median (range) | 4.76 (2.26–10.56) | 3.13 (2.11–5.82) | 3.13 (2.11–10.56) |
| Reason for VKA therapy, *n* (%) | | | |
| Atrial fibrillation | 1 (17) | 4 (80) | 5 (46) |
| Aortic valve replacement | 2 (33) | 0 | 2 (18) |
| Cerebral infarction | 1 (17) | 0 | 1 (9) |
| Deep vein thrombosis | 1 (17) | 0 | 1 (9) |
| Myocardial infarction | 1 (17) | 0 | 1 (9) |
| Tricuspid valve incompetence | 0 | 1 (20.0) | 1 (9) |

*FAS* full analysis set, *INR* international normalized ratio, *VKA* vitamin K antagonist

**Table 3** Summary of bleeding events or procedures, and dosing details (FAS)

| Bleeding group | | | | | | |
|---|---|---|---|---|---|---|
| Patient | Bleeding event (preferred term) | 4F-PCC dose | | | | IV vitamin K dose (mg) |
| | | IU | IU/kg | mL | Infusion time (min) | |
| B1 | Traumatic intracranial hemorrhage | 1150 | 25 | 46 | 10 | No vitamin K* |
| B2 | Thalamus hemorrhage | 1650 | 25 | 66 | 11 | 20 |
| B3 | Face injury | 1550 | 25 | 62 | 8 | 10 |
| B4 | Pulmonary alveolar hemorrhage | 3650 | 50 | 146 | 17 | 20 |
| B5 | Hemorrhage subcutaneous (subcutaneous limb hemorrhage) | 2900 | 50 | 116 | 23 | 20 |
| B6 | Postprocedural hemorrhage (shoulder synovectomy wound) | 2850 | 50 | 114 | 18 | No vitamin K* |
| Surgical group | | | | | | |
| Patient | Surgical/invasive procedure | 4F-PCC dose | | | | IV vitamin K dose (mg) |
| | | IU | IU/kg | mL | Infusion time (min) | |
| S1 | Transarterial embolization (left hip traumatic bleeding) | 1750 | 25 | 70 | 10 | 20 |
| S2 | Blood access catheter insertion (internal jugular vein; hemodialysis) | 1085 | 35 | 43 | 15 | 10 |
| S3 | Hematoma evacuation (lower back) | 1275 | 25 | 51 | 16 | 20 |
| S4 | Upper gastrointestinal endoscopy | 1500 | 25 | 60 | 30 | 10 |
| S5 | Endoscopic biliary sphincterotomy | 1625 | 25 | 65 | 10 | 10 |

*4F-PCC* four-factor prothrombin complex concentrate, *FAS* full analysis set, *IU* international unit, *IV* intravenous

[a] Vitamin K was due to be administered to all patients; however, two patients did not receive any vitamin K treatment

vitamin K within 24 h of 4F-PCC infusion (before 4F-PCC, $n = 6$; after 4F-PCC, $n = 3$).

## Efficacy

### *Primary endpoint: INR reduction*

Overall, INR reduction to ≤1.3 at 0.5 h postinfusion end was achieved in 9/11 (81.8%) patients: 5/6 (83.3%) in the bleeding group and 4/5 (80.0%) in the surgical group (Table 4). The two patients who did not achieve INR ≤1.3 at this time point did not achieve this over the 24-h period, with lowest recorded INR values of 1.38 (patient in the bleeding group) and 1.92 (patient in the surgical group).

### *Main secondary endpoint: hemostatic efficacy*

Hemostatic efficacy was evaluable in 5/6 patients in the bleeding group; it was deemed unevaluable in one patient who had a subarachnoid hemorrhage that precluded hematoma volume measurement. Effective hemostasis was achieved in 3/5 (60%) evaluable patients, all of whom achieved INR ≤1.3 at 0.5 h postinfusion end (Table 4). In the surgical group, hemostasis was assessed as effective in all patients (5/5; 100%).

### *Other secondary efficacy endpoints*

Figure 1a, b shows the individual INR values in the bleeding and surgical groups at 0.5, 1, 3, 6, 12, and 24-h post 4F-PCC infusion end. Median INR decreased from 4.76 at baseline to 1.11 at 0.5 h postinfusion end in the bleeding group, while in the surgical group, the corresponding decrease was 3.13–1.25. In both groups, median INR was ≤1.3 at every time point, except the 3-h time point in the surgical group. Overall, 6/11 (54.5%) patients (bleeding group, $n = 4$; surgical group, $n = 2$) maintained an INR ≤1.3 at all time points; Fig. 1c shows the proportion of patients with INR ≤1.3 at each time point.

Vitamin K-dependent coagulation factor levels rapidly increased after administration of 4F-PCC in patients in both groups, remaining at physiologically relevant levels over the 24-h period (data not shown). These increases were observed consistently in all patients, regardless of baseline INR. Median concentrations of factors II, VII, IX, X, and proteins C and S increased by more than 100% in patients in

**Table 4** Summary of primary and key secondary endpoint achievement (FAS)

| Patient | Baseline INR | INR at 0.5 h | INR correction[a] | Hemostatic efficacy |
|---|---|---|---|---|
| Bleeding group | | | | |
| B1 | 2.71 | 1.25 | Yes | Non-evaluable[b] |
| B2 | 2.56 | 1.14 | Yes | Non-effective |
| B3 | 2.26 | 1.01 | Yes | Effective |
| B4 | 6.80 | 1.07 | Yes | Effective |
| B5 | 10.56 | 1.02 | Yes | Effective |
| B6 | 7.08 | 1.38 | No | Non-effective |
| Surgical group | | | | |
| S1 | 2.11 | NR | Yes[c] | Effective |
| S2 | 5.82 | 1.92 | No | Effective |
| S3 | 3.13 | 1.15 | Yes | Effective |
| S4 | 3.97 | 1.26 | Yes | Effective |
| S6 | 2.26 | 1.25 | Yes | Effective |

Hemostatic efficacy was assessed by the treating physician based on prespecified criteria, using the descriptive terms excellent, good, or poor/none in the bleeding group and very good, satisfactory, questionable or none in the surgical group. These were further categorized to give a binary endpoint of effective or non-effective. In the bleeding group, effective was defined as a rating of excellent or good; non-effective was defined as a rating of poor/none. In the surgical group, effective was defined as a rating of very good or satisfactory; non-effective was defined as a rating of questionable or none

*FAS* full analysis set, *INR* international normalized ratio, *NR* not recorded

[a] ≤1.3 at 0.5 h postinfusion end

[b] Hemostatic efficacy could not be evaluated in one patient with subarachnoid hemorrhage that precluded hematoma volume measurement

[c] The INR at 0.5 h was missing for one patient in the surgical group and the value at 1 h was used (INR: 1.07), as prespecified in the statistical analysis plan

the bleeding group and by ≥70% in patients in the surgical group from baseline to 0.5 h postinfusion end.

Red blood cell transfusions were given to 6/11 (54.5%) patients (bleeding group, $n = 2$; surgical group, $n = 4$).

Two patients in the bleeding group presented with ICH. Supplementary Table 2 shows detailed information regarding outcomes in these patients.

In all patients in the surgical group, actual estimated blood loss during the procedure was equal to or less than predicted estimated blood loss (data not shown).

### Safety

In total, 41 AEs were reported for 10/11 (90.9%) patients (Table 5). No AEs led to treatment discontinuation and most (39/41) were not considered treatment-related by the investigator. The two treatment-related events occurred in the surgical group. Nine SAEs were reported for 5/11 (45.5%) patients; there were 2 SAEs reported in 2 patients in the bleeding group and 7 SAEs reported in 3 patients in the surgical group. Two SAEs occurring in the surgical group, both thromboembolic events (TEEs; left atrial appendage thrombosis on day 3, splenic infarction on day 2) were reported as related to 4F-PCC treatment by investigators; however, the treating physicians considered both of these events to be mild and of minor clinical significance, so further follow-up after the study end was not conducted. Neither patient had reinitiated anticoagulant treatment at the time of the TEE. Coagulation factor levels in patients with and without TEEs were analyzed and no relationship between elevated factor levels and TEEs after 4F-PCC administration was found.

No deaths, fluid overload events, or cases of viral transmission were reported during the study.

One patient in the surgical group experienced a recurrent bleeding event (hematoma), which required surgical evacuation on the first postoperative day. No other bleeding AEs were reported.

## Discussion

In this Japanese patient cohort, 4F-PCC was effective for INR reduction to ≤1.3 in the majority of patients experiencing acute major bleeding or requiring urgent surgical/invasive procedures. This INR reduction was associated with effective hemostasis and increases in plasma levels of coagulation factors 0.5 h postinfusion end. It is unlikely that vitamin K contributed to these increases as it takes approximately 6–12 h for vitamin K infusion to affect coagulation factor levels.

Results in Japanese patients were consistent with those observed in the two large, multinational RCTs evaluating the use of this 4F-PCC for rapid VKA reversal in cases of major bleeding or before urgent surgical/invasive procedures [22, 23]. The proportion of patients meeting the INR endpoint (≤1.3 at 0.5 h postinfusion end) was slightly lower in the multinational RCTs than the Japanese study (62.2 vs 83.3% for bleeding patients and 55.2 vs 80.0% for surgical patients, respectively), although the sample size in the present study was small. Proportions of patients achieving the hemostatic efficacy endpoint were similar across the multinational and Japanese studies (72.4 vs 60.0% for bleeding patients and 89.7 vs 100% for surgical patients, respectively).

While the present study did not include a comparator group, in the multinational RCTs, 4F-PCC was non-inferior to plasma for hemostatic efficacy in patients with major bleeding and superior to plasma for this endpoint in patients requiring urgent VKA reversal before an emergency surgical/invasive procedure; 4F-PCC was also superior for rapid INR reduction in both settings [22, 23].

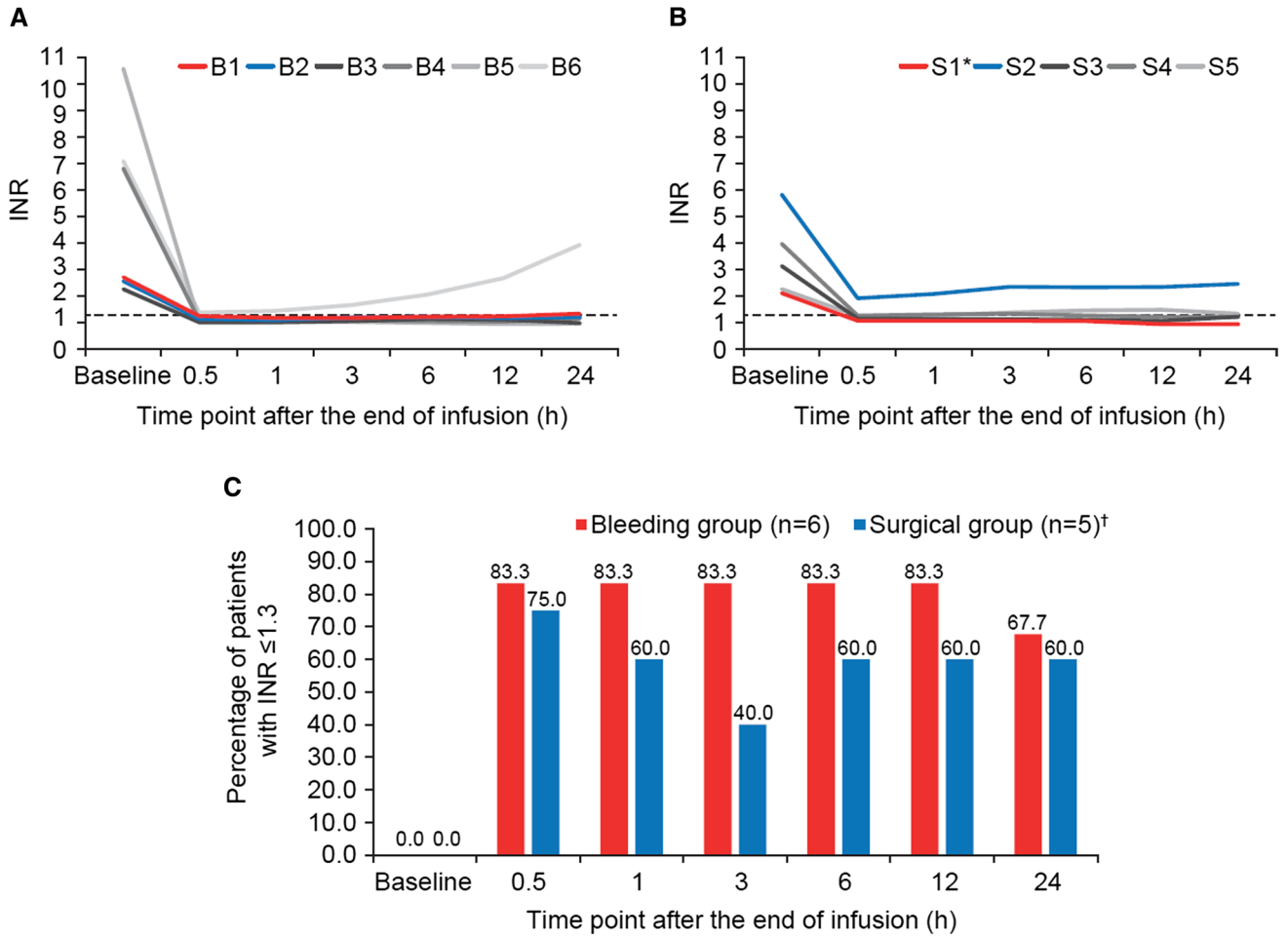


**Fig. 1** Change in INR values over time in the bleeding group (**a**) and surgical group (**b**), and proportion of patients achieving INR ≤1.3 in each group (**c**). *Asterisks* the INR at 0.5 h was missing for one patient in the surgical group and the value at 1 h was used, as prespecified in the statistical analysis plan. *Dagger* $n = 4$ for the 0.5 h time point. The *dotted line* represents the target INR (≤1.3). *FAS* full analysis set, *INR* international normalized ratio

## Use of PCC for VKA reversal in Japanese patients

Another 4F-PCC product (PPSB-HT, Nihon Pharmaceuticals, Japan) has also been used off-label in Japanese patients requiring VKA reversal [19–21]. In one study in 17 patients presenting with major hemorrhagic complications, 4F-PCC administration with or without vitamin K was more effective for rapid INR correction than vitamin K alone [20]. Median INR decreased from 2.70 at baseline to 1.13 and from 6.23 to 1.36 at 10 min in those receiving 4F-PCC with and without vitamin K, respectively. Though we did not measure INR at 10 min in the present study, decreases were observed 0.5 h postinfusion end.

In the previous study by Yasaka et al. [20], INR remained unchanged at 10 min in the group receiving vitamin K alone. This is to be expected given that VKA reversal with vitamin K takes several hours and is not recommended as a monotherapy for major bleeding [15, 26]. Administration of 4F-PCC without vitamin K was associated with increases in INR after the initial decrease, whereas INR decreases in the group receiving concomitant 4F-PCC and vitamin K, and in the present study, were sustained for 24 h. This provides further confirmation that these treatments should be administered concomitantly.

In medical chart review of 50 warfarin-treated Japanese patients presenting with ICH, rapidly reversing INR with 4F-PCC was effective in preventing hematoma expansion (lower proportion of patients with expansion vs controls) [19]. In our present study, two patients with ICH were included; both met the INR correction endpoint, but hemostasis was unevaluable in one patient and categorized as non-effective in the other. As the information available is limited, the efficacy of PCCs in patients with ICH should be evaluated further.

In a study in 42 Japanese patients requiring warfarin reversal for major hemorrhagic complications or before

**Table 5** Summary of adverse events (safety population)

| *n* (%) | Treatment group | | |
|---|---|---|---|
| | Bleeding ($N = 6$) | Surgical ($N = 5$) | Overall ($N = 11$) |
| Any AE | 5 (83.3) | 5 (100) | 10 (90.9) |
| Treatment-related AE | 0 | 2 (40.0) | 2 (18.2) |
| AE leading to treatment discontinuation | 0 | 0 | 0 |
| SAE[a] | 2 (33.3) | 3 (60.0) | 5 (45.5) |
| Treatment-related SAE | 0 | 2 (40.0) | 2 (18.2) |
| TEE | 0 | 2 (40.0) | 2 (18.2) |
| Treatment-related TEE | 0 | 2 (40.0) | 2 (18.2) |
| Fluid overload | 0 | 0 | 0 |
| Viral transmission | 0 | 0 | 0 |
| AE leading to death (up to day 45) | 0 | 0 | 0 |

Treatment-related events were defined as events whose relationship to study treatment was considered related by the investigator. AEs were reported to day 14 (visit window day 12–16) and SAEs were reported to day 45 (visit window day 43–47)

*AE* adverse event, *SAE* serious adverse event, *TEE* thromboembolic event

[a] The SAEs reported in the bleeding group were subdural hematoma and organizing pneumonia, each reported in one patient. One patient in the surgical group had 2 SAEs (chondrocalcinosis pyrophosphate and atrial thrombosis) and another had 4 SAEs (hypercapnia, ileus paralytic, pneumothorax, and splenic infarction). The third patient in the surgical group had a single SAE (sepsis)

invasive procedures, 4F-PCC 500 IU (range 6.0–17.9 IU/kg) rapidly reduced INR to <1.5 in 96% of patients with an initial INR <5.0; however, this dose was inadequate in those with a higher initial INR [21]. Furthermore, most patients administered PCC 200 IU (range 2.6–5.3 IU/kg) did not achieve INR <1.5. Though the optimal dose in Japanese patients has not been definitively established, data suggest that higher doses are needed in patients with higher INR values, and that vitamin K use is synergistic in maintaining INR reduction for 12–24 h.

### Safety of 4F-PCC

Interpretation of safety data for PCCs has been confounded by the complexity of the patient population requiring urgent VKA reversal. Patients receiving VKAs typically have significant comorbidities; superimposed on an already complex medical history, use of VKA therapy carries additional risks, such as acute major bleeding episodes, and bleeding during urgent surgical/invasive procedures. Furthermore, reversal of anticoagulation exposes patients to underlying thromboembolic risks, for which the anticoagulant was originally prescribed.

This study provides data on the safety of 4F-PCC in Japanese patients that can be evaluated in the context of the multinational RCTs [22, 23], which compared the safety profile of 4F-PCC with plasma, both of which are included in guidelines but not formally approved for VKA reversal in Japan [18, 27]. Safety findings in the present study were consistent with the multinational RCTs [22, 23] and post-marketing experience with this 4F-PCC. Though the sample size was small, 4F-PCC (dosed at 25–50 IU/kg) was well tolerated, and no new safety concerns were identified in Japanese patients. The types and incidence of AEs reported were reflective of the age and comorbidities of this study population.

A historic concern with PCC treatment has been the potential association with TEEs. This concern originated from repeat dosing of activated PCCs in patients with hemophilia [28]; however, most modern formulations of PCC, including the one used in this study, have no activated components. A systematic review of patients treated with PCCs for VKA reversal conducted in 2011 estimated a low risk for TEEs [29]. In our study, there were two TEEs in two patients, and neither event was subject to further follow-up as investigators considered them not clinically relevant. It is important to note that VKA reversal, or even just the withdrawal of VKA therapy, exposes patients to the underlying risk of TEEs for which the VKA was initially prescribed. As such, patients may experience TEEs due to a delay in reinitiating or the complete withdrawal of VKA therapy [30], rather than the anticoagulation reversal strategy used. An integrated analysis of the two multinational RCTs showed that TEEs occurred with similar frequency in the 4F-PCC and plasma treatment arms (7.3 and 7.1%, respectively) [31]. Accordingly, it is important for anticoagulant treatment to be reinitiated once the risk of thrombosis outweighs the risk of bleeding.

Compared with plasma, PCCs have several advantages in terms of safety. In the large, multinational RCTs, plasma use was associated with a higher risk of fluid overload and similar cardiac events versus 4F-PCC [31]. In the present study,

no events suggestive of fluid overload were reported. These findings are to be expected given the low volume of 4F-PCC required to adequately reduce the INR. Another benefit of PCCs is that their manufacturing process involves several viral inactivation steps, minimizing the risk of viral transmission. Consequently, in this study, the multinational RCTs and a pharmacovigilance study of the same 4F-PCC, there was no evidence of confirmed viral transmission in patients treated with this product [32, 33].

### Study limitations

Limitations of this study include the lack of a control treatment group, and that comparison of different 4F-PCC doses was not a study objective. The doses used in this study are slightly higher than those described in the previous Japanese studies, but the optimal dose for use in Japanese patients may be refined in clinical practice. The highest baseline INR reported in this study was 10.56, so there are no data in Japanese patients with higher INRs. Given the small number of patients included, results should be interpreted with caution. Obtaining additional clinical data in specific clinical situations such as ICH would require trials with more focused recruitment.

Common limitations among clinical trials of hemostasis are that many lack defined time points for analysis and most endpoints have some subjective elements; here, time points were clearly defined, and we increased objectivity using predefined hemostatic efficacy definitions rather than relying only on individual physicians' assessments. In addition, it is not always possible to perform direct hemostatic assessments for some types of bleeding, such as GI bleeding and ICH; therefore, actual hemostasis may have been achieved earlier than observed. INR reduction and factor level repletion may also have occurred before 0.5 h after the end of infusion; a detailed analysis of 4F-PCC pharmacokinetics/pharmacodynamics in Japanese people would be of interest.

## Conclusions

This was the first study to assess the efficacy and safety of this 4F-PCC for urgent reversal of VKA anticoagulation in a Japanese population; findings were consistent with those observed in the multinational RCTs. Overall, the results showed that 4F-PCC has an acceptable safety profile and is an effective alternative to plasma for rapid reversal of VKA therapy in Japanese patients presenting with acute major bleeding or requiring urgent surgical/invasive procedures.

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**Compliance with ethical standards**

**Conflict of interest** AB, AH, and TC are employees of CSL Behring. SK is on an advisory board for CSL Behring. TF, AK, KT, and MY declare that they have no conflicts of interest.

**Ethical approval** The study was 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 their legally authorized representatives.

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