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ORIGINAL RESEARCH

Real-World Safety and Effectiveness of a 4-Factor Prothrombin Complex Concentrate in Japanese Patients Experiencing Major Bleeding: A Post-marketing Surveillance Study

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ABSTRACT

Introduction: Limited data are available regarding the safety and effectiveness of 4-factor prothrombin complex concentrate (4F-PCC) in patients experiencing major hemorrhage or requiring expeditious surgical intervention, both globally and within Japan.

Methods: We executed a prospective, observational post-marketing surveillance study of patients receiving 4F-PCC for the first time between September 19, 2017 and August 15, 2018 in Japan. Patients were subjected to a comprehensive follow-up for a duration of 4 weeks.

Results: Of 1381 eligible patients, 1271 (92%) received a vitamin K antagonist. Among these, 58% were aged ≥ 75 years, 49% manifested atrial fibrillation, 17% presented with valvular heart disease, and 6% exhibited venous thromboembolism. The median (range) international normalized ratio was 2.67 (0.96–27.11) at baseline and 1.21 (0.45–6.61) at first measurement post-administration of 4F-PCC. The most common reason for 4F-PCC administration was intracranial hemorrhage (59.6%), followed by gastrointestinal bleeding (6.6%). Hemostatic effectiveness was achieved in 85.8% of patients. The incidences of adverse drug reactions (ADRs) and serious ADRs were 3.9% and 2.8%, respectively. Thromboembolic events (TEEs) occurred in 20 (1.5%) patients, with a mean onset of 10 days. The majority of TEEs were classified as

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nervous system disorders (55%). At the time of TEE, only 13% of patients resumed anticoagulant therapy.
Conclusion: The incidence of TEEs following treatment with 4F-PCC did not surpass those observed in phase 3 trials. No novel safety signals were identified. The safety and effectiveness of 4F-PCC in Japanese real-world practice were in harmony with the observations of prior studies.

Keywords: Anticoagulants; Bleeding; Intracranial hemorrhage; Japan; Prothrombin complex concentrates; Vitamin K antagonist

Key Summary Points

Why carry out this study?

Patients presenting with acute hemorrhage require rapid VKA reversal via restoration of vitamin K-dependent coagulation factors.

While small phase 3 studies have demonstrated that 4-factor prothrombin complex concentrate (4F-PCC) is well tolerated and effective, there have been no large-scale studies.

What was learned from the study?

4F-PCC was well tolerated and effective for major bleeding or needing urgent surgery in a real-world setting in Japan.

Thromboembolic events (TEE) occurred in 1.5% patients, but only 13% restarted anticoagulant therapy at the time of TEE.

INTRODUCTION

Vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) exhibit a favorable benefit–risk profile in managing thrombotic events (TEEs). However, they may precipitate or exacerbate acute major bleeding, leading to significant morbidity and mortality [1–6]. Current guidelines endorse the use of DOACs over VKAs for stroke prevention in most patients with atrial fibrillation (AF) [7–9]. For patients with AF and a history of valvular replacement, mechanical heart valves, or a diagnosis of mostly rheumatic mitral stenosis, VKAs are indicated whereas DOACs are not. In patients with AF and creatinine clearance (CCr) < 15 mL/min, warfarin remains the sole anticoagulant for ischemic stroke prevention. VKA therapy heightens bleeding risk especially during surgical interventions, events are typically minor, but can be life-threatening [10, 11]. A global review of VKA-treated AF found an annual major hemorrhage rate of 1.3–7.2% and an annual intracranial hemorrhage (ICH) rate of 0.1–2.5% [12]. ICH is a major cause of mortality and morbidity in these patients [13, 14]. Prompt VKA reversal is imperative for acute hemorrhage, requiring discontinuation of antithrombotic agents for bleeding cessation, and blood pressure reduction particularly in ICH. Prothrombin complex concentrates (PCCs), containing three or four vitamin K-dependent coagulation factors (3-factor PCC with significant quantities of factors II, IX, X; 4-factor PCCs (4F-PCC) with the addition of factor VII) are recommended [15, 16]. Administration of both 4F-PCC and vitamin K is recommended for fast and reliable reversal [7, 17]. Three phase 3 studies consistently demonstrate effective hemostasis and a notable international normalized ratio (INR) reduction with 4F-PCC [18–20], with a total incidence of thromboembolic events (TEEs) possibly related to treatment of 3.8%. The incidence rate is no means insignificant, warranting continued attention, particularly in the Japanese population.

The dosage of 4F-PCC is determined by the prothrombin time-INR (PT-INR) and patient body weight. Phase 3 studies have not investigated usage and dosage for patients with INR < 2.0. However, analysis of the Japanese J-RHYTHM registry suggests INR 1.6–2.6 as the range where thromboembolism and major bleeding risks are minimal [21–23], aligning with the current Japanese guideline [7], while the global guidelines advocate PT-INR 2.0–3.0. To date, no extensive study has assessed the safety and effectiveness of 4F-PCC globally or in

Japan including patients with INR < 2.0. Thus, we conducted a prospective, observational post-marketing surveillance study to investigate the safety and effectiveness of 4F-PCC in clinical practice collecting real-world data from all patients treated between September 19, 2017 and August 15, 2018 in Japan. Here, we report the results of that analysis.

METHODS

Study Design and Patients

This regulatory post-marketing surveillance study, conducted between September 2017 and August 2018, was a prospective, observational, noncontrolled, multicenter, single-arm study. Patients experiencing major bleeding or requiring urgent surgical intervention, and subsequently administered 4F-PCC at 482 Japanese medical centers, underwent a follow-up period of 4 weeks. Given the limited representation of Japanese patients in the 4F-PCC in phase 3 trial [24], this investigation included an all-encompassing surveillance approach, designed to enroll all patients treated with 4F-PCC post-market launch.

The administration doses of 4F-PCC are indicated according to the Japanese label, i.e., based on patient INR and body weight: 25 IU/kg for INR $\geq$ 2.0 and < 4.0, 35 IU/kg for INR $\geq$ 4.0 and $\leq$ 6, or 50 IU/kg for INR > 6.0. The administration protocols for patients with an INR below 2.0 lacked official recognition. In this study, the dose of 4F-PCC was determined at the discretion of the attending physician.

Determinations regarding initiation of 4F-PCC and the resumption of anticoagulant therapy were left to the discretion of the attending physicians. Subgroup classifications included all patients (safety analysis set) and those who had received VKAs.

The study was conducted according to the Declaration of Helsinki (1964 and its later amendments). The study also complied with adhered to the tenets of the Japanese Good Postmarketing Study Practice (GPSP) regulations. The protocol was reviewed and approved by the Japanese regulatory authority, the Pharmaceuticals and Medical Devices Agency (PMDA), and received ethical committee approvals. Comprehensive, written informed consent was obtained from all participating patients. The medical institutions that agreed to provide anonymized data signed a contract with the sponsor (CSL Behring K.K.).

Information was collected via case report forms (CRFs) for patients who had been administered 4F-PCC. While the original target number of patients was 900 as described below, enrollment continued until the conditions of the regulatory approval were satisfied according to the Japanese authority. The registration period was from September 2017 to March 2021 when the conditions of the approval were removed. All sites that administered 4F-PCC to patients after the drug was approved in Japan participated in the study; if a study site had already administered 4F-PCC at the time of contracting with the sponsor, data were collected retrospectively.

Study Endpoints

This was a descriptive study based on surveillance. The primary objective of the study was the incidence of TEEs. Sample size estimation for the primary objective is described Sect. "Statistical Analyses". The secondary objectives were the incidence of ADRs other than TEEs and unexpected ADRs and hemostatic effectiveness.

ADRs were encoded by attending physicians utilizing the Medical Dictionary for Regulatory Activities Japan (MedDRA/J) version 22.1, and causality and seriousness of ADRs were evaluated at the physician's discretion. ADRs encompassed all events for which a causal relationship with 4F-PCC could not be excluded, as determined by the attending physician. TEEs, shock, and anaphylaxis were assessed as priority survey items based on the discernment of the PMDA. The timing of anticoagulant therapy resumption and the nature of the drug employed upon therapy recommencement were also scrutinized. Day 1 was operationally defined as the day of administration of 4F-PCC.

Hemostatic effectiveness was assessed at the physician's discretion. The timing of PT-INR

measurement before and after administration of 4F-PCC adhered to routine clinical practice. The INR values measured immediately before the initial 4F-PCC dose were designated as the baseline INR. The initial measured INR values constituted the post-administration INR values for subsequent analysis.

Data Collection, Management, and Analysis

Physicians used CRFs to collect patient data. Observations were made at prespecified time points: during 4F-PCC administration and 4 weeks after administration or discontinuation of 4F-PCC. ADRs were defined as adverse events (AEs) that the investigator assessed as related to 4F-PCC, in which there was at least a reasonable probability of a causal relationship between 4F-PCC and an AE. A serious AE was defined as any AE that (1) resulted in death, (2) was life-threatening, (3) resulted in persistent or significant disability/incapacity, (4) required inpatient hospitalization or prolongation of existing hospitalization, (5) was medically significant, or (6) was a congenital anomaly/birth defect. The safety dataset was the basis of all demographic, baseline, and safety analyses, which included all patients who were registered, received at least one dose of 4F-PCC, and had available CRFs.

Statistical Analyses

On the basis of the observed TEEs incidence rate of 3.8% (9 of 234 patients) in phase 3 trials [18–20], a target sample size of 900 was set to detect an incidence of 5.8%. The primary objective of this study was to statistically guarantee that the incidence of TEEs is $\leq$ 5.8%, which was calculated by multiplying the incidence 3.8% by 1.5. With an assumed true incidence of TEEs of 3.8%, we run simulations with a sample size of 900 evaluable patients; the resulting power to detect (1 − beta) was 0.867, the maximum allowable incidence of adverse events was 4.4% (40 of 900 patients), and the upper limit of the one-sided 95% CI was 5.7%.

Descriptive statistics (number of patients, mean and standard deviation [SD]) were employed to succinctly summarize continuous effectiveness variables. The change in INR from baseline to administration was analyzed using a paired *t* test. Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Japan).

RESULTS

Patient Disposition

A total of 482 centers actively engaged in this investigative survey. Of 1973 registered patients who were eligible for the study, 1387 provided informed consent, and case report forms were not collected from 6 patients; therefore, data from 1381 patients were analyzed for safety and effectiveness (the overall study populations group). Of these, 1271 (92.0%) patients received a VKA (the VKA treatment group) (Fig. 1). Of 110 patients (8.0%) with records of not receiving a VKA, 7 were treated with DOAC and 103 were not treated with any anticoagulants.

Patient Characteristics at Baseline

Patient baseline characteristics were similar between both groups (Supplementary materials, Table S1). Table 1 shows that 61.4% and 38.6% of patients were male and female, respectively; 57.7% were aged $\geq$ 75 years and 21.0% were $\geq$ 85 years; 81.5% had comorbidities. The mean doses of 4F-PCC of both groups were 28 IU/kg. Baseline INR was 2.0 to < 4.0 in the majority of patients (52.6%), and < 1.6 or 1.6 to < 2.0 in substantial numbers (9.7%, 11.1%, respectively). A total of 13 patients (0.9%) received additional administration of 4F-PCC; 10 patients received two doses, 3 patients received three or more doses.

In the VKA treatment group (Supplementary materials, Table S1), AF was the most frequent reason for use of warfarin (48.7%), followed by valvular heart disease (16.5%) and cerebral infarction (8.3%). The proportion of patients with concomitant vitamin K was 72.6%.

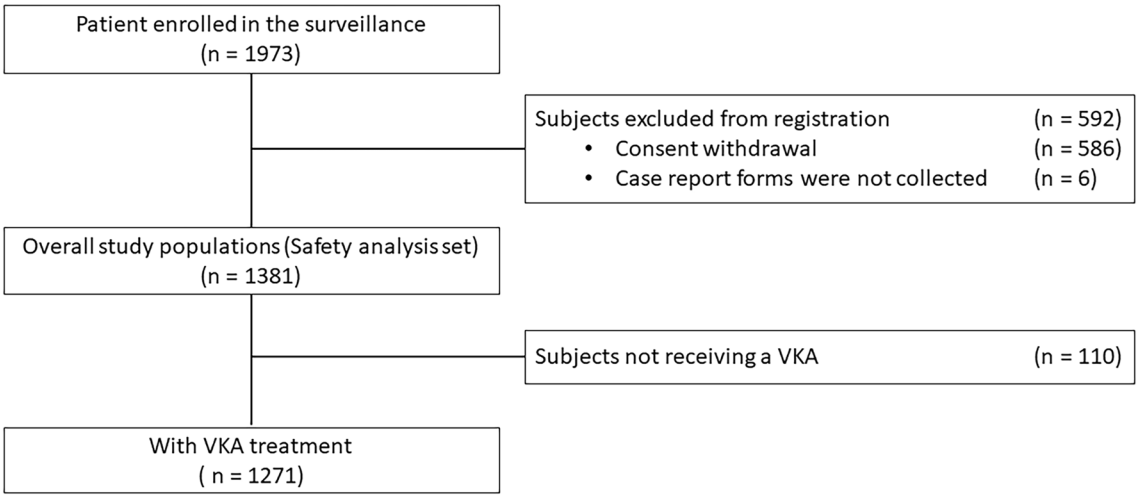

Fig. 1 Patient disposition and analysis sets. VKA, vitamin K antagonist

Reason for Utilization of 4F-PCC

The most common reasons for the administration of 4F-PCC were ICH at 59.6%, inclusive of 28.8% for non-traumatic ICH and 17.9% for traumatic ICH, followed by gastrointestinal (GI) bleeding at 6.6%, with 14.8% of patients receiving 4F-PCC for urgent surgical interventions and/or invasive procedures. A marginal 1.2% of cases exhibited overextension of PT-INR (Table 2).

Effectiveness

In patients who received a VKA, hemostatic effectiveness was achieved 1091/1271 (85.8%), not achieved in 8 (0.6%), and unknown in 172 (13.5%) patients. Treatment with 4F-PCC significantly reduced INR ($p < 0.001$); median (range) INRs at baseline and post-administration were 2.67 (0.96–22.11) and 1.21 (0.45–6.61), respectively (Fig. 2). The median (interquartile range) time between 4F-PCC administration and the first INR measurement was 2.34 (0.97–12.0) h. The first measured INRs was ≤ 1.30 in 67.2% of patients and < 1.50 in 84.7% of patients.

Safety

ADRs were reported in 54 (3.9%) patients; and serious ADRs were reported in 38 (2.8%) patients. The most common serious ADRs were cerebral infarction ($n = 6$, 0.4%), embolic stroke, deep vein thrombosis, and abnormal hepatic function ($n = 3$ for each, 0.2%).

Assessing priority survey items, shock and anaphylaxis were reported in one and no patients, respectively. A total of 31 TEEs reported in 20 (1.5%) patients (Table 3).

Characteristics of TEEs

The characteristics of the TEEs are presented in Table 4. The majority of TEEs were categorized as nervous system disorders (55%); further details are available in the supplementary materials (Table S2); and 35.5% of events developed ≥ 8 days and 61.2% developed ≥ 4 days post-administrations of 4F-PCC. Only 12.9% of patients were receiving anticoagulant therapy at the time of the TEE event.

Baseline characteristics of patients who experienced TEEs are presented in Table 5. Among patients with TEEs, the mean dose of 4F-PCC used was 33 IU/kg, and 65.0% received concomitant vitamin K. Overall, the characteristics of patients who experienced TEEs were

Table 1 Patient characteristics at baseline

Characteristics	Overall study populations (n = 1381)
Sex, male, n (%)	848 (61.4)
Age, years, mean (SD)	74.0 (14.2)
Age group, years, n (%)	
< 65	236 (17.1)
≥ 65 to < 75	347 (25.1)
≥ 75 to < 85	507 (36.7)
≥ 85	290 (21.0)
Weight, kg, mean (SD)	56.0 (12.9)
BMI, mean (SD)	21.9 (3.9)
Comorbidity, n (%)	1126 (81.5)
Dose of 4F-PCC, IU/kg (SD)	28.4 (9.7)
Baseline PT-INR, median (minimum, maximum)	2.6 (0.92–27.11)
Distribution of baseline PT-INR, n (%)	
< 1.6	134 (9.7)
1.6 to < 2.0	153 (11.1)
2.0 to < 4.0	727 (52.6)
4.0–6.0	140 (10.1)
6.01 to < 10.0	94 (6.8)
≥ 10.0	57 (4.1)
Not available	76 (5.5)

BMI body mass index, *IU* international units, *PT-INR* prothrombin time international normalized ratio, *SD* standard deviation, *VKA* vitamin K antagonist, *VTE* venous thromboembolism

comparable with those of the overall population (Table 1).

Resumption of Anticoagulant Therapy After 4F-PCC administration

In the VKA treatment group, 62.8% of patients resumed anticoagulants. Of these, 25.3%

Table 2 Reasons for the administration of 4F-PCC

Reason	Overall study populations (n = 1381), n (%)
Acute major bleeding	
Intracranial hemorrhage	823 (59.6)
Non-traumatic ICH (except for subarachnoid hemorrhage)	397 (28.8)
Traumatic ICH (except for chronic subdural hematoma)	247 (17.9)
Chronic subdural hematoma	115 (8.3)
Subarachnoid hemorrhage	32 (2.3)
Other	6 (0.4)
Unclassifiable	26 (1.9)
GI bleeding	91 (6.6)
Upper	49 (3.6)
Lower	22 (1.6)
Unclassifiable	20 (1.5)
Other bleeding (including major bleeding in cardiovascular system)	229 (16.6)
Non-traumatic	185 (13.4)
Traumatic	44 (3.2)
Urgent surgery/invasive procedure	
Abdominal surgery/ intervention	76 (5.5)
Cardiovascular surgery/ intervention	69 (5.0)
Orthopedic surgery	18 (1.3)
Neurological surgery/ intervention	8 (0.6)
Other surgery/intervention	33 (2.4)

Table 2 continued

Reason	Overall study populations (n = 1381), n (%)
PT-INR overextension (prolonged)	16 (1.2)
Unknown	18 (1.3)

GI gastrointestinal, *ICH* intracranial hemorrhage, *PT-INR* prothrombin time international normalized ratio

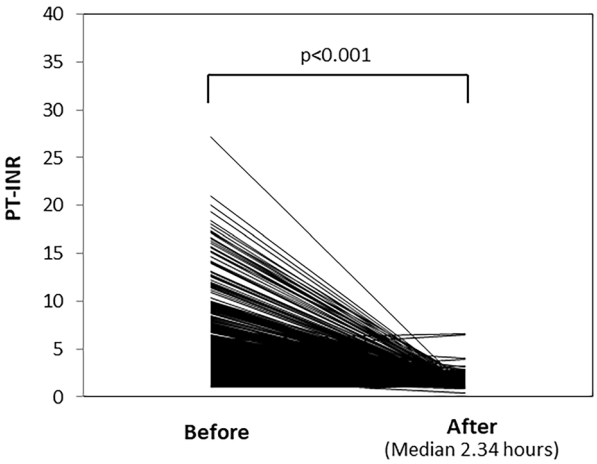

Fig. 2 PT-INR before and after initial administration of 4F-PCC (VKA treatment). PT-INR between before and after initial administration of 4F-PCC was analyzed using a paired t test. 4F-PCC, four prothrombin complex concentrate; PT-INR, prothrombin time-international normalized ratio

Table 3 Incidence of ADRs

ADRs	Patients, n (%)
Any ADRs	54 (3.9)
Serious ADRs	38 (2.8)
Assessing priority survey items	
Shock	1 (0.07)
Anaphylaxis	0 (0)
TEE	20 (1.5)

ADR adverse drug reaction, *TEE* thromboembolic events

Table 4 Summary of TEEs

	31 TEEs
Type of TEE, n	
Nervous system disorders	17 (54.8)
Cardiac disorders	2 (6.5)
Vascular disorders	8 (25.8)
Other	4 (12.9)
Date of onset of TEE	
Mean (SD), days	10.4 (13.4)
Median (range), days	5.0 (1–42)
$\geq$ 8 days, n (%)	11 (35.5)
4–7 days, n (%)	8 (25.8)
$\leq$ 3 days, n (%)	10 (32.3)
Unknown, n (%)	2 (6.5)
Resumption of anticoagulant therapy at time of event, n (%)	4 (12.9)

TEE thromboembolic events, *SD* standard deviation
[a]To recuperate but retain pathological conditions resulting from the prior disease or injury

resumed anticoagulant use within 3 days of 4F-PCC administration, 54.0% resumed use within 7 days, and 80.5% resumed use within 14 days. The following anticoagulants were used: warfarin (60.7%), heparin (10.0%), and DOACs. Similarly, anticoagulant use was resumed in 56.9% of patients with ICH; 17.1% resumed use within 3 days, 46.2% resumed use within 7 days, and 74.3% resumed use within 14 days.

DISCUSSION

In this study, information concerning 1381 patients between September 2017 and August 2018 was amassed through a comprehensive surveillance initiative, designed to encompass all individuals subjected to 4F-PCC treatment following its market launch in Japan. Preceding

Table 5 Baseline characteristics of patients who experienced TEEs

	20 subjects with TEE
Sex, male; mean (%)	10 (50.0)
Age; mean (SD)	76.2 (17.3)
Age group, ≥ 75 years; mean (%)	13 (65.0)
Baseline INR	
Median, range	3.1 (1–12)
< 2.00, *n* (%)	6 (30)
History of treatment with warfarin, *n* (%); yes	17 (85)
Reason for the use of warfarin, *n* (%)	
Atrial fibrillation	8 (40)
Valvular heart disease	2 (10)
Cerebral infarction	3 (15)
VTE	2 (10)
Ischemic heart disease	1 (5)
Other	1 (5)
Reasons for the use of 4F-PCC, *n* (%)	
Major bleeding	18 (90)
Intracranial hemorrhage	12 (60)
Gastrointestinal bleeding	1 (5)
Other bleeding	5 (25)
Surgery/procedure	1 (5)
Other	1 (5)

4F-PCC 4-factor prothrombin complex concentrate, *INR* international normalized ratio, *SD* standard deviation, *VTE* venous thromboembolism

multinational phase 3 trials delineated the experiences of 100 and 80 patients who received 4F-PCC [19, 20]. In a Japanese phase 3 study, a cohort of 11 patients received 4F-PCC [24]. To our knowledge, the present study is the largest one investigating the safety and effectiveness of 4F-PCC both globally and within Japan.

4F-PCC treatment effectively reduced INR to levels below 1.3, demonstrating commendable hemostatic efficacy, when used concomitantly with vitamin K, as observed in the majority of patients. The results are consistent with findings from the two large global phase 3 trials [19, 20]. Treatment with 4F-PCC displayed hemostatic effectiveness in 85.8% of patients, which is similar to the observations in the phase 3 trials [19, 20]. A comparative analysis showed that Japanese patients in the current study exhibited advanced age (74.3 vs. 69.8 years) and a lower body mass index (21.9 vs. 27.7 kg/m^2) compared with a phase 3 study [19]. Consequently, patients in the current study appeared to be at higher risk of bleeding than those in the phase 3 studies.

Comparative evidence from global phase 3 trials with fresh frozen plasma demonstrated the non-inferiority and superiority of 4F-PCC over plasma in achieving effective hemostasis and the rapid attainment of the INR target [19, 20]. Consequently, the current Japanese guidelines recommend the administration of 4F-PCC plus vitamin K over plasma [7]. Nevertheless, the observed 3.8% incidence rate of TEEs in global phase 3 trials is by no means insignificant, warranting continued attention, particularly in the Japanese population. Importantly, this study is the first adequately statistically powered assessment of incidence of TEEs. The data revealed that the incidence of TEEs (1.5%) in this study was numerically lower than the global phase 3 trials [19, 20]. This large-scale investigation is provided on the management of patients undergoing 4F-PCC treatment, with particular emphasis on TEEs the real-world setting in Japan.

A parallel observation was noted in cases involving the reversal of other anticoagulant therapies using andexanet alfa, a specific reversal agent for factor Xa (FXa) inhibitor activity [25, 26], a phenomenon partially documented in Japanese patients with acute major bleeding [27]. Similarly, analogous trends were observed in Asian populations treated with idarucizumab, a monoclonal antibody fragment used for dabigatran reversal [28, 29]. The low rates of TEEs associated with anticoagulant therapy reversal may be attributed to differences in

ethnicity. Notably, the study populations were predominantly composed of patients with AF who appeared to discontinue anticoagulants at the time of TEE. This may suggest differences in ethnicity in the susceptibility to TEE in patients with AF. The divergence in risk factors for thromboembolism on ethnicity and region is underscored by the use of $CHADS_2$ score in Japan for thromboembolic risk stratification in patients with nonvalvular AF, as opposed to the global use of the CHA_2DS_2-VASc score [30]. This notion is further supported by a comprehensive meta-analysis of genome-wide association studies for AF revealing the existence of ethnicity specific loci associated with AF [31].

The majority of TEEs were categorized as nervous system disorders (55%) and the remainder were coronary and peripheral vessels. Notably, over 35% of TEEs manifested at least 8 days after 4F-PCC administration. The total number of patients who received multiple doses was 0.9%, but TEEs were not observed in patients with multiple dosing, so we conclude that multiple doses do not affect the occurrence of TEE. It should be noted that 87.1% of TEEs occurred in patients who were not receiving anticoagulant therapy at the time of the event. A post hoc analysis comparing treatment-related TEEs following VKA reversal using 4F-PCC and plasma demonstrated similar percentages of TEEs deemed related to treatment in both groups [32]. Most patients were not receiving anticoagulants at the time of the event, and the failure to reinitiate anticoagulants treatment in patients with pre-existing thromboembolic risks, coupled with their heightened risk due to acute illness, may have contributed to observed rate of thromboembolism. Indeed, in some patients, anticoagulants might be indicated at the time of the event.

Currently, medications including 4F-PCC are sanctioned in Japan, the USA, and the EU for the treatment of patients with life-threatening or uncontrolled bleeding linked to anticoagulants. Nonetheless, disparities in epidemiologic characteristics and stroke management practices exist between Japan and Western countries, notably the higher prevalence of ICH in Japan [33–35]. While the majority of patients in this study received 4F-PCC for ICH, global phase 3 trials predominantly featured patients with GI bleeding [18–20]. Importantly, patients with ICH did not experience a higher rate of TEEs, defying expectations due to post-ICH immobilization. It has been proposed that VKA-associated ICH could be partially attributed to genetic differences affecting warfarin metabolism or treatment response [36, 37]. However, the elevated incidence of ICH in Asian populations does not seem to be linked to drug metabolism, as evidenced by observations with andexanet alfa for FXa inhibitors in Japanese patients [27]

Based on evidence from Japanese registries, the Japan guideline recommends maintaining an optimal INR range of 1.6–2.6 under warfarin treatment [7]. It is noteworthy that, for this target range, physicians are advised to target a PT-INR of 2.0, rather than lower values such as 1.6 or 1.7 to mitigate the risk of TEE. However, the official indication for usage and dosage of 4F-PCC in patients with INR < 2.0 is currently absent. This study provided an opportunity to assess the safety and effectiveness of 4F-PCC in 215 patients with INR < 2.0. The data revealed that the mean dose of 4F-PCC in patients with INR < 2.0 was 24.5 IU/kg, and the effects appeared comparable to those in patients with INR 2 to 4. A prior pharmacometric simulation model suggested that lower 4F-PCC doses (15–20 IU/kg) for INR < 2.0 might be considered [38]. Retrospective studies from US groups also suggested the usefulness of administering 15–25 IU/kg of 4F-PCC for INR < 2.0 [39, 40]. The current study expands these important earlier observations, reinforcing the rationale for utilizing 4F-PCC in patients with INR < 2.0.

This regulatory-mandated all-case post-marketing surveillance study is an observational study and it therefore has inherent limitations. First, the single-cohort design prevented comparisons with conventional therapy. Second, possible misclassifications of events and hemostatic effectiveness cannot be ruled out because these were assessed by treating physicians and were not confirmed by an independent adjudication committee. Third, the dose of 4F-PCC and the time of INR measurement particularly for post-4F-PCC administration was variable because data originated from daily medical

practice. Finally, relative risk estimates or absolute incidence rates cannot be confirmed as completely unbiased.

CONCLUSION

This prospective, observational study elucidated the favorable tolerability and efficacy of 4F-PCC, with a prompt reduction of INR and substantial hemostatic efficacy in the real-world setting for a large dataset of patients requiring urgent VKA reversal because of an acute major bleed or an urgent surgery/invasive procedure. TEEs manifested in 1.5% patients, yet a mere 13% recommenced anticoagulant therapy during the occurrence of TEE. This underscores the pivotal significance of expeditiously reinstating anticoagulant therapy to avert TEEs when clinically warranted.

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Author Contributions. Masahiro Yasaka: data interpretation. Michiyasu Suzuki: data interpretation. Shigeki Kushimoto: data interpretation. Ayako Kiyonaga: data analysis, data interpretation. Antoinette Mangione: data interpretation, Yuki Niwa: data interpretation. Naoki Terasaka: data interpretation, drafting the manuscript.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Ayako Kiyonaga, Antoinette Mangione, Yuki Niwa, Naoki Terasaka are full-time employees of CSL Behring. Masahiro Yasaka has received lecture, advisory, and travel fees from Bristol-Myers Squibb, Nippon Boehringer Ingelheim, Bayer, Daiichi Sankyo, and CSL Behring, as well as scholarship funds or nonrestricted grants from Nippon Boehringer Ingelheim. Michiyasu Suzuki has received lecture fees from Nippon Boehringer Ingelheim and CSL Behring. Shigeki Kushimoto has received lecture fee from CSL Behring.

Ethical Approval. The study was conducted according to the Declaration of Helsinki (1964 and its later amendments). The study was also complied in accordance with Japanese Good Postmarketing Study Practice (GPSP) regulations. The protocol was reviewed and approved by the Japanese regulatory authority, PMDA, and by the ethics committees; written informed consent was obtained from all patients.

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