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blood advances

INR and vitamin K–dependent factor levels after vitamin K antagonist reversal with 4F-PCC or plasma

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Key Points

- 4F-PCC rapidly restores vitamin K–dependent factors to hemostatic levels in patients treated with VKA immediately after infusion.
- Postreversal INR may not accurately reflect vitamin K–dependent factor restoration after a 4F–PCC infusion.

Restoration of the international normalized ratio (INR) to values <1.5 is commonly targeted to achieve hemostasis in patients with major bleeding or undergoing urgent surgery who are treated using vitamin K antagonists (VKAs). However, the relationship between corrected INR and vitamin K–dependent factor (VKDF) levels for hemostasis is uncertain. We aim to examine the impact of 4-factor prothrombin complex concentrate (4F-PCC) or plasma on INR correction and VKDF restoration and evaluate the relationship between INR values and VKDF levels in patients with acute major bleeding or patients requiring an urgent surgical procedure. Adult patients treated with VKA with an elevated INR (≥2.0 within 3 hours before study treatment) who received 4F-PCC or plasma after major bleeding or before an urgent surgery or invasive procedure were included in this retrospective analysis of data from 2 prospective phase 3b randomized controlled trials. Of the 370 patients included in this analysis, 185 received 4F-PCC, and 185 received plasma. In the 4F-PCC group, 159 of 185 (85.9%) had an INR ≤1.5 at 30 minutes after the end of infusion compared with only 72 of 184 (39.1%) in the plasma group. After 4F-PCC treatment, all VKDF levels exceeded 50% activity regardless of the postinfusion INR value. However, after plasma administration, mean activity levels for factors II and X were <50% at all time points assessed within 3 hours after starting the infusion, regardless of the postinfusion INR value. This retrospective analysis demonstrated that treatment with 4F-PCC among patients treated with VKA rapidly restores VKDFs to hemostatic levels irrespective of the postinfusion INR value, whereas treatment with plasma does not.

Introduction

Vitamin K antagonists (VKAs) are the preferred oral anticoagulants for several clinical indications.[1] Patients taking VKAs require anticoagulation reversal at instances of acute major bleeding or before urgent surgical or invasive procedures.[2,3] Reversal of VKAs involves the replacement of vitamin K–dependent coagulation factors (VKDF) (factor II [FII], FVII, FIX, and FX), which was historically achieved using plasma. However, the use of plasma typically achieves a slow or inadequate reversal of the international normalized ratio (INR) and comes with the risk of a circulatory volume overload because of the large transfusion volume required, allergic reactions, and rarely, infection transmission

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The full-text version of this article contains a data supplement.

and transfusion-related acute lung injury.[4,5] Prothrombin complex concentrates (PCCs) are purified concentrates of VKDF that can be administered in a smaller volume because they have a concentration of VKDF ~25× higher than that of plasma, which results in an immediate restoration of VKDF and a decrease in INR.[6,7] The standard of care for reversal of VKA is now 4-factor PCC (4F-PCC), as recommended by several society guidelines.[5,8-11]

Two phase 3b studies have demonstrated the superiority of nonactivated 4F-PCC (Kcentra, CSL Behring) compared with plasma for a rapid INR correction among patients requiring a VKA reversal because of major bleeding or before an urgent surgical or invasive procedure.[7,12] Both studies demonstrated that 4F-PCC was effective at achieving hemostasis and provided a more rapid INR reversal than plasma with a similar safety profile.

Restoration of the INR to values <1.5 is commonly targeted to achieve hemostasis in patients treated with VKA, but the relationship between INR values, VKDF activities, and the level of hemostasis has not been demonstrated. Of the 4 VKDFs, FII and FX are considered critical for the surgical hemostasis (>40%-50% activity), whereas FVII is required in a very small quantity to initiate the coagulation cascade (15%-20%) for major surgery, and FIX >50% seems adequate for surgical hemostasis.[13] The aims of this study are to examine the impact of 4F-PCC vs plasma on INR reduction and VKDF restoration and explore the relationship between INR values and VKDF levels in patients with acute major bleeding or patients requiring an urgent surgical procedure, with an additional focus on the impact in the population undergoing surgery.

Methods

A retrospective exploratory analysis of data from 2 prospective phase 3b randomized controlled trials that compared the efficacy of 4F-PCC with that of plasma for VKA reversal was performed (NCT00708435 and NCT00803101).[7,12] These trials included patients treated with VKA (≥18 years of age) with an elevated INR (≥2.0 within 3 hours before study treatment) receiving either 4F-PCC or plasma after major bleeding or requiring an urgent surgical or invasive procedure within 24 hours (see supplemental Figures 1 and 2 for the patient flow of these studies). Weight- and INR-based dosing of 4F-PCC and plasma was used in both trials. Rapid INR reduction (≤1.3) at 30 minutes after the end of infusion and plasma levels of VKDF and proteins C and S were included among the secondary end points of these clinical trials.[7,12] In the individual clinical trials, only INR values obtained within the specified time frame of 30 minutes (±15 minutes) after infusion were included in the final analysis.[7,12] To replicate real-world practice, this retrospective analysis included all postinfusion INR values assessed, irrespective of time of the laboratory sampling. The main outcomes of this analysis were postinfusion INR values and VKDF levels. Patients were dichotomized based on postinfusion INR values to assess differences in VKDF activity. Analyses of VKDF activity focused on the proportion of patients with activity levels >40% to 50%, the level considered sufficient for surgical hemostasis.[13]

The overall objectives of the study are to (1) examine the impact of 4F-PCC vs plasma on INR correction and VKDF restoration and (2) evaluate the relationship between INR values and VKDF levels in patients with acute major bleeding or those in need of an urgent surgical/invasive procedure. Data were aggregated to reflect INR correction and VKDF levels, with additional data analysis focused on the population that underwent surgery.

Statistical analysis

Descriptive statistics were used to summarize the quantitative data based on the median and interquartile range (IQR) and the categorical data based on percentages or proportions. To compare proportions between defined study subgroups, the χ^2 test for homogeneity was used.

Results

Study population

In total, 202 patients with major bleeding (n = 98 received 4F-PCC and n = 104 received plasma; supplemental Figure 1) and 168 patients requiring emergency and surgical/invasive procedure (n = 87 received 4F-PCC and n = 81 received plasma; supplemental Figure 2) were included in these analyses. Patients were pooled based on the treatment, resulting in 185 patients in the 4F-PCC group and 185 patients in the plasma group. Postinfusion INR was not available for 1 patient in the plasma group. The average 4F-PCC dose was 2238 IU (28.1 IU/kg), and the average plasma dose was 832 mL (10.6 mL/kg).

Postinfusion INR values

In total, 159 of 185 (85.9%) patients treated with 4F-PCC had an INR ≤1.5 at the first time point, assessed at the end of infusion (mean, 32 minutes; range, 1-151 minutes) compared with only 72 of 184 (39.1%) patients treated with plasma (mean, 54 minutes; range, 1-1250 minutes) (Figure 1A). Inclusive of infusion times, the INR corrected within 55 minutes after administering 4F-PCC and 209 minutes after administering plasma in these patients.

For the population that underwent surgeries, the mean infusion time for 4F-PCC was 20.9 minutes (range, 7-85 minutes), and the mean infusion volume was 90 mL (range, 48-200 mL). Treatment with 4F-PCC rapidly corrected the INR, from a median baseline value of 2.9 (IQR, 2.3-3.8) to a median of 1.3 (IQR, 1.2-1.6) recorded 30 minutes after the end of the infusion (Figure 1B). Patients treated with plasma received a mean infusion volume of 819 mL (range, 430-1500 mL) for a mean infusion time of 140.7 minutes (range, 28-590 minutes). Plasma corrected the INR more slowly and incompletely than 4F-PCC (Figure 1B), from a median baseline value of 2.9 (IQR, 2.5-4.1) to a median value of 1.7 (IQR, 1.5-2.1) recorded 30 minutes after the end of the infusion.

Postinfusion coagulation factor levels

Thirty minutes after starting the infusion, mean activity levels of all VKDFs (FII, FVII, FIX, and FX) in the 4F-PCC group exceeded 50% regardless of whether the patients achieved a postinfusion INR ≤1.5 or >1.5 (Figure 2; supplemental Table 1), with FII and FX levels (key hemostatic factors for thrombin generation) >50% in >90% and >89% of patients, respectively, compared with 14.7% and 9.8%, respectively, in the plasma group (Table 1). The proportion of patients with FII or FX levels >50% was significantly higher at all measured time points post–4F-PCC treatment than that of postplasma treatment (Table 1). All VKDF levels were significantly higher in patients treated with 4F-PCC than in patients treated with plasma regardless of patients achieving a postinfusion INR ≤1.5 or >1.5 (supplemental Table 1).

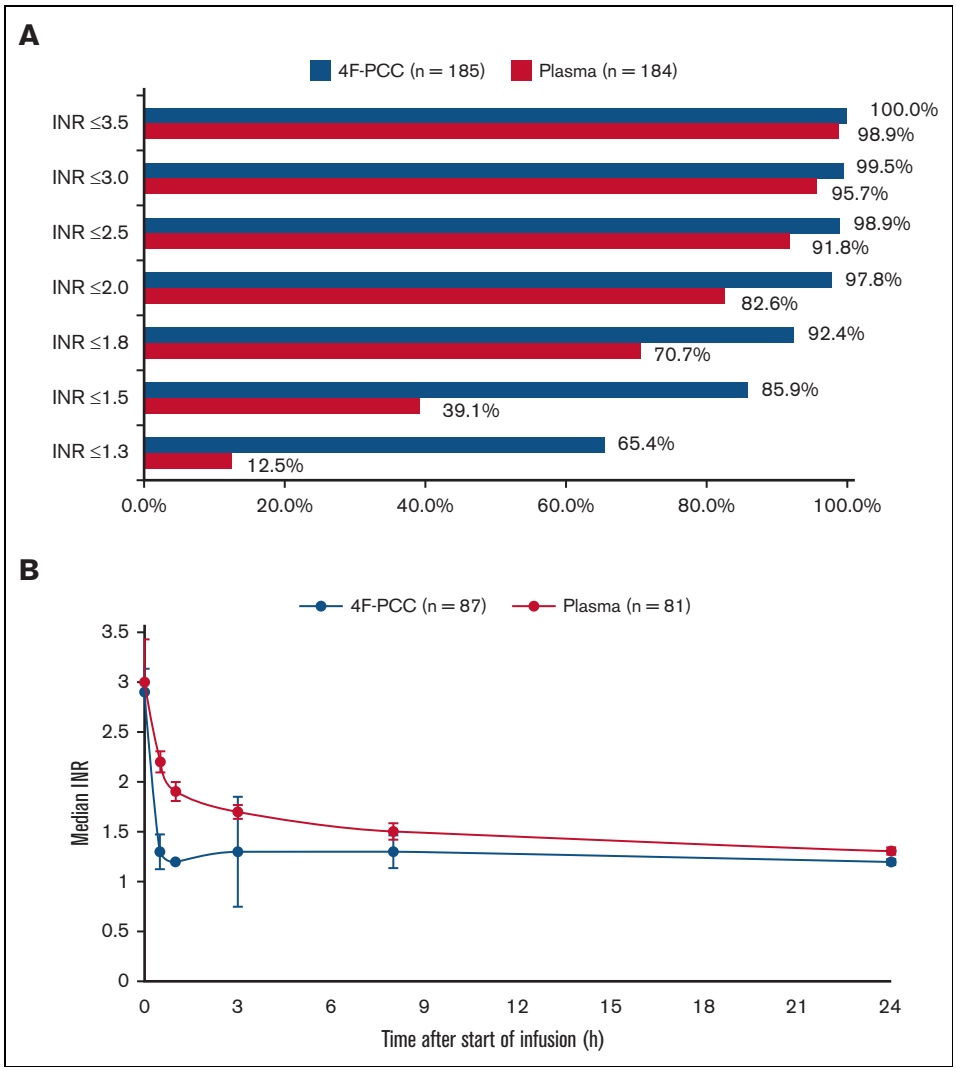

Figure 1. Postinfusion INR rates. (A) Cumulative frequency distribution of INR values at 30 minutes after infusion and (B) Median INR values after treatment with 4F-PCC or plasma (surgical population).

The normalization of VKDF levels was slower for patients treated with plasma than for patients treated with 4F-PCC (Figure 2). Mean activity levels for FII and FX were <50% at all time points assessed within 3 hours after starting the infusion, regardless of whether the patient achieved a postinfusion INR ≤1.5 or >1.5 (Figure 2; supplemental Table 1). At the end of the plasma infusion, 27.2% and 13.9% of the patients had FII and FX levels >50%, respectively (3 hours after start of infusion time point; Table 1).

Average VKDF levels at the time of hemostasis assessment (end of surgery) were no different after treatment with 4F-PCC in those patients achieving effective hemostasis (n = 45) compared with those with ineffective hemostasis (n = 5), with mean FII and FX levels >80% in both groups (Table 2). However, in patients receiving plasma, average VKDF levels were significantly higher in patients achieving effective hemostasis after surgery (n = 44, mean FII 65% and FX 56%) than those with ineffective hemostasis (n = 6, mean FII 45% and FX 32%). Notably, patients with FVII >50% seemed to have an INR <1.5, and as such may reflect INR variation depending upon the international sensitivity index and VKDF sensitivity of each prothrombin time reagent (Table 2).

Time to surgery after infusion

Patients receiving 4F-PCC were able to start surgery significantly earlier after the start of infusion as compared with those receiving plasma (median, 4F-PCC 3.6 hours vs plasma 8.8 hours; $P = .04$) (Figure 3). Patients were able to start surgery in <3 hours after starting the infusion in 44.8% of patients receiving 4F-PCC vs 28.4% of patients receiving plasma ($P = .027$).

Discussion

This retrospective analysis of data from 2 prospective phase 3b randomized controlled trials demonstrated that 4F-PCC achieves not only rapid correction of INR values but also rapid restoration of hemostatic levels of VKDF, even when the postinfusion INR is still elevated at >1.5 compared with plasma. Also, significantly higher number of patients were able to undergo urgent surgery within 3 hours with 4F-PCC compared with plasma.

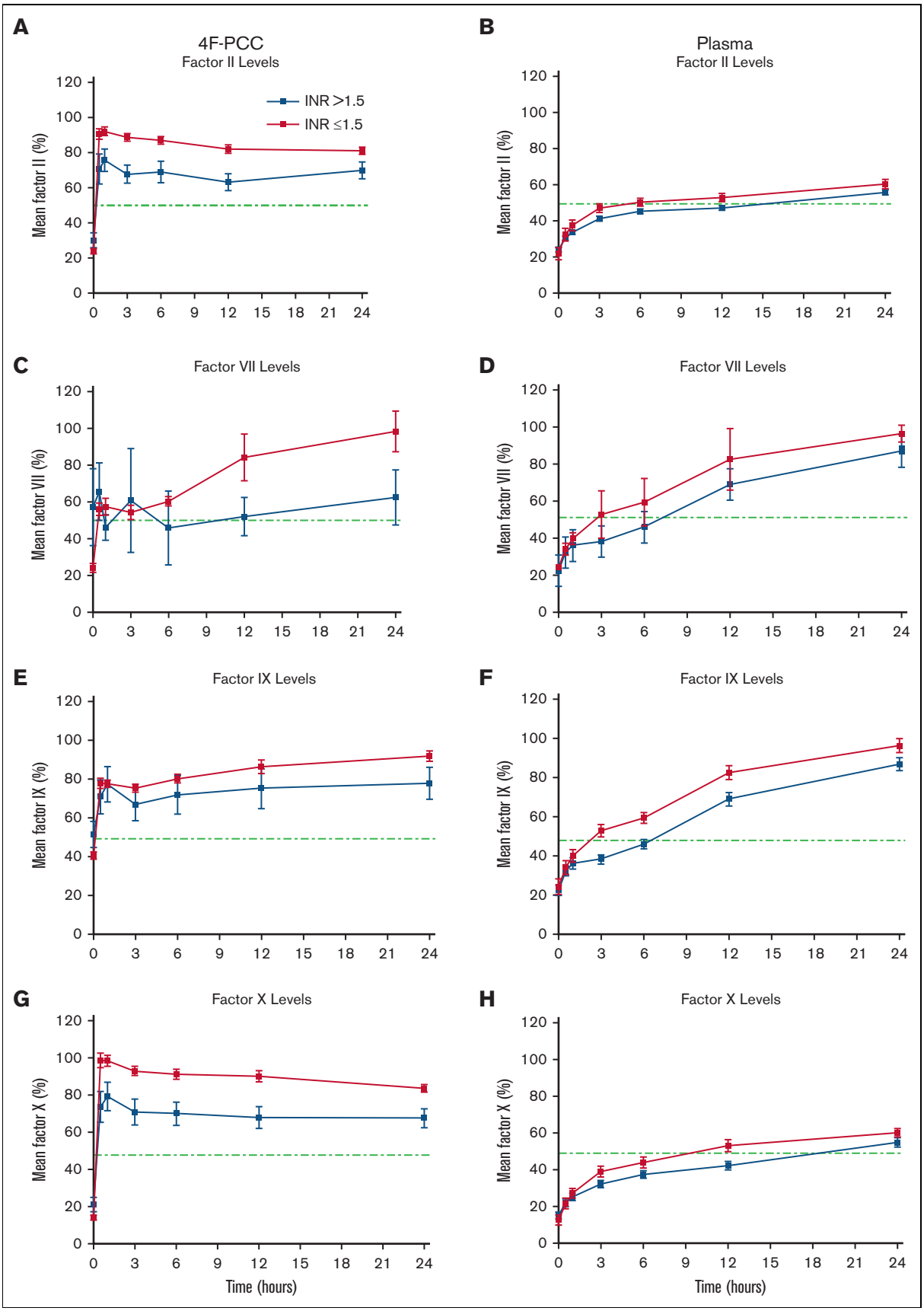

Figure 2.

Table 1. Proportion of patients (%) with coagulation factor levels >50% from the start of infusion after treatment with 4F-PCC or plasma

	4F-PCC (n = 185) (%)			Plasma (n = 184) (%)			*P*-value (4F-PCC vs plasma)		
Factor	**All**	**INR ≤1.5**	**INR >1.5**	**All**	**INR ≤1.5**	**INR >1.5**	**All**	**INR ≤1.5**	**INR >1.5***
FII									
Time after start of infusion									
0.5 hours	144 (90.6)	130 (95.6)	14 (60.9)	24 (14.7)	11 (17.7)	13 (13.0)	< .0001	< .0001	< .0001
1 hour	158 (93.5)	141 (96.6)	17 (73.9)	30 (17.9)	14 (20.6)	16 (16.2)	< .0001	< .0001	< .0001
3 hours	150 (96.2)	136 (97.8)	14 (82.4)	41 (27.2)	20 (35.7)	21 (22.1)	< .0001	< .0001	< .0001
6 hours	136 (93.8)	122 (96.8)	14 (73.7)	54 (35.1)	27 (45.8)	27 (28.4)	< .0001	< .0001	.0002
12 hours	89 (92.7)	77 (95.1)	12 (80.0)	49 (50.0)	24 (68.6)	25 (39.7)	< .0001	.0003	.0082
24 hours	156 (90.2)	141 (94.6)	15 (62.5)	121 (69.9)	56 (81.2)	65 (63.1)	< .0001	.0017	.96
FVII									
Time after start of infusion									
0.5 hours	83 (52.2)	74 (54.4)	9 (39.1)	32 (19.6)	13 (21.0)	19 (19.0)	< .0001	< .0001	.038
1 hour	84 (49.7)	79 (54.1)	5 (21.7)	44 (26.2)	22 (32.4)	22 (22.2)	< .0001	.003	.96
3 hours	77 (49.4)	72 (51.8)	5 (29.4)	49 (32.4)	29 (51.8)	20 (21.0)	.0026	.999	.45
6 hours	85 (58.6)	79 (62.7)	6 (31.6)	69 (44.8)	37 (62.7)	32 (33.7)	.017	.999	.86
12 hours	68 (70.8)	62 (76.5)	6 (40.0)	75 (76.5)	33 (94.3)	42 (66.7)	.37	.033	.056
24 hours	138 (79.8)	125 (83.9)	13 (54.2)	150 (86.7)	66 (95.6)	83 (80.6)	.084	.014	.0067
FIX									
Time after start of infusion									
0.5 hours	126 (79.2)	116 (85.3)	10 (43.5)	77 (47.2)	36 (58.1)	40 (40.0)	< .0001	< .0001	.76
1 hour	140 (82.8)	128 (87.7)	12 (52.2)	78 (46.4)	42 (61.8)	35 (35.4)	< .0001	< .0001	.14
3 hours	132 (84.6)	122 (87.8)	10 (58.8)	87 (57.6)	38 (67.9)	49 (51.6)	< .0001	.001	.58
6 hours	125 (86.2)	113 (89.7)	12 (63.2)	118 (76.6)	51 (86.4)	67 (70.5)	.034	.52	.52
12 hours	79 (82.3)	70 (86.4)	9 (60.0)	86 (87.8)	34 (97.1)	52 (82.5)	.29	.1	.057
24 hours	144 (83.2)	130 (87.2)	14 (58.3)	159 (91.9)	67 (97.1)	91 (88.4)	.015	.025	.0005
FX									
Time after start of infusion									
0.5 hours	142 (89.3)	127 (93.4)	15 (65.2)	16 (9.8)	7 (11.3)	9 (9.0)	< .0001	< .0001	< .0001
1 hour	156 (92.3)	140 (95.9)	16 (69.6)	17 (10.1)	8 (11.8)	9 (9.1)	< .0001	< .0001	< .0001
3 hours	144 (92.3)	134 (96.4)	10 (58.8)	21 (13.9)	11 (19.6)	10 (10.5)	< .0001	< .0001	< .0001
6 hours	134 (92.4)	121 (96.0)	13 (68.4)	34 (22.1)	16 (27.1)	18 (19.0)	< .0001	< .0001	< .0001
12 hours	88 (91.7)	77 (95.1)	11 (73.3)	35 (35.7)	17 (48.6)	18 (28.6)	< .0001	< .0001	.0023
24 hours	153 (88.4)	139 (93.3)	14 (58.3)	110 (63.6)	53 (76.8)	56 (54.4)	< .0001	.0005	.73

Number and percentage of patients treated with 4F-PCC or plasma with FII, FVII, FIX, and FX levels >50% at 0.5 hours, 1 hour, 3 hours, 6 hours, 12 hours, and 24 hours after the start of infusion. Patients were stratified based on their INR being ≤1.5 or >1.5; the number and percentage of patients with INR ≤1.5 who had VDKF levels >50% after treatment with 4F-PCC or plasma and equally for patients with INR >1.5 are also reported.

* The statistical significance between 4F-PCC and plasma for all patients, patients with INR ≤1.5, and with INR >1.5 for each VKDF and time after the start of infusion is provided in the last column.

Our results are consistent with those of previously published studies, including those from a systematic review and meta-analysis that concluded that PCCs are more likely to achieve INR correction within a shorter time.[14] In a study among patients with intracranial hemorrhage and requiring VKA reversal, the time to reach INR <1.3 after plasma administration was 32 hours.[15] Even when targeting INR <1.4, patients treated with plasma exhibited significant delays in INR correction at an average of 29 hours and for INR ≤1.5, an average of 25 hours.[15]

PCC administration has previously been shown to have greater efficacy than plasma in correcting all VKDF levels.[16] Accordingly, our data have shown an increase of 61% in FII levels in patients

Figure 2. Postinfusion coagulation factor levels. Mean factor activity levels (%) from the start of infusion after treatment with 4F-PCC or plasma according to postinfusion INR level (INR >1.5, INR ≤1.5). Dotted green line indicates factor activity level of 50% which is considered to be the minimum threshold for hemostatic levels.

Table 2. Factor activity levels and INR assessed at the time of hemostasis

	Hemostasis: yes (mean ± SD)	Hemostasis: no (mean ± SD)	*P*-value
4F-PCC			
Factor activity levels*	n = 45	n = 5	
FII	90.2 ± 25.2	85.8 ± 24.2	.72
FVII	65.7 ± 47.4	59.6 ± 13.9	.52
FIX	77.2 ± 29.4	70.8 ± 24.1	.6
FX	88.6 ± 27.7	83.4 ± 27.6	.71
Median INR†	1.2 (n = 62)	1.35 (n = 6)	.40
Plasma			
Factor activity levels*	n = 44	n = 6	
FII	64.6 ± 30.3	45.2 ± 12.7	.013
FVII	72.1 ± 56.0	44.5 ± 16.1	.016
FIX	77.5 ± 30.6	57.5 ± 7.8	.001
FX	56.3 ± 26.6	32.2 ± 7.9	< .001
Median INR†	1.4 (n = 56)	1.6 (n = 16)	.002

Effective hemostasis was observed in 78 of 87 (90%) patients receiving 4F-PCC and in 61 of 81 (75%) patients receiving plasma ($P = .0142$). The values reflect data available within ±3 hours of the time of hemostasis assessment.

SD, standard deviation.

*Student t-test used for factor activity levels *P*-value.

†Brown-mood test used for INR *P*-value.

receiving 4F-PCC (from 25.7% baseline to 86.7% after treatment with 4F-PCC) compared with only an 18.1% increase in FII levels in those receiving plasma (from 28.1% baseline to 46.2% after treatment with plasma), suggesting that each unit of plasma increases FII levels by ~5%. In a study of patients requiring VKA reversal, administration of ~4 units of plasma resulted in a decrease of median INR from 8.95 to 2.3, whereas the activity levels of factors II, VII, IX, and X increased from 3% to 10% to 17% to 20%.[16] Similar results were observed in a second study in which a median of 3 units of plasma resulted in an increase in the activity levels of factors II, V, and VII (from 25%-48% to 37%-58%; a median increase of 10% to 12% in activity levels).[17] Taking these findings together, each unit of plasma increased factor activity levels by ~3% to 5%,[16,17] leading to a situation in which INR values may be considered to be corrected (because of early increases in FVII activity compared with FII or FX, mainly because of intravenous vitamin K administered together with PCC or plasma), although the risk of bleeding remains high.[18] Therefore, complete normalization of the hemostatic defect cannot be assumed to have occurred with plasma administration alone.[16,18] It is important to note that our data reflect 2 studies that used a weight-based dosing approach for plasma (10, 12, and 15 mL/kg based on INR), which is not routinely done in clinical practice, and thus, often underdosed.

Our data further highlight that the VKDF levels and INR normalized after administering 4F-PCC in both patients achieving and those not achieving hemostasis. This suggests that other confounding patient characteristics may be attributed to the ineffective hemostasis; however, this needs further exploration. On the contrary, after receiving plasma, INR and VKDF levels were significantly higher (FII and FX activity levels were 65% and 56%, respectively) only in patients achieving hemostasis compared with those not achieving hemostasis (FII and FX activity levels were 45% and 32%, respectively).

The rapid and effective correction of INR and restoration of hemostatic levels of VKDFs affect the ability to operate on patients treated with VKA who require urgent/emergent surgery. The

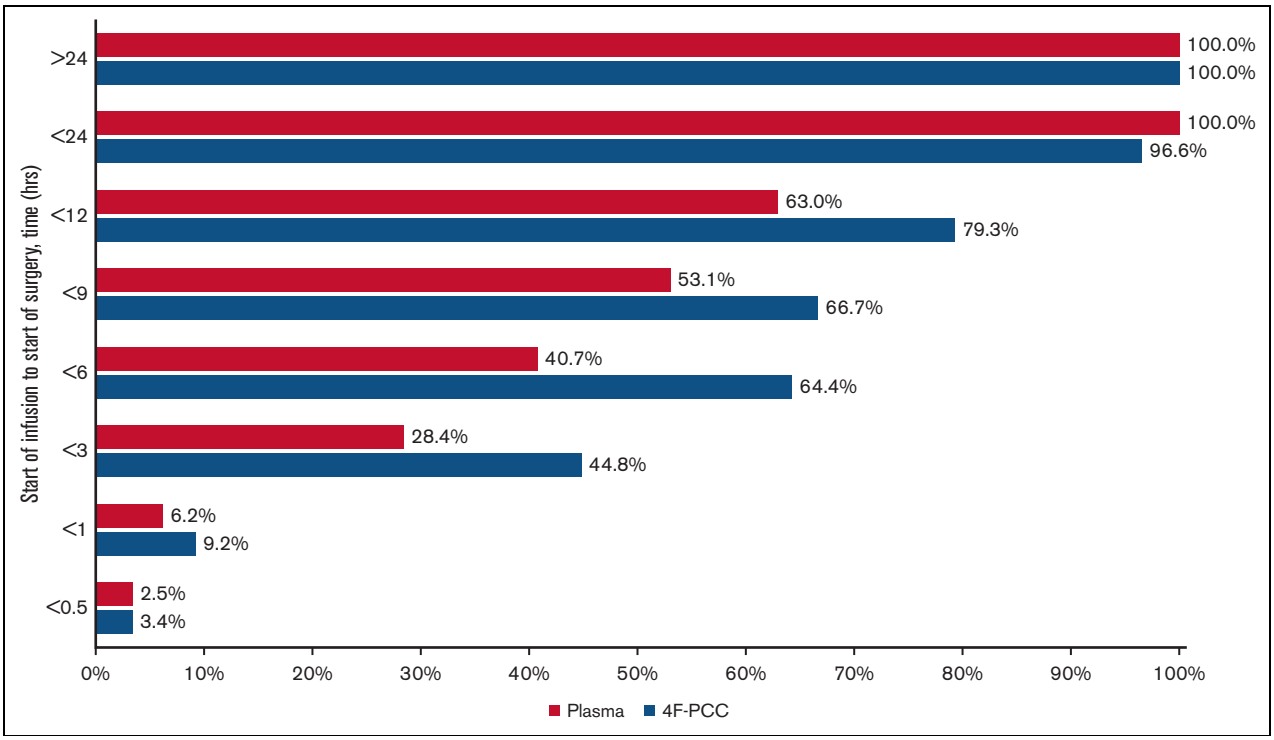

Figure 3. Cumulative frequency distribution of the time from the start of infusion to the start of surgery (hours) after treatment with 4F-PCC or plasma.

majority of such patients will have a correction of INR or VKDF and be ready for surgery immediately after infusion of 4F-PCC, compared with only a small proportion of patients receiving plasma.

The relationship between the extent of INR correction and VKDF levels is probably variable. This may be because of variations among different prothrombin time reagents based on their individual international sensitivity index and their sensitivities to different VKDF, especially FVII.[19,20] Complete INR correction after VKA reversal is often considered to be ≤1.5, and this level has been used as a primary end point in clinical studies assessing the ability of PCCs to correct INR after VKA reversal.[7,12,21,22] However, the target INRs for VKA reversal vary widely depending on the clinical context. In the perioperative setting, the postinfusion target INR is typically <1.3 for neurosurgery and <1.5 for others, depending on the level of bleeding risk associated with the procedure.[3,23-25] In this retrospective analysis, 4F-PCC rapidly restored VKDFs, irrespective of elevated INR levels (>1.5), suggesting that postinfusion INR may not accurately reflect restoration of VKDF levels. Thus, individual coagulation factor levels, FII and FX, provide a better assessment of hemostasis than the INR of patients receiving 4F-PCC for instances of major bleeding or before urgent surgical or invasive procedures.[26-28] With an adequate 4F-PCC dose, there is a predictable increase in VKDF levels; therefore, there is no need to monitor these factor levels in real life.

The strength of this study is that the INR and VKDF data are obtained from 2 prospective randomized clinical trials with hemostatic efficacy being the primary end point. This allowed us to perform post hoc analyses, comparing INR, VKDF levels, and clinical hemostasis.

There are limitations to this study that clinicians should be aware of when interpreting these data. Firstly, this study was a retrospective exploratory analysis that included many post hoc descriptive statistical analyses of 2 prospective randomized trials. Despite the exploratory nature, descriptive values derived are representative of clinical practice and are consistent with those of previously published literature. Secondly, VKDF levels are a surrogate outcome, and thus the relationship between these and patient outcomes requires further research. Thirdly, institutions use different prothrombin time reagents with different international sensitivity indices, leading to potential variability in the INR values drawn at different institutions in these trials; however, this also reflects true clinical practice. In this study, the use of centralized coagulation factor measurement was, therefore, a unique strength that supported published literature using FII and FX >40% to 50% as the surgical hemostatic levels.[13] However, further research is required to provide more data with regard to the VKDF levels required for hemostasis in different clinical situations.

Conclusions

The results from this study demonstrate that 4F-PCC restores VKDFs rapidly in most patients treated with VKA compared with those treated with plasma, even if the postinfusion INR is >1.5. These findings suggest that postinfusion INR may not accurately reflect VKDF restoration because of the variability in prothrombin time reagents at instances of major bleeding or before urgent surgical/invasive procedures. Thus, patients receiving a sufficient dose of 4F-PCC may be taken to the operating room irrespective of complete INR correction.

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Authorship

Contribution: C.H., J.N.G., T.J.M., M.A.R., P.B., B.G., and R.S. designed the study, collected, statistically analyzed and interpreted the data, and drafted and critically revised the manuscript.

Conflict-of-interest disclosure: J.N.G. has received research funding from Pfizer, Takeda, Octapharma and consulting fees from CSL Behring, Alexion-AstraZeneca, Ncontrol, and Cayuga. T.J.M. is a consultant for CSL Behring, Octapharma, Alexion-AstraZeneca, and Cellphire. M.A.R. is in the advisory committees and is a consultant for Cerus, Stago diagnostica, CSL Behring, and Octapharma. R.S. was a consultant for CSL Behring and currently is a consultant for Octapharma. C.H., P.B., and B.G. are employees of CSL Behring.

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References

1. Baugh CW, Levine M, Cornutt D, et al. Anticoagulant reversal strategies in the emergency department setting: recommendations of a multidisciplinary expert panel. *Ann Emerg Med*. 2020;76(4):470-485.

2. Levy JH, Connors JM, Steiner ME, Douketis J, Spyropoulos AC. Management of oral anticoagulants prior to emergency surgery or with major bleeding: a survey of perioperative practices in North America: communication from the scientific and standardization committees on perioperative and critical care haemostasis and thrombosis of the International Society on Thrombosis and Haemostasis. *Res Pract Thromb Haemost*. 2020;4(4):562-568.

3. Hirsh J, Fuster V, Ansell J, Halperin JL. American Heart Association/American College of Cardiology Foundation. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. *J Am Coll Cardiol*. 2003;41(9):1633-1652.

4. Hemphill JC 3rd, Greenberg SM, Anderson CS, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46(7):2032-2060.

5. Tomaselli GF, Mahaffey KW, Cuker A, et al. 2017 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Task Force on expert consensus decision pathways. *J Am Coll Cardiol*. 2017;70(24):3042-3067.
6. Yee J, Kaide CG. Emergency reversal of anticoagulation. *West J Emerg Med*. 2019;20(5):770-783.
7. Goldstein JN, Refaai MA, Milling TJ Jr, 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(9982):2077-2087.
8. Acosta RD, Abraham NS, Chandrasekhara V, et al. The management of antithrombotic agents for patients undergoing GI endoscopy. *Gastrointest Endosc*. 2016;83(1):3-16.
9. Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. *Blood Adv*. 2018;2(22):3257-3291.
10. 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(2 Suppl):e152S-e184S.
11. Greenberg SM, Ziai WC, Cordonnier C, et al. 2022 Guideline for the management of patients with spontaneous intracerebral hemorrhage: a guideline from the American Heart Association/American Stroke Association. *Stroke*. 2022;53(7):e282-e361.
12. Sarode R, Milling TJ Jr, 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(11):1234-1243.
13. Burbury KL, Milner A, Snooks B, Jupe D, Westerman DA. Short-term warfarin reversal for elective surgery–using low-dose intravenous vitamin K: safe, reliable and convenient*. *Br J Haematol*. 2011;154(5):626-634.
14. Chai-Adisaksopha C, Hillis C, Siegal DM, et al. Prothrombin complex concentrates versus fresh frozen plasma for warfarin reversal. A systematic review and meta-analysis. *Thromb Haemost*. 2016;116(5):879-890.
15. Woo CH, Patel N, Conell C, et al. Rapid warfarin reversal in the setting of intracranial hemorrhage: a comparison of plasma, recombinant activated factor VII, and prothrombin complex concentrate. *World Neurosurg*. 2014;81(1):110-115.
16. Makris M, Greaves M, Phillips WS, Kitchen S, Rosendaal FR, Preston EF. Emergency oral anticoagulant reversal: the relative efficacy of infusions of fresh frozen plasma and clotting factor concentrate on correction of the coagulopathy. *Thromb Haemost*. 1997;77(3):477-480.
17. Muller MC, Straat M, Meijers JC, et al. Fresh frozen plasma transfusion fails to influence the hemostatic balance in critically ill patients with a coagulopathy. *J Thromb Haemost*. 2015;13(6):989-997.
18. Steiner T, Rosand J, Diringer M. Intracerebral hemorrhage associated with oral anticoagulant therapy: current practices and unresolved questions. *Stroke*. 2006;37(1):256-262.
19. Jackson CM, Esnouf MP. Has the time arrived to replace the quick prothrombin time test for monitoring oral anticoagulant therapy? *Clin Chem*. 2005;51(3):483-485.
20. van den Besselaar A, Chantarangkul V, Angeloni F, et al. International collaborative study for the calibration of proposed International Standards for thromboplastin, rabbit, plain, and for thromboplastin, recombinant, human, plain. *J Thromb Haemost*. 2018;16(1):142-149.
21. Pabinger I, Brenner B, Kalina U, et al. Prothrombin complex concentrate (Beriplex P/N) for emergency anticoagulation reversal: a prospective multinational clinical trial. *J Thromb Haemost*. 2008;6(4):622-631.
22. Preston FE, Laidlaw ST, Sampson B, Kitchen S. Rapid reversal of oral anticoagulation with warfarin by a prothrombin complex concentrate (Beriplex): efficacy and safety in 42 patients. *Br J Haematol*. 2002;116(3):619-624.
23. Tran HA, Chunilal SD, Harper PL, et al. An update of consensus guidelines for warfarin reversal. *Med J Aust*. 2013;198(4):198-199.
24. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 Suppl):e326S-e350S.
25. Levy JH, Tanaka KA, Dietrich W. Perioperative hemostatic management of patients treated with vitamin K antagonists. *Anesthesiology*. 2008;109(5):918-926.
26. Xi M, Beguin S, Hemker HC. The relative importance of the factors II, VII, IX and X for the prothrombinase activity in plasma of orally anticoagulated patients. *Thromb Haemost*. 1989;62(2):788-791.
27. Allen GA, Wolberg AS, Oliver JA, Hoffman M, Roberts HR, Monroe DM. Impact of procoagulant concentration on rate, peak and total thrombin generation in a model system. *J Thromb Haemost*. 2004;2(3):402-413.
28. Dielis AW, Castoldi E, Spronk HM, et al. Coagulation factors and the protein C system as determinants of thrombin generation in a normal population. *J Thromb Haemost*. 2008;6(1):125-131.