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Impact of infusion speed on the safety and effectiveness of prothrombin complex concentrate

A prospective clinical trial of emergency anticoagulation reversal

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Abstract Prothrombin complex concentrate (PCC) infusion is preferred for emergency reversal of coumarin therapy. Rapid infusion can potentially save crucial time; however, the

possible impact of high infusion speed on PCC safety and effectiveness has not been delineated. In a prospective multinational clinical trial with 43 patients receiving PCC (Beriplex® P/N) for emergency reversal of coumarin therapy, infusion speeds were selected by the investigators. In a two-phase statistical analysis, the influence of baseline patient variables and dose on selected infusion speed was assessed. Then, the effect of infusion speed on reduction in international normalized ratio (INR) and on thrombogenicity marker pharmacokinetics was evaluated. Infusion speed ranged widely from 2.0 to 40.0 mL min⁻¹ with a median of 7.5 mL min⁻¹. Selection of infusion speed was not significantly influenced by gender, age, body mass index, presence of acute bleeding, indication for coumarin therapy, baseline INR, or PCC dose. Infusion speed was higher by a median of 2.2 mL min⁻¹ (95% confidence interval, 1.0–4.3 mL min⁻¹) among patients receiving Beriplex P/N volumes ≥80 mL compared with smaller infusion volumes. Infusion speed did not affect INR attained 30 min following PCC infusion. None of the evaluated thrombogenicity marker pharmacokinetic parameters was affected by infusion speed. Infusions in one patient with questionable hemostatic efficacy and another with a possibly PCC-related thromboembolic event were at moderate and slow speeds, respectively. This study provides the first direct evidence that Beriplex® P/N can be rapidly infused for emergency coumarin therapy reversal without altering safety or effectiveness.

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Introduction

As long-term oral anticoagulant therapy with warfarin and other coumarins has continued to increase, the incidence of coumarin-induced bleeding complications has also risen [1]. In particular, warfarin-associated intracranial hemorrhage (ICH) is an increasing problem as more elderly patients with atrial fibrillation are anticoagulated [2]. The mortality resulting from these bleeds remains high: half the patients with coumarin-associated ICH die within 30 days [3].

When patients receiving coumarin therapy experience major bleeding or require emergency surgery, rapid reversal of coumarin anticoagulation becomes imperative. Recommended therapy consists of fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) in conjunction with vitamin K [4–9]. Coumarins inhibit the maturation of functional vitamin K-dependent coagulation factors II (FII), VII (FVII), IX (FIX), and X (FX), and hence cause a functional deficiency of these proteins. Both FFP and PCC can restore the levels of these four coagulation factors, but PCC can reverse warfarin-related coagulopathy more rapidly than FFP, and usually more completely [10–12]. FFP is more cumbersome and slower to administer than PCC. The necessary thawing and warming of FFP to 37°C expend at least 30 min in an emergency setting [13]. Second, the concentrations of the vitamin K-dependent coagulation factors in FFP equal only approximately 4% of the levels in PCC and, hence, necessitate much higher infusion volumes [14]. For effective anticoagulation reversal, 1 to 2 L of FFP can be required. Third, the relatively well-defined composition of PCC allows more accurate calculation of the dose needed to attain desired coagulation factor levels. Fourth, the PCC purification process removes certain unwanted plasma constituents such as functional isohemagglutinins. Thus, PCC obviates ABO blood type matching that may be needed prior to FFP infusion for optimal safety.

The appropriate rate of FFP infusion depends on the condition of the patient. For an uncompromised adult, infusion of one FFP unit (approximately 220 mL) in 30 min is recommended. However, advanced age and cardiac compromise, both of which are common among patients under coumarin therapy, usually necessitate slow infusion in order to avoid fluid overload. In such cases, hours may elapse before delivery of the full FFP volume is completed. In a retrospective study of patients with warfarin-associated ICH, a median of 6.25 h was needed to administer a mean of five FFP units [15].

In contrast, the lower volumes of PCC can generally be administered within 10 to 60 min [16–27]. Consequently, international normalized ratio (INR) can be very rapidly decreased with PCC, and critical time can be saved under emergency circumstances [24]. Accordingly, the most recent update from the British Committee for Standards in

Haematology recommends that, for reversal of anticoagulation in patients with major bleeding, PCC should be administered in preference to FFP [9].

The impact of infusion speed on PCC safety and effectiveness has thus far not been well characterized. There has been concern that rapid infusion of PCC-containing concentrated coagulation factors might increase the risk of thromboembolic complications. As a precaution, a slow rate of PCC infusion, such as a maximum of 1 mL min⁻¹, has been advocated [28]. It has also been proposed that rates exceeding 1 mL min⁻¹ be reserved exclusively for cases of life-threatening bleeding, and then only during administration of the first PCC doses [29]. Most manufacturers recommend a maximum infusion rate of 2 to 4 mL min⁻¹. However, more recent reports in the literature indicate that PCC can safely be infused more rapidly [16–27]. The present prospective multinational study is the first to empirically assess the influence of infusion rate on PCC safety and effectiveness in emergency reversal of coumarin therapy.

Materials and methods

This prospective clinical cohort study was conducted at 15 centers in Austria, Germany, Hungary, Israel, Lithuania, The Netherlands, Poland, and Switzerland. Eligibility criteria included age ≥18 years old, current oral anti-coagulant therapy with warfarin, acenocoumarol, or phenprocoumon, and INR >2. Study patients required either (1) an emergency surgical or urgent invasive diagnostic intervention or (2) INR normalization due to acute bleeding. Informed written consent was obtained, and the study protocol was approved by the ethics committees or Institutional Review Boards at all participating centers and by the regulatory authorities of the corresponding countries. Further study details are reported elsewhere [30].

One 25-, 35-, or 50-IU kg⁻¹ dose of PCC (Beriplex® P/N, CSL Behring, Marburg, Germany) was administered to patients with baseline INR of <4, 4–6, or >6, respectively. Infusion rate was at the discretion of the investigators up to a recommended maximum of 8.4 mL min⁻¹ (equivalent to 210 IU min⁻¹ or 3 IU kg⁻¹ min⁻¹). Total volume and the duration of infusion were prospectively recorded.

Assessments Effectiveness endpoints for the infusion speed analysis were INR attained 30 min after the end of PCC infusion and clinical rating of hemostatic efficacy. Safety endpoints were thrombogenicity marker pharmacokinetic parameters and the occurrence of adverse events categorized as possibly related to PCC infusion. Evaluated thrombogenicity markers were prothrombin activation fragments 1+2 (F₁₊₂), thrombin–antithrombin complex (TAT) and D-dimer. Pharmacokinetic parameters consisted of the baseline-

adjusted maximum concentration (C_{\max}) observed over the 48-h study period and area under the time-concentration curve (AUC) calculated by the linear trapezoidal method.

Analysis plan In this study, patients were not randomly assigned to particular infusion speeds. Consequently, the possibility of confounding existed, since investigators might have systematically chosen speed of infusion based upon perceived responsiveness to PCC therapy or risk of complications. In order to address that possibility, the first phase of the analysis was focused on the effect, if any, of preinfusion patient attributes on selected infusion speed. These attributes were composed of gender, age, body mass index (BMI), presence of acute bleeding, and indication for coumarin therapy. Dose was also evaluated as a parameter influencing infusion speed since doses were selected according to a patient attribute, namely, baseline INR. Though not a patient attribute and, hence, not an expected source of confounding, volume infused was also evaluated, since investigators may have reserved higher infusion speeds for patients receiving larger PCC volumes in order to reduce the needed duration of infusion. In the second phase of the analysis the effects of infusion speed on the above listed effectiveness and safety endpoints were assessed.

Statistical methods A target enrollment of at least 40 patients was estimated on the basis of previous clinical studies involving Beriplex P/N. The objective in selecting this sample size was to ensure an exact 95% confidence interval (CI) width of <20% around the proportion of patients achieving INR normalization, under the assumption that proportion would equal or exceed 90%.

Descriptive statistics for continuous data were the median and interquartile range (IQR). Normality of continuous data was ascertained by inspection of stem-and-leaf plots. Differences in binary predictors such as gender or presence of acute bleeding were determined by exact Wilcoxon–Mann–Whitney test. Median differences and their CI were quantified by exact Hodges–Lehmann estimation. Unordered ternary predictors such as coumarin therapy indication category (atrial fibrillation, thrombosis, or other) were compared by exact Kruskal–Wallis test and ordered ternary predictors, e.g., the baseline INR categories <4, 4–6, and >6 defined in the study protocol, by exact Jonckheere–Terpstra test.

The influence of infusion speed on thrombogenicity marker pharmacokinetics was evaluated by linear regression. Inability to reject the null hypothesis of zero slope was interpreted as evidence of no effect. Continuous infusion speed and pharmacokinetic parameter data were log transformed to improve normality prior to linear regression analysis. All analyses were conducted using R version 2.5.0 (The R Foundation for Statistical Computing, Vienna,

Austria) and StatXact 7.0 (Cytel Software, Cambridge, MA, USA) statistical software.

Results

Forty-three patients participated in the study: 22 (51%) women and 21 (49%) men. All were Caucasian. Their median age was 70 years (IQR, 66–79 years), and their median body weight was 74.1 kg (IQR, 66.0–84.0 kg). Seventeen patients (40%) were under oral anticoagulant therapy with acenocoumarol, 17 (40%) with phenprocoumon, and nine (20%) with warfarin. The most prevalent indication for coumarin therapy was atrial fibrillation, accounting for 44% (19) of study patients. Other indications included thrombosis in eight patients, pulmonary embolism in four, heart valve replacement and myocardial infarction in three each, and aortic bypass, myocardial ischemia, thrombophlebitis, vascular stent insertion, venous embolism, and ill-defined disorder in one each. Interventional procedures were performed in 26 patients, and 23 patients were experiencing acute bleeding. Baseline INR was <4 in 27 patients (64%), 4–6 in eight (18%), and >6 in eight (18%). The minimum and maximum individual patient baseline INR values were 1.9 and 17.4, respectively.

PCC doses of <30, 30–40, and >40 IU kg^{-1} were administered to 16, 13, and 14 patients, respectively. The total IU of PCC infused, in terms of FIX content, ranged from 1,560 to 6,400. The median volume infused was 90 mL (IQR, 80–105 mL). Figure 1 shows the individual patient infusion speeds, which were $\leq 5 \text{ mL min}^{-1}$ in nine patients (21%), between 5 and 10 mL min^{-1} in 28 (65%), and $\geq 10 \text{ mL min}^{-1}$ in six (14%). The median infusion speed was 7.5 mL min^{-1} (IQR, $5.8\text{--}8.3 \text{ mL min}^{-1}$), equivalent to 188 IU min^{-1} or $2.5 \text{ IU kg}^{-1} \text{ min}^{-1}$. The respective minimum and maximum individual patient values were 2.0 and 40.0 mL min^{-1} . Infusion speed exceeded 15 mL min^{-1} in four patients, of whom three were enrolled at one study center (Table 1; Fig. 1). All four patients had presented with acute bleeding, but otherwise, they differed in their demographic characteristics, indications for coumarin therapy, and baseline INR (Table 1). In three of four patients with ICH, infusions were performed at rates (2.0, 2.8, and 3.2 mL min^{-1}) in the slowest quartile.

Patient attributes vs infusion speed The distributions of infusion speeds were similar in men and women (Fig. 2a). Advanced age (≥ 80 years), obesity ($\text{BMI} \geq 30 \text{ kg m}^{-2}$), and the presence of acute bleeding did not significantly influence the selection of infusion speed (Fig. 2b–d). Infusion speeds were also similar among patients with differing indications for coumarin therapy and baseline INR values (Fig. 3a–b). Thus, no systematic effect of patient

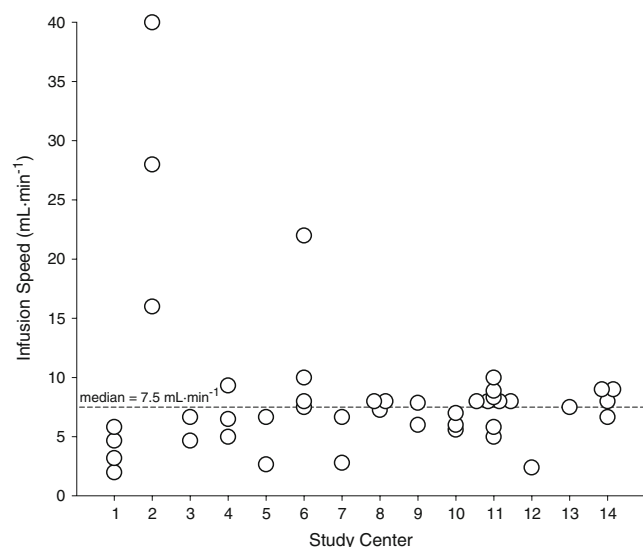


Fig. 1 Individual patient infusion speeds at each study center. After enrollment of 44 total patients, the single patient enrolled at one center withdrew consent to participate in the study prior to PCC infusion. Accordingly, infusion speed data were available from 14 rather than 15 centers

attributes on infusion speed was apparent. Since baseline INR did not affect infusion speed and PCC dose was selected on the basis of baseline INR, it was expected that infusion speeds would not vary according to dose, as was proven to be the case (Fig. 3c).

Volume infused The only significant predictor of infusion speed was volume infused. Larger volumes of PCC were infused at higher speeds (Fig. 3d). For instance, in patients receiving PCC volumes ≥ 80 mL, infusion speed was higher by a median of 2.2 mL min^{-1} (CI, $1.0\text{--}4.3 \text{ mL min}^{-1}$) vs smaller infusion volumes.

Post-infusion INR Individual patient INR values attained 30 min after PCC infusion are displayed in Fig. 4. Infusion speed did not significantly alter INR at 30 min.

Hemostatic efficacy In 40 patients (93%) hemostatic efficacy was classified as “very good” and in two patients as “satisfactory.” A rating of “questionable” hemostatic effi-

cacy was assigned to one patient with a malignant bladder tumor because of persistent post-infusion bladder bleeding. Because hemostatic efficacy ratings other than very good were rare, a formal statistical analysis with respect to this endpoint could not be conducted with adequate precision. In the two cases of satisfactory hemostatic efficacy, both of which involved acute bleeds, the infusion speeds were 9.0 and 28.0 mL min^{-1} . The single patient with questionable hemostatic efficacy was infused at a rate (8.0 mL min^{-1}) closely similar to the study median (7.5 mL min^{-1}).

Thrombogenicity In patients with baseline INR <4 , $4\text{--}6$, and >6 , the median baseline concentrations of F_{1+2} were 0.17 nmol L^{-1} (IQR, $0.12\text{--}0.27 \text{ nmol L}^{-1}$), 0.26 nmol L^{-1} (IQR, $0.16\text{--}0.66 \text{ nmol L}^{-1}$), and 0.20 nmol L^{-1} (IQR, $0.10\text{--}0.27 \text{ nmol L}^{-1}$), respectively. Corresponding medians were $1.0 \mu\text{g L}^{-1}$ (IQR, $1.0\text{--}2.2 \mu\text{g L}^{-1}$), $4.7 \mu\text{g L}^{-1}$ (IQR, $2.0\text{--}6.1 \mu\text{g L}^{-1}$), and $1.8 \mu\text{g L}^{-1}$ (IQR, $1.0\text{--}6.8 \mu\text{g L}^{-1}$) for TAT and $126 \mu\text{g L}^{-1}$ (IQR, $86\text{--}193 \mu\text{g L}^{-1}$), $146 \mu\text{g L}^{-1}$ (IQR, $75\text{--}302 \mu\text{g L}^{-1}$), and $100 \mu\text{g L}^{-1}$ (IQR, $63\text{--}136 \mu\text{g L}^{-1}$) for D-dimer. There was no significant relationship between baseline INR and baseline F_{1+2} ($p=0.90$), TAT ($p=0.064$), or D-dimer ($p=0.45$).

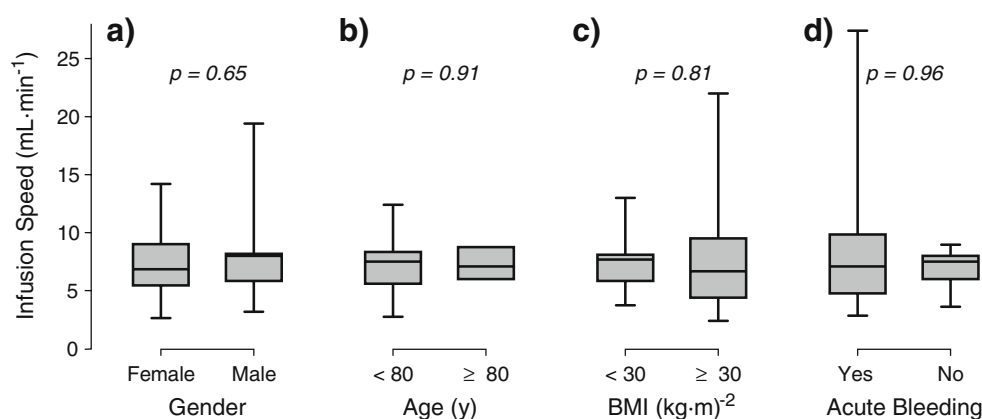
The impact of infusion speed on thrombogenicity marker pharmacokinetic parameters as evaluated by linear regression is depicted in Fig. 5. There was no significant effect of infusion speed on either C_{max} or AUC for any of the three evaluated thrombogenicity markers.

Only one patient experienced an adverse event judged to be possibly related to PCC infusion. A 70-year-old man with metastatic gastrointestinal cancer and atrial fibrillation developed a fatal suspected pulmonary embolism following a second PCC infusion 4 days after the first. Despite laboratory evidence of coagulation activation prior to the initial infusion, this adverse event was judged to have been possibly related to PCC infusion. Although the rate of the second PCC infusion was not documented, the initial infusion was delivered at 4.7 mL min^{-1} , a rate within the slowest quartile for the study. Thus, there was no evidence that rapid initial infusion might have contributed to the thromboembolic event. The low incidence of possibly PCC-related adverse events in this trial precluded a formal statistical analysis for this endpoint.

Table 1 Patients infused at $>15 \text{ mL min}^{-1}$

	Gender	Age (years)	Weight (kg)	Indication	Acute bleeding ^a	INR	
						Baseline	30min
INR international normalized ratio	Female	74	60	Venous thrombosis	Yes	15.9	1.0
	Male	70	72	Atrial fibrillation	Yes	16.6	1.0
^a Intracranial hemorrhage was not present in any of these four patients	Female	66	80	Atrial fibrillation	Yes	3.0	1.1
	Male	84	106	Atrial fibrillation	Yes	7.5	1.0

Fig. 2 Effect on infusion speed of **a** gender, **b** age, **c** BMI, and **d** presence of acute bleeding. Box bottoms and tops depict lowest and highest quartiles, respectively, error bars the lowest and highest deciles, and horizontal lines within the boxes the medians. Abbreviation: BMI, body mass index; *n*, number of patients



Discussion

In this multinational clinical trial, Beriplex P/N was infused over a wide range of rates from 2.0 to 40.0 mL min⁻¹. A detailed statistical analysis of the study data provides the first evidence that the safety and effectiveness of PCC administration for coumarin therapy reversal are not compromised by increased infusion speed, and that infusion speeds higher than previously recommended in the literature can be utilized. A number of prior reports have indicated that PCC can be safely and effectively infused in a rapid manner for coumarin therapy reversal (Table 2). Rapid Beriplex P/N infusion (median 6 mL min⁻¹) has additionally been described in patients with hemostatic defects due to severe liver disease [21]. Healthy volunteers participating in a pharmacokinetic study have also received Beriplex P/N rapidly (mean 7.9 mL min⁻¹) [25].

The feasibility of rapidly infusing PCC for coumarin therapy reversal can afford valuable time savings in the context of acute, possibly life-threatening bleeding or the urgent need for a procedural intervention. Beyond direct medical benefit to the patient, rapid infusion might also help conserve health care provider resources. Using the median volume of 90 mL and the median rate of 7.5 mL min⁻¹ in the present trial, 78 min would be saved

per patient in comparison with the 1.0 mL min⁻¹ 1998 recommendation of Kohler et al [28]. The Paul-Ehrlich-Institut, the German regulatory authority responsible for biological medicinal products, has cleared Beriplex P/N for infusion up to approximately 8 mL min⁻¹, the highest approved infusion rate for any PCC currently available.

The patients enrolled in this trial were diverse in age, indication for coumarin therapy, and BMI and, thus, representative of the population of patients under coumarin therapy commonly encountered in routine clinical practice. None of the evaluated baseline patient variables affected choice of infusion speed by the investigators. Hence, confounding due to non-randomized allocation to infusion speed was not apparent. The only significant predictor of infusion speed was volume infused, with larger volumes being infused faster.

PCC was judged to provide effective clinical control of hemorrhage in 98% of the study patients. By 30 min, INR declined to ≤1.4 in all patients, despite the 20-fold range of infusion speeds in this study (2.0–40.0 mL min⁻¹). The study was designed to determine the magnitude of INR decrease at 30 min, but not its rapidity. As demonstrated in another study of emergency coumarin therapy reversal with Beriplex P/N, the desired INR reduction can be achieved by as soon as 10 min post-infusion [24]. Further studies with sampling earlier than 30 min would be needed to

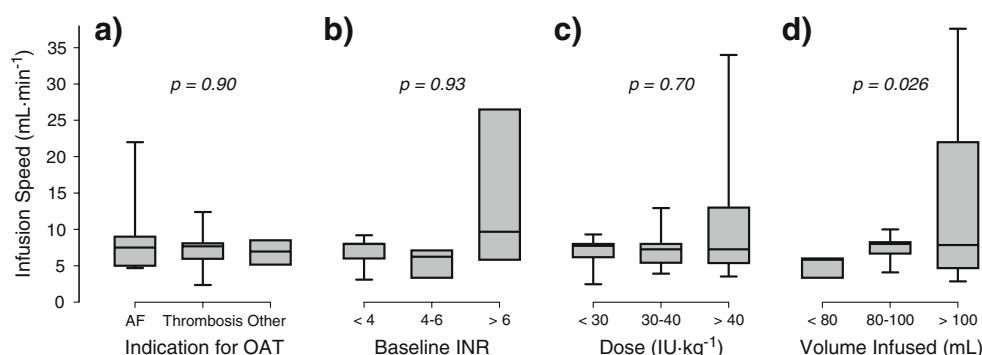


Fig. 3 Effect on infusion speed of **a** indication for coumarin therapy, **b** baseline INR, **c** Beriplex P/N dose, and **d** volume infused. Graphic conventions as in Fig. 2. Abbreviations: INR, international normalized ratio; *n*, number of patients

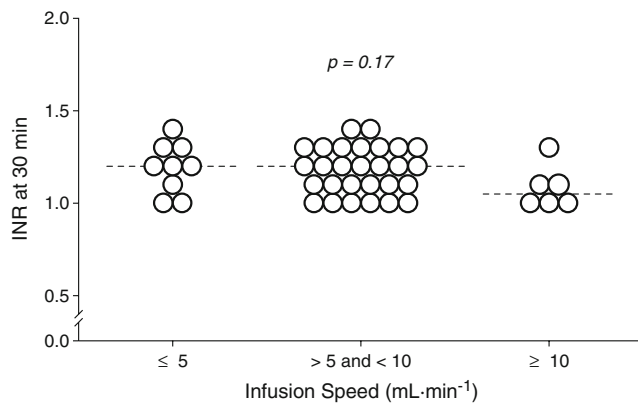


Fig. 4 Effect of infusion speed on INR at 30 min. Dashed lines show median values. Abbreviation: INR, international normalized ratio

investigate any impact of infusion speed on the rapidity of INR reduction by PCC.

In the past, avoidance of rapid PCC infusion has been advised because of concern that a resulting spike in plasma

coagulation factor levels might potentially trigger a thrombotic event. However, in this study, faster infusion speed was not associated with either higher peak levels (C_{\max}) of thrombogenicity markers or greater cumulative elevation (AUC) in these markers. These findings are encouraging. Nevertheless, while F_{1+2} , TAT, and D-dimer are established surrogate markers of thrombogenicity thought to signal a prothrombotic state, their association with the risk of overt thromboembolic events remains uncertain. Because only one thrombotic event possibly related to PCC infusion occurred in the present study, a formal analysis of actual infusion speed in relation to risk of overt thrombotic events could not be conducted due to the low event rate. In any case, coumarin therapy is routinely prescribed for patients whose medical conditions place them at high risk for thrombosis, and nonetheless, the occurrence of thrombotic events following PCC infusion for coumarin therapy reversal has been rare. No thromboembolic or other adverse events were encountered during a recently reported study

Fig. 5 Effect of infusion speed on pharmacokinetic parameters for thrombogenicity markers: **a** F_{1+2} C_{\max} , **b** F_{1+2} AUC, **c** TAT C_{\max} , **d** TAT AUC, **e** D-dimer C_{\max} , and **f** D-dimer AUC. Dashed curves indicate CI of regression slopes and dotted curves 95% prediction intervals for new observations; p values correspond to hypothesis of zero slope. F_{1+2} and TAT data for one patient excluded due to marked pre-infusion elevations in these markers. Abbreviations: AUC, area under the time-concentration curve; C_{\max} , maximum concentration; CI, 95% confidence interval; F_{1+2} , prothrombin activation fragments 1+2; TAT, thrombin–antithrombin complex

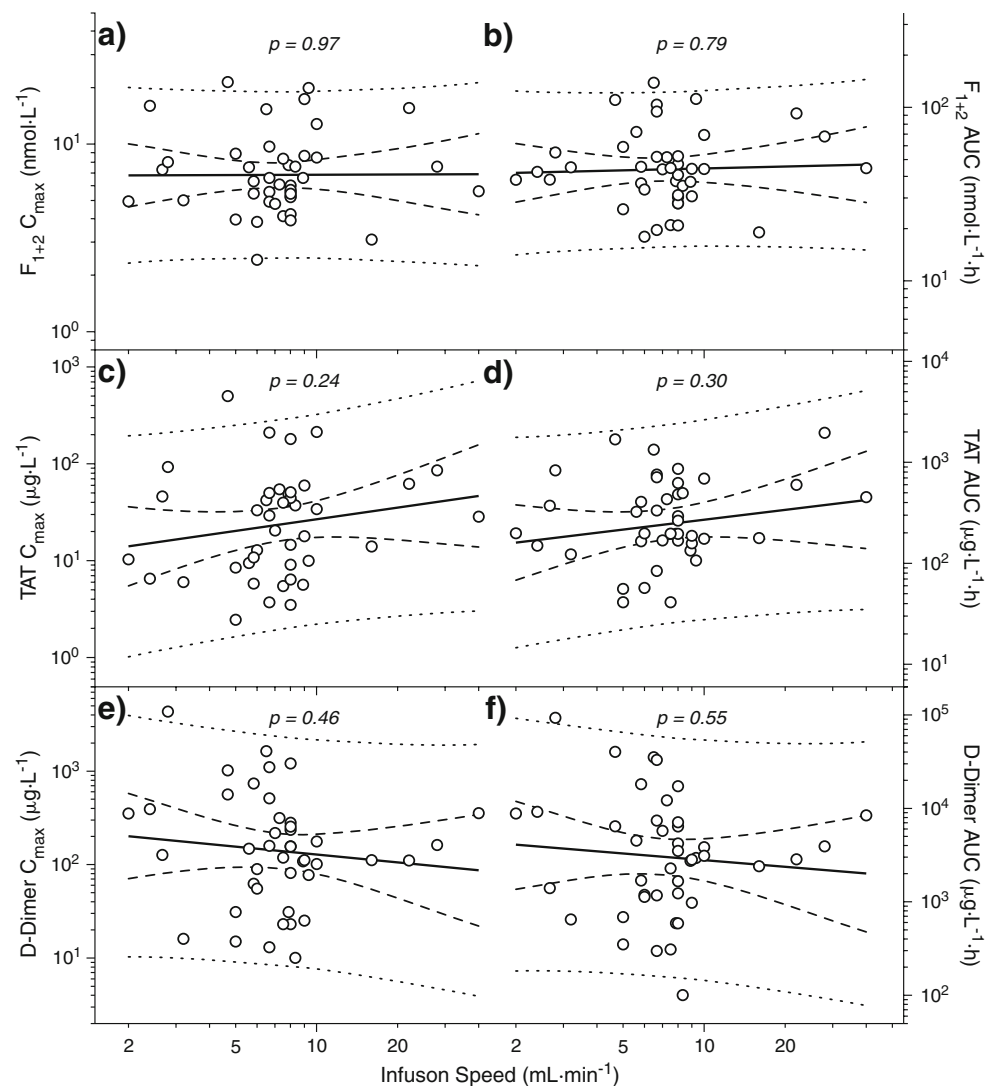


Table 2 PCC infusion speed in clinical studies of coumarin therapy reversal

Study	<i>n</i>	PCC	Indication	Infusion speed
Boulis et al., 1999 [16]	5	Konyne	Warfarin-related ICH	100 IU min ⁻¹
Evans et al., 2001 [18]	10	Beriplex P/N	Reversal of warfarin anticoagulation in patients with major bleeding	30 IU kg ⁻¹ over 10–15 min
Preston et al., 2002 [19]	42	Beriplex P/N	Requirement for immediate reversal of warfarin therapy	25, 35, or 50 IU kg ⁻¹ ; all infusions completed within 10 min
Yasaka et al., 2002 [20]	13	PPSB-HT Nichiyaku	Major hemorrhagic complications during warfarin treatment	500 or 1,000 IU infused in 5–10 min
Lubetsky et al., 2004 [22]	20	Octaplex	Major bleeding or urgent surgery	≤2–3 mL min ⁻¹
van Aart et al., 2006 [23]	93	Cofact	Major bleeding or urgent surgical interventions	2 mL min ⁻¹
Lorenz et al., 2007 [24]	8	Beriplex P/N	Urgent invasive procedures or bleeding in patients under phenprocoumon anticoagulation	Median 17.0 mL min ⁻¹
Riess et al., 2007 [26]	60	Octaplex	Bleeding complications or invasive procedures	Mean 6.42 mL min ⁻¹
Vigué et al., 2007 [27]	18	Kaskadil	ICH	20 IU kg ⁻¹ over 3 min
Present study	43	Beriplex P/N	Interventional procedures or acute bleeding	Median 7.5 mL min ⁻¹

ICH intracranial hemorrhage, *n* number of subjects, PCC prothrombin complex concentrate

in which the median rate of Beriplex P/N infusion (17.0 mL min⁻¹) was more than twice that employed in the present study [24].

This study furnishes the first direct demonstration that the important clinical advantages of rapid PCC infusion can be secured without sacrificing safety or effectiveness. Hence, higher rates of PCC infusion appear to offer an opportunity for expediting the emergency reversal of coumarin therapy.

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Appendix

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References

1. Wysowski DK, Nourjah P, Swartz L (2007) Bleeding complications with warfarin use: a prevalent adverse effect resulting in regulatory action. Arch Intern Med 167:1414–1419

2. Flaherty ML, Kissela B, Woo D, Kleindorfer D, Alwell K, Sekar P, Moomaw CJ, Haverbusch M, Broderick JP (2007) The increasing incidence of anticoagulant-associated intracerebral hemorrhage. *Neurology* 68:116–121
3. Aguilar MI, Hart RG, Kase CS, Freeman WD, Hoeven BJ, Garcia RC, Ansell JE, Mayer SA, Norrving B, Rosand J, Steiner T, Wijdicks EF, Yamaguchi T, Yasaka M (2007) Treatment of warfarin-associated intracerebral hemorrhage: literature review and expert opinion. *Mayo Clin Proc* 82:82–92
4. Executive Committee and Scientific Advisory Committee of the Federal Physicians Chamber (2002) Prothrombin complex concentrate. In: *Guidelines for Therapy with Blood Components and Plasma Derivatives*, 2nd edn. Deutscher Ärzte-Verlag GmbH, Köln, pp 95–111
5. Hirsh J, Fuster V, Ansell J, Halperin JL (2003) American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. *Circulation* 107:1692–1711
6. Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E (2004) The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 126:204S–233S
7. Baker RI, Coughlin PB, Gallus AS, Harper PL, Salem HH, Wood EM (2004) Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. *Med J Aust* 181:492–497
8. O'Shaughnessy DF, Atterbury C, Bolton Maggs P, Murphy M, Thomas D, Yates S, Williamson LM (2004) Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. *Br J Haematol* 126:11–28
9. Baglin TP, Keeling DM, Watson HG (2006) Guidelines on oral anticoagulation (warfarin): third edition—2005 update. *Br J Haematol* 132:277–285
10. Makris M, Greaves M, Phillips WS, Kitchen S, Rosendaal FR, Preston EF (1997) Emergency oral anticoagulant reversal: the relative efficacy of infusions of fresh frozen plasma and clotting factor concentrate on correction of the coagulopathy. *Thromb Haemost* 77:477–480
11. Cartmill M, Dolan G, Byrne JL, Byrne PO (2000) Prothrombin complex concentrate for oral anticoagulant reversal in neurosurgical emergencies. *Br J Neurosurg* 14:458–461
12. Yasaka M, Sakata T, Naritomi H, Minematsu K (2005) Optimal dose of prothrombin complex concentrate for acute reversal of oral anticoagulation. *Thromb Res* 115:455–459
13. Erber WN, Perry DJ (2006) Plasma and plasma products in the treatment of massive haemorrhage. *Best Pract Res Clin Haematol* 19:97–112
14. Schulman S, Bijsterveld NR (2007) Anticoagulants and their reversal. *Transfus Med Rev* 21:37–48
15. Lee SB, Manno EM, Layton KF, Wijdicks EF (2006) Progression of warfarin-associated intracerebral hemorrhage after INR normalization with FFP. *Neurology* 67:1272–1274
16. Boulis NM, Bobek MP, Schmaier A, Hoff JT (1999) Use of factor IX complex in warfarin-related intracranial hemorrhage. *Neurosurgery* 45:1113–1118
17. Staudinger T, Frass M, Rintelen C, Quehenberger P, Wagner O, Stoiser B, Locker GJ, Laczika K, Knapp S, Watzke H (1999) Influence of prothrombin complex concentrates on plasma coagulation in critically ill patients. *Intensive Care Med* 25:1105–1110
18. Evans G, Luddington R, Baglin T (2001) Beriplex P/N reverses severe warfarin-induced overanticoagulation immediately and completely in patients presenting with major bleeding. *Br J Haematol* 115:998–1001
19. Preston FE, Laidlaw ST, Sampson B, Kitchen S (2002) Rapid reversal of oral anticoagulation with warfarin by a prothrombin complex concentrate (Beriplex): efficacy and safety in 42 patients. *Br J Haematol* 116:619–624
20. Yasaka M, Sakata T, Minematsu K, Naritomi H (2002) Correction of INR by prothrombin complex concentrate and vitamin K in patients with warfarin related hemorrhagic complication. *Thromb Res* 108:25–30
21. Lorenz R, Kienast J, Otto U, Egger K, Kiehl M, Schreiter D, Kwasny H, Haertel S, Barthels M (2003) Efficacy and safety of a prothrombin complex concentrate with two virus-inactivation steps in patients with severe liver damage. *Eur J Gastroenterol Hepatol* 15:15–20
22. Lubetsky A, Hoffman R, Zimlichman R, Eldor A, Zvi J, Kostenko V, Brenner B (2004) Efficacy and safety of a prothrombin complex concentrate (Octaplex) for rapid reversal of oral anticoagulation. *Thromb Res* 113:371–378
23. van Aart L, Eijkhout HW, Kamphuis JS, Dam M, Schattenkerk ME, Schouten TJ, Ploeger B, Strengers PF (2006) Individualized dosing regimen for prothrombin complex concentrate more effective than standard treatment in the reversal of oral anticoagulant therapy: An open, prospective randomized controlled trial. *Thromb Res* 118:313–320
24. Lorenz R, Kienast J, Otto U, Kiehl M, Schreiter D, Haertel S, Barthels M (2007) Successful emergency reversal of phenprocoumon anticoagulation with prothrombin complex concentrate: a prospective clinical study. *Blood Coagul Fibrinolysis* 18:565–570
25. Ostermann H, Haertel S, Knaub S, Kalina U, Jung K, Pabinger I (2007) Pharmacokinetics of Beriplex P/N prothrombin complex concentrate in healthy volunteers. *Thromb Haemost* 98:790–797
26. Riess HB, Meier-Hellmann A, Motsch J, Elias M, Kursten FW, Dempfle CE (2007) Prothrombin complex concentrate (Octaplex®) in patients requiring immediate reversal of oral anticoagulation. *Thromb Res* 121:9–16
27. Vigué B, Ract C, Tremey B, Engrand N, Leblanc PE, Decaux A, Martin L, Benhamou D (2007) Ultra-rapid management of oral anticoagulant therapy-related surgical intracranial hemorrhage. *Intensive Care Med* 33:721–725
28. Köhler M, Hellstern P, Lechler E, Überfuhr P, Müller-Berghaus G (1998) Thromboembolic complications associated with the use of prothrombin complex and factor IX concentrates. *Thromb Haemost* 80:399–402
29. Pindur G, Morsdorf S (1999) The use of prothrombin complex concentrates in the treatment of hemorrhages induced by oral anticoagulation. *Thromb Res* 95:S57–61
30. Pabinger I, Brenner B, Kalina U, Knaub S, Nagy A, Ostermann H (2008) Prothrombin complex concentrate (Beriplex® P/N) for emergency anticoagulation reversal: a prospective multinational clinical trial. *J Thromb Haemost* 6:622–631