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Citation



Brekelmans, M. P. A., Abdoellakhan, R. A., Scheres, L. J. J., Biedermann, J. S., Hutten, B. A., Meijer, K., ... Coppens, M. (2018). Clinical outcome of patients with a vitamin K antagonist-associated bleeding treated with prothrombin complex concentrate. *Research And Practice In Thrombosis And Haemostasis*, 2(1), 77-84. doi:10.1002/rth2.12055

Version: Not Applicable (or Unknown)
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Note: To cite this publication please use the final published version (if applicable).

ORIGINAL ARTICLE

Clinical outcome of patients with a vitamin K antagonist-associated bleeding treated with prothrombin complex concentrate

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Funding information

This study was funded by ZonMW Goed Gebruik Geneesmiddelen (project number 836021017) and Sanquin Blood Supply.

Abstract

Background: Vitamin K antagonists (VKA) are used for the treatment of thromboembolism. Patients with severe VKA-associated bleeding require immediate restoration of haemostasis. Clinical studies on the effect of prothrombin complex concentrate (PCC) are heterogeneous with respect to outcome of bleeding.

Objective: To evaluate the clinical outcome of patients treated with PCC for VKA-associated bleeding.

Methods: We performed a cohort study of consecutive patients who received PCC for VKA-related bleeding in five Dutch hospitals. Data were collected by chart review on the bleeding event, international normalized ratio (INR), haemostatic efficacy, thromboembolic (TE) complications, and mortality. The primary outcome was effective haemostasis, assessed by an adaptation of the Sarode criteria with a surrogate outcome for patients with ICH without repeat CT.

Results: One hundred patients were included. Mean age was 74 years, 54% were male and 79% received VKA for atrial fibrillation. Most patients presented with ICH (41%) or GI bleeding (36%). Effective haemostasis was achieved in 67/98 (68%) patients using the adapted classification. Surrogate outcomes were applied for 32 patients and data for two patients was missing. Median pre-treatment INR was 3.9 (IQR 2.9-5.8). One hour after PCC infusion, the INR was available for 50 patients and of these, 35 (70%) had an INR \leq 1.4. TE complications occurred in five patients and 22 died (60% bleeding-related) within 30 days.

Conclusion: PCC achieved effective haemostasis in 68% of evaluable patients with VKA-associated bleeding. TE complication rates were low, but mortality rates were high, due to the large number of patients with ICH.

KEYWORDS

anticoagulants, coumarins, haemorrhage, prothrombin, vitamin K

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Essentials

- Data on clinical outcome of vitamin K antagonist (VKA)-associated bleeding is scarce.
- Cohort study of patients with VKA bleeds treated with prothrombin complex concentrate (PCC).
- Effective haemostasis was achieved in 68% of patients with a VKA-associated bleeding.
- Thromboembolism rates were low and mortality rates high at 30 days after PCC administration.

1 | INTRODUCTION

Vitamin K antagonists (VKA) are frequently prescribed oral anticoagulants and are effective in the treatment and prevention of venous and arterial thromboembolic diseases.¹ An important complication of VKA treatment is the occurrence of bleeding events, which typically involve the gastrointestinal system, central nervous system, or soft tissues.² The annual incidence rate of major bleeding episodes in VKA treated patients is 1-3%.³⁻⁶ Life-threatening bleeding occurs in approximately 0.25% of patients annually.⁴

Patients with severe VKA-associated bleeding require immediate restoration of haemostasis by reversing the anticoagulant effect of VKA as part of the bleeding management.¹ The first step in reversal is usually vitamin K administration.^{7,8} Intravenously administered vitamin K normalizes the international normalized ratio (INR) within 12-16 hours,⁹ whereas oral administration of vitamin K will take up to 24 hours to take effect.¹⁰ Since immediate reversal is indicated in these patients, several international treatment guidelines recommend the use of prothrombin complex concentrate (PCC).^{1,11,12} Three-factor PCC contains the vitamin K-dependant coagulation factors II, IX, and X, and protein C and S. Four-factor prothrombin complex concentrate (PCC) additionally contains factor VII.^{13,14} PCC products are highly effective in normalizing INR.^{3,15} Advantages of PCC over substitution with fresh frozen plasma (FFP) are a smaller volume and shorter duration of infusion and a low pathogen transmission risk.¹⁶ In the Netherlands, PCC has been widely available for decades in all national hospitals and there is ample experience with its use in patients with bleeding or in those that need to undergo emergency invasive procedures.

In 2013, a new standard was introduced to evaluate haemostatic efficacy of reversal agents in bleeding complications related to anticoagulant use.¹⁷ This classification scheme was developed in collaboration with the Food and Drug Administration (FDA) for a randomized controlled trial (RCT) comparing Beriplex (PCC) with FFP.¹⁷ In the current studies testing antidotes for the direct oral anticoagulants,^{18,19} this classification scheme is standardly used to assess haemostatic efficacy of the reversal agent. Both the FDA and the European Medicines Agency (EMA) have accepted this standard for ongoing and future studies. This endpoint was not used previously in studies of reversing VKA in the setting of haemorrhage. Therefore, the current study addressed this endpoint in order to provide comparison to the results of ongoing studies of antidotes to DOACs. The aim of this cohort study was to evaluate clinical outcome parameters, including haemostatic efficacy, thromboembolic complications, and mortality in patients treated with PCC for VKA-associated bleeding complications.

2 | METHODS

2.1 | Study design and study population

We performed a retrospective cohort study of consecutive patients who received PCC for a VKA-associated bleeding between September 2014 and December 2015 in five Dutch tertiary university medical centers (Amsterdam, Maastricht, Rotterdam, Leiden, and Groningen). Every participating hospital included 20 patients. The study was performed in accordance with local ethics regulations, and the Institutional Review Board of the Academic Medical Center, Amsterdam waived the need for a formal review of this study. Informed consent was not obtained from the patients, because all data was retrospectively and anonymously collected from medical charts and discharge letters.

Patients 18 years or older receiving PCC therapy for a VKA-related acute bleeding event were eligible for inclusion. Each of the participating hospitals started the retrospective data collection at a different time point, and data were collected consecutively for the first 20 patients that received PCC in the prior 4-6 months. Patients were identified through PCC distribution lists and administration files from the hospital blood bank or pharmacy. Data were collected on medical history, concomitant medication, VKA-related bleeding event, PCC treatment, other procedures and interventions to treat the bleeding, INR, haemostatic efficacy, thromboembolic (TE) complications, and mortality. All information was recorded in standardized case report forms.

Patients all received 4-factor PCC (Cofact; Sanquin Blood Supply, Amsterdam, the Netherlands) according to local hospital protocol. Each mL of PCC contains 14 IU factor II, 7 IU factor VII, 25 IU factor IX, 14 IU factor X, 11 IU protein C, and 1 IU protein S. PCC was administered intravenously and the dose was dependent on INR at presentation and body weight. The speed of administration was variable and not recorded for study purposes. In Dutch clinical practice, FFP is not considered to be a VKA reversal method. Hence, if a VKA-related bleeding was severe enough, PCC was administered.

2.2 | Outcome parameters

2.2.1 | Haemostatic efficacy

The primary outcome parameter was haemostatic efficacy of PCC at 24 hours after the start of infusion, assessed by a modification of the Sarode et al. criteria,¹⁷ based on Dutch clinical practice. Haemostatic efficacy was classified as excellent, good, or poor for different bleeding localizations based on haemoglobin decrease over 24 hours

(gastrointestinal [GI] bleeding), hematoma expansion (intracranial haemorrhage [ICH]), or cessation of visible blood loss.¹⁷ Effective haemostasis was defined as the efficacy ratings excellent or good (Table S1). When no repeat CT scanning was performed within 24 hours due to standard clinical practice policy, surrogate outcome categories for haemostatic efficacy ("surrogate efficacy") in ICH patients were set. Patients were first classified as stable neurological condition since admission, cessation of further medical treatment due to a poor neurological condition, or no records available. The category "stable neurological condition since admission" was surrogate for effective haemostasis, whereas the category "cessation of further medical treatment due to a poor neurological condition" was indicative of non-effective or poor haemostasis. Data on the Glasgow Coma Scale score, neurological signs and symptoms, neurological examination, and clinical course, were used to evaluate these patients on the surrogate outcome and were retrieved by chart review.

The secondary analysis described the results of the original haemostatic efficacy classification¹⁷ and the surrogate efficacy outcome separately.

2.2.2 | Clinical presentation and course

Bleeding events were classified as major or minor bleeding. Major bleeding was defined according to the ISTH criteria as clinically overt and causing a decrease in haemoglobin of ≥ 2 grams per decilitre or requiring two or more units of packed cells or whole blood, occurring in a critical organ or site, or being fatal.²⁰ All other bleedings were considered minor bleedings.

All major bleeding events were classified using two classification schemes that were developed and published previously.²¹⁻²³ The first classification was used to assess the severity of the major bleeding event at presentation (Table S2A). The second classification was used to assess the applied procedures and interventions for treatment and the clinical outcome of the bleeding event (Table S2B). Both classification schemes consist of four different categories, with one being the mildest and four the most severe.²¹⁻²³

2.3 | Statistical analysis

Continuous variables are described by measures of central tendency and variability. Categorical variables are presented as proportions (n/N) and percentage (%). Comparisons between patients from the different centers were made using the one-way analysis of variance (ANOVA) for continuous variables, and by Chi-square test for categorical variables. A *P*-value of less than .05 was considered to be statistically significant. All statistical analyses were performed using the SPSS package (version 24.0, Chicago, Illinois).

3 | RESULTS

3.1 | Study population

Demographic and clinical characteristics of the 100 patients with a VKA-associated bleeding event treated with PCC at presentation are

detailed in Table 1. The mean age was 74 ± 12 years and 54 (54%) of the patients were male. There were no significant differences in age, sex, or weight between the five centers. Almost three-quarters of the study population had a history of hypertension (71%) and approximately one-quarter had as history of type 2 diabetes mellitus (24%). Antiplatelet drugs were used in 17 (17%) of patients; of whom seven patients clopidogrel and six aspirin.

TABLE 1 Demographics and characteristics of patients with a VKA-associated bleeding event

Total patients	N = 100
Age in years, mean (SD)	74.4 \pm 11.6
Male sex, n (%)	54 (54)
Weight in kg, mean (SD) ^a	
Males	85.0 \pm 18.0
Females	70.2 \pm 15.1
Medical history, n (%)	
Hypertension	71 (71)
Diabetes mellitus	24 (24)
Cancer	18 (18)
Heart valve disease	16 (16)
Peripheral vascular disease	11 (11)
Stroke	10 (10)
Thyroid disease	6 (6)
Medication use, n (%)	
Antiplatelet agents	17 (17)
NSAIDs	9 (9)
Type of VKA, n (%)	
Acenocoumarol	65 (65)
Phenprocoumon	33 (33)
Warfarin	1 (1)
Unknown	1 (1)
Indication for VKA therapy, n (%)	
Atrial fibrillation	79 (79)
Venous thromboembolism	7 (7)
Mechanical heart valve	6 (6)
Other	8 (8)
Type of bleeding, n (%)	
Intracranial	41 (41)
Gastrointestinal	36 (36)
Intramuscular/subcutaneous	11 (11)
Retroperitoneal	4 (4)
Epistaxis	4 (4)
Genitourinary	2 (2)
Hemoptysis	2 (2)

NSAIDs, non-steroidal anti-inflammatory drugs; SD, standard deviation; VKA, vitamin K antagonist.

^aData missing for 17 males and 18 females.

The most frequently prescribed type of VKA was acenocoumarol (65 [65%]). Of the included patients, in 79 (79%) the indication for VKA was atrial fibrillation, in seven (7%) venous thromboembolism and in the remainder mechanical heart valves or other conditions. The majority of patients (72 [72%]) were treated with VKA for >12 months at the time of bleeding.

A total of 86 (86%) patients presented with a major bleeding and 14 (14%) had a minor bleeding; 41 (41%) patients presented with an ICH and 36 (36%) patients with a GI bleeding. The mean age of patients with an ICH was 72 ± 12 years and 49% of them were male. The 36 patients with GI bleeding had a mean age of 76 ± 11 years and 67% were male. When combining the other types of bleeding ($n = 23$), the mean age was 75 ± 12 years and 44% were male. The distribution of bleeding types differed significantly between the five centers ($p = .01$); two centers included predominantly ICH, two included mostly GI bleeds, and one included a variety of bleeding types.

3.2 | Treatment of VKA-related bleedings

The median dose of administered PCC was 2000 international units (IU) for men (median 25 IU per kg body weight) and 1500 IU for women (median 22 IU per kg body weight). Vitamin K was given to 79 (79%) patients in addition and parallel to PCC treatment. In 45 (57%) of 79 patients, vitamin K was administered intravenously and 61 (77%) received a dose of 10 mg vitamin K. Packed cells were administered in 45 (45%), platelet transfusions in 6 (6%), and FFP in 8 (8%) of the patients. In 39 (39%) patients a procedure was indicated

to control or stop the bleeding; in 15 (38%) a surgical, in 21 (54%) an endoscopic, and in three (8%) a radiological procedure was performed (Table 2).

3.3 | Outcome parameters

3.3.1 | Haemostatic efficacy

Assessment of the adapted classification of haemostatic efficacy showed that effective haemostasis was achieved in 67 (68%) of 98 patients; 31 (31%) of 98 had non-effective or poor haemostasis, and for two patients effective haemostasis could not be assessed primarily or using the surrogate efficacy outcome measurement (Table 3).

Using the Sarode criteria for haemostatic efficacy,¹⁷ assessment was possible in 66/100 patients. In 34 (34%) patients the rating was missing, mostly due to the absence of repeat CT scans for ICH. Effective haemostasis was achieved in 47 (71%) of 66 evaluable patients (Table 3).

Stratification by type of bleeding showed that in nine (22%) of 41 patients with an ICH the haemostatic efficacy could be assessed using the Sarode criteria,¹⁷ which was excellent in four and poor in five patients. Surrogate efficacy analyses were performed for patients with ICH without haemostatic efficacy assessment (32 [78%]). Of the 32 ICH patients, 20 (63%) were classified as having a stable neurological condition since admission, 10 (31%) as cessation of further medical treatment due to poor neurological condition, and two (6%) as no records available (Table 3).

TABLE 2 Treatment of VKA-associated bleeding events

	Total cohort N = 100	ICH N = 41	GI bleeds N = 36	Other bleeds N = 23
Dose of PCC administered in IU				
Males, median (IQR)	2000 (1500-2250)	2000 (1750-2500)	2000 (1500-2250)	1750 (1125-1750)
Females, median (IQR)	1500 (1000-1750)	1500 (1250-2000)	1250 (1000-1500)	1250 (1000-2000)
Dose of PCC in IU per kg, median (IQR)				
Males	25 (20-25)	25 (22-26)	25 (28-26)	23 (18-26)
Females	22 (16-28)	21 (12-29)	22 (14-29)	20 (10-25)
Other medical treatment, n (%)				
Vitamin K	79 (79)	34 (83)	25 (69)	20 (87)
Tranexamic acid	4 (4)	1 (2)	1 (3)	2 (9)
Administration of blood products, n (%)				
Red blood cells	45 (45)	2 (5)	28 (78)	15 (65)
Platelets	6 (6)	4 (10)	2 (6)	0
Fresh frozen plasma	8 (8)	1 (2)	5 (14)	2 (9)
Procedures to control the bleeding, n (%)				
Type of procedure, n/N (%)				
Surgical	15/39 (38)	12/12 (100)	0	3/6 (50)
Endoscopic	21/39 (54)	0	20/21 (95)	1/6 (17)
Radiologic	3/39 (8)	0	1/21 (5)	2/6 (33)

GI, gastrointestinal; iCH, intracranial haemorrhage; IQR, interquartile range; IU, international units; PCC, prothrombin complex concentrate; VKA, vitamin K antagonist.

TABLE 3 Haemostatic efficacy of VKA-associated bleeding events

Total patients	N = 100
Adapted assessment of haemostatic efficacy, n/N (%) ^a	
Effective haemostasis	67/98 (68)
Poor haemostasis	31/98 (32)
Missing or no record	2/100 (2)
Secondary outcomes	
Haemostatic efficacy rating by category according to Sarode, n/N (%)	
Excellent	35/100 (35)
Good	12/100 (12)
Poor	19/100 (19)
Missing primary rating	34/100 (34)
Surrogate haemostatic efficacy, n/N (%) ^b	
Effective haemostasis	20/32 (63)
Non-effective or poor haemostasis	12/32 (37)

ICH, intracranial haemorrhage; VKA, vitamin K antagonist.

^aCombined haemostatic efficacy and surrogate efficacy.

^bIn patients with ICH.

In the 36 patients presenting with GI bleeding, 20 (56%) had excellent haemostatic efficacy, nine good, six poor and in one patient the rating was not assessable.

3.3.2 | INR correction

At presentation, the median INR was 3.85 with an interquartile range (IQR) of 2.9-5.8. Data on INR correction after receiving PCC was not available for 50 patients. For the remaining 50 patients, INR correction was rapid; 1 hour after start of infusion, 35 (70%) of patients had an INR \leq 1.4. The baseline INR of the patients who had a follow up INR was a median 3.8 with an IQR of 2.7-6.2.

For patients who achieved effective haemostasis ($n = 67$), the median baseline INR was 4.4 (IQR 3.1-6.6). INR after PCC administration was available for 61 (94%) patients and was \leq 1.4 in 40 of 61 (66%) within the hour. For patients with poor haemostatic outcome ($n = 31$ in total), median baseline INR was 3.59 with an IQR of 2.7-4.5. For 23 (74%) of them the INR was available after PCC administration and the INR lowered to \leq 1.4 in 15 of 23 (65%) patients.

In patients with ICH, the median INR at presentation was 3.25 (IQR 2.6-5.1). Data on INR normalization after PCC administration was available for 34 of 41 (83%) ICH patients and 27 of them achieved an INR \leq 1.4 within 1 hour.

INR measurement at 24 hours after PCC infusion was performed in 77 patients and the median INR value was 1.3 (IQR 1.1-1.6).

3.3.3 | Safety outcomes

Thromboembolic complications were reported in 5 (5%) patients (Table 4). Four of these were venous thromboembolic events.

TABLE 4 Safety outcomes of VKA-associated bleeding events

Total patients	N = 100
Thromboembolic complications <30 days, n (%)	5 (5)
Type of complication, n/N (%)	
Myocardial infarction	1/5 (20)
Deep vein thrombosis or pulmonary embolism	4/5 (80)
Bleeding complications < 30 days, n (%)	11 (11)
Type of complication, n/N (%)	
Intracranial bleeding	1/11 (9)
Gastro-intestinal bleeding	5/11 (46)
Other	4/11 (36)
Unknown	1/11 (9)
Mortality, n (%)	22 (22)
Cause of death, n/N (%)	
Ischemic stroke	1/22 (5)
Bleeding	13/22 (59)
Other	8/22 (36)
Length of hospital stay in days, median (IQR)	7 (5-13)
Admission at ICU, n (%)	21 (21)
Length of stay in ICU in days, median (IQR)	3 (1-5)

ICU, intensive care unit; IQR, interquartile range; TIA, transient ischemic attack; VKA, vitamin K antagonist.

Eleven (11%) patients had a new bleeding complication within 30 days after the VKA associated bleeding event. Most of these were re-bleedings at the same location as the initial bleeding event.

By day 30 after PCC administration, 22 (22%) deaths were observed (Table 4), of which 18 were in patients with ICH. The mortality rate in ICH patients was 44% (18 of 41) and in patients with GI bleeding 8% (3 of 36). The cause of death was related to the bleeding event in 13 (59%) of 22 of the patients. None of the deaths were attributed to thrombosis, ie, pulmonary embolism or myocardial infarction. The median duration of hospital stay was 7 days, and 21% of patients was admitted in the ICU for a median of 3 days.

3.3.4 | Clinical presentation and course

Figure 1 details the results of the classification of the VKA-associated major bleeding events at presentation ($N = 86$). None of the major bleeding episodes were classified as category 1; ie, presenting without any clinical emergency. A severe clinical presentation (category 3 or 4) was observed in 64% of the patients. One patient presented with a bleeding event that was fatal before or almost immediately after entering the hospital (category 4).

The clinical course of VKA-associated major bleeding events treated with PCC was categorized as 3 or 4 in 50% of patients (Figure 1). Four (5%) major bleeds met the criteria for severest clinical course in which death was unavoidable and life-saving attempts were not undertaken (category 4).

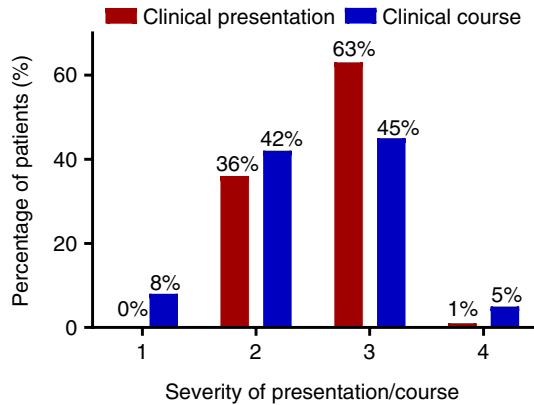


FIGURE 1 Clinical presentation and clinical course of major bleeding episodes (n = 86) on vitamin K antagonists

4 | DISCUSSION

The present multicenter cohort study shows that infusion of PCC was able to achieve effective haemostasis in 68% of patients with VKA-associated bleeding complications based on an adapted assessment of haemostatic efficacy using our surrogate efficacy outcome for ICH patients. In addition, TE complication rates were low and mortality rates rather high within 30 days after PCC administration. Sub-classification of clinical presentation and course of major VKA-associated bleeding showed that two-thirds of patients had a severe clinical presentation, and half also had a severe clinical course, meaning that the bleeding was life-threatening and required elaborate measures to avoid death, could still be fatal after interventions and could lead to permanent disability, or death was unavoidable.

In a previously published randomized controlled trial, PCC was compared to plasma for immediate reversal of VKA-associated major bleedings.¹⁷ In that study, effective haemostasis was achieved in 72% of patients receiving PCC, which is consistent with our findings. An advantage of our cohort study is that we included all consecutive patients with bleeding events in comparison to trial patients that had to fulfill in- and exclusion criteria.¹⁷

The rapid and almost complete INR normalization observed in the current analysis is consistent with findings from previous studies.^{3,17,24–27} In addition, the reported TE event rate (5%) is comparable to those from earlier reports (range 3.9–6.2%).^{17,25,28,29} The possible association between the administration of PCC and the occurrence of TE complications remains a concern. In most studies, including ours, it is impossible to disentangle the potentially thromboembolic effects of PCC from the effects of cessation of anticoagulation.^{27,29} Finally, the observed mortality rate was 22%. This rate was similar to numbers reported (25%) in a recent systematic review of PCC,²⁵ but somewhat higher than in other studies (range 5.8–7.8%).^{17,30} The high mortality rate in this study can be explained by the large number of patients included with ICH compared to other studies, reflecting the presence of severe bleeding complications of VKA treatment.

Strengths of the present study include consecutive sampling, the relative homogeneous population of patients with VKA-related

bleeding events that were all treated with PCC, the representativeness of the patients from daily practice, the comprehensive and standardized data retrieval on standardized report forms, the use of the extensive predefined criteria for haemostatic efficacy, the evaluation of clinically relevant outcome parameters (INR normalization, thromboembolic complications, and mortality), and the long-term availability and experience with PCC in all national hospitals in the Netherlands.

Some methodological aspects of our study require further comment. First, no repeat CT scan after reversal with PCC was performed in almost 80% of patients with ICH. This is explained by local treatment protocols in which repeat CT imaging is only done in patients with neurological deterioration and not in patients that are neurologically stable or in patients with infaust prognosis who are considered beyond repair. We believe our surrogate outcome to be a valid surrogate for haemostatic efficacy. Haematoma expansion is unlikely and arguably clinically irrelevant in patients without neurological deterioration and vice versa a poor neurological condition might be indicative of an increase in haematoma volume partly due to cessation of further medical treatment. Second, our study was a retrospective cohort study. It is therefore not possible to implicate causal relations between PCC and clinical study outcome parameters. Due to the observational nature of our study and the variable follow-up data available, the results of this study can be particularly used for hypothesis-generating purposes. In addition, one should be careful with the interpretation of the results, as there may be a selection bias; patients that have a very poor prognosis beforehand will not be treated as aggressively, hence there may be a selection of patients that do receive PCC based on a better prognosis at presentation. Furthermore, all centers that participated in this study were tertiary university medical hospitals. These hospitals usually treat patients with the very worst prognoses, but on the other hand do have elaborate treatment options and interventions available, for example neurosurgical departments. This could have also introduced selection bias leading to over- or underestimation of true treatment effects. A third limitation is that we did not include a control group of patients receiving other treatment to restore haemostasis. We are therefore not able to compare the results directly with other treatment options. Given the current guidelines, a meaningful comparison with no haemostatic treatment is not possible from observational data. Especially in ICH, where retrospective studies are hampered by the absence of repeat CT, prospective and possibly interventional data on efficacy are needed. Furthermore, this study had a small sample size of 100 patients which might have influenced the results; possible existing differences in treatment, management or outcomes between different types of bleeding may not have been detected. Another limitation is that data on INR correction were not available for 50% of the patients. Therefore, these findings need to be interpreted with caution, since they do not represent the total study population. The described INR values after PCC administration might be an over- or underrepresentation of the true INR values for all patients. Finally, 14% of patients were classified as having a minor bleeding. The decision to treat with PCC was at the discretion of the treating physician, and the diagnosis of major or minor bleeding was made in retrospect by chart review. However, one could speculate that events classified as minor bleeding

might not have needed PCC, and including these events could have slightly overestimated the haemostatic efficacy outcome.

Overall, the results from this study support the use of PCC as primary treatment for VKA-associated bleeding events as recommended by recent guidelines.^{1,11,12} Since we included real-world patients experiencing bleeding complications of VKA treatment, our results are likely to be generalizable to other patients needing PCC for VKA-associated bleeding.

In conclusion, our study assessed clinical outcomes, haemostatic efficacy and INR normalization in patients treated with PCC for VKA-associated bleeding complications. The most frequently observed bleeding was ICH. PCC administration was shown to achieve effective haemostasis in 68% of patients with VKA-associated bleeding. TE complication rates were low, but mortality rates high, due to the large number of patients presenting with ICH.

AUTHOR CONTRIBUTIONS

M.P.A. Brekelmans, S. Middeldorp, and M. Coppens were responsible for the study concept and design. M.P.A. Brekelmans, R.A. Abdoellakhan, L.J.J. Scheres, and J.S. Biedermann were responsible for collecting data. M.P.A. Brekelmans, B.A. Hutten, and M. Coppens were responsible for analysis of the data and drafting of the manuscript. All authors revised and approved the final version of the manuscript. All authors had full access to the data in the study.

RELATIONSHIP DISCLOSURE

M.P.A. Brekelmans reports grants from ZonMW Goed Gebruik Geneesmiddelen, and grants from Sanquin Blood Supply, during the conduct of the study; and travel and accommodation fees from Bayer, outside the submitted work. R.A. Abdoellakhan has nothing to disclose. L.J.J. Scheres has nothing to disclose. J.S. Biedermann has nothing to disclose. B.A. Hutten has nothing to disclose. K. Meijer reports grants from Bayer, Sanquin and Pfizer, consulting fees from Uniqure, travel support from Baxter, Bayer, Sanquin and Pfizer, speaker fees from Bayer, Sanquin, Boehringer Ingelheim, BMS and Aspen, outside the submitted work. H. ten Cate is Chair of the Dutch Federation of Anticoagulation Clinics, but has no other relevant conflicts. M.V. Huisman reports research grants and personal fees as well as honoraria for presentations from Boehringer Ingelheim, Bayer HealthCare, Pfizer-Bristol-Myers Squibb, GlaxoSmithKline, Aspen, and Actelion Pharmaceuticals outside this work, outside the submitted work. M.J.H.A. Kruip reports grants from Daiichi Sankyo, Boehringer Ingelheim, Bayer, Pfizer (Nederland), and personal fees from Bayer, outside the submitted work. S. Middeldorp reports Grant or Research Support from GSK/Aspen, BMS/Pfizer, Sanquin and Bayer, Consultant fees from Bayer, BMS/Pfizer, Boehringer Ingelheim and Daiichi Sankyo, Paid Instructor at Bayer, GSK BMS/Pfizer, Boehringer Ingelheim and Daiichi Sankyo, outside the submitted work. M. Coppens reports grants from ZonMW Goed Gebruik Geneesmiddelen, grants from Sanquin Blood Supply, during the conduct of the study; other from

Boehringer Ingelheim, grants, personal fees, non-financial support and other from Bayer, grants, personal fees, non-financial support and other from Daiichi Sankyo, other from Pfizer, personal fees from Bristol Myers Squibb, other from Portola, personal fees and non-financial support from CSL Behring, personal fees from Aspen Pharma Group, outside the submitted work.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Brekelmans MPA, Abdoellakhan RA, Scheres LJJ, et al. Clinical outcome of patients with a vitamin K antagonist-associated bleeding treated with prothrombin complex concentrate. *Res Pract Thromb Haemost*. 2018;2: 77–84. <https://doi.org/10.1002/rth2.12055>