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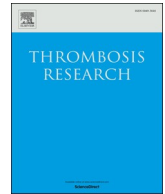
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Full Length Article

Outcome of intracranial bleeding managed with prothrombin complex concentrate in patients on direct factor Xa inhibitors or vitamin K antagonists



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A B S T R A C T

Intracranial hemorrhage (ICH) is the most feared complication of anticoagulation with a high mortality and morbidity. Before registration of a specific reversal agent for factor Xa inhibitors (FXa-I), international guidelines recommended prothrombin complex concentrate (PCC), which also is the specific reversal agent for vitamin K antagonists (VKA). In two contemporary cohorts, we compared clinical outcomes between patients with FXa-I and VKA related ICH treated with PCC between 2014 and 2018. Primary outcome was effective hemostasis after 24 h, according to the International Society of Thrombosis and Hemostasis definition. Safety outcomes were defined as venous and arterial thromboembolic complications and death within 30 days. Thirty-six patients with FXa-I-ICH and 39 patients with VKA-ICH were available for analysis. Baseline characteristics were comparable between both groups, except for time from start of symptoms to presentation at the hospital. In the FXa-I-ICH cohort, 24 (73%) patients achieved effective hemostasis compared to 23 (62%) patients in the VKA-ICH cohort (crude odds ratio [OR] 1.62 [95%CI 0.59–4.48], adjusted OR 1.45 [95%CI 0.44–4.83]). Eight (24%) patients with FXa-I-ICH deceased compared to 17 (45%) patients with VKA-ICH (crude OR 0.38 [95%CI 0.14–1.24], adjusted OR 0.41 [95%CI 0.12–1.24]). In this observational cohort study, the outcome of ICH managed with PCC was similar in patients with FXa-I-ICH and in patients with VKA-ICH.

1. Introduction

Due to the high mortality and morbidity, intracranial hemorrhage (ICH) is the most feared complication in patients using anticoagulant drugs [1]. Almost half of patients die after ICH and two thirds of the survivors suffer from significant functional dependencies [2–4]. As a consequence anticoagulant related ICH is eminently the type of emergency for which reversal of an oral anticoagulant is thought crucial to improve the outcome of the bleed [5]. Reported ICH incidences with use of direct oral anticoagulants (DOACs) are half of the reported ICH incidences with the use of vitamin K antagonists (VKA) [6,7]. In parallel, reported incidences of DOAC-related fatal bleeding are half that of VKA-related fatal bleeding [6,8].

Four-factor prothrombin complex concentrate (PCC) is a specific

reversal agent for VKA and consists of the vitamin K dependent coagulation factors II, VII, IX and X. Therefore, international guidelines recommend the use of PCC when immediate VKA reversal is indicated [9,10]. Upon regulatory approval of the DOACs, physicians were concerned about the absence of a reversal agent, especially for patients with a high bleeding risk. Before the registration of andexanet alfa for reversal of direct factor Xa inhibitors (FXa-I), PCC was recommended by several guidelines as part of the management in patients with FXa-I related emergencies [11,12]. This recommendation was based on a randomized crossover study in healthy non-bleeding volunteers on rivaroxaban showing that administration of PCC immediately restored thrombin generation [13].

Importantly, the prognosis of FXa-I-ICH managed with PCC is unknown, as well as whether its prognosis differs from the prognosis of

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VKA-ICH managed with PCC. Since several clinical registries have suggested that PCC is effective and safe for FXa-I reversal, current clinical guidelines also suggest treatment with PCC for life-threatening FXa-I emergencies [9,14,15].

We compared the clinical outcomes of two contemporary cohorts of patients with ICH, either on a FXa-I or on a VKA, both managed with PCC. We hypothesized that the prognosis of the patients in both cohorts are similar.

2. Methods

2.1. Study population and design

Participants in this study were selected from two Dutch observational studies: the DOAC emergency registry and the ROVAP cohort [20,21]. The DOAC emergency study consisted of 121 consecutively included patients who presented with a DOAC-related emergency between 2014 and 2018 [16]. The ROVAP cohort consisted of 100 consecutive patients that presented with a VKA related major bleeding between September 2014 and December 2015 for which PCC was administered as a reversal agent [17]. For the present study, we included those patients who had an ICH and received PCC. All patients using direct factor Xa inhibitors or VKA were eligible, patients using dabigatran were excluded. The choice to use PCC and the choice of the PCC dose was at the discretion of the treating physician in both studies, as was the choice of adding other hemostatic measures to the ICH management. For management of DOAC emergencies, national guidelines in the Netherlands suggests PCC in a dose of 25–50 international units (IU)/kilogram (kg) and for management of VKA emergencies the PCC dose is based on the patient's weight and international normalized ratio (INR).

In both cohorts data on medical history, anticoagulant use, ICH characteristics and concomitant medication use were collected by chart review, along with details on management of the bleed. ICH volume was measured centrally by one investigator (RB) using the ABC/2 score for intracerebral hemorrhage [23]. For subdural or epidural ICH, the diameter of the bleeding was measured. Volumes of subarachnoid hemorrhages were not calculated. When in doubt, the volumes were discussed with an independent radiologist (LB), who was blinded for the cohort (DOAC or VKA) the patient belonged to.

2.2. Clinical outcomes

The definitions of clinical outcomes were identical in both cohorts. The efficacy outcome was effective hemostasis 24 h after presentation or PCC administration [16,17]. Effective hemostasis was defined according to the ISTH criteria [18]. According to these criteria hemostasis can be classified as excellent, good or poor according to the site of bleeding (musculoskeletal, intracranial or other non-visible bleeding), wherein effective hemostasis is defined as either excellent or good hemostasis. The hemostatic classification of patients with intracranial bleeding can be either assessed by repeated imaging to evaluate hematoma expansion or by clinical evaluation on the neurological condition after 24 h, assessed by neurological scores such as Glasgow Coma Score (GCS). Worsening of the neurological condition or cessation of treatment is considered as poor hemostasis [19].

In the DOAC emergency registry, effective hemostasis was evaluated by four site investigators and reviewed by the national coordinator (RB) of the study. In case of doubt, classification was made by consensus with the last author (MC) [18]. For the VKA cohort, effective hemostasis had been evaluated by the national coordinator (MB) and, when in doubt, discussed with the last author (MC).

Safety outcomes consisted of thromboembolic events and mortality up to 30 days after presentation. Thromboembolic events were defined as venous and arterial events comprising pulmonary embolism, deep

vein thrombosis, myocardial infarction, transient ischemic attack, ischemic stroke and systemic embolisms. Patients were followed until 30 days after inclusion or death.

2.3. Statistical analysis

Differences in continuous variables between patients of the DOAC cohort and the VKA cohort were evaluated using the independent sample *t*-test; variables with a skewed distribution were compared by the non-parametric Mann-Whitney *U* test. Chi-square tests were applied for comparing distributions of dichotomous data.

The association between the different outcomes (efficacy and safety) and treatment (DOAC-I or VKA) were explored using logistic regression analyses. We adjusted for potential confounders by means of multiple logistic regression analyses in two different ways. First, all variables that were considered clinically relevant by the authors were joined in a full model. With the use of stepwise backward elimination (significance level to stay [SLS] in the model < 0.1), a final model, that always contained the variable anticoagulant treatment (VKA or DOAC), was derived. These variables in the model considered clinically relevant by the authors consisted of age, center, indication anticoagulation, ICH location, baseline GCS, hypertension, baseline systolic blood pressure, trauma, procedure, history of stroke, concomitant NSAID/antiplatelet use and cancer.

The second model was derived by including those variables that had a *p*-value below 0.25 for both the relationship with the determinant (DOAC or VKA) and the outcome. In line with the first model, stepwise backward elimination (SLS < 0.1) was applied. Variables with more than 30% missing values, were not taken into account as possible confounders. A *p*-value of less than 0.05 was considered to be statistically significant. All statistical analyses were performed using the SPSS package (version 26.0, Chicago, Illinois).

3. Results

3.1. Study population

Of 221 patients, 36 (30%) of the DOAC emergency registry cohort and 39 (39%) patients of the ROVAP cohort had ICH and received PCC; these patients comprised our study population. All 36 DOAC-ICH patients were using factor-Xa inhibitors (from now on referred to as the “FXa-I-ICH”). Demographic and clinical characteristics of both cohorts are shown in Table 1. Most patients (36%) presented with an intracerebral bleeding. The median intracerebral bleeding volume was 15 ml (IQR 4–34) in the FXa-I-ICH compared to 22 ml (IQR 3–54) in the VKA-ICH cohort (*p* = 0.695). The median time from symptoms of ICH to presentation in the hospital was reported in 36 (48%) patients and was 135 min (IQR 71–253 min) for the FXa-I-ICH and 360 min (IQR 116–1440 min) for the VKA-ICH cohort (*p* = 0.006). Bleeding management did not differ between both cohorts, except for the dose of PCC (Table 2). Patients in the FXa-I-ICH cohort were treated with a median dose of 50 IU/kg (IQR 50–50) and patients in the VKA-ICH cohort were treated with a median PCC dose of 20 IU/kg (IQR 20–25) (*p* < 0.001). Thirty-three out of 39 patients in the VKA-ICH cohort also received vitamin K as part of the reversal management.

3.2. Outcomes

3.2.1. Efficacy

Effective hemostasis after 24 h was not assessable in five patients of which three belonged to the FXa-I-ICH cohort and two belonged to the VKA-ICH cohort. All five patients were transferred to another regional hospital within 24 h. Effective hemostasis was achieved after treatment with PCC in 26 (73%) patients with FXa-I-ICH and 23 (62%) patients with VKA-ICH (Fig. 1), corresponding to a crude odds ratio (OR) of 1.62

Table 1
Demographic and clinical characteristics at presentation.

	VKA-ICH N = 39	FXa-I-ICH N = 36	p-Value
Age (years), mean (SD)	73.1 (10.9)	76.1 (8.9)	0.197
Male, no. (%)	20 (51)	20 (56)	0.771
Weight (kg), mean (SD)*	81.2 (17.4)	77.1 (14.3)	0.363
Indication anticoagulant, no. (%)*			
Atrial fibrillation	30 (77)	33 (92)	
Venous thromboembolism	4 (10)	2 (6)	
Mechanical heart valve	2 (5)	0	0.247
Medical history, no. (%)			
Hypertension	17 (44)	22 (61)	0.129
Diabetes mellitus	10 (26)	10 (28)	0.834
Stroke	5 (13)	8 (22)	0.283
Cancer	4 (10)	6 (17)	0.415
Thyroid disease	3 (8)	6 (17)	0.232
Peripheral arterial disease	5 (13)	2 (6)	0.280
Heart valve disease	2 (5)	3 (8)	0.578
Concomitant medication use, no. (%)			
Antiplatelet drugs	5 (12.8)	2 (5.6)	0.280
NSAIDs	3 (8)	1 (3)	0.344
Bleeding characteristics			
Time from start symptoms to presentation (minutes), median (IQR)*	360 (116–1440)	135 (71–253)	0.006
Systolic blood pressure (mmHg), median (IQR)*	140 (118–171)	156 (139–187)	0.016
ICH localization, no. (%)			
Intracerebral	16 (33)	14 (39)	
Subdural	11 (23)	6 (17)	0.2
Subarachnoidal	6 (15)	4 (11)	
Cerebellar	0	5 (14)	
Epidural	1 (3)	1 (3)	
Other	0	1	
Combination	5 (13)	5 (14)	
Trauma, no. (%)*	15 (39)	14 (39)	0.602
Baseline GCS, median (IQR)*	13 (7–15)	14 (11–15)	0.314
Volume, median (IQR)*			
Intracerebral bleeding (mL)	22 (3–54)	15 (4–34)	0.695
Subdural bleeding (mm)	11.7 (4.0–15.3)	11.0 (10.7–12.0)	0.958

VKA: vitamin K antagonist; ICH: intracranial hemorrhage; FXa-I: factor-Xa inhibitor; SD: standard deviation, no.: number; kg: kilogram; IQR: interquartile range; IU: international units; HVD: heart valve disease; PVD: peripheral arterial disease; TD: thyroid disease; NSAID: non-steroidal anti-inflammatory drugs; GCS: Glasgow Coma Scale; mL: milliliter. * Weight was missing in 17 VKA patients and 8 FXa-I patients; indication anticoagulant was missing in 13 VKA patients and 1 FXa-I patient; time to presentation was missing in 24 VKA patients and 18 FXa-I patients; systolic blood pressure was missing in 2 VKA patients and 3 FXa-I patients; ICH localization was missing in 5 VKA patients; trauma was missing in 13 VKA patients and 3 FXa-I patients; GCS was missing in 6 VKA patients and 1 FXa-I patient; volume in mL was missing in 11 VKA patients and 12 of the FXa-I patients. † Subclassification for ISTH major bleeding according to the severity of bleeding, previously described in methods section of this paper.

(95%CI 0.59–4.48) (Table 3). After adjustment for age and baseline GCS, the adjusted OR for effective hemostasis was 1.45 (95%CI 0.44–4.83).

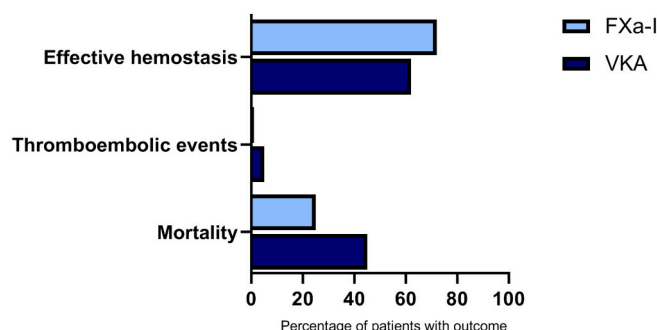
We observed a significant difference in time to presentation between FXa-I-ICH and VKA-ICH, but could not adjust for this variable, because of missing values in 39 (52%) patients.

We performed four different sensitivity analyses including the five patients for whom the efficacy outcome effective hemostasis was missing. The first analysis assumed all five patients had poor hemostasis, the second analysis assumed all five patients had effective hemostasis, the third analysis assumed all three FXa-I-ICH patients had effective hemostasis and both VKA-ICH patients had poor hemostasis, and the fourth analysis assumed all three FXa-I-ICH patients had poor

Table 2
Details on ICH course and management.

ICH course and management	VKA-ICH N = 39	FXa-I-ICH N = 36
Dose of PCC (IU/kg), median (IQR)*	20 (20–25)	50 (50–50)
Total dose of PCC (IU), median (IQR)*	1750 (1250–2250)	3500 (3000–4000)
Admission intensive care unit, no. (%)	12 (30.8)	11 (30.6)
Administration packed cells, no. (%)	2 (5)	0
Administration of tranexamic acid, no. (%)	0	2 (6)
Administration of vitamin K, no. (%)	33 (85)	N.A.
Hospital stay (days), median (IQR)	6 (5–12)	7 (3–15)
Intervention for bleeding, no. (%)	10 (26)	9 (25)

VKA: vitamin K antagonist; ICH: intracranial hemorrhage; FXa-I: factor-Xa inhibitor; SD: standard deviation, no.: number; kg: kilogram; IQR: interquartile range; IU: international units; PCC: prothrombin complex concentrate. * Dose of PCC in IU/kg was missing in 14 VKA patients and 2 FXa-I patients; total dose PCC was missing in 2 VKA patients; intervention for bleeding was missing in 1 VKA patient; packed cells was missing in 1 FXa-I patient.

**Fig. 1.** Overview of proportion of patients encountering the outcomes, stratified for VKA and FXa-I.

FXa-I = factor Xa inhibitor; VKA = vitamin K antagonist.

hemostasis and both VKA-ICH patients had effective hemostasis. The results of the sensitivity analyses were not substantially different from the original analyses (data not shown).

3.2.2. Safety

Thromboembolic events were not assessable due to loss-to-follow up in three patients. Two of three patients belonged to the FXa-I-ICH and the one to the VKA-ICH. No thromboembolic events occurred within 30 days after presentation in the FXa-I-ICH cohort and two thromboembolic events occurred in the VKA-ICH cohort, hence no OR was calculated for thromboembolic events.

Mortality was not assessable due to loss-to-follow-up in three patients, of which two belonged to the FXa-I-ICH cohort and the other two to the VKA-ICH cohort. Mortality within 30 days was observed in eight (24%) patients in the FXa-I-ICH cohort and in 17 (45%) patients in the VKA-ICH cohort (Fig. 1). The corresponding crude OR for mortality for FXa-I-ICH vs. VKA-ICH was 0.38 (95%CI 0.14–1.24) and the OR adjusted for age and baseline GCS was 0.41 (95%CI 0.12–1.42) (Table 3).

Analogous to the efficacy outcome, we performed four different sensitivity analyses including the three patients in which the safety outcomes (30-day thrombosis and 30-day mortality) were missing. The results of these sensitivity analyses were not substantially different from the original analyses (data not shown).

4. Discussion

In this study we did not observe a significant difference in hemostatic efficacy between patients with a direct factor Xa inhibitor related

Table 3

Efficacy and safety outcomes per treatment group in the bleeding population after administration of PCC.

Efficacy outcome, no. (%; 95% CI)	FXa-I (n = 36)	VKA (n = 39)	Crude OR (95% CI)	Adjusted OR [*] (95% CI)	Adjusted OR ^{**} (95% CI)
Effective hemostasis after 24 h	24 (73%, 56%–85%)	23 (62%, 46%–76%)	1.62 (0.59–4.48)	1.56 (0.43–5.54)	1.45 (0.44–4.83)
Safety outcomes, no. (%; 95% CI)	FXa-I (n = 36)	VKA (n = 39)	Crude OR (95% CI)	Adjusted OR [*] (95% CI)	Adjusted O ^{**} (95% CI)
30-day thromboembolic rate	0 N.A.	2 (5%, 2%–17%)	N.A.	N.A.	N.A.
30-day mortality rate	8 (24%, 12%–40%)	17 (45%, 30%–60%)	0.38 (0.14–1.24)	0.39 (0.11–1.44)	0.41 (0.12–1.42)

95% CI = 95% confidence interval; VKA = vitamin K antagonist; FXa-I = factor Xa inhibitor; OR = odds ratio; n = number; N.A. = not applicable.

In 5 patients (2 VKA and 3 FXa-I) effective hemostasis was not assessable. For 30-day thromboembolic events there is 1 missing value for VKA and 2 for thromboembolic events. For mortality 1 value is missing in the VKA cohort and 2 values are missing in FXa-I cohort.

^{*} Odds ratio adjusted for age, baseline GCS (missing in 4 patients) and type ICH (intracerebral vs non-intracerebral). This model was based on clinical reasoning.^{**} Odds ratio for when adjusted for age and baseline GCS (missing in four patients). This model was based on selecting associations with a *p*-values < 0.25.

intracranial hemorrhage and patients with a vitamin K antagonist related intracranial hemorrhage treated with PCC, nor in mortality and thromboembolic outcomes. Our findings suggest that the prognosis for FXa-I-ICH patients managed with PCC does not seem worse than the prognosis for VKA-ICH patients treated with PCC. This study does not answer the questions if PCC is efficacious and safe for treatment of FXa-I-ICH as this would require patients with FXa-I-ICH that did not receive PCC. However, in an observational study such as the present one this would lead to considerable confounding by indication which cannot be reliably adjusted for. We therefore chose to compare with VKA-ICH since a specific reversal agent has been available for VKAs for years, and both cohorts represent a similarly urgent clinical situation in which the use of a reversal agent is deemed necessary.

Our findings can be interpreted in different ways. First, these findings could suggest that PCC is an effective reversal agent for FXa-I. This is plausible as PCC contains coagulation factor X which, after activation at the site of bleeding may compete with the circulating FXa-I and restore thrombin generation sufficiently to control bleeding. This interpretation is supported by our recent study showing that PCC swiftly increases endogenous thrombin potential in patients with a FXa-I related major bleeding, which is also in line with previous studies in healthy volunteers [13,20]. Secondly, our findings could also suggest that PCC does *not* improve effective hemostasis for both FXa-I-ICH and VKA-ICH. In ICH, the prognosis of the bleed may be determined mostly before presentation to the emergency room and not so much by the strategy to restore functional hemostasis [21]. This interpretation is supported by the results of the trial randomizing patients with a major VKA related bleeding to either PCC or fresh frozen plasma, demonstrating swift INR reversal did not influence effective hemostasis [19]. Thirdly, these findings could also be explained by a different prognosis between FXa-I-ICH and VKA-ICH, in our study or in general. In our study we observed a significant difference in time to presentation (135 min in the FXa-I-ICH cohort vs. 360 min in the VKA-ICH cohort, *p* = 0.006). However, we were not able to adjust for this difference in our multivariate model as this variable was missing in 52% of the patients. We do not have a plausible explanation for this finding, other than chance, but we cannot rule out that this partially explains our findings. It is also possible that there is an intrinsic difference in prognoses of FXa-I-ICH and VKA-ICH, determined by differences in other factors such as baseline hematoma volume. Consequently, the prognosis of FXa-I-ICH may be better than VKA-ICH and balance out the disadvantage of the lack of specific reversal agents. This is plausible as the majority of published studies within this field implies that DOAC-ICH may have smaller volumes and hence better prognoses in comparison with VKA-ICH [22–24].

Strengths of this study are that both the FXa-I cohort and the VKA-cohort are contemporary and had identical inclusion criteria, clinical outcome definitions and follow-up. Moreover, the primary outcome “effective hemostasis” for both cohorts was according to the ISTH definition, which is considered the benchmark for studies evaluating the efficacy of reversal agents [17,20,25–27]. Some limitations of our study warrant consideration. The main limitation is the observational nature of this study by which we cannot establish the true efficacy and safety of PCC in FXa-I-ICH. Our observations can only be interpreted as associations of FXa-I-ICH and VKA-ICH treated with PCC with the clinical outcomes and do not evince a causal pathway as we cannot account for uncontrolled confounders, such as the oral anticoagulant preference of the initial prescriber and time period in which the patients were included. We realize that for evaluating the efficacy and safety of PCC in patients with FXa-I-ICH a randomized controlled trial (RCT) would be necessary. However, by using a multiple regression model with adjustment for measured confounders such as age and baseline GCS, we minimized the potentially induced bias by these confounders. A second limitation is the relatively small number of patients that was included in this study. One could argue that due to lack of statistical power we did not detect significant differences in outcome variables between the two cohorts. However, the calculated 95% confidence intervals around the point estimates (hemostatic efficacy, mortality) in the FXa-I cohort and the VKA-ICH overlap substantially and we therefore believe that this limitation does not preclude our conclusions. Furthermore, we did not adjust for potential confounders with more than 30% missing values, such as hematoma volume and time from start of symptoms to presentation. To counterbalance this limitation, we performed regression analyses in two different ways and performed sensitivity analyses, as described in the method section. These additional analyses did not change the main conclusions of this study. Unfortunately no information was collected on the renal insufficiency.

Now that andexanet alfa is approved for reversal of rivaroxaban and apixaban in patients with life-threatening bleeding, the American Society of Hematology guideline recommends either PCC or andexanet alfa for FXa-I reversal [9]. Our study design does not allow for a comparative efficacy and safety analysis between PCC and the recently approved specific antidote andexanet alfa. Indirect comparisons between the subgroup FXa-I-ICH in two cohorts managed with PCC and one cohort managed with andexanet alfa (ANNEXA-4) yields effective hemostasis rates according to the ISTH definition of 72.8%, 83.3% and 80.4%, respectively [25–27]. The comparison of these two agents in a randomized trial is relevant as andexanet alfa is much more expensive than PCC. Currently an RCT is ongoing in patients with an FXa-I-ICH in which the efficacy and safety of andexanet alfa is

compared with usual care (trialregister.gov; [NCT03661528](#)). The expectation is that PCC will be opted as standard of usual care in the majority of the patients randomized to the 'usual of care' arm and therefore in this study, andexanet alfa will likely be compared with PCC. Until this trial establishes what the optimal reversal strategy for FXa-I-ICH is, our study suggests that if PCC is used for management of FXa-I-ICH, the prognosis will not be worse than what we have come to know from patients with VKA-ICH reversal [28].

Declaration of competing interest

R.B. has nothing to disclose. R.A. has nothing to disclose. L.B. has nothing to disclose. M.B. has nothing to disclose. R.O. has received travel grants from Sanofi and Pfizer/BMS, is in the advisory board of Bayer and has received speaker fees from Leo Pharma. H.C. received research support Bayer, Pfizer, consultancy Alveron, is in the advisory board of Bayer, Pfizer/BMS, Leo Pharma. H.C. is unpaid chairman of board, Dutch Federation of Anticoagulation clinics. M.H. reports grants from ZONMW; Boehringer-Ingelheim; Bayer Health Care, and Pfizer-BMS outside the submitted work. M.K. has nothing to disclose. S.M. reports grants and fees paid to her institution from GSK, BMS/Pfizer, Aspen, Daiichi Sankyo, Bayer, Boehringer Ingelheim, Sanofi, and Portola. K.M. received research grants from Bayer, Pfizer and Sanquin, speaker fees from Aspen, Bayer, BMS, Boehringer Ingelheim, Sanquin and consulting fees from Uniquire. B.H. has nothing to disclose. M.C. has received research support, consultancy fees or travel support from Bayer, Boehringer Ingelheim, Bristol-Myers Squib, CSL Behring, Daiichi Sankyo, Pfizer, Portola, and Sanquin Blood Supply.

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CRedit authorship contribution statement

R.B. contributed towards collection of data, data analysis and drafting the manuscript; A.R. contributed towards drafting the manuscript; L.B. contributed towards the data collection on ICH volume and drafting the manuscript; M.B. contributed towards the study concept, drafting the study protocol and collection of data; R.O. contributed towards collection of data and drafting the manuscript; H.C. contributed towards collection of data and drafting the manuscript; M.H. contributed towards collection of data and drafting the manuscript; M.K. contributed towards collection of data and drafting the manuscript; S.M. contributed towards the study concept and drafting the manuscript; K.M. contributed towards collection of data and drafting the manuscript; B.H. contributed towards data analysis and drafting the manuscript; M.C. contributed towards the study concept, drafting the study protocol and drafting the manuscript.

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