Association of Prothrombin Complex Concentrate Administration and Hematoma Enlargement in Non–Vitamin K Antagonist Oral Anticoagulant–Related Intracerebral Hemorrhage

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Objective: To investigate parameters associated with hematoma enlargement in non–vitamin K antagonist oral anticoagulant (NOAC)-related intracerebral hemorrhage (ICH).
Methods: This retrospective cohort study includes individual patient data for 190 patients with NOAC-associated ICH over a 5-year period (2011–2015) at 19 departments of neurology across Germany. Primary outcome was the association of prothrombin complex concentrate (PCC) administration with hematoma enlargement. Subanalyses were calculated for blood pressure management and its association with the primary outcome. Secondary outcomes include associations with in-hospital mortality and functional outcome at 3 months assessed using the modified Rankin Scale.

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Members of the RETRACE II study group are available as an online supplementary file.

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Results: The study population for analysis of primary and secondary outcomes consisted of 146 NOAC-ICH patients with available follow-up imaging. Hematoma enlargement occurred in 49/146 (33.6%) patients with NOAC-related ICH. Parameters associated with hematoma enlargement were blood pressure $\geq$ 160mmHg within 4 hours and—in the case of factor Xa inhibitor ICH—anti-Xa levels on admission. PCC administration prior to follow-up imaging was not significantly associated with a reduced rate of hematoma enlargement either in overall NOAC-related ICH or in patients with factor Xa inhibitor intake (NOAC: risk ratio [RR] = 1.150, 95% confidence interval [CI] = 0.632–2.090; factor Xa inhibitor: RR = 1.057, 95% CI = 0.565–1.977), regardless of PCC dosage given or time interval until imaging or treatment. Systolic blood pressure levels < 160mmHg within 4 hours after admission were significantly associated with a reduction in the proportion of patients with hematoma enlargement (RR = 0.598, 95% CI = 0.365–0.978). PCC administration had no effect on mortality and functional outcome either at discharge or at 3 months.
Interpretation: In contrast to blood pressure control, PCC administration was not associated with a reduced rate of hematoma enlargement in NOAC-related ICH. Our findings support the need of further investigations exploring new hemostatic reversal strategies for patients with factor Xa inhibitor–related ICH.

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The most significant complication of oral anticoagulation (OAC) is the occurrence of intracerebral hemorrhage (ICH).[1] As compared to primary ICH patients, patients with OAC-ICH are characterized by a significantly poorer prognosis (increased mortality and unfavorable functional outcome).[2–4] Several established outcome predictors in OAC-ICH contribute to this prognosis, such as advanced age, larger hematoma volumes, more extensive intraventricular involvement, and notably hematoma enlargement.[4–6]

The occurrence of hematoma enlargement in OAC-ICH is based on an altered coagulation which—in vitamin K antagonist (VKA)-related ICH—is targeted by effective hemostatic treatment. Data from randomized trials and large observational studies provide evidence that rapid reversal and normalization of VKA using prothrombin complex concentrates (PCCs), alongside with specific systolic blood pressure management, lead to lower rates of hematoma enlargement and to reduced mortality.[4,6,7]

However, in non-VKA oral anticoagulant (NOAC)-related ICH, data on acute hemostatic strategies hardly exist.[8] For patients treated with dabigatran-related bleeding complications the antidote idarucizumab is available and effective,[9] but so far specific antidotes for factor Xa inhibitor–related hemorrhage, such as andexanet alfa, are unavailable for routine management.[10]

Current international guidelines recommend administration of PCC[11]; however, several hemostatic considerations question the efficacy of PCC in Xa inhibitor–associated bleeding.[8,11–15] This German-wide multicenter analysis explored the influence of PCC administration on hematoma enlargement (primary outcome), mortality, and functional outcome (secondary outcomes) in patients with NOAC-related ICH.

Patients and Methods

Study Design and Patient Selection

This observational cohort study integrated individual patient data from 19 tertiary care centers in Germany during 2011–2015 (start of enrollment at January 1, 2011, end of enrolment at December 31, 2015). The study was approved by the local ethics committees and institutional review boards based on the central vote from Friedrich-Alexander University Erlangen–Nuremberg, Erlangen, Germany (reference numbers 4409 and 30_16B). Consent was obtained from patients or legal representatives. The current investigation represents the second part of the registered RETRACE program (German-Wide Multicenter Analysis of Oral Anticoagulation–Associated Intracerebral Hemorrhage; first part: NCT01829581,[4] second part: NCT03093233). ICH was considered NOAC-related if patients were known to be on treatment with NOAC at ICH onset.[8,14,15] We excluded ICH patients with secondary etiologies, such as ICH related to trauma, tumor, arteriovenous malformation, aneurysmal subarachnoid hemorrhage, acute thrombolysis, or other coagulopathies.[4]

Data Acquisition

As previously described,[4] we assessed data on demographics, medical history, pre-ICH medication exposures, admission status (Glasgow Coma Scale, National Institutes of Health Stroke Scale [NIHSS], ICH score), indication for oral anticoagulation, in-hospital measures, and laboratory data, as well as all data regarding the interventions (see below) through review of patient's medical charts and institutional databases at each individual institution. We obtained the respective NOAC agent, daily dosage, time point of last intake, and serial NOAC levels. Any available NOAC levels (drug-specific anti-Xa activity in factor Xa inhibitors[16] and hemoclot in dabigatran[17], NOAC level on admission (ie, blood sampling within 3 hours after admission), and last NOAC intake—documented in the hours prior to hospital admission—were recorded. We evaluated all available computed tomography and magnetic resonance imaging scans of each patient similarly as described previously.[4] We obtained follow-up data on mortality and functional outcome using the modified Rankin Scale (mRS) at 3 months (see also below).[18]

Analyses of Primary and Secondary Outcomes

Analyses of primary and secondary outcomes were based on patients with available second imaging, without surgical evacuation prior to follow-up imaging, and without isolated intraventricular haemorrhage (Fig 1). The primary outcome measure

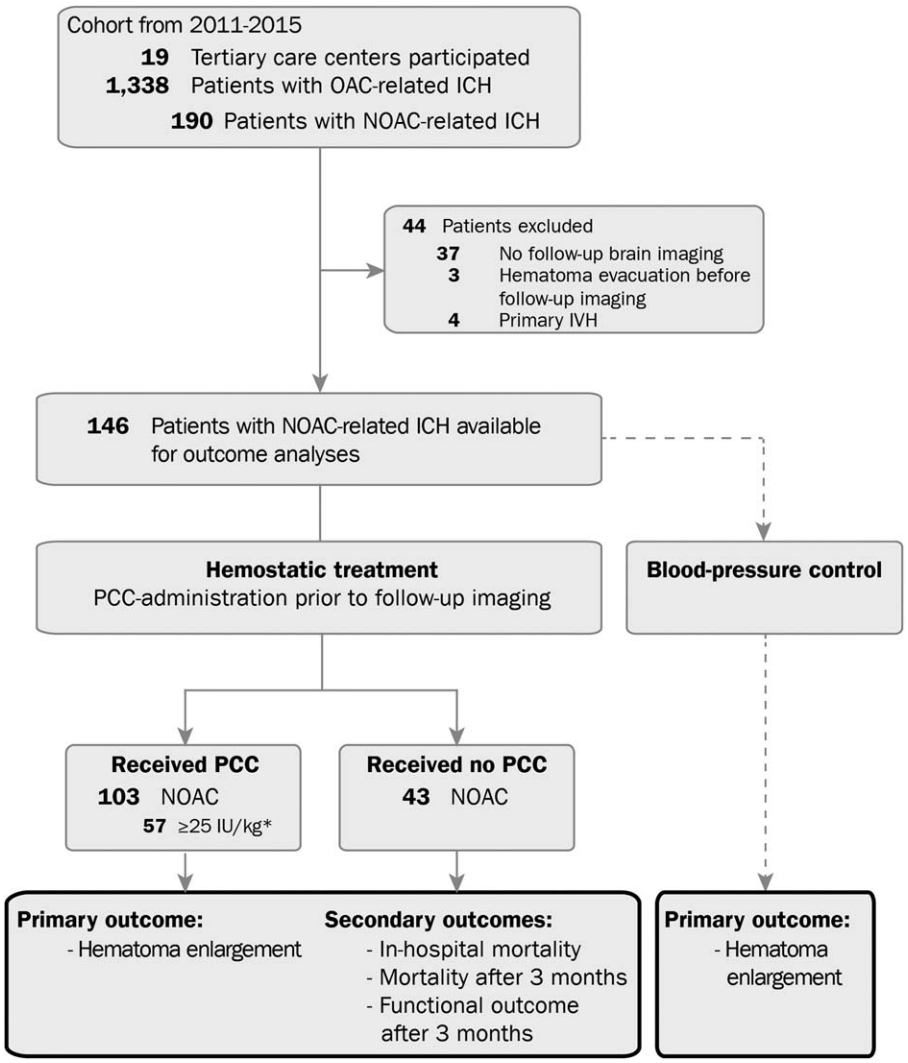

FIGURE 1: Flow chart of study participants. Overall, data of 1,338 patients with oral anticoagulation–related intracerebral hemorrhage (ICH)—admitted between 2011 and 2015—were provided by 19 tertiary care centers across Germany. Of those, 190 patients were identified with non–vitamin K antagonist oral anticoagulant (NOAC)-related ICH. After exclusion of 44 patients because of missing follow-up imaging, hematoma evacuation, or primary intraventricular hemorrhage, 146 ICH patients with NOAC intake remained for analysis of primary and secondary outcomes. *Information on administered weight-adapted dosage of prothrombin complex concentrate (PCC) was available in 85 patients (≥25IU/kg: n = 57, <25IU/kg: n = 28). IVH = intraventricular hemorrhage; OAC = oral anticoagulation.

was occurrence of hematoma enlargement defined as a relative parenchymal volume increase of >33% from initial to follow-up imaging.[4,19] Secondary outcomes were the proportion of patients with (1) in-hospital mortality, (2) mortality at 3 months, and (3) functional outcome at 3 months. Functional outcome was categorized, according to current definitions used in randomized trials,[20,21] into favorable (mRS = 0–3) and unfavorable (mRS = 4–6). We compared baseline clinical and radiological characteristics in patients with hematoma enlargement versus those without, and functional outcome among patients with versus without hemostatic treatment (see below).

Definition of Interventions

We assessed the associations of hemostatic treatment with primary and secondary outcomes. We defined hemostatic intervention as the administration of PCC given prior to follow-up cranial imaging. Administered PCC comprised a 4-factor concentrate only, containing coagulation factors II, VII, IX, and X, as well as proteins C and S. All additional agents used for anticoagulation reversal including dosages and time points of administration were assessed. Both the amount of PCC received and the total amount given prior to follow-up brain imaging were recorded. PCC treatment was subanalyzed according to weight-adjusted dosages ≥ 25IU/kg bodyweight according to existing guideline recommendations during the study period.[22–24]

Additional subanalyses were calculated for the association of blood pressure values with the primary outcome. Therefore, all consecutive blood pressure levels (systolic, diastolic, and mean blood pressure stratified into 4-hour intervals) within 16 hours after admission were recorded. Associations of systolic blood pressure levels at these time points with hematoma

enlargement were analyzed by categorical frequency distributions (increasing 20mmHg categories), as described previously,[4] and tested for heterogeneity.

Analysis of Confounding Factors

All available time intervals possibly confounding the associations of hemostatic treatment with hematoma enlargement were recorded: that is, time from symptom onset (1) to admission, (2) to first cranial imaging, (3) to hemostatic treatment, and (4) to follow-up brain imaging. We conducted subgroup analyses for time-dependent associations of the interventions with the primary outcome in the aforementioned time intervals dichotomized by the median split.

Analysis of Missing Data

For further analyses of primary and secondary outcomes, we decided to perform multiple imputation analysis after appropriate evaluation (Little missing completely at random test) to minimize bias because of missing data.[25] Multiple imputation (10 imputed datasets) was performed separately—using fully conditional specification—to account for missing outcome data (n = 34/190) in all patients, and for missing data on hemostatic treatment (n = 3/106) and blood pressure levels (n = 7/146) in patients available for analysis of primary and secondary outcomes.[25,26] Parameters used for prediction of the imputation model are listed in Supplementary Table 1.

Statistical Analysis

Statistical analyses were performed using the SPSS 21.0 software package (www.spss.com) and R 2.12.0 (www.r-project.org). For group comparisons, data were tested for normal distribution by Kolmogorov–Smirnov and Shapiro–Wilk tests. In the case of normal distribution, data were presented as mean (standard deviation) compared using the Student *t* test, otherwise as median (interquartile range) and compared using the Mann–Whitney *U* test or Kruskal–Wallis test. For comparison of frequency distribution of categorized variables, Pearson's chi-square test or Fisher's exact test were used. Significance level was set at $\alpha = 0.05$, 2-sided. In a second step, the Bonferroni correction was applied to correct for accumulation of type 1 error in multiple testing. Receiver operating characteristic (ROC) analysis was conducted to investigate the association of anti-Xa levels on admission with hematoma enlargement in patients with factor Xa inhibitor–related ICH. The best cutoff point for discriminating the risk of hematoma enlargement was identified by the Youden index.

All multivariate models consisted of a generalized linear model using log-Poisson regression utilizing a robust estimator as covariance matrix to account for bias introduced by skewed distributions and outliers (ie, treatment years and center effects). Multivariate adjusted regression analyses were performed to identify parameters independently associated with hematoma enlargement in patients with NOAC-related ICH. For analyses of hemostatic treatment and systolic blood pressure levels on hematoma enlargement, we carried out regression analyses adjusted for identified and validated predictors of hematoma enlargement in ICH: that is, NIHSS, intraventricular hemorrhage, systolic blood pressure levels time from symptom onset until initial imaging, and time from symptom onset until repeat imaging. The associations of hemostatic treatment (PCC prior to follow-up imaging vs no PCC) and blood pressure levels (systolic blood pressure < 160mmHg vs ≥ 160mmHg within 4 hours after admission) with hematoma enlargement were presented as risk ratios (RRs) with 95% confidence intervals (CIs) and graphically shown as forest plots. Heterogeneity for differences between the aforementioned subgroups were determined by inclusion of interaction terms. Secondary outcomes were compared using Pearson's chi-square test and presented as mRS plot at discharge and after 3 months.

Results

We investigated a total of 190 patients with NOAC-ICH (see Fig 1) over a 5-year period (see Supplementary Table 2a for sites and patient enrollment). Among patients with NOAC-related ICH, 22 patients were treated with dabigatran, 142 with rivaroxaban, and 26 with apixaban, and none of the patients received edoxaban. To specifically explore the effects of hemostatic PCC treatment with parenchymal hematoma enlargement, we excluded patients without second cranial imaging, those with primary ventricular hemorrhage, and patients who received surgical hematoma evacuation before follow-up imaging (see Fig 1). Subsequently, 146 patients with NOAC-related ICH—131 patients with factor Xa inhibitor and 15 with dabigatran intake—remained for final analyses.

Analysis of Parameters Associated with Hematoma Enlargement

Hematoma enlargement occurred in 49/146 (33.6%) patients with NOAC-related ICH (Table 1). In univariate testing, there was no parameter that differed significantly among patients with and without hematoma enlargement in overall NOAC patients. For each specific NOAC agent, the occurrence of hematoma enlargement and associated parameters are given in Table 2. Rates of hematoma enlagement were not significantly different ($p = 0.21$) among patients with rivaroxaban (32.7%), apixaban (47.6%), and dabigatran (20.0%). In patients with rivaroxaban-related ICH, we observed associations ($p < 0.05$) with the occurrence of hematoma enlargement for higher anti-Xa levels, worse clinical condition on admission (NIHSS), greater initial ICH volume, and shorter time between onset and follow-up imaging (see Table 2).

Factors associated with hematoma enlargement in multivariate analysis are shown in Supplementary Table 3. Besides presence of intraventricular hemorrhage on initial imaging, systolic blood pressure levels at 4 hours after admission were independently associated with

TABLE 1. Comparison of Patients with and without Hematoma Enlargement

Parameter	Patients with NOAC-Related ICH and Follow-up Imaging, n = 146		*p*
	HE Present, n = 49	HE Absent, n = 97	
Age, mean yr (SD)	76.6 (7.3)	77.9 (7.9)	0.34
Female sex, No. (%)	18 (36.7%)	51 (52.6%)	0.07
Prior comorbidities			
Premorbid mRS, median (IQR)	0 (0–2)	1 (0–2)	0.03[a]
Hypertension, No. (%)	43 (87.8%)	93 (95.9%)	0.09
Admission status, median (IQR)			
GCS	13 (9–15)	14 (10–15)	0.46
NIHSS	11 (7–19)	10 (5–17)	0.16
ICH score	1 (1–2)	1 (1–3)	0.52
Initial imaging			
ICH volume, median cm^3 (IQR)	13.3 (6.4–30.2)	9.3 (3.4–28.9)	0.18
Intraventricular hemorrhage, No. (%)	26 (53.1%)	34 (35.1%)	0.04[a]
Location, No. (%)			
Deep	29 (59.2%)	50 (51.5%)	0.38
Lobar	17 (34.7%)	33 (34.0%)	0.94
Cerebellar	3 (6.1%)	11 (11.3%)	0.39
Brainstem	0	3 (3.1%)	0.55
Symptom onset, admission, median min (IQR)	96 (53–240)	118 (57–438)	0.26
Symptom onset, first imaging, median min (IQR)	117 (75–192)	149 (80–543)	0.05
Follow-up imaging			
ICH volume, median cm^3 (IQR)	28.5 (13.5–60.5)	9.4 (2.8–24.4)	<0.001
Absolute volume increase, median cm^3 (IQR)	11.6 (4.0–25.9)	0 (0–1.1)	<0.001
Symptom onset, follow-up imaging, median h (IQR)	16.0 (6.7–26.0)	24.9 (12.0–37.8)	0.02[a]
First imaging, follow-up imaging, median h (IQR)	9.9 (4.0–23.7)	20.0 (8.2–25.4)	0.06
Hemostatic treatment			
Reversal therapy, No. (%)	36 (73.5%)	72 (74.2%)	0.92
Symptom onset, reversal treatment, median min (IQR)	198 (120–299)	230 (155–550)	0.07
Admission, reversal treatment, median min (IQR)	76 (54–141)	120 (70–173)	0.11
Blood pressure values, mean mmHg (SD)			
Admission systolic	169.7 (33.4)	167.2 (35.1)	0.68
4-hour systolic	142.6 (24.1)	137.7 (24.2)	0.24
8-hour systolic	133.3 (18.6)	136.2 (20.1)	0.40

Complete case analysis of patients with and without hematoma enlargement in patients with NOAC-related ICH. Hematoma enlargement was defined as volume increase of >33% compared to initial imaging. Multiple imputation was applied to address missing data in blood pressure values. Significance level was adjusted according to the Bonferroni correction to control for accumulation of type 1 error in multiple testing.

[a]Not significant after Bonferroni correction.

GCS = Glasgow Coma Scale (ranging from 3, comatose, to 15, alert); HE = hematoma enlargement; ICH = intracerebral hemorrhage; IQR = interquartile range; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale (ranging from 0, no deficit, -40, severe neurological deficit; 40 is the maximum because in comatose ataxia is not scored); NOAC = non–vitamin K antagonist oral anticoagulant; SD = standard deviation.

TABLE 2. Overview of Hemostatic Treatment according to NOAC Agent

Parameter	Patients with NOAC-Related ICH and Follow-up Imaging, n = 146			*p*
	Rivaroxaban, n = 110	Apixaban, n = 21	Dabigatran, n = 15	
Initial coagulation parameter, median (IQR)				
INR	1.30 (1.13–1.75)	1.20 (1.11–1.36)	1.20 (1.11–1.29)	0.09
aPTT, s	35.5 (31.0–38.5)	32.6 (28.3–35.6)	40.7 (31.7–54.0)	0.01[a]
Anti-Xa activity, ng/ml	115.6 (61.3–215.0)	82.7 (25.3–107.2)	—	—
Dabigatran level, ng/ml	—	—	130.0 (54.0–253.5)	—
Hemostatic treatment, No. (%)				
Any	85 (77.3%)	13 (61.9%)	10 (66.7%)	0.27
PCC	81 (73.6%)	13 (61.9%)	9 (60.0%)	0.36
Fresh frozen plasma	2 (1.8%)	1 (4.8%)	0	0.58
Platelet concentrate	5 (4.5%)	2 (9.5%)	0	0.39
Tranexamic acid	0	1 (4.8%)	0	0.25
Activated factor VII	0	0	3 (20.0%)	<0.001
Hemostatic treatment using PCC				
Amount, median IU (IQR)	2,000 (1,500–2,600)	2,400 (1,500–3,000)	2,000 (1,650–3,000)	0.85
≥ 25 IU/kg, No. (%)[b]	45 (47.9%)	9 (42.9%)	3 (23.1%)	0.23
≥ 50 IU/kg, No. (%)[c]	5 (4.8%)	2 (10.0%)	1 (7.7%)	0.34
Time from admission to reversal treatment, median min (IQR)	95 (56–154)	87 (73–224)	130 (112–270)	0.22
Hematoma enlargement on follow-up imaging				
Overall, No. (%)	36 (32.7%)	10 (47.6%)	3 (20.0%)	0.21
Received PCC, No./total No. (%)	27/81 (33.3%)	6/13 (46.2%)	2/9 (22.2%)	0.49
Did not receive PCC, No./total No. (%)	9/29 (31.0%)	4/8 (50.0%)	1/6 (16.7%)	0.43
Parameters associated with hematoma enlargement at $p < 0.05$	Anti-Xa activity, NIHSS, ICH volume, time from ictus until follow-up imaging	n/a[d]	n/a[d]	

Complete case analysis of initial coagulation parameters and hemostatic treatment for each NOAC agent. In addition to type of hemostatic agent, total amount of administered PCC prior to follow-up imaging and dichotomized into ≥25IU/kg and ≥50IU/kg are provided. Comparisons were calculated for group differences between the 3 NOAC agents. Multiple imputation was used for missing data in hemostatic treatment variables. Hematoma enlargement was defined as volume increase of >33% compared to initial imaging. Significance level was adjusted according to the Bonferroni correction to control for accumulation of type 1 error in multiple testing. Parameters associated with hematoma enlargement at $p < 0.05$ in rivaroxaban-related ICH are listed in the last row.

[a]Not significant after Bonferroni correction (adjusted $p = 0.0045$).

[b]Information available in 68 rivaroxaban/13 apixaban/7 dabigatran patients.

[c]Information available in 5 rivaroxaban/12 apixaban/7 dabigatran patients.

[d]Too few patients available for further analyses.

aPTT = activated partial thromboplastin time; ICH = intracerebral hemorrhage; IQR = interquartile range; n/a = not applicable; NIHSS = National Institutes of Health Stroke Scale; NOAC = non–vitamin K antagonist oral anticoagulant; PCC = prothrombin complex concentrate.

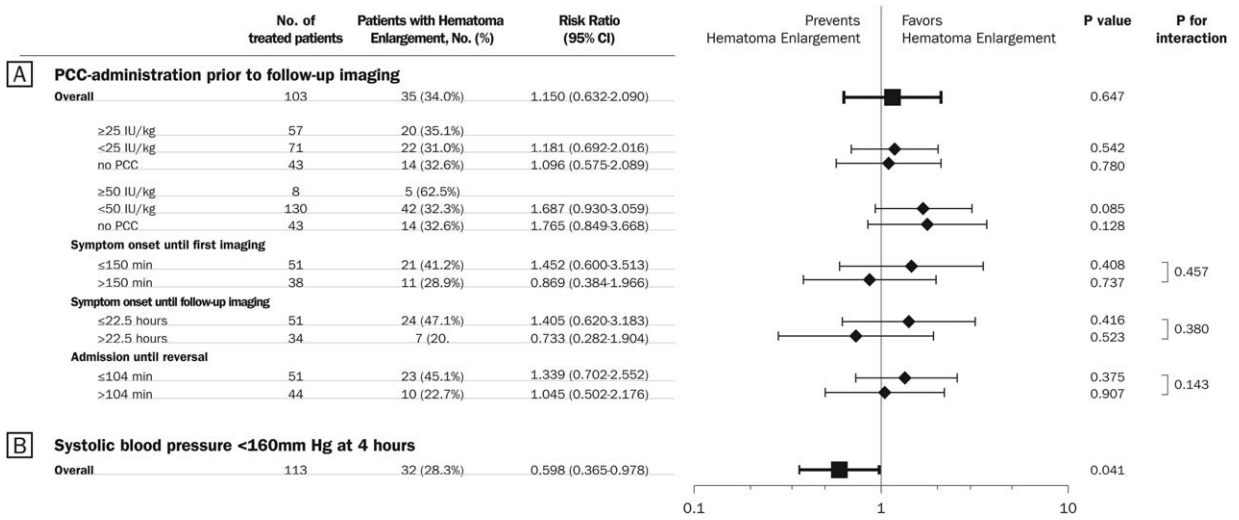

FIGURE 2: Association of hemostatic treatment and systolic blood pressure with hematoma enlargement in patients with non–vitamin K antagonist oral anticoagulant (NOAC)-related intracerebral hemorrhage (ICH). Regression analysis (log-Poisson with robust estimator) is shown for the association of (A) hemostatic treatment, that is, prothrombin complex concentrate (PCC) administration and (B) systolic blood pressure values at 4 hours with hematoma enlargement in patients with NOAC-related ICH. Hematoma enlargement was defined as volume increase of >33% compared to initial imaging. Subanalyses for time windows (median split) from symptom onset until first imaging and admission until treatment were calculated for patients with PCC treatment prior to follow-up imaging versus those without. Systolic blood pressure values were dichotomized into <160mmHg versus ≥160mmHg. Risk ratios (95% confidence interval [CI]) are adjusted for identified predictors of hematoma enlargement (see Supplementary Table 3: time from symptom onset to initial imaging, time from initial imaging to follow-up imaging, National Institutes of Health Stroke Scale score on admission, intraventricular hemorrhage on initial imaging, and systolic blood pressure at 4 hours). Heterogeneity was tested for the comparison between subgroups regarding time intervals by inclusion of an interaction term.

hematoma enlargement (RR = 1.004, 95% CI = 1.000–1.008 per mmHg increase; $p = 0.03$). Further analyses of blood pressure revealed a significantly reduced risk of hematoma enlargement in patients with systolic blood pressure < 160mmHg 4 hours after admission (RR = 0.550, 95% CI = 0.353–0.856; $p = 0.01$; Supplementary Table 4).

In factor Xa inhibitor–related ICH (n = 131), there were 40 patients available for additional analysis of anti-Xa levels on admission. ROC analysis revealed a strong, positive association between this parameter and hematoma enlargement (area under the curve = 0.711, 95% CI = 0.645–0.777; $p < 0.01$; Supplementary Table 5a). Occurence of hematoma enlargement was significantly more frequent in patients with anti-Xa level greater than the identified best discriminative threshold of 118ng/ml (hematoma enlargement: >118ng/ml 9/16 [56.2%] vs ≤118ng/ml 4/24 [16.7%]; RR = 3.375, 95% CI = 1.245–9.115; $p = 0.01$; see Supplementary Table 5b).

Hemostatic Treatment in NOAC-Related ICH

The initial hemostatic strategies applied for anticoagulation reversal—alongside with initial laboratory values—are shown in Table 2. The rate of any reversal treatment was 73.9% (108/146), and there were no significant differences in the proportion of patients who received reversal treatment among patients with specific NOACs (NOAC group comparison: $p = 0.27$). Hemostatic treatment consisted primarily of administration of PCC at a median dosage of 2,000IU (range = 1,500-3,000) in all patients, followed by vitamin K, platelet concentrates, fresh frozen plasma, tranexamic acid, desmopressin, and antithrombin III. Less than half of the patients received PCC at dosages recommended by international guidelines during the study period (PCC ≥ 25IU/kg).[22]

Association of PCC Administration and Blood Pressure Values with the Primary Outcome

We performed multivariate regression analyses, corrected for possible confounding variables (as shown in Supplementary Table 3), to specifically explore associations of PCC administration and systolic blood pressure levels with hematoma enlargement in NOAC-related ICH (Fig 2). PCC was administered in 103/146 (70.5%) patients prior to follow-up imaging. PCC treatment—at a any dose, at ≥25IU/kg bodyweight, and at ≥50IU/kg bodyweight, respectively—was statistically not significantly associated with a reduced risk for hematoma enlagement in the overall NOAC cohort (RR = 1.150, 95% CI = 0.632–2.090). Focusing on patients with factor Xa inhibitor intake only also revealed no significant association of PCC administration with the occurrence of hematoma enlargement (RR = 1.057, 95%

TABLE 3. Association of PCC Administration with Hematoma Enlargement in Factor Xa Inhibitor–Related ICH

PCC prior to Follow-up Imaging	Patients, No.	Hematoma Enlargement, No. (%)	Risk Ratio (95% CI)	*p*
Yes	94	33 (35.1%)		
No	37	13 (35.1%)	1.057 (0.565–1.977)	0.863
≥25IU/kg	54	19 (35.2%)		
<25IU/kg	61	20 (32.8%)	1.137 (0.647–1.999)[a]	0.656[a]
No PCC	37	13 (35.1%)	1.011 (0.516–1.982)[b]	0.974[b]
≥50IU/kg	7	4 (57.1%)		
<50IU/kg	118	40 (33.9%)	1.483 (0.731–3.010)[c]	0.275[c]
No PCC	37	13 (35.1%)	1.547 (0.679–3.522)[d]	0.299[d]

Regression analysis (log-Poisson with robust estimator) for the association of hemostatic treatment using PCC with hematoma enlargement in patients with Xa inhibitor–related ICH (ie, rivaroxaban and apixaban; n = 131). Risk ratios (95% CIs) are adjusted for identified predictors of hematoma enlargement (see Supplementary Table 3: time from symptom onset to initial imaging, time from initial imaging to follow-up imaging, National Institutes of Health Stroke Scale score on admission, intraventricular hemorrhage on initial imaging, and systolic blood pressure at 4 hours). Hematoma enlargement was defined as volume increase of >33% compared to initial imaging.

[a]PCC ≥ 25IU/kg versus PCC < 25IU/kg.

[b]PCC ≥ 25IU/kg versus no PCC.

[c]PCC ≥ 50IU/kg versus PCC < 50IU/kg.

[d]PCC ≥ 50IU/kg versus no PCC.

CI = confidence interval; ICH = intracerebral hemorrhage; PCC = prothrombin complex concentrate.

CI = 0.565–1.977; see Table 3 and Supplementary Table 6 for further subanalyses).

Systolic blood pressure levels < 160mmHg at 4 hours after admission were achieved in 113 patients and were significantly associated with a lower proportion of patients with hematoma enlargement (RR = 0.598, 95%CI = 0.365–0.978; $p = 0.04$; see Fig 2B).

Association of PCC Treatment with Secondary Outcomes

The mortality rates were 29/146 (19.9%) at discharge and 43/146 (29.5%) after 3 months without differences among patients with and without PCC treatment (Fig 3). Only one-third of patients achieved a favorable outcome after 3 months without any significant difference in the proportion with favorable functional outcome among patients with and without PCC administration (mRS = 0–3 at 3 months: PCC 32/103 [31.1%] vs no PCC 17/43 [39.5%]; $p = 0.32$).

Discussion

To our knowledge, the present study represents the largest analysis of patients with NOAC-related ICH. As key findings, this study demonstrates that hemostatic treatment with PCC—regardless of timing and dosage—was not associated with a reduced risk for hematoma enlargement, mortality, or unfavorable functional outcome either in overall NOAC-related ICH or specifically in factor Xa inhibitor–related ICH. Notably, systolic blood pressure levels < 160mmHg 4 hours after admission were significantly associated with a lower rate of hematoma enlargement. Several aspects need consideration.

First, in patients with VKA-related ICH, recent studies stressed the importance of an immediate international normalized ratio normalization to reduce the risk for hematoma enlargement,[4] and—according to the INCH study—neutralization of altered coagulation should preferentially be achieved by administration of PCC.[6] Contrary to growing evidence in VKA-related ICH, data on risk factors for hematoma enlargement and hemostatic management in NOAC-related ICH are limited.[8] International guidelines, available during the study period, recommended application of at least 25IU/kg bodyweight PCC, although the strength of the recommendations are weak ("should consider PCC" or "suggest reversal with PCC").[11,22,27–30] In addition, guideline recommendations were mainly based on animal studies, which do not necessarily translate to humans,[31,32] and pharmacological considerations raised doubt on any PCC efficacy in patients with NOAC-related ICH.[13,33] Since the introduction of idarucizumab, the therapeutic dilemma of hemostatic management in NOAC-related ICH is now restricted to patients with factor Xa inhibitor–related ICH.[9] In the absence of specific antidotes,

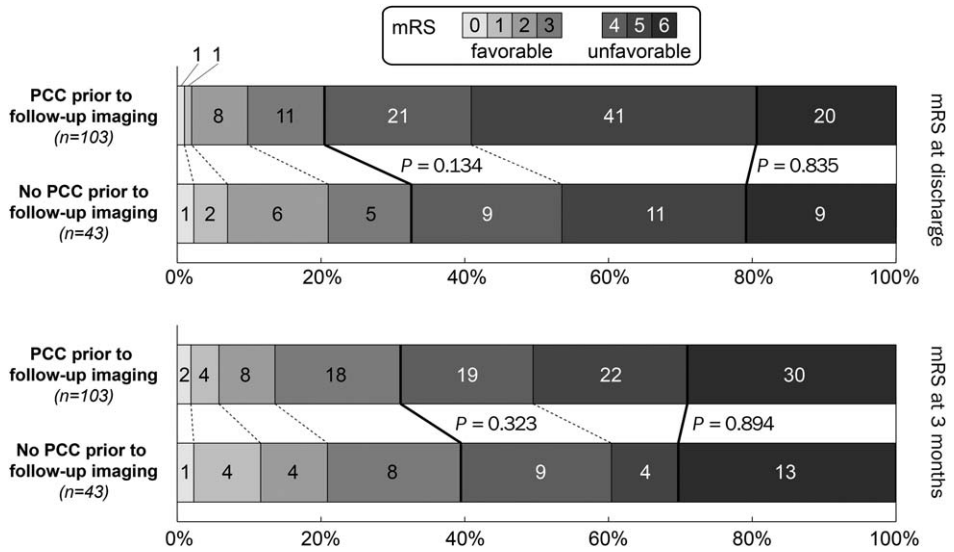

FIGURE 3: Functional outcome according to prothrombin complex concentrate (PCC) treatment. Distribution of functional outcome was assessed at discharge and after 3 months using the modified Rankin scale (mRS) dichotomized into patients with and without PCC administration. Multiple imputed data were used for outcome analysis. Dashed lines separate each score on the mRS. The thick lines illustrate the proportion of patients with unfavorable outcome and mortality, respectively. mRS 0 indicates no symptoms; mRS 1, no significant disability; mRS 2, slight disability and inability to carry out all prestroke activities; mRS 3, moderate disability, but able to walk without personal assistance or wheelchair; mRS 4, moderate to severe disability, needs assistance to attend to own bodily needs, unable to walk without assistance; mRS 5, severe disability, requires constant attention and care, bedridden; mRS 6, death.

such as andexanet alfa or ciraparantag (PER977), PCC administration remains the most intuitive hemostatic treatment approach for coagulation reversal in the case of factor Xa inhibitor–related ICH.[27]

However, the present study did not identify any significant reduction in the risk of hematoma enlargement by PCC administration both in overall NOAC-related ICH and in the subgroup of patients with intake of factor Xa inhibitors. Specifically, subgroup analyses identified no subset of NOAC-related ICH patients in whom PCC would exert a significant risk reduction of hematoma enlargement. Of note, international guidelines are dynamically adopting and were recently updated such that the PCC dosage recommendation now refers to $\geq$50IU PCC.[24,27] Again, these expert opinions and recommendations still are not backed by clinical studies. However, reconciling the data presented here, in essence only 8 patients (of whom 5 showed hematoma enlargement) were treated with high PCC dosages of $\geq$50IU/kg bodyweight, so meaningful conclusions on high-dose PCC efficacy cannot be drawn at this time. It seems valuable to seek new therapeutic hemostatic options for factor Xa inhibitor–related ICH as soon as possible.[10,34,35]

In addition to the acute hemostatic treatment, rigorous systolic blood pressure control appears likewise important. In patients with primary ICH, the INTERACT and ATACH study programs provided nonsignificant evidence in favor of intensive blood pressure regimens and clinical outcomes[21,36]; however, a recent meta-analysis verified the influence of blood pressure control on hematoma enlargement.[37] In NOAC-related ICH, existing data on blood pressure management were limited and remained inconclusive because of low patient numbers and residual heterogeneity.[8,14] As demonstrated here, systolic blood pressure levels were significantly associated with reduced risk for hematoma enlargement in NOAC-related ICH. Given the absent associations of a hemostatic treatment with hematoma enlargement, systolic blood pressure management appears even more important in NOAC-related ICH. Controlled trials are needed to establish the effect of hemostatic treatments and blood pressure management on hematoma enlargement in patients with NOAC-related ICH.[4,6,33,38]

This study has several important limitations. Shortcomings include mainly the retrospective study design, implying reduced data quality. As stated previously,[4] a certain level of imprecision remained in terms of hematoma enlargement and blood pressure assessments, and multiple imputation was used to compensate for missing outcome data. In addition, patients were excluded because of absent second imaging. Furthermore, the retrospective design did not allow exploration of the association of exact time points of achieving blood pressure control with the primary outcome, as recording of blood pressure levels within the first day was restricted to 4-hour intervals after hospital admission. Although this study represents the largest cohort of patients with

NOAC-related ICH, there were few patients in the subgroup analyses for associations of various PCC dosages with hematoma enlargement as well as for a meaningful head-to-head-comparison between specific NOACs. Furthermore, the cutoff value for anti-Xa levels and prediction of hematoma enlargement was based on only few patients with available data. In addition, it cannot be fully excluded that the nonsignificant findings in NOAC-related ICH regarding PCC are based on a power issue and small patient numbers. Furthermore, data on safety of administered coagulation reversal strategies, specifically potentially procoagulatory effects of PCC, were not obtained.[39] In addition, despite a rigorous statistical design including extensive adjustments, residual center effects cannot be completely ruled out.

In conclusion, among patients with NOAC-related ICH, there were no significant differences between those with PCC treatment compared to those without regarding rate of hematoma enlargement, mortality, or functional outcome at 3 months. In this study, systolic blood pressure control < 160mmHg at 4 hours after admission was associated with a lower risk of hematoma enlargement in patients with NOAC-related ICH.

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Author Contributions

S.T.G., J.B.K., S.S., and H.B.H. contributed to the concept and design of the study. S.T.G., J.B.K., J.A.S., M.I.S., K.G.H., J.P., T.R., H.St., H.Sc., H.N., D.M., and H.B.H. contributed to the acquisition and analysis of data. S.T.G., J.B.K., M.E., P.V., P.A.R., J.P., T.R., F.E., P.D.S., G.R.F., J.R., J.C., A.D., S.S., and H.B.H. contributed to drafting the text and preparing the figures. All authors participated in editing and approving of the final manuscript.

Potential Conflicts of Interest

J.B.K., M.E., K.G.H., P.A.R., T.R., F.E., P.D.S., G.R.F., and J.R. report personal fees outside the submitted work from Bayer Healthcare (rivaroxaban). J.B.K., M.E., K.G.H., P.A.R., J.P., T.R., F.E., P.D.S., and J.R. report personal fees outside the submitted work from Bristol-Myers Squibb/Pfizer (apixaban). M.E., K.G.H., P.A.R., J.P., T.R., F.E., P.D.S., G.R.F., H.N., J.R., S.S., and H.B.H. report personal fees outside the submitted work from Boehringer Ingelheim (dabigatran, idarucizumab). M.E., K.G.H., P.A.R., T.R., F.E., P.D.S., H.N., S.S., and H.B.H. report personal fees/grants outside the submitted work from Daiichi Sankyo (edoxaban). H.B.H. reports personal fees outside the submitted work from CSL Behring (Beriplex [PCC]). Potential conflicts of interest of collaborators are available as an online supplementary file.

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