UniversitätsKlinikum Heidelberg

Name of Sponsor/Company: University hospital Heidelberg	**Sponsor-Code of Study:** ICH-VKA (INCH)		*(For National Authority Use only)*
Name of (Finished) Product: Octaplex® Fresh frozen Plasma	**Name of Active Ingredient:** PCC (prothrombin complex-concentrate) human plasma		
EudraCT-No.: 2008-005653-37	**BfArM Vorlage No.:** 790/01	**Ethic application No.:** AFmu-344/2008	

SYNOPSIS

Title of Study:

Multicenter, prospective randomized trial on the use of prothrombin complex and fresh frozen plasma in patients with intracerebral hemorrhage related to vitamin K antagonists (VKA)
Short title: ICH-VKA

INCH - (**IN**R normalization in patients with **c**oumarin related intracerebral **h**emorrhages)

Last approved version of the trial protocol: **12Jan2009**/ Version 03

There was one site specific amendment (only applicable for the site no 08/ university hospital Koeln).
Approved version of the site specific protocol-amendment: **05Jan2012**

The amendment describes a different procedure for the informed consent process in case the subject is not able to give consent on his/her own and no legal representative is available in time.
The local ethics committee for the University hospital Koeln recommended that a.m. subjects should only be enclosed after the potential will of the subject had been clarified by asking a relative. Also the written assent of the relative should be obtained. In a second step the local judge had to be informed and had to give his written assent for subject enrollment.
This procedure differs from the procedure described originally in the trial protocol whereas the subject can be enrolled after written assent of an independent physician who confirms the presence of an emergency situation.

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Publication (reference):

Publication has been submitted to the journal "Lancet Neurology". Reviewer's comments are in process. Final acceptance of the article is pending.

Corresponding Author: Thorsten Steiner

Title: International Normalized Ratio normalization in patients with coumarin associated intracranial haemorrhages (INCH) trial: Results of a randomized trial comparing fresh frozen plasma (FFP) versus prothrombin complex concentrate (PCC) in patients with intracranial haemorrhages.

Study period: **(date of first enrolment)** **(date of last completed)**	07Aug2009 (First patient in) 11Oct2013 (Last patient in) 09Jan2014 (Last patient out) **18Oct2013:** study on-hold (stop of recruitment by the Sponsor / substantial amendment)) for preparing a safety report after inclusion of 50 subjects (procedure was recommended by and agreed with the competent authority (CA; PEI)). No un-blinding of investigators or outcome assessors regarding group assignment was necessary and the primary endpoint was not included in the safety analyses. **26May2014**: application of a substantial amendment (CA and EC) for the re-start of recruitment. **29Sep2014:** Withdrawal of the first approval by the CA for safety reasons. The Sponsor has been given the opportunity to comment on the opinion of the CA. **23Jan2015:** CA rejects the objection of the Sponsor and maintains its withdrawal. **06Feb2015**: Sponsor`s official date of premature study end **09Feb2015:** official notification of premature study end to CA and EC
Study Phase:	IV

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Background:
Hematoma expansion (HE) predicts mortality in vitamin K antagonist related intracranial hemorrhage (VKA-ICH). Normalizing the international normalized ratio (INR) is recommended but optimal hemostatic management is controversial. We compared the effect of fresh frozen plasma (FFP) and prothrombin complex concentrate (PCC) on early coagulation and HE.

Introduction:
Intracranial hemorrhage (ICH) related to vitamin K antagonists (VKA-ICH) is responsible for up to 36% of bleeding-associated deaths during long-term anticoagulation. The annual rate of VKA-ICH was between 0.33 and 0.85% in randomized controlled trials of warfarin versus non-vitamin K antagonists and as high as 1.9% in observational cohorts. Hematoma expansion (HE) remains a major cause of mortality occurring most frequently in the first few hours after hemorrhage onset in 36% to 54% of patients.
Therapeutically, it is reasonable to consider the administration of coagulation factors in order to normalize coagulation and to prevent HE. However, evidence for the efficacy of different reversal strategies is limited in VKA-ICH, and only a small number of patients have been included in randomized controlled trials of anticoagulation reversal. Some observational studies have suggested that normalization of INR reduces the risk of HE but which treatment has the biggest impact on mortality remains controversial. Prothrombin complex concentrate (PCC) was more effective than fresh frozen plasma (FFP) in some studies whereas another study only found an effect on mortality with a combination of FFP and PCC. In the absence of evidence from randomized controlled trials specifically dedicated to VKA-ICH, treatment guidelines either recommend using PCC or FFP based on plausibility or refrain altogether from making any recommendations.

This clinical trial compared the efficacy and safety of FFP and four-factor PCC in patients with VKA-ICH in the acute phase. The null hypothesis was defined as follows: FFP and PCC are equally effective in normalizing the INR ≤1·2 within three hours after the start of treatment.

Objectives:
Efficacy and safety of PCC compared to FPP in patients with ICH-VKA

Primary endpoint/ outcome parameter: Efficacy
- INR ≤ 1.2 within 3 hours after start of drug infusion

Secondary endpoints/ outcome parameter:
- Efficacy:
  - Hematoma growth: percentage of volume increase within 24 hours
  - NIHSS, mRS, BI, GOS, EQ-5D
  - Number of patients with normalization of INR within 30 minutes and 3 hours
  - Time to reach normalization of vitamin-K-dependent coagulation factors
- Safety:
  - Number of adverse events until the end of the trial (day 90) (AEs of special interest)
  - Number of serious adverse events (SAEs) until the end of the trial (day 90)

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Methodology:
Randomized, open (observer-blinded), multi-center, two parallel groups.

This investigator-initiated trial had a multicentre, prospective, randomized, controlled, open, blinded endpoint design. Patients with VKA-ICH presenting within 12 hours after symptom-onset with an INR ≥2.0 were intended to receive FFP or four-factor PCC within one hour after initial cerebral computed tomography. The primary endpoint was the proportion of patients with INR ≤1.2 within three hours. Secondary endpoints included HE, early mortality and thromboembolic events.

Number of patients (planned and analysed):

Planned:	**74**
Enrolled:	**54**
Analysed:	**50**

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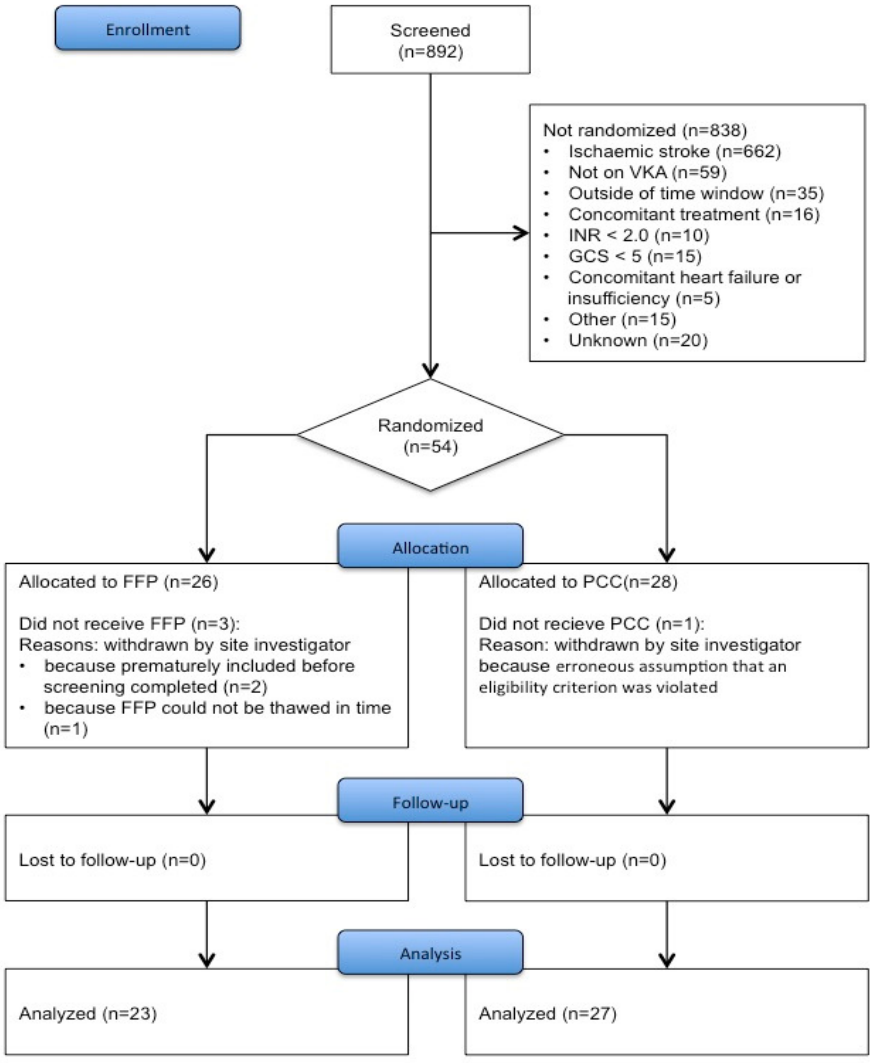
Figure 1: Flow diagram of trial progress



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EudraCT-No.:	BfArM Vorlage No.:	Ethic application No.:
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Diagnosis and main criteria for inclusion:

Diagnosis:
Intracerebral hemorrhage (ICH) in patients related to vitamin K antagonists (VKA)

Criteria for inclusion:
1. Spontaneous ICH (intraparenchymal), subdural hematoma (SDH) diagnosed by CT scanning ≤ 12 hours after onset of symptoms. In case of unknown time of symptom onset: time between last seen in healthy condition and first CCT ≤ 12 hours.
2. Therapy receiving vitamin K antagonists (VKA)
3. International Normalized Ratio (INR) ≥ 2
4. Male or female subjects, age ≥ 18 years
5. Signed informed consent form, or signed informed consent by a legal representative, judicial consent in cases where no legal representative is available in time, or consent of an independent physician familiar with the indication in cases where the first three possibilities can not be realized.

Criteria for exclusion:
1. Patients with primary ICH
2. Patients with secondary ICH related to infarction, hemophilia or other coagulopathy, tumor, hemorrhagic infarction, cerebrovenous thrombosis, aneurysm, arteriovenous malformations (AVM) or severe trauma
3. Deep Coma (GCS ≤ 5) at the time of admission or before intubation if intubated outside the hospital
4. Known thrombocytopenia (platelets <50,000/µL), hemorrhagic diathesis (primary defects of coagulation, fibrinolysis, platelets)
5. Pregnancy and lactation
6. Acute myocardial ischemia, acute septicemia, acute crush injury, any history of acute hemorrhagic disseminated intravascular coagulation, acute thrombotic stroke
7. Acute or known congestive heart failure (NYHA III, IV)
8. Pulmonary edema
9. Known history of claudicatio intermittens
10. Known recent thrombotic event < 30 days
11. Known active malignant disease
12. Known alcohol or other drug abuse
13. Known previous disability (mRS > 2 before stroke occurred)
14. Known liver failure (child-pugh-score C)
15. History of hypersensitivity to the investigational products or to any drug with similar chemical structure or to any excipient present in the pharmaceutical form of the investigational product
16. Known allergy to heparin or history of heparin induced thrombocytopenia.
17. Previous participation in this trial
18. Participation in ANY clinical trial within 30 days of entry into the trial and during the trial
19. Concomitant use of antithrombotic (with PTT > 1.5 of normal PTT), thrombolytic treatment. – Use of aspirin, clopidogrel or dipyridamole or combinations thereof (e.g. Aggrenox®) is not an exclusion criterion. These drugs should be discontinued and not restarted earlier than 24 hours after normalization of INR if indicated.

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Test product, dose and mode of administration:

Subjects were randomly assigned to treatment with PCC or FFP.
Both investigational products were administered intravenously. In addition 10 mg of intravenous Vitamin-K was given for both treatment groups.

Test product:

Prothrombin complex concentrate (PCC): 30 IU/ kg, max. total initial dose 3000 IU; i.v.

Duration of treatment: PCC

Treatment started within 1 hour after first cerebral computer tomography (CCT) on admission.

The initial dose of PCC was 30 IU/kg (but not more than a total initial dose of 3000 IU).

If the primary endpoint was not reached, additional PCC was prescribed as per protocol.

Reference therapy, dose and mode of administration:

Fresh frozen plasma: at least 20 mL/kg i.v.

Duration of treatment: FFP
Treatment started within 1 hour after first cerebral computer tomography (CCT) on admission.
FFP had to be administered at the highest infusion rate clinically tolerated within 3 hours (clinical threshold of no tolerance reached when signs of fluid overload became apparent).

Dosing of PCC/ FFP and re-dosing of PCC

The INR was measured at 3 hours after start of infusion (primary endpoint). If INR was > 1.2, all patients independent of randomization received PCC. The dose of PCC depended on the INR value at hour 3.

	INR	Treatment A (PCC)	Treatment B (FFP)
Hour 0	---	30 IU/ kg	20 ml/ kg
Hour 3	≤ 1.2	---	---
	1.2 < INR ≤ 2	10 IU/ kg **(PCC)**	
	> 2	30 IU/ kg **(PCC)**	

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Criteria for evaluation: (efficacy, safety)

Primary endpoint/ outcome parameter: Efficacy

- INR ≤ 1.2 within 3 hours after start of drug infusion

Secondary endpoints/ outcome parameter:

- Efficacy:
  - Hematoma growth: percentage of volume increase within 24 hours (measured at 3 hours and 24 hours)
    (A difference of 15% between both groups was regarded as clinically significant)
  - National Institute of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), Barthel Index (BI), extended Glasgow Outcome Scale (eGOS), Quality of Life (EQ-5D questionnaire)
  - Number of patients with normalization of INR within 30 minutes and 3 hours
  - Time to reach normalization of vitamin-K-dependent coagulation factors

- Safety:
  - Number of adverse events until the end of the trial (day 90) (AEs of special interest)
  - Number of serious adverse events (SAEs) until the end of the trial (day 90)

Additional not pre-specified measurements:
Relative hematoma growth of ≥33% was also analyzed as previous trials on spontaneous ICH had used this threshold.

Changes in the planned analysis/ statistical analysis plan

The data collected in this trial were analyzed as planned in the trial protocol. Additionally, the 15-day and 90-day modified Rankin scale was tested for treatment effect using a proportional-odds logistic regression (shift analysis).

Statistical methods:

As specified in the trial protocol, Wald test in a logistic regression model (including treatment site and baseline INR (values higher than 4.6 set to 4.6) was used to assess the treatment effect on the primary endpoint. All tests were two-sided and p-values less than 0.05 were considered to be statistically significant. Modified Rankin Score after 15 and 90 days was modeled using a Cox proportional odds model for shift analysis. The confidence interval for linear difference and shift odds ratio were generated using Wald approximations. Haematoma volumes were replaced by the highest preceding measurement on the same patient if the patient died or had haematoma reduction surgery before the planned CCT.
Statistical tests were obtained by parameter tests in of logistic regression models (for binary outcomes), linear regression models (for outcomes on the interval scale) or log-rank test (for time-to-event outcomes). Where appropriate, the baseline value of the response parameter and study site have been included as explanatory variables for an adjusted analysis. P-values and confidence intervals were not corrected for multiplicity and should be interpreted with appropriate caution.

Four patients were withdrawn by the site investigator after randomization and before the beginning of infusion (for details see next section). No data have been obtained for these patients. We followed an intention-to-treat approach for all 54 patients using multiple imputation for missing baseline and 3 h INR values. All other analyses have been performed on a "treated as randomized" approach, where these four patients were excluded from.

Four patients were withdrawn by the site investigator after randomization and before the beginning of infusion: Two patients were randomized (both into fresh frozen plasma group) before screening was completed, by the investigator after an exclusion criterion had become apparent. Another patient (prothrombin complex concentrate group) was excluded after randomization under the erroneous assumption that an eligibility criterion was violated. One patient was randomized into the fresh frozen plasma group but the plasma could not be thawed rapidly enough to start treatment in time. In any of these cases no further data were collected by the site investigator, and although these four patients technically were part of the full analysis data set, they remained excluded. A sensitivity analyses to check for the influence of these exclusions on the primary endpoint was carried out using the "randomised-as-treated" set, from which those four patients were excluded. The resulting effect on the primary endpoint was estimated to be OR=30.6 [4.7; 197.9], p=0.0003.
Another sensitivity analysis was carried out for the per protocol set. The expectation was that FFP would fare comparatively better, as patients with administration of study medication over more than three hours had been excluded from the set. The reverse turned out to be true, however, as only one out of 17 FFP patients compared to 15 out of 23 PCC patients experienced normalization (p=0.002).

Primary Endpoint: INR ≤ 1.2 within 3 hours after start of drug infusion

Statistical model: logistic regression
Variables: assigned treatment group, site, baseline INR

The dichotomous variable "normalization of INR to ≤ 1.2 after 180 minutes": dependence on treatment arm by two-sided test on a parameter in a logistic model involving baseline INR (winsorized at 4.6), site, and assigned treatment as the explanatory variables.
A similar model was applied to the variable "normalization of INR to ≤ 1.2 after 180 minutes or treatment readjustment, whatever comes first".

Test of the study hypothesis: Wald test of the parameter „treatment group", α = 0.05 of the null hypothesis „no association between treatment group and primary endpoint".
Presentation of the effects: Odds ratios as exp (estimates of parameters) for the treatment group with a likelihood based 95% confidence interval.

Secondary objectives:
Hematoma growth as response in a linear model using baseline ICH, site, and treatment group as explanatory variables. Additionally, it was dichotomized at +15 percent and assessed in a logistic model using the same explanatory variables.
Clinical scales such as modified Rankin Scale, Barthel Index and National Institute of Health Stroke Scale were primarily interpreted as continuous for analysis and included in a linear using baseline and baseline heamatoma volume, site, and treatment group.

Tabular and graphical (box-and-whiskers-plots) description of PT (Quick), INR, aPTT, coagulation activities of factors II, VII, IX, X, Protein C and free Protein S by visit. Time to normalization was depicted for each coagulation separately.
Adverse events were tabulated by System Organ Class (SOC), severity and relatedness vs. treatment group displaying frequency of events (according to preferred term (PT)) and number of subjects with at least one event. The safety laboratory parameters were tabulated the same way as the coagulation parameters.

Analysis set:

ITT (intention to treat/ **f**ull **a**nalysis **s**et (**FAS**))**:**
all randomized patients who received study medication at least once. Within this population all patients were analyzed according to their randomized treatment arm, following an intention-to-treat approach.

PP: The Per Protocol population includes all patients of the FAS who received at least 80 % of the planned study medication. The complete list of reasons for exclusion of patients from the PP population are:

- Less than 50 % of prescribed study medication used,
- Screening cerebral CT was performed more than 12 hours after onset of clinical symptoms,
- Subsequent cerebral CTs were performed outside of the pre-planned time frames (3 hours ± 90 minutes, 24 hours ± 6 hours),
- Hemorrhage volume estimation was not performed or was not possible,
- Blood sample for INR scheduled at 3 hours outside the time frame (3 hours ± 1.5 hours)
- Application of study medication not within prescribed time frame (within 3 hours for FFP treatment arm),
- Violation of in-/exclusion criteria.

The Safety population (**SP**) includes all patients who received at least one dose of study medication. Within this population the patients will be analyzed according to the treatment actually received. Since some patients of the FFP treatment arm subsequently received PCC as rescue medication the FFP treatment group was subdivided into 2 subgroups for the analysis of safety: those patients receiving a PCC rescue treatment and those who did not.

- PCC (n= 27)
- FFP (n= 4)
- FFP and PCC as rescue medication after 3 hours (n= 19)

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Summary – Conclusions:

Efficacy Results:

The trial was terminated after the inclusion of 50 patients following the second safety analysis (first after 24 patients) on the demand of the competent authority due to a strong trend towards more pronounced haematoma expansion in the FFP-group (Figure 2).

Recruitment of patients took place in six out of eight centres.

50 of 54 randomized patients received a study drug (FFP: 23; PCC: 27). Four patients were withdrawn by the site investigator before study treatment. A sensitivity analysis demonstrated no influence of these exclusions on the primary endpoint.
According to the protocol, patients with an INR >1.2 at three hours were to receive PCC. This was the case in 19/23 (83%) patients assigned to FFP and 7/27 (26%) allocated to PCC.

The mean age of patients was 75.6 years, with 19/50 patients (38%) being women. Baseline values are displayed in Table 1.

The primary analysis was on all treated patients and the primary endpoint was reached in 2/23 patients in the FFP-group, and 18/27 patients in the PCC-group (adjusted odds ratio 29.5, 95%-confidence interval (CI): [4.2; 206.7], p =0.0007), (Table 2). 30 minutes after the start of drug infusion, an INR of ≤1.2 was observed in 17/26 patients in the PCC-group but in 0/19 in the FFP-group (Figure 3).

The adjusted difference in haematoma expansion at three hours between FFP and PCC was 16.9 ml (95%-CI: [2.5; 31.3], p=0.023) and thus significantly different in favour of PCC. Haematoma expansion exceeding 15% from baseline at three hours occurred in 16/22 FFP and 15/26 PCC patients (adjusted odds ratio 2.0 [0.6; 7.3]; 2 CCTs were not done at the 3 hour time point). Only 20/23 patients in the FFP-group were available for analysis at 24 hours due to poor general condition, inability to perform CCT and performance of magnetic resonance tomography (MRI) instead of CCT. In three patients who died prior to 24 hours, the highest haematoma value on CT was carried forward. At 24 hours, the adjusted difference in haematoma expansion was 16.4 ml (95%-CI: [2.9-29.9], p=0.018), and HE of more than 15% had occurred in 14/20 surviving FFP patients (three died within 24 hours), and 12/27 PCC patients (all surviving to 24 hours) (adjusted odds ratio 3.9 [1.0; 17.6]) (Table 2).

Nineteen of 23 (83%) patients assigned to FFP and 7/27 (26%) allocated to PCC failed to attained an INR of 1.2 at three hour.

Figure 2: Volume of intracranial haematoma at different time points according to treatment group
Circles and crosses: mean; horizontal bar within box: median

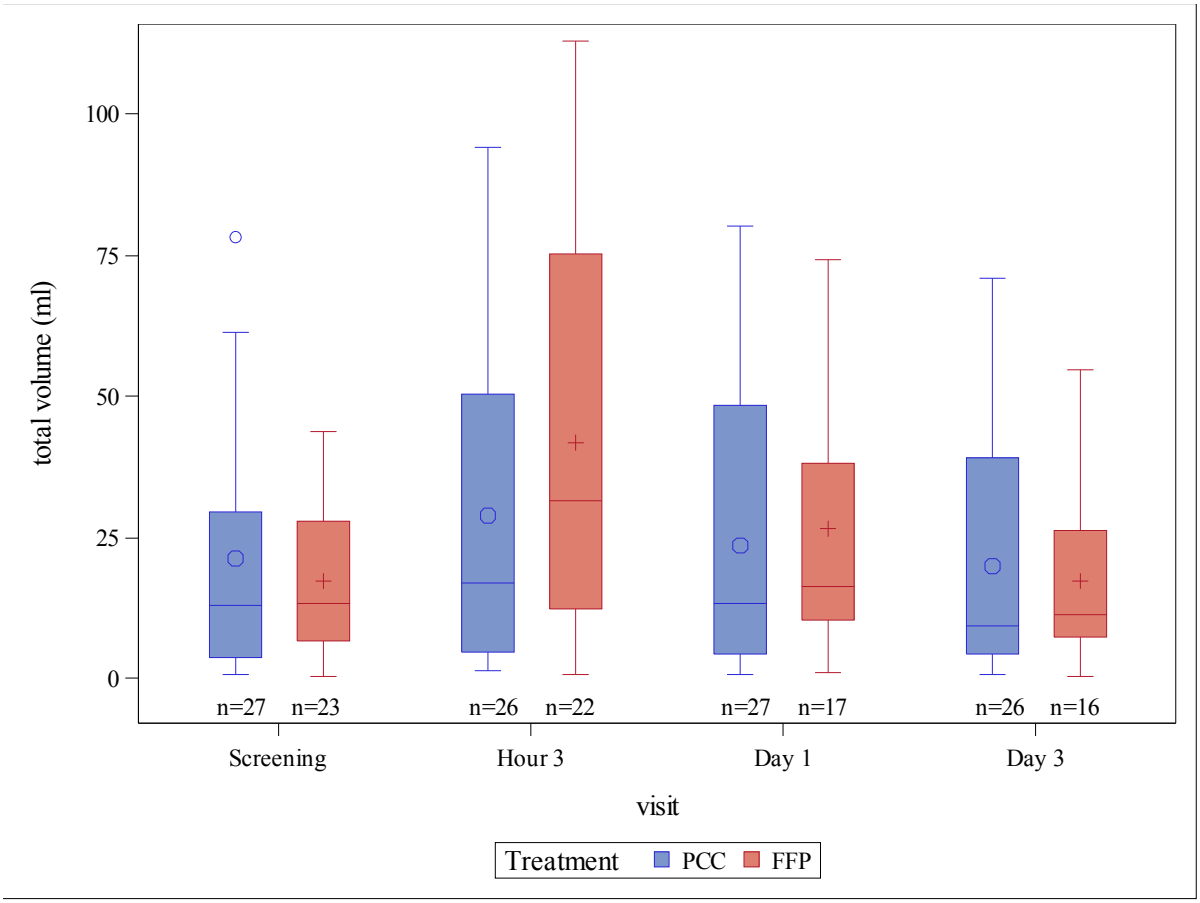

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Table 1: Demographic data and clinical characteristics

Variable	**FFP**	**PCC**
Number	23	27
INR at baseline, mean, ±SD	3.26 ± 1.22	2.83 ± 0.68
Age, mean	76.6	74.7
Female [N (%)]	8 (35)	11 (41)
Blood pressure, systolic, mean, ±SD [mmHg]	178 ± 21	165 ± 37
Blood pressure, diastolic, mean, ±SD [mmHg]	97 ± 18	88 ± 25
Haematoma volume at baseline, mean (min, max) [ml]	17.3 (0.2, 43.9)	21.2 (0.6, 78.1)
Body mass index, mean, ±SD [kg/m2]	26.9 ± 4.3	25.9 ± 3.9
Diabetes [N (%)]	6 (26)	4 (15)
Hypertension [N (%)]	21 (91)	24 (89)
Myocardial infarction	5 (22)	3 (11)
Atrial fibrillation	20 (87)	17 (63)
Clinical status at baseline		
Premorbid Modified Rankin Scale, median (min, max)	4 (0, 5)	4 (1, 5)
NIHSS, median (min, max)	7 (2, 19)	10 (0, 22)
Glasgow Coma Score (GCS) admission, median (min, max)	15 (10, 15)	13 (9; 15)
Site of haematoma location		
Basal ganglia, [N (%)]	12 (52)	13 (48)
Thalamus, [N (%)]	0 (0)	1 (4)
Lobar, [N (%)]	7 (30)	4 (15)
Brain stem, [N (%)]	1 (4)	3 (11)
Intraventricular, [N (%)]	0 (0)	2 (7)
Cerebellar, [N (%)]	1 (4)	0 (0)
Subdural, [N (%)]	2 (9)	4 (15)
Time from onset to baseline CCT, mean, SD [minutes]	202 ± 152	199 ± 160

Table 2: Outcomes

	FFP N=23	PCC N=27	Treatment effect	95% CI	p-value
Primary outcome					
INR ≤1.2 within three hours	2	18	OR: 29.5	4.2 –206.7	0.0003
Secondary outcomes					
***Efficacy outcome* - Imaging data**					
At 3 hours					
Haematoma expansion, mean ± SD [ml]	23.7 (28.4)	9.7 (20.9)	16.9	2.5 – 31.3	0.023
15% Growth, N (%)	16 (72.7)	15 (57.7)	OR: 2.0	0.6 – 7.3	0.29
33% Growth, N (%)	13 (59.1)	12 (44.4)	OR: 3.8	1.1 – 16.0	0.048
At 24 hours					
Haematoma expansion, mean ± SD [ml]	22.1 (27.1)	8.3 (18.3)	16.4	2.9 – 29.9	0.018
15% Growth, N (%)	14 (70.0)	12 (44.4)	OR: 3.9	1.0 –17.7	0.044
33% Growth, N (%)	12 (60.0)	8 (29.6)	OR: 4.8	1.3 – 20.4	0.024
Clinical outcomes					
Functional independence at day 15 or discharge* no (%)	7 (30.4)	7 (25.9)	OR: 2.3	0.5 – 13.1	0.31
Functional independence at day 90*	9 (39.1)	10 (37.0)	OR: 1.7	0.4 – 6.8	0.47
Deaths at day 90	8	5	No proportional hazard assumed	No proportional hazard assumed	0.14**
Quality of life at day 90[x]	8.21	9.25	-0.7	-5.6 – 4.2	0.78
Barthel Index (BI) at Day 90	52.5 ± 40.3	70.0 ± 37.7	-16.0	-44.9–12.8	0.27
Trial performance outcomes					
Time from onset to baseline CCT, mean, SD [minutes]	202 ± 152	199 ± 160	-6	-98 – 90	0.90
Time from baseline CCT to start of treatment, mean, SD [minutes]	80 ± 33	59 ± 20	26	13 – 39	0.0002

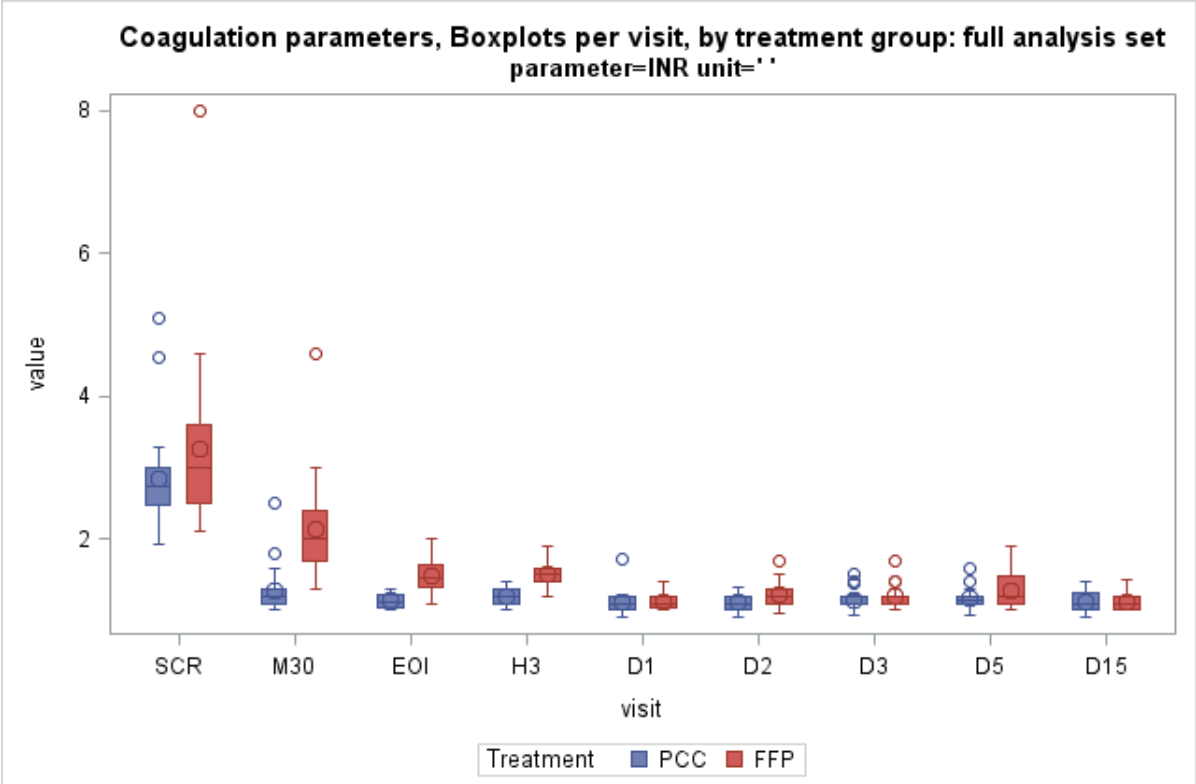
Duration of infusion mean, SD [minutes]	129 ± 69	34 ± 31	103	75 – 130	<0.0001

Haematoma growth is defined as 15% change of mean volume between baseline and follow-up CTT

* modified Rankin Scale of 0, 1, 2, 3
** Logrank test
x Quality of Life assessment EQ-5D self-report questionnaire (QoL/EQ-5D)

Of 20 patients in the FFP-group, three patients had missing values for 24 hours due to poor general condition, not done and MRI instead of CCT taken
Number of available CCT at three hours: 48; at 24 hours: 44

Figure 3: Course of INR over time according to treatment group



SCR= Screening, M30= minute 30, EOI= End of infusion, H3= hour 3; D1= day1, D2= day2, D3= day3, D5= day5, D15= day15)

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Safety Results:

The mortality rate at day 90 was 35% (8/23) vs. 19% (5/27) in the FFP and PCC-groups, respectively (p=0.14). Five deaths in the FFP-group were related to HE as assessed by the investigators; these five deaths occurred within the first 48 hours. No patient in the PCC-group died from HE (Figure 4) during this period. The remaining three later deaths in the FFP-group were classified as sequelae from ICH but did not directly result from HE. In the PCC-group, the first death occurred on day five due to cardiac arrest. At 90 days, the median mRS score was four in the FFP and four in the PCC-group (Table 2).

In total, there were 43 serious adverse events (SAE) in 26 patients. Thereof, 20 events were observed in the FFP-group and 23 in the PCC-group. Six SAEs were assessed as FFP-related (four cases of haematoma expansion, one anaphylactic reaction and one ischaemic stroke) and two SAEs as PCC-related (ischaemic stroke and pulmonary embolism). No case of fluid overload was reported after either treatment.

Thromboembolic events are listed in Table 3. Three out of nine thromboembolic events occurred within the first three days after the start of treatment (two ischaemic strokes, and one pulmonary embolism, Table 3). All other thromboembolic events occurred 12 days or later after the start of investigational treatment.

Figure 4: Kaplan-Meier curve and haematoma expansion

Blue (FFP-group), red (PCC-group) circles indicate the time point when haematoma expansion occurred. The corresponding line (blue, red) indicates the time point of death for this individual patient.

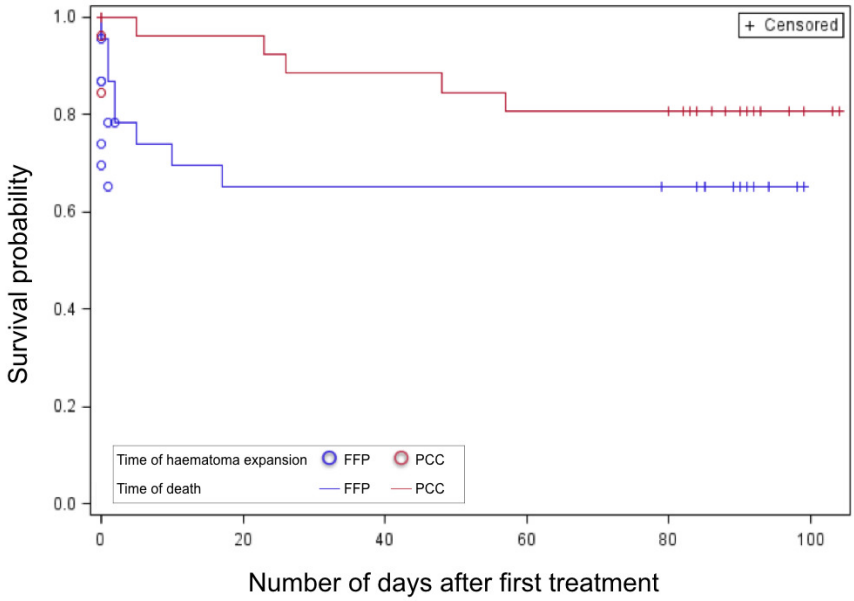

Table 3: Safety outcomes

	FFP (N=23)		PCC (N=27)	Odds Ratio FFP+PCC vs. PCC	95% CI	p (Fisher's exact test)
	FFP N=4	+ PCC (after 3 hours) N=19*				
Thromboembolic events						
Myocardial infarction	0		0	N/A	N/A	N/A
Ischaemic stroke	1**	1	2	N/A	N/A	N/A
Pulmonary embolism	0	0	4**	N/A	N/A	N/A
Deep vein thrombosis	0	0	1	N/A	N/A	N/A
Number of patients with at least one SAE	2	8	16	0.65	0.16–2.49	0.55
Number of SAEs	5	15	23			
SAE classified as haematoma expansion	2	7	7			
SAE classified as haematoma expansion leading to death	2	4	1			

N/A: Not applicable
* According to the protocol patients in whom the INR after three hours was not below or equal 1·2 received PCC
** Three within first three days, all other thromboembolic events occurred at day 12 or later, SAE: serious adverse event

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Discussion:

The INCH trial was undertaken to compare the acute haemostatic effect of FFP and PCC in patients with VKA-ICH. The trial demonstrates that PCC is superior to FFP in normalizing the INR within three hours. Furthermore, HE at three hours and 24 hours was significantly less extensive in patients treated with PCC. The only five deaths within the first 48 hours were related to haematoma expansion and occurred exclusively in the FFP-group, three of them within 24 hours). This indicates that haematoma expansion is an acute phenomenon and leads to death if not treated immediately. A difference in clinical endpoints at three months was not demonstrated, but the trial was not designed for this endpoint, as it allowed early ”rescue” therapy with PCC in both groups after three hours.

Despite the introduction of novel oral anticoagulants which carry a substantially lower risk of ICH, VKA-ICH is likely to remain a substantial challenge for the foreseeable future as VKA are still frequently prescribed in many countries for stroke prevention in atrial fibrillation and remain indispensable for other indications. We chose FFP as a comparator to PCC as both drugs are routinely used in many countries despite a preference for PCC in some guidelines (Steiner T, Al-Shahi Salman R, Beer R, et al. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. Int J Stroke 2014; 9(7): 840-55; Hemphill JC, 3rd, Greenberg SM, Anderson CS, et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2015; 46(7): 2032-60).
Intriguingly, a recent retrospective international study found no evidence for superiority of FFP or PCC in VKA-ICH.[11] Normalization of the INR was defined as the primary endpoint in INCH to achieve a feasible sample size in this challenging condition. The primary endpoint was measured at three hours to allow sufficient time for administration of FFP, which requires high volume infusion, cross-matching and thawing. Despite choosing the three-hour time point and despite optimizing the organizational delivery of FFP in the trial, the vast majority of patients in the FFP-group failed INR-normalization as late as three hours after start of treatment. Moreover, anticoagulation reversal using PCC might be further accelerated in clinical routine by using serial bedside point-of-care coagulation-testing (Rizos T, Jenetzky E, Herweh C, et al. Point-of-care reversal treatment in phenprocoumon-related intracerebral hemorrhage. *Ann Neurol* 2010; **67**(6): 788-93).

In accordance with two trials of VKA reversal in other settings (Sarode R, Milling TJ, Refaai MA, et al. Efficacy and Safety of a Four-Factor Prothrombin Complex Concentrate (4F-PCC) in Patients on Vitamin K Antagonists Presenting with Major Bleeding: A Randomized, Plasma-Controlled, Phase IIIb Study. Circulation 2013; 128(11): 1234-43.), our findings clearly favour PCC over FFP in terms of speed of INR normalization. The majority of patients in the FFP-group (83 % vs. 26% in the PCC-group) subsequently received PCC because the INR was not normalized at three hours. This is likely to have accelerated anticoagulation reversal in the FFP-group. Nevertheless, haematoma volumes at 24 hours were smaller in the PCC than in the FFP-group. This and our exploratory analysis regarding the effect of early effective reversal on HE independent of group assignment support the importance of an immediate start of treatment with high concentrations of coagulation factors that was also suggested by a retrospective study (Kuramatsu JB, Gerner ST, Schellinger PD, et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. JAMA 2015; 313(8): 824-36).

Conclusions regarding safety of PCC versus FFP should be made with caution, because of the small simple size:

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Three thromboembolic events occurred within the first three days in both groups. All other thromboembolic events occurred after 12 days and the number of events was higher in the PCC-group than in the FFP-group. However, only one patient (in the FFP group) was anticoagulated at that time, and the number of early deaths in the FFP needs to be taken into consideration. An anaphylactic reaction occurred only in the FFP-group.

Our trial has several strengths. It was the first randomized controlled trial with a rigorous design of anticoagulation reversal in the devastating condition of VKA-ICH. Compared to other types of major bleedings related to VKA, VKA-ICH is clearly defined and quantifiable in terms of haematoma size. Another strength is that the INCH protocol included serial CCT imaging and measures of clinical outcome. The findings of this proof-of-concept approach suggest that failure to rapidly antagonize anticoagulation effectively increases the risk of HE and early death.

This trial also has limitations: The sample size was small as it was powered to compare the effect on acute haemostasis and not designed for clinical endpoints. Investigators were not blinded to treatment allocation but main outcomes including INR values, haematoma volumes and clinical outcomes were assessed blinded to treatment allocation. Randomization was based on envelopes and was used because of the low expected event rate, the tight protocol schedule within the emergency situation. The trial was stopped prematurely by the competent authority (Paul-Ehrlich-Institute) based on differences in HE between treatment groups. This reduced power but as this was observed during the trial, the observed effect is prone to bias away from the null hypothesis of no effect. Nevertheless, an upward bias cannot be ruled out. The assumption that elevated blood pressure favoured haematoma growth was abandoned after two safety analyses had not supported this hypothesis.
Some imbalances were observed in baseline values but the differences in absolute numbers were small and appeared unlikely to be relevant with regards to the primary endpoint and haematoma expansion. Although bleeding locations that are associated with worse prognosis (e.g. intraventricular, brainstem, basal ganglia) were more frequently present in the PCC-group, this did not affect the overall better outcomes in the PCC-group. Finally, the number of recruiting centres was small and one centre enrolled a large number of patients, thus possibly limiting the generalizability of our findings. A sensitivity analysis for the influence of the centres revealed no influence.

In conclusion, the significantly faster effect of four-factor PCC on anticoagulation reversal compared to FFP corresponded to decreased early HE at three and 24 hours, and a lower rate of early death in the PCC-group. This trial lends biological plausibility to the concept that rapid and effective anticoagulation reversal reduces HE in VKA-ICH.

Date of report: February 04th, 2016

Signatures

The present synopsis of trial results was subject to critical review and has been approved in the present version by the persons undersigned.

Prof. Dr. Thorsten Steiner
Name in Blockletters

05.02.2016
Date and Signature Coordinating Investigator