



Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial

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Summary

Background Haematoma expansion is a major cause of mortality in intracranial haemorrhage related to vitamin K antagonists (VKA-ICH). Normalisation of the international normalised ratio (INR) is recommended, but optimum haemostatic management is controversial. We assessed the safety and efficacy of fresh frozen plasma (FFP) versus prothrombin complex concentrate (PCC) in patients with VKA-ICH.

Methods We did an investigator-initiated, multicentre, prospective, randomised, open-label, blinded-endpoint trial. Patients aged at least 18 years with VKA-ICH who presented within 12 h after symptom onset with an INR of at least 2·0 were randomly assigned (1:1) by numbered sealed envelopes to 20 mL/kg of intravenous FFP or 30 IU/kg of intravenous four-factor PCC within 1 h after initial cerebral CT scan. The primary endpoint was the proportion of patients with INR 1·2 or lower within 3 h of treatment initiation. Masking of treatment was not possible, but the primary analysis was observer masked. Analyses were done using a treated-as-randomised approach. This trial is registered with EudraCT, number 2008-005653-37, and ClinicalTrials.gov, number NCT00928915.

Findings Between Aug 7, 2009, and Jan 9, 2015, 54 patients were randomly assigned (26 to FFP and 28 to PCC) and 50 received study drug (23 FFP and 27 PCC). The trial was terminated on Feb 6, 2015, after inclusion of 50 patients after a safety analysis because of safety concerns. Two (9%) of 23 patients in the FFP group versus 18 (67%) of 27 in the PCC group reached the primary endpoint (adjusted odds ratio 30·6, 95% CI 4·7–197·9; $p=0\cdot0003$). 13 patients died: eight (35%) of 23 in the FFP group (five from haematoma expansion, all occurring within 48 h after symptom onset) and five (19%) of 27 in the PCC group (none from haematoma expansion), the first of which occurred on day 5 after start of treatment. Three thromboembolic events occurred within 3 days (one in the FFP group and two in the PCC group), and six after day 12 (one and five). 43 serious adverse events (20 in the FFP group and 23 in the PCC group) occurred in 26 patients. Six serious adverse events were judged to be FFP related (four cases of haematoma expansion, one anaphylactic reaction, and one ischaemic stroke) and two PCC related (ischaemic stroke and pulmonary embolism).

Interpretation In patients with VKA-related intracranial hemorrhage, four-factor PCC might be superior to FFP with respect to normalising the INR, and faster INR normalisation seemed to be associated with smaller haematoma expansion. Although an effect of PCC on clinical outcomes remains to be shown, our data favour the use of PCC over FFP in intracranial haemorrhage related to VKA.

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Introduction

Intracranial haemorrhage related to vitamin K antagonists (VKA-ICH) is responsible for up to 36% of bleeding-associated deaths during long-term anticoagulation.^{1,2} The incidence of VKA-ICH was between 0·33% and 0·85% per year in randomised controlled trials of warfarin versus non-VKAs,^{3–6} and as high as 1·9% in a cohort study.⁷ Haematoma expansion remains a major cause of mortality, occurring in 36–54% of patients with VKA-ICH, most frequently in the first few hours after haemorrhage onset.^{1,8}

Since VKAs lead to the depletion of coagulation factors II, VII, IX, and X, repletion of coagulation factors using fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC; three or four factor) might normalise coagulation and prevent haematoma expansion. Only

two randomised trials have compared PCC and FFP for urgent VKA reversal.^{9,10} Findings from both trials suggest superiority of PCC regarding international normalised ratio (INR) reversal and effective haemostasis. However, only a few patients in these trials had VKA-ICH or were in need of VKA reversal before urgent neurosurgical intervention. In a retrospective international study in 2015, no difference in mortality between FFP and PCC in VKA-ICH was found.¹¹ Four-factor PCC might be superior to three-factor PCC for INR reversal, but only two retrospective studies have directly compared both PCC types and data from prospective randomised trials are absent.^{12,13}

In the absence of evidence from randomised controlled trials specifically of VKA-ICH, treatment guidelines recommend using PCC or FFP on the basis of plausibility

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Research in context

Evidence before this study

No evidence from randomised controlled trials on management of intracranial haemorrhage related to vitamin K antagonists (VKA-ICH) was available when this trial was started in 2009. We did a broad literature search without language restrictions between 1966 and Nov 30, 2015, in MEDLINE, the Cochrane Library, and ClinicalTrials.gov using the terms “randomized controlled trial”, “prothrombin complex concentrate”, and “fresh frozen plasma” as subject headings and text words. We found one systematic Cochrane review published in 2015 and one randomised controlled trial published later the same year. The Cochrane review contained all data from six data banks from 1950 to 2014 on trials of prothrombin complex concentrate (PCC) versus fresh frozen plasma (FFP) and on PCC versus other haemostatic drugs as well as data from four randomised controlled trials. The Cochrane review investigators concluded that evidence from available randomised controlled trials did not support superiority of FFP or PCC, and that both treatments might cause serious adverse events. All included trials had a high risk of bias and were underpowered to detect an effect on mortality. The randomised controlled trial from 2015 compared FFP and a four-factor PCC for emergency

reversal of VKAs in patients with the need for urgent surgery or other procedures (n=181). However, only two patients needing a neurosurgical procedure were enrolled, limiting the relevance for the management of patients with VKA-ICH.

Added value of this study

Previous observational trials yielded controversial results regarding the clinical effectiveness of FFP and PCC in VKA-ICH, and a previous randomised controlled trial in major bleeding was not designed to address specific aspects such as intracranial haemorrhage and haematoma enlargement in patients with ICH. Our trial is the first randomised controlled trial to compare anticoagulation reversal with FFP or PCC in patients with ICH specifically. In addition to showing more rapid INR normalisation in patients treated with PCC, faster anticoagulation reversal was associated with reduced early intracranial haematoma expansion.

Implications of all the available evidence

Although an effect of the modification of early intracranial haematoma on clinical endpoints remains to be shown in a phase 3 trial, our findings support the notion of rapid anticoagulation reversal in VKA-ICH with PCC treatment.

or refrain from making any recommendations.^{14,15} In this trial, we compared the safety and efficacy of FFP and four-factor PCC in patients with VKA-ICH in the acute phase.

Methods

Study design and participants

We did an investigator-initiated, multicentre, prospective, randomised, open-label, blinded-endpoint trial (PROBE design). The trial protocol has been described in detail previously.¹⁶ Patients aged at least 18 years who had ICH (ie, intracerebral or subdural) diagnosed by cerebral CT scanning within 12 h of the onset of symptoms or after they were last seen well, who were receiving VKA treatment, and whose INR at admission was at least 2.0 were eligible for inclusion. Exclusion criteria were traumatic or secondary ICH (eg, due to vascular malformations, transformation of cerebral infarction, cerebral venous thrombosis, tumour, haemophilia, or other coagulopathies), Glasgow Coma Score of 5 or lower, concurrent acute ischaemic events, congestive heart failure (to prevent cardiac decompensation by fluid overload in the FFP group), thrombotic events within the past 30 days, liver failure (Child-Pugh score C), and moderate-to-severe pre-morbid disability (ie, Modified Rankin Scale [mRS] score >2). Patient recruitment took place in certified stroke centres in Germany with experience in the treatment of VKA-ICH (five centres were initially invited to participate); the German Stroke Society has developed and published certification criteria for stroke units and oversees the certification process.

The trial was done according to good clinical practice and was consistent with the principles stated in the Declaration of Helsinki in 1964 and subsequent revisions. The trial protocol was approved by the competent legal authority (Paul-Ehrlich-Institute, Langen, Germany), a central medical ethics committee (reference number AFmu-344/2008), and the local ethics committees of each participating centre. No changes to the protocol were made since the start of the trial. Written informed consent was obtained from the patient or the patient's legal representative before trial participation.¹⁷

Randomisation and masking

Patients were randomly assigned (1:1) to 20 mL/kg of intravenous FFP (after blood group typing or by using AB group plasma supplied by local transfusion units) or 30 IU/kg of intravenous four-factor PCC (Octaplex, Octapharma, Lachen, Switzerland). The allocation sequence was implemented with a randomisation list computer generated at the Coordination Centre for Clinical Trials at Heidelberg University Hospital (Heidelberg, Germany). The randomisation list linked sequential numbers to treatment codes allocated at random in site-stratified blocks of varying length (four, six, eight, and ten, with a probability 0.25 each) using a customised R program. The person responsible for generation of the randomisation list was independent of all other trial procedures. Because of the emergency situation and the need to randomise without delay, every site was provided with a sufficient number of closed, non-transparent envelopes containing treatment allocation.

For the **study protocol** see <http://wso.sagepub.com/content/6/3/271.full>

For the **German Stroke Society** see <http://www.dsg-info.de>

Each envelope had an individual randomisation number on the outside. The investigators were instructed to assign the patient according to the envelope with the lowest randomisation number.

Masking of treatment was not possible because of the different appearance of the two products and study drug preparation at bedside. The trial was observer masked for all laboratory data, including the primary endpoint, and for neuroradiological and clinical outcome assessments.

Procedures

Infusion of haemostatic drugs was intended to be started within 1 h after diagnostic cerebral CT. The speed of the infusion was as fast as the condition of the patient would allow. All patients also received 10 mg of intravenous vitamin K (appendix). Patients with an INR greater than 1.2 at 3 h after the start of treatment received PCC as a rescue treatment.

Image analyses were done on a Siemens Leonardo VD10B Syngo Workstation (Version VX49B, OS: WinNT 5.1 SP1, Siemens Healthcare, Erlangen, Germany) by an experienced radiologist (JK) who was masked to clinical data. Blood volume in each patient and in each CT scan (baseline, 3 h, 24 h, and 72 h) was measured separately for supratentorial and infratentorial brain regions, and

automatically by setting the required minimum Hounsfield unit to +45 and the maximum to +90. In case of intraventricular haemorrhage, blood volume was manually segmented on each slice (by JK).

The trial was monitored by an independent data safety and monitoring board (DSMB). Working procedures of the DSMB were prespecified in a DSMB charter. The DSMB had access to all safety endpoints and were masked to the primary endpoint.

Outcomes

The primary endpoint was the effect of the investigational product on anticoagulation reversal, measured as the proportion of patients with an INR of 1.2 or lower at 3 h after the start of treatment. If the primary endpoint was not reached, additional PCC was prescribed as per the protocol (appendix).

Secondary clinical endpoints were death and haematoma expansion by day 90 after start of treatment; mRS score¹⁸ and National Institute of Health Stroke Scale¹⁹ on day 15 (or discharge if earlier); day 90 mRS, Barthel Index²⁰ and Extended Glasgow Outcome Scale by telephone interview;²¹ quality of life at day 90, assessed by the EQ-5D self-report questionnaire;²² and time until INR 1.2 or lower. In an exploratory analysis, we assessed feasibility of application of the two reversal strategy treatments by measurement of time from onset to baseline cerebral CT, time from baseline cerebral CT to start of treatment, and duration of infusion (min).

Prespecified secondary imaging outcomes were the adjusted difference in absolute change in haematoma volume and relative haematoma growth defined as at least 15% changes, at 3 h and 24 h. Relative haematoma growth of at least 33% with respect to baseline was also analysed because previous trials on spontaneous ICH had used this threshold.^{23–25} Planimetric measuring procedures were predefined in a specific imaging protocol and related to all subtypes of bleeding.

Safety endpoints, including adverse events and serious adverse events, were recorded and assessed by the investigators throughout the trial until day 90. Thromboembolic events of special interest—myocardial infarction, ischaemic stroke, pulmonary embolism, and deep vein thrombosis—were prespecified according to international recommendations.^{26–29} All serious adverse events were forwarded to a medical expert for assessment of relatedness to the study drug treatment.

Statistical analysis

The null hypothesis was that FFP and PCC are equally effective in normalising the INR to 1.2 or lower within 3 h after the start of treatment. We calculated that 64 participants were needed to successfully reject the two-sided null hypothesis of independence using a χ^2 test at the prespecified level α of 0.05, with a probability $1-\beta$ of 0.8, assuming that the proportion of INR normalisation was 0.9 in the PCC group and 0.6 in the FFP group,

See Online for appendix

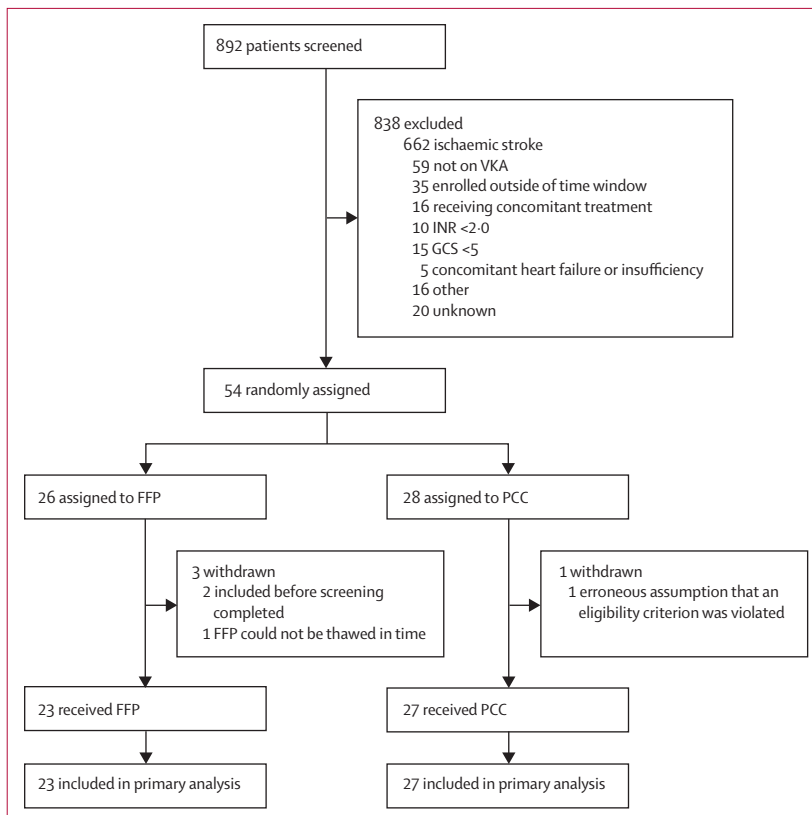


Figure 1: Trial profile

VKA=vitamin K antagonist. INR=international normalised ratio. GCS=Glasgow Coma Score. FFP=fresh frozen plasma. PCC=prothrombin complex concentrate.

amounting to a probability difference of 0.3. We increased the sample size to 74 to account for a dropout rate of 7%.

We did safety analyses after the enrolment of 24 and 50 patients upon the request of the competent legal authority (Paul-Ehrlich-Institute), to check for an association between blood pressure and haematoma growth (appendix). No unmasking of investigators or outcome assessors was needed and the primary endpoint was not included in the safety analyses.

We used a Wald test in a logistic regression model (including treatment site and baseline INR [values higher than 4.6 set to 4.6] along with treatment group) to assess the treatment effect on the primary endpoint.³⁰ All tests were two-sided and p values of less than 0.05 were deemed significant. We modelled the mRS score after 15 days and 90 days using a Cox proportional odds model for shift analysis. We generated the CI for the linear difference and shift odds ratio using Wald approximations. Haematoma volumes were replaced by the highest preceding measurement from the same patient if the patient died or had haematoma reduction surgery before the planned cerebral CT.

We did parameter tests in logistic regression models for binary outcomes and linear regression models for outcomes on the interval scale, and the log-rank test for time-to-event outcomes. Where appropriate, we included the baseline value of the response parameter and study site as explanatory variables for an adjusted analysis. p values and CIs were not corrected for multiplicity and should be interpreted with appropriate caution.

As a sensitivity analysis, we followed an intention-to-treat approach for all randomly assigned patients using multiple imputation for INR values missing at baseline and 3 h. All other analyses were done using a treated-as-randomised approach, defined as all patients who received the randomised treatment, regardless of protocol violations. In these analyses, we used worst observation carried forward for imputation in 24 h haematoma expansion, whereas we used complete case analysis for all other analyses.

This trial is registered with EudraCT, number 2008-005653-37, and ClinicalTrials.gov, number NCT00928915.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Aug 7, 2009, and Jan 9, 2015, 54 patients were randomly assigned (26 to FFP and 28 to PCC). Four patients were withdrawn by the site investigator immediately after randomisation and before the beginning of infusion (appendix), leaving 50 who received study

drug (23 FFP and 27 PCC; figure 1). No data were recorded for the four excluded patients by local investigators. A sensitivity analysis showed no effect of these exclusions on the primary endpoint (appendix). The trial was

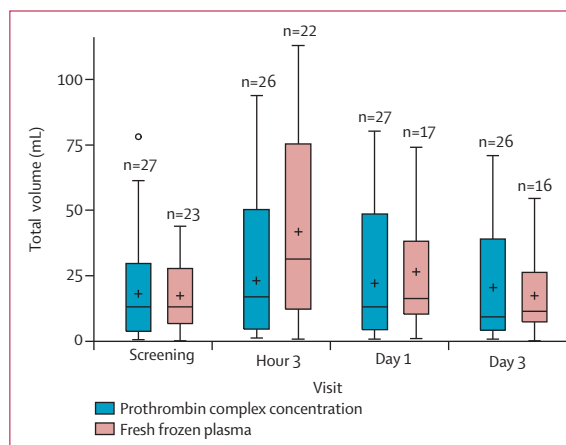


Figure 2: Volume of intracranial haematoma at different timepoints according to treatment group

Numbers are patients who received cerebral CT at each timepoint. +=group mean. Circle shows outlier.

	Fresh frozen plasma (n=23)	Prothrombin complex concentrate (n=27)
Mean age (years)	76.6 (7.6)	74.7 (8.7)
Sex		
Female	8 (35%)	11 (41%)
Male	15 (65%)	16 (59%)
International normalised ratio	3.26 (1.22)	2.83 (0.68)
Mean systolic blood pressure (mm Hg)	178 (21)	165 (37)
Mean diastolic blood pressure (mm Hg)	97 (18)	88 (25)
Median haematoma volume (mL)	13.2 (0.2–43.9)	13.0 (0.6–78.1)
Mean body-mass index (kg/m ²)	26.9 (4.3)	25.9 (3.9)
Diabetes	6 (26%)	4 (15%)
Hypertension	21 (91%)	24 (89%)
Myocardial infarction	5 (22%)	3 (11%)
Atrial fibrillation	20 (87%)	17 (63%)
Clinical status at baseline		
Premorbid Modified Rankin Scale score	4 (0–5)	4 (1–5)
National Institutes of Health Stroke Scale score	7 (2–19)	10 (0–22)
Glasgow Coma Score	15 (10–15)	13 (9–15)
Site of haematoma		
Basal ganglia	12 (52%)	13 (48%)
Thalamus	0 (0%)	1 (4%)
Lobar	7 (30%)	4 (15%)
Brainstem	1 (4%)	3 (11%)
Intraventricular	0 (0%)	2 (7%)
Cerebellar	1 (4%)	0 (0%)
Subdural	2 (9%)	4 (15%)
Time from onset to baseline cerebral CT (min)	202 (152)	199 (160)

Data are mean (SD), number (%), or median (range).

Table 1: Demographics and baseline clinical characteristics

	Fresh frozen plasma (n=23)	Prothrombin complex concentrate (n=27)	Treatment effect (95% CI)	p value
Primary outcome				
INR \leq 1.2 within 3 h	2 (9%)	18 (67%)	OR 30.6 (4.7 to 197.9)*	0.0003
Secondary clinical outcomes				
Deaths at day 90	8 (35%)	5 (19%)	No proportional hazard assumed	0.14†
Functional independence (mRS score 0–3)				
At day 15 or discharge	7 (30%)	7 (26%)	OR 2.3 (0.5 to 13.1)*	0.31
At day 90	9 (39%)	10 (37%)	OR 1.7 (0.4 to 6.8)*	0.47
NIHSS score at day 15 or discharge	10.9	12.2	-1.9 (-8.3 to 4.4)‡	0.53
Barthel index at day 90	52.5 (40.3)	70.0 (37.7)	-16.0 (-44.9 to 12.8)‡	0.27
Quality of life at day 90§	8.21	9.25	-0.7 (-5.6 to 4.2)‡	0.78
Extended Glasgow Outcome Scale at day 90	4.60	4.18	0.39 (-0.84 to 1.63)‡	0.52
Secondary imaging outcomes				
Time until INR \leq 1.2 normalisation of INR (min)	1482 (1335–1610)	40 (30–1610)	No proportional hazard assumed	0.050†
Imaging data at 3 h¶				
Haematoma expansion (mL)	23.7 (28.4)	9.7 (20.9)	16.9 (2.5 to 31.3)‡	0.023
\geq 15% growth	16/22 (73%)**	15/26 (58%)**	OR 2.0 (0.6 to 7.3)*	0.29
\geq 33% growth	13/22 (59%)**	12 (44%)**	OR 3.8 (1.1 to 16.0)*	0.048
Imaging data at 24 h				
Haematoma expansion (mL)	22.1 (27.1)	8.3 (18.3)	16.4 (2.9 to 29.9)‡	0.018
\geq 15% growth or death	14/20 (70%)††	12/27 (44%)	OR 3.9 (1.0 to 17.6)*	0.044
\geq 33% growth or death	12/20 (60%) ††	8/27 (30%)	OR 4.8 (1.3 to 20.4)*	0.024
Secondary exploratory outcomes				
Time from onset to baseline CCT (min)	202 (152)	199 (160)	-6 (-98 to 90)‡	0.90
Time from baseline CCT to start of treatment (min)	80 (33)	59 (20)	26 (13 to 39)‡	0.0002
Duration of infusion (min)	129 (69)	34 (31)	103 (75 to 130)‡	<0.0001

Data are number, median (IQR), or mean (SD). INR=international normalised ratio. mRS=Modified Rankin Scale. NIHSS=National Institute of Health Stroke Scale. OR=odds ratio. CCT=cerebral CT. *Obtained using logistic regression analysis including treatment group, baseline value of outcome and site as explanatory variables. †Log-rank test. ‡Obtained using linear regression analysis including treatment group, baseline value of outcome and site as explanatory variables. §Assessed by EQ-5D self-report questionnaire. ¶Two cerebral CTs (one in each group) were not done at the 3 h timepoint. ||Change in mean volume between baseline and follow-up cerebral CT. **One patient in each group had no CT taken. ††Three patients in the fresh frozen plasma group were unavailable for analysis because of poor general condition, inability to undertake cerebral CT, or use of magnetic resonance tomography instead of cerebral CT.

Table 2: Outcomes

terminated on Feb 6, 2015, after the inclusion of 50 patients after the second safety analysis on the request of the competent legal authority because of weak evidence of more pronounced haematoma expansion in the FFP than in the PCC group (figure 2). The DSMB had favoured continuation of the trial.

The mean age of patients was 75.6 years and 19 (38%) were women. Table 1 and the appendix list baseline values. Some baseline characteristics seemed to differ between groups; haematoma volumes seemed to be higher and more haematomas seemed to be located in the brainstem and within the ventricles in the PCC group than in the FFP group. Recruitment of patients took place in six of eight centres (appendix). Two centres did not recruit because of a short timeframe between site initiation and study termination. One of these centres also had a change in the referral system such that patients were not able to be enrolled quick enough.

Two (9%) of 23 patients in the FFP group and 18 (67%) of 27 in the PCC group had an INR of 1.2 or lower within

3 h (adjusted odds ratio 30.6, 95% CI 4.7–197.9; $p=0.0003$; table 2).

Haematoma expansion at 3 h was higher in the FFP than in the PCC group (adjusted difference 16.9 mL, 95% CI 2.5–31.3; $p=0.023$; table 2). Death or haematoma expansion of at least 15% expansion from baseline at 3 h occurred in 16 (73%) of 22 patients in the FFP group and 15 (58%) of 26 in the PCC group (adjusted odds ratio 2.0, 95% CI 0.6–7.3; $p=0.29$). In three patients who died before 24 h, the highest haematoma value on previous cerebral CT was carried forward. At 24 h, the adjusted difference in haematoma expansion was 16.4 mL (95% CI 2.9–29.9; $p=0.018$), and haematoma expansion of at least 15% had occurred in 14 (70%) of 20 patients with cerebral CT available (reasons for missing values are reported in table 2), and 12 of 27 in the PCC group (all surviving to 24 h; adjusted odds ratio 3.9, 95% CI 1.0–17.6; $p=0.044$).

At day 90, eight (35%) of 23 patients in the FFP group and five (19%) of 27 in the PCC group had died ($p=0.14$; figure 3; table 2). Five deaths in the FFP group were due to haematoma expansion as assessed by local

investigators; these five deaths occurred within the first 48 h. No patient in the PCC group had fatal haematoma expansion. The remaining three deaths in the FFP group were classified as sequelae from initial ICH, but not from haematoma expansion. In the PCC group, the first death occurred on day 5 and was due to cardiac arrest. At 90 days, the median mRS score was four (IQR 2–6) in the FFP group and four (3–5) in the PCC group.

43 serious adverse events occurred in 26 patients: 20 events in the FFP group and 23 in the PCC group (table 3). Six serious adverse events were judged to be FFP related (four cases of haematoma expansion, one anaphylactic reaction, and one ischaemic stroke) and two PCC related (ischaemic stroke and pulmonary embolism). No case of fluid overload was reported after either treatment. Three of nine thromboembolic events occurred within the first 3 days after the start of treatment (two ischaemic strokes, one in each group) and one pulmonary embolism in the PCC group). All other thromboembolic events occurred 12 days or later after the start of investigational treatment.

In a post-hoc analysis, 30 min after the start of drug infusion, 17 (65%) of 26 patients in the PCC group and none of 19 in the FFP group had an INR of 1.2 or lower (appendix).

Discussion

Our findings in the INCH trial suggest that PCC is better than FFP in normalising the INR within 3 h. Furthermore, haematoma expansion at 3 h and 24 h was significantly less extensive in patients treated with PCC than with FFP. The five deaths within the first 48 h were related to haematoma expansion and occurred exclusively in the FFP group, and three patients died within 24 h. This finding suggests that haematoma expansion is an acute phenomenon and leads to death if not treated immediately. We did not identify a difference in clinical endpoints at day 90, but the trial was not designed for this endpoint, because it involved early rescue treatment with PCC in both groups after 3 h.³¹

Despite the introduction of novel oral anticoagulants, which carry a substantially lower risk of ICH,^{3–6} VKA-ICH is likely to remain a great challenge for the foreseeable future, because VKAs are still frequently prescribed in many countries for stroke prevention in atrial fibrillation and remain indispensable for other indications.³² We chose FFP as a comparator to PCC because both drugs are routinely used in many countries despite a preference for PCC in some guidelines.^{14,15} We defined normalisation of the INR as the primary endpoint in INCH to achieve a feasible sample size in this challenging disorder. The primary endpoint was measured at 3 h to allow sufficient time for administration of FFP, which requires high-volume infusion, group typing, and FFP thawing. Despite choosing the 3 h timepoint and despite optimising the organisational delivery of FFP in the trial, most patients in the FFP group did not reach INR

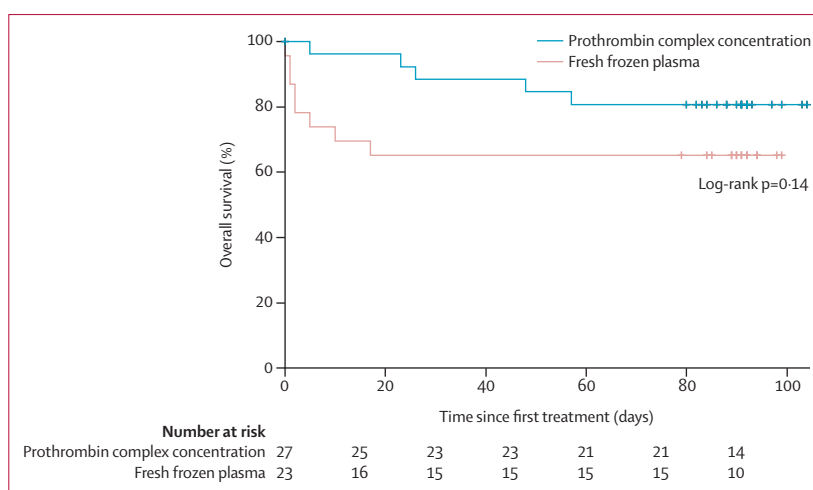


Figure 3: Kaplan-Meier survival curve

Crosses represent censored patients.

	FFP (n=23)		PCC (n=27)	Odds ratio (95% CI)*	p value†
	FFP only (n=4)‡	FFP plus PCC (after 3 h; n=19)‡§			
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	N/A	N/A
SAE classified as haematoma expansion	2	7	7	N/A	N/A
SAE classified as haematoma expansion leading to death	2	4	1	N/A	N/A
Thromboembolic events¶					
Myocardial infarction	0	..	0	N/A	N/A
Ischaemic stroke	1	1	2	N/A	N/A
Pulmonary embolism	0	0	4	N/A	N/A
Deep vein thrombosis	0	0	1	N/A	N/A

FFP=fresh frozen plasma. N/A=not applicable. PCC=prothrombin complex concentrate. SAE=serious adverse event. *FFP plus PCC vs PCC only. †Fisher's exact test. ‡Two of 21 patients who did not reach the primary endpoint in the FFP did not receive PCC (protocol violation). §According to the protocol, patients in whom the international normalised ratio after 3 h was not below or equal to 1.2 received PCC. ¶One stroke in the FFP only group and one stroke and one pulmonary embolism in the PCC group occurred within the first 3 days after start of treatment.

Table 3: Safety outcomes

normalisation within 3 h after the start of treatment. Moreover, anticoagulation reversal using PCC might be further accelerated in routine clinical practice by using serial bedside point-of-care coagulation testing.³³

In accordance with findings from another trial of VKA reversal in other settings,⁹ our findings favour PCC over FFP in terms of speed of INR normalisation. Most patients in the FFP group (83% vs 26% in the PCC group) subsequently received PCC because the INR was not normalised at 3 h, which is likely to have accelerated anticoagulation reversal in the FFP group. Nevertheless, haematoma volumes at 24 h were smaller in the PCC group than in the FFP group. This finding supports the importance of an immediate start of treatment with high

concentrations of coagulation factors, which was also suggested in a retrospective study.⁸

Conclusions regarding safety of FFP versus PCC should be made with caution because of the small sample size. Three of four thromboembolic events occurred within the first 3 days (one in the FFP group and two in the PCC group). All other thromboembolic events occurred after 12 days and the number of events was higher in the PCC group (five events) than in the FFP group (one event). However, only one patient (in the FFP group) was anticoagulated at that time, and the high number of early deaths in the FFP group compared with the PCC group needs to be taken into consideration. An anaphylactic reaction occurred only in one patient in the FFP group.

This trial is, to our knowledge, the first randomised controlled trial of anticoagulation reversal in VKA-ICH. Compared with other types of major bleedings related to VKA, VKA-ICH is clearly defined and quantifiable in terms of haematoma size. Additionally, the INCH protocol included serial cerebral CT imaging and measures of clinical outcome. The findings of this proof-of-concept approach suggest that inability to rapidly antagonise anticoagulation effectively increases the risk of haematoma expansion and early death.

This trial has several 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 masked to treatment allocation, but main outcomes including INR values, haematoma volumes, and clinical outcomes were assessed by researchers masked to treatment allocation. Randomisation was done using envelopes because VKA-ICH is a rare event, and because of the tight protocol schedule within the emergency situation. The trial was stopped prematurely by the competent authority (Paul-Ehrlich-Institute) because of differences in haematoma expansion between the treatment groups. Since this termination was unplanned, effect of treatment on haematoma expansion might have been biased away from the null. Although the primary endpoint was never looked at during discussion with authorities, some of the bias might have carried over to the primary endpoint. The assumption that raised blood pressure favoured haematoma growth was abandoned after two safety analyses did not support this hypothesis (appendix). We noted some imbalances in baseline values, but the differences in absolute numbers were small and seemed unlikely to be relevant with regards to the primary endpoint and haematoma expansion. Although numerically more patients in the PCC than the FFP group had bleeding in locations that are associated with worse prognosis (eg, intraventricular, brainstem, or basal ganglia), this difference 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 generalisability of our findings. A prespecified sensitivity analysis revealed no effect of the centres on the primary outcome (data not shown).

The findings from our trial suggest that rapid and effective reversal of anticoagulation reduces haematoma expansion in patients with VKA-ICH.

Contributors

TS planned and organised the trial, analysed data, and wrote the manuscript. SP designed the study protocol, did the literature search, collected and interpreted data, and wrote the manuscript. MG collected and interpreted data, and reviewed the manuscript. JHü provided the biostatistical contribution to the protocol, created the randomisation lists and envelopes, provided reports to the DSMB, provided statistical advice during negotiations with the competent authority, wrote the statistical analysis plan, did the statistical analysis, and wrote the Statistical analysis section. JHa edited the pharmacovigilance section of the trial protocol, coordinated serious adverse event management and safety surveillance of the trial, provided pharmacovigilance-related interaction with regulatory bodies, interpreted the data, and proofread the manuscript. AF did the literature search, designed the study, collected and interpreted data, and reviewed the manuscript. MB did the literature search, designed the imaging portion of the study; and collected, analysed, and interpreted data. JB, HC, CD, MH, HS, KEW, and CW collected data and reviewed the manuscript. JK collected, analysed, and interpreted data, and proofread the manuscript. WH designed the study and collected and interpreted data. RV designed the study protocol, did the literature search, collected and interpreted data, and wrote the manuscript.

Steering Committee: Thorsten Steiner, Boris Invandic*, Anja Freiberger, and Johannes Hüsing. *BI left the institution before trial termination.

Declaration of interests

TS has received research grants from Octapharma, and speaker and consulting honoraria from Bayer, Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, and Daiichi Sankyo. SP has received speakers and consulting honoraria and research support from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, and Daiichi Sankyo. JHü, JHa, and AF have received research grants from Octapharma. MB has received grants from DFG, EORTC, Covidien, and Stryker; grants and personal fees from Novartis and Guerbet; and personal fees from Roche, Codman, and Bayer. RV has received speakers and consulting honoraria and research support from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, Daiichi Sankyo, CSL Behring, MorphoSys, Medtronic, Sanofi, St Jude Medical, and Apoplex Medical technologies. MG, JB, HC, CD, MH, JK, HS, KEW, CW, and WH declare no competing interests.

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