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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Goldstein JN, Refaai MA, Milling TJ Jr, et al. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial. *Lancet* 2015; published online Feb 27. http://dx.doi.org/10.1016/S0140-6736(14)61685-8.

Appendix

Biased coin randomisation method[1]

Patients were assigned to treatment groups using a biased coin randomisation technique based on the method of minimisation [see, for example, Pocock 1975].[1] Using this approach, the goal was to balance the treatment groups with respect to centre, urgent surgical and urgent invasive procedure (but not on the combination of these simultaneously). As each patient was entered into the study, the randomisation was adapted to reflect the under-represented treatment group as a function of those three variables. As a result, the randomisation was offset from the usual 50:50 to favour the under-represented group. This methodology ultimately allowed for treatment balance within each of the individual stratification variables.

Inclusion/exclusion criteria

Inclusion criteria

- Male and female patients ≥18 years of age
- Patients currently on oral VKA therapy
- Patients requiring an urgent surgical or urgent invasive procedure* within 24 hours of the start of the IMP
- Indication for withdrawal of oral VKA therapy and infusion of plasma to reverse the VKA effect, due to the nature of the procedure
- INR ≥2 within 3 hours before start of IMP
- Informed consent obtained

Exclusion criteria

- Patients requiring urgent surgical procedures where, according to the surgeon's clinical judgment, an accurate estimate of blood loss was not possible (e.g., ruptured aneurysm)
- Patients for whom administration of IV vitamin K and VKA withdrawal, alone, can adequately correct the patient's coagulopathy before initiation of the urgent surgical procedure
- Administration of IV vitamin K more than 3 hours before, or administration of oral vitamin K more than 6 hours before, the infusion of IMP
- Patients in whom lowering the INR to within the normal range may have presented an unacceptable risk for a thromboembolic complication where the INR goal is to lower, but not normalise, the INR because of risk of procedure-associated stroke
- Patients who, despite medical management that includes close monitoring and diuretics, may not, by Investigator assessment, tolerate the total volume of IMP required by the protocol
- Expected need for additional nonstudy blood products before the infusion of IMP (Note: Administration of PRBCs was not an exclusion criterion)
- Expected need for platelet transfusions or desmopressin before day 10
- Acute trauma for which reversal of VKAs alone would not be expected to control or resolve an acute bleeding complication and/or control the acute bleeding event
- Use of unfractionated or low molecular weight heparin within 24 hours before randomisation or potential need before completion of procedure
- Patients with a history of TEE, MI, unstable angina pectoris, critical aortic stenosis, CVA, TIA, severe peripheral vascular disease, or disseminated intravascular coagulation within 3 months of enrolment
- Patients in whom reversal of VKA therapy alone may not have resolved coagulopathy (e.g., patients receiving a potent antiplatelet agent [such as clopidogrel or prasugrel] or those with advanced liver disease)
- Patients with a known history of antiphospholipid antibody syndrome or lupus anticoagulant antibodies
- Suspected or confirmed serious viral or bacterial infection (e.g., meningitis or sepsis at time of enrolment)
- Administration of whole blood, plasma, plasma fractions or platelets within 2 weeks before inclusion into study (Note: Administration of PRBCs was not an exclusion criterion)
- Pre-existing progressive fatal disease with a life expectancy of less than 2 months
- Known inhibitors to coagulation factors II, VII, IX, or X; hereditary protein C or protein S deficiency; or heparin-induced type II thrombocytopenia
- Treatment with any other IMP within 30 days prior to inclusion into the study
- Presence or history of hypersensitivity to components of study product
- Pregnant or breastfeeding women
- Prior inclusion in study or any other CSL Behring-sponsored 4F-PCC study
- For patients with ICH:
  - GCS <10
  - mRS score >3 prior to ICH
  - Intracerebral haemorrhage
  - Epidural haematomas
  - Infratentorial haemorrhage
  - Patients with SAH with a Hunt and Hess Scale >2[2]
  - Subdural haematomas that:
    - were judged to be an acute subdural haematoma (based on neurosurgeon review)
    - had a concurrent SAH or parenchymal contusion

*Enrolment of patients requiring an urgent invasive procedure was halted following protocol amendment 3.0 (07-Sep-2011). 4F-PCC, four-factor prothrombin complex concentrate; CVA, cerebrovascular accident; GCS, Glasgow coma score; ICH, intracranial haemorrhage; IMP, investigational medicinal product; INR, international normalised ratio; IV, intravenous; MI, myocardial infarction; mRS, modified Rankin scale; PRBCs, packed red blood cells; SAH, subarachnoid haemorrhage; TEE, thromboembolic event; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

Exploratory endpoints for future analyses

- Response and *in vivo* recovery: The classical and incremental in-vivo recovery (IVR) for each component was obtained from the maximum plasma level within 3 hours after administration of study product.
- Time to INR correction from randomisation: summarised per treatment group in life-tables and respective Kaplan–Meier survival-time graphs with log-rank p-values
- Intraoperative haemostasis by surgeon or performing physician: The surgeon's or performing physician's assessments of the patient's intraoperative haemostasis immediately after the end of the urgent surgical procedure (normal, mildly abnormal, moderately to severely abnormal) was tabulated by treatment group and category, as counts and as frequencies
- Use of non-study prescribed blood products (except PRBCs) and non-study haemostatic agents from randomisation to 24 hours after start of infusion (or until the end of the urgent surgical procedure, whichever comes later)
- Transfusion of red blood cells: Transfusion of red blood cells (PRBCs and whole blood) assessed for the time period from the start of study product administration to 24 h from the start of the administration (or until the end of surgery, whichever is later)
- 45-day all-cause mortality: Summarised by treatment group in tables, including the number and percentage of deaths. A possible difference between treatment groups was estimated by a risk ratio with 95% confidence interval. In addition, the survival times were summarised by treatment group using Kaplan–Meier plots with log rank p-value
- Difference in actual and estimated blood loss: summarised by treatment group, stratified by the type of surgery
- Estimates of actual blood loss: assessed via ANCOVA with ABL as the response variable and treatment group and type of surgery or procedure as explanatory variables
- Decrease in INR from infusion start: proportion of subjects in each treatment group, stratified by type of surgery, who achieve INR $\leq 1 \cdot 3$ at $0 \cdot 5$ h after the start of study product infusion
- Neurological outcome assessment for ICH subjects - Modified Rankin Scale: assessed at baseline (prior to randomisation) at 24 h, at time of hospital discharge, and at study Day 45
- Newly prescribed diuretics: total mg of diuretics administered within 24 hours of start of study product infusion, by treatment group and stratified by type of surgery
- Volume of wound drainage: total volume of wound drainage (sanguineous or serosanguineous)
- Treatment-emergent wound haematomas: rates were compared between treatment groups using the Fisher Exact test. Confidence intervals of the rates and difference in rates were also provided
- Change in haemoglobin value: The change in haemoglobin value from pre-infusion to lowest haemoglobin value during the 24 hours after the end of the surgical/invasive procedure was analysed by ANCOVA with treatment as factor and pre-infusion haemoglobin value as covariate
- Proportion of patients with decreased INR (i.e., INR $\leq 1 \cdot 3$) at 1, 3, 6, and 24 hours from the start of infusion (only utilising results obtained pre-operatively).

List of surgeries and procedures (ITT-E population)

Category	Procedure	4F-PCC (N=87)	Plasma (N=81)
Orthopaedic	**Total**	**31**	**21**
	Hip	16	7
	Lower extremity	12	11
	Upper extremity	3	3
Gastrointestinal	**Total**	**21**	**27**
	Cholecystectomy	6	13
	Hernia repair	7	3
	Laparoscopy/laparotomy	5	3
	Appendectomy	2	5
	Other abdominal	0	3
	Gastrectomy	1	0
Invasive procedure	**Total**	**13**	**15**
	Endoscopy	5	2
	Thoracentesis	3	3
	Cystoscopy	1	2
	Laparocentesis	1	2
	Lumbar puncture	1	1
	Colonoscopy	1	0
	Radiofrequency ablation of coronary isthmus	1	0
	Angiography	0	1
	Cardiac catheterisation	0	1
	CT-guided abscess drainage	0	1
	Knee arthrocentesis	0	1
	Lung biopsy	0	1
Skin	**Total**	**11**	**8**
	Incision and drainage of abscess/haematoma	7	7
	Wound closure	3	0
	Fasciotomy	1	0
	Primary debridement	0	1
Cardiac	**Total**	**3**	**3**
	Pacemaker	2	1
	Mitral valve replacement	1	1
	Bronchoscopy	0	1
Vascular	**Total**	**2**	**3**
	Haemodialysis catheter placement	2	0
	Femoral-popliteal bypass	0	2
	Carotid endarterectomy	0	1
Maxillofacial	**Total**	**2**	**2**
	Facial reconstruction	1	1
	Periapical abscess drainage	1	0
	Dental extraction	0	1
Genitourinary	**Total**	**2**	**0**
	Orchiectomy	1	0
	Transurethral resection of prostate	1	0
Neurological	**Total**	**1**	**1**
	Subdural haematoma drainage	1	1
Gynaecological	**Total**	**0**	**1**
	Oophorectomy	0	1
Respiratory	**Total**	**1**	**0**
	Tracheostomy	1	0

4F-PCC, four-factor prothrombin complex concentrate; ITT-E, intention-to-treat efficacy.

Haemostatic efficacy and rapid INR reduction (mITT population)

Co-primary endpoint	% (n/N) of patients [95% CI]		Difference 4F-PCC minus plasma % [95% CI]
	4F-PCC	Plasma	
Effective haemostasis*	87·6 (78/89) [80·8; 94·5]	67·8 (61/90) [58·1; 77·4]	19·9 [7·7; 31·4]
Rapid INR reduction†	53·9 (48/89) [43·6; 64·3]	11·1 (10/90) [4·6; 17·6]	42·8 [29·7; 54·0]

Haemostatic efficacy and rapid INR reduction (per-protocol population)

Co-primary endpoint	% (n/N) of patients [95% CI]		Difference 4F-PCC minus plasma % [95% CI]
	4F-PCC	Plasma	
Effective haemostasis*	90·7 (78/86) [84·6; 96·8]	76·3 (58/76) [66·8; 85·9]	14·4 [3·0; 26·0]
Rapid INR reduction†	55·8 (48/86) [45·3; 66·3]	10·5 (8/76) [3·6; 17·4]	45·3 [31·5; 56·5]

*Effective haemostasis was defined as: (1) intraoperative (or intraprocedural) blood loss not exceeding predicted blood loss by 30% or 50 mL, *and* (2) "normal" or "mildly abnormal" haemostasis (surgeon assessed), *and* (3) no administration of non-study coagulation products.

†INR ≤1·3 at 0·5 hours after the end of infusion.

4F-PCC, four-factor prothrombin complex concentrate; CI, confidence interval; INR, international normalised ratio; mITT, modified intention-to-treat.

Listing of TEAEs reported in at least 5% of patients of any treatment group, by decreasing frequency (ITT-S population)

Preferred term*	4F-PCC, n (%) (N=88)	Plasma, n (%) (N=88)
Anaemia	11 (12.5)	10 (11.4)
Constipation	10 (11.4)	4 (4.5)
Hypokalaemia	7 (8.0)	8 (9.1)
Hypotension	7 (8.0)	6 (6.8)
Nausea	7 (8.0)	4 (4.5)
Oedema peripheral	6 (6.8)	6 (6.8)
Atrial fibrillation	6 (6.8)	4 (4.5)
Tachycardia	5 (5.7)	1 (1.1)
Pyrexia	3 (3.4)	5 (5.7)
Pulmonary oedema	1 (1.1)	5 (5.7)

*TEAEs are listed in descending order based on frequency in the 4F-PCC group and are coded according to the Medical Dictionary for Regulatory Activities version 12.0. TEAEs defined as adverse events reported from start of study product infusion to the reporting time window (day 10 [visit window days 7–11] for adverse events; day 45 [visit window days 43–51] for serious adverse events).4F-PCC, four-factor prothrombin complex concentrate; ITT-S, intention-to-treat safety; n (%), number (percentage) of patient reporting a TEAE; N, total number of patient in each group; TEAE, treatment-emergent adverse event.

Listing of late bleeding SAEs

Event (reported term)	Study day	Relationship to treatment	Abbreviated patient narrative
4F-PCC group (n=3)			
Respiratory failure	7	Not related	• 85-year-old male was randomised to 4F-PCC prior to laparoscopy and chest tube placement after a gunshot wound. 7 days after randomisation he developed respiratory failure with bloody secretions • The patient was not receiving anticoagulation therapy at the time of the event
Upper GI haemorrhage	5	Not related	• 71-year-old female was randomised to 4F-PCC prior to laparoscopic cholecystectomy; EGD with biopsy and ERCP with biliary sphincterotomy, papillotomy and common bile duct stone extraction were also conducted. On Day 5, she experienced upper GI bleeding, which was assessed as serious on Day 6; EGD revealed oozing at the ERCP site • The patient was receiving anticoagulation therapy at the time of the event (enoxaparin)
GI bleeding	6	Not related	• 68-year-old female was randomised to 4F-PCC prior to endocardial electrophysiological study and radiofrequency ablation of the isthmus • On Day 4, she was diagnosed with a retroperitoneal haematoma; laparotomy revealed an IVC perforation. On Day 6 he was diagnosed with haemorrhagic erosive esophagitis, erosive haemorrhagic gastroduodenitis and an ulcer of the stomach body with evidence of bleeding • The patient was receiving anticoagulation therapy at the time of the event
Plasma group (n=4)			
Persistent wound drainage	16	Not related	• 73-year-old female was randomised to plasma prior to irrigation and debridement at a total hip replacement site followed by implantation of a new hip prosthesis. 15 days later she developed "persistent wound drainage" • The patient was receiving anticoagulation therapy at the time of the event
Left subarachnoid haemorrhage, bilateral subdural haematoma/ haemorrhage	16	Not related	• 93-year-old female was randomised to plasma for open reduction and internal fixation of a right shoulder fracture. 36 days later she presented with nausea, vomiting, and headache, and was diagnosed with subdural and subarachnoid haemorrhages. The patient was withdrawn from the study on day 42 • The patient was receiving anticoagulation therapy at the time of the event (initially enoxaparin, and then warfarin)
Postoperative bleeding	3	Not related	• 81-year-old male was randomised to plasma for incarcerated right inguinal hernia repair. On day 2 post-randomisation, he experienced post-operative bleeding. The patient was then treated with vitamin K, 2 units of plasma, and 2 units of packed red blood cells • The patient was receiving anticoagulation therapy at the time of the event
Right neck haematoma	5	Not related	• 73-year-old female was randomised to plasma for right carotid endarterectomy. On Day 5 she was diagnosed with neck haematoma, which was treated with surgical neck exploration and haematoma evacuation • The patient was receiving anticoagulation therapy at the time of the event (aspirin and heparin)

"Late bleeding" was defined by the DSMB as an SAE of bleeding that occurred after the end of surgery (i.e., at time of wound closure) or procedure and within 10 days of study product infusion. The DSMB requested that late bleeding events be reviewed by the blinded SAB. A total of 7 patients experienced possible late bleeding events that were reviewed by the SAB. All of the late bleeding events were considered not related to study product by the SAB.

4F-PCC, four-factor prothrombin complex concentrate; DSMD, data and safety monitoring board; EGD, esophagogastroduodenoscopy; ERCP, endoscopic retrograde cholangiography procedure; GI, gastrointestinal; IVC, inferior vena cava; SAB, safety adjudication board; SAE, serious adverse event.

Listing of patients who died up to Day 45 (visit window Days 43–51) (ITT-S population)

Cause of death (reported term)	Study day	Age	Comfort care	Relationship to treatment (as adjudicated by the SAB)
4F-PCC group (n=3)				
GI haemorrhage	6	78	No	Not related
Intestinal obstruction	7	68	No	Not related
Worsening advanced-stage lung cancer	26	66	Yes	Not related
Plasma group (n=8)				
Cardiorespiratory arrest	6	74	No	Not related
Acute MI	8	61	No	Possible
Worsening CHF	13	85	Yes	Not related
Pulmonary embolism	16	92	No	Not related
Cardiac arrest	17	68	No	Not related
Death (unknown)	17	72	No	Not related
Septic shock	22	71	No	Not related
Tumour haemorrhage	41	62	No	Not related

Note: One additional patient (81 years of age) in the 4F-PCC group died on study day 48. The cause of death was listed 'unclear' and was recorded as most likely due to underlying cardiopulmonary disease. The event was judged to be not related to treatment. 4F-PCC, four-factor prothrombin complex concentrate; CHF, congestive heart failure; GI, gastrointestinal; ITT-S, intent-to-treat evaluable for safety; MI, myocardial infarction; SAB, safety adjudication board.

References

1 Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975; **31(1)**: 103–15.

2 Hunt WE, Hess RM. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. *J Neurosurg* 1968; **28(1)**: 14–20.