Treatment of bleeding patients during therapy with direct oral anticoagulants

Results from the French registry: GIHP-NACO

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Presents results from a registry detailing information about the management of bleeding patients in the emergency room, operating room or intensive care unit during therapy with direct oral anticoagulants.

Background

There is a large literature on the efficacy of direct oral anticoagulants (DOAC) to prevent stroke or systemic embolic events in patients with atrial fibrillation or to treat venous thromboembolism. DOAC, which include direct anti-Xa and thrombin inhibitors, have a favourable risk-benefit profile. However, as for any anticoagulant, they are associated with spontaneous or provoked haemorrhagic risk. The meta-analysis by Ruff and colleagues of trials comparing patients treated with Vitamin K antagonists (VKA) to patients treated with DOAC showed that with DOAC there were significant reductions in stroke, intracranial haemorrhage and mortality, similar to warfarin, but increased gastrointestinal bleeding.

The challenge remains to manage bleeding, emergency surgery or invasive procedures in patients treated with DOAC. Current French and European guidelines recommend use of haemostatic agents, such as prothrombin complex concentrate (PCC) and antidotes for the treatment of life-threatening bleeding associated with the use of DOAC (Albaladejo et al. 2017a; Kozek-Langenecker et al. 2017).

However, there is a lack of data and we are still trying to develop strategies to manage patients receiving DOAC who are bleeding and who need urgent surgery.

DOAC and coagulation assays

Steiner and colleagues showed that the sensitivity of usual coagulation tests to DOAC is quite variable (Steiner et al. 2013). It depends on the test and the DOAC.

For patient management in anaesthesia and critical care, we need a test that can:

1. Detect significant plasma concentration that could interfere with haemostasis.
2. Eventually attest that a reversal strategy is effective.

The mechanism of action of PCC is different to reverse the anticoagulation effects of VKA or DOAC (**Figure 1**).

In patients anticoagulated with VKA, PCC will replace the factors. In patients anticoagulated with DOAC, PCC acts by overwhelming inhibition of factor IIa or factor Xa, depending on the DOAC involved.

There are several animal studies on direct oral anticoagulants. For example, the study by Pragst and colleagues showed that with 50 IU/kg you reduce bleeding to control animals. Similar studies for apixaban or rivaroxaban have been completed.

In a study that measured thrombin generation times in healthy volunteers receiving a dose of 20 mg rivaroxaban or 150 mg dabigatran, after 2 hours a new measurement was performed for the drug effect of increasing doses of PPSB or FEIBA or rFVIIa. These showed partial or total correction, or even overcorrection (Marlu et al. 2012).

DOAC were first developed without reversal strategies, and antidotes were developed several years after DOAC were approved. Reversal agents include idarucizumab, andexanet alfa (PRT064445) and aripazine (PER977).

Pollack and colleagues (2017) in a prospective cohort study of safety and efficacy of idarucizumab in patients who had serious bleeding or needed an urgent procedure, found that 5g (2 x 2.5g administered within 15 minutes) of idarucizumab reversed the effect of dabigatran.

Lu and colleagues described an antidote for reversal of anticoagulation (Lu et al. 2013). This modified rFXa is produced in Chinese hamster ovary cells. It has no intrinsic procoagulatory effect, but it binds the direct anti-FXa inhibitors.

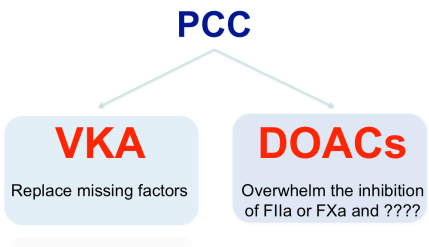


Figure 1.

DOAC direct oral anticoagulant FXa activated factor X PCC prothrombin complex concentrate VKA vitamin K antagonist

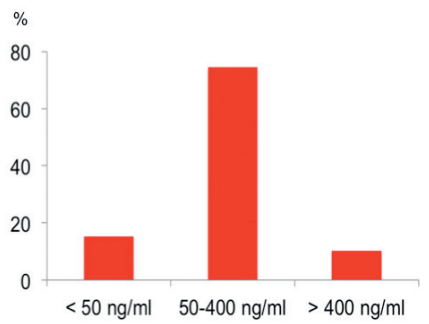


Figure 2.

Plasma concentration of DOAC on admission

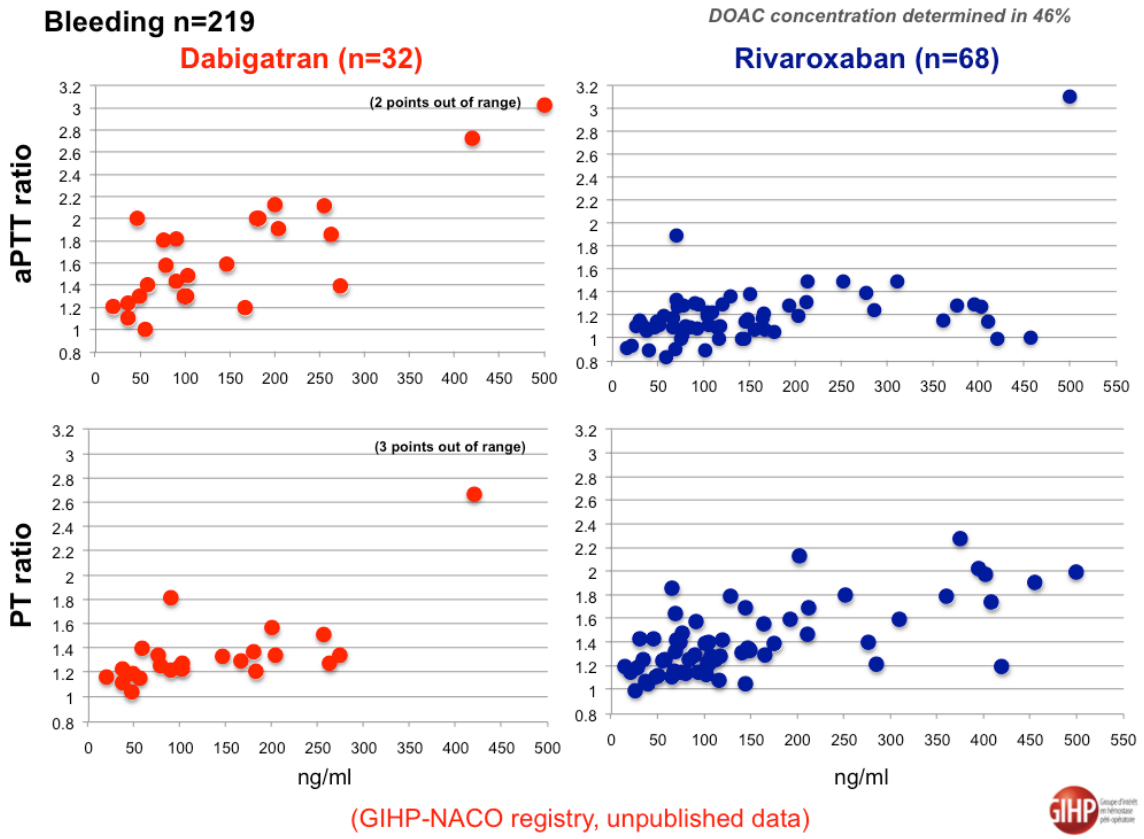


Figure 3 .

aPTT activated partial thromboplastin time DOAC direct oral anticoagulant PTT partial thromboplastin time

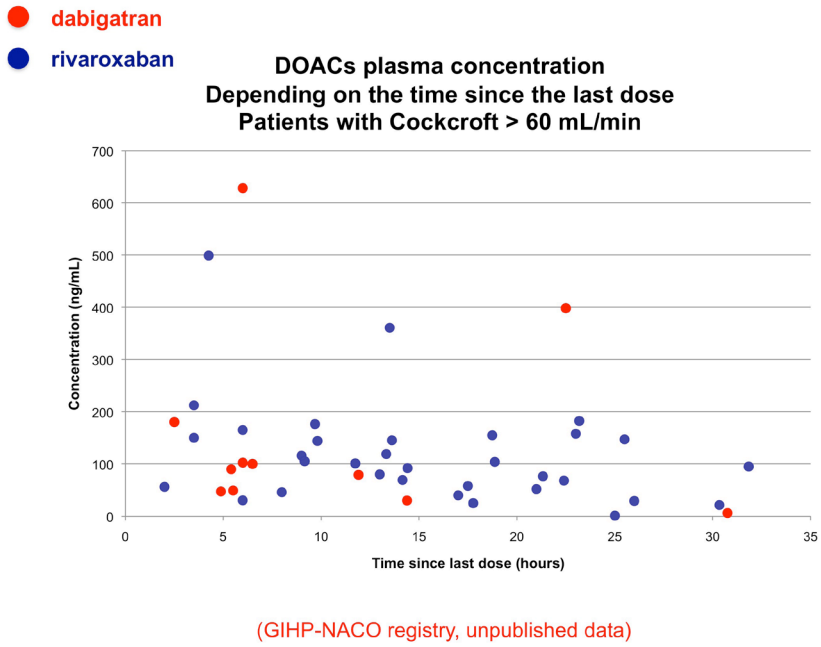


Figure 4.

An investigation of andexanet alfa for acute major bleeding associated with factor Xa inhibitors (Connolly et al. 2016) found that an initial bolus and subsequent 2-hour infusion of andexanet substantially reduced anti-factor Xa activity in patients with acute major bleeding associated with factor Xa inhibitors. Effective haemostasis occurred in 79% of the patients.

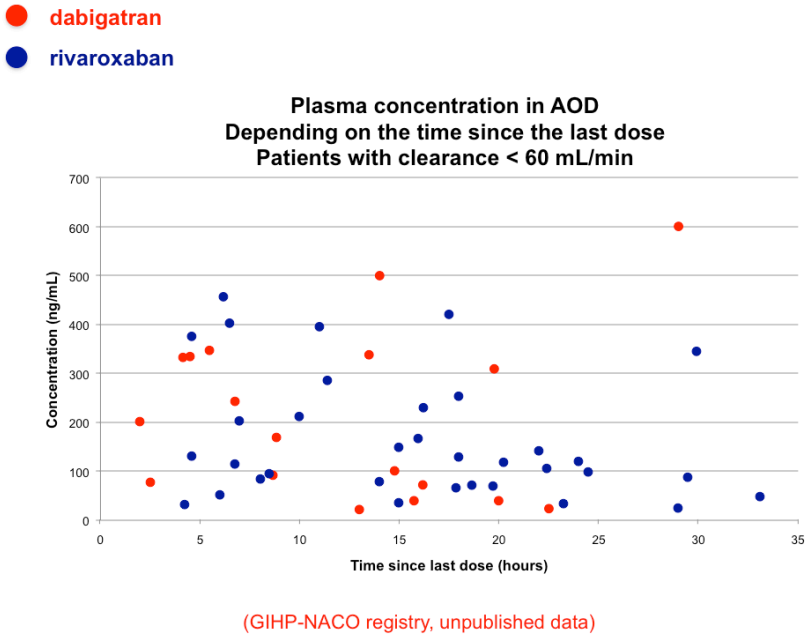
Connolly's study raises all the problems related to the use of antithrombotic antidotes:

What is the relationship between reversion and a clinical effect? How long is this reversion necessary? Is the antidote prothrombotic? And how to highlight it?

Bleeding in patients treated with DOAC

When we have a patient bleeding while treated by any anticoagulant, we must always consider the use of appropriate supportive and symptomatic treatment:

- Compression
- Surgery
- Embolisation



(GIHP-NACO registry, unpublished data)

Figure 5.

- Specific procedures
- Fluids
- Transfusion
- Clotting factors
  - Fresh frozen plasma (FFP)
  - Prothrombin complex concentrate (PCC)

Reversal strategies

After all these treatments are used, there are several options to specifically reverse either VKA or DOAC.

Alter the pharmacokinetics of the DOAC by:

a) Time

Waiting is the best antidote. Elimination half-lives are short, unless the patient has a renal dysfunction, particularly with dabigatran.

b) Antidotes

Antidotes exist for dabigatran, and are being developed for anti-Xa agents, and phase III studies are in progress for idarucizumab, for example.

c) Dialysis

This can be considered if the patient is treated with dabigatran, but it is not a simple situation.

d) Charcoal

e) Clotting factors

Administration of clotting factors should be included in local guidelines. In France we have a labelling for VKA, but it is off label to reverse DOAC.

- 4F-PCC First-line
- aPCC First- or second-line

FFP and recombinant activated clotting factor VII (rFVIIa) are not effective, or safe in this indication.

As clinicians, we have to ask: Is it efficient? Is it safe? Is it recommended in guidelines?

GIHP-NACO registry results

The GIHP (French Working Group on Perioperative Haemostasis) established a registry in June 2013 across 41 emergency centres in France and Belgium to collect data on the management of major bleeding in patients receiving DOAC (dabigatran, rivaroxaban or apixaban), who have been hospitalised for major bleeding or emergency surgery (Albaladejo et al. 2017b). The registry prospectively collected data on patient management, focusing on the use of haemostatic agents and the plasma concentration of DOAC. This registry data can be compared with data from large series treated with DOAC antidotes.

Our published results are from 35 centres, between June 2013 and November 2015 (Abaladejo et al. 2017b).

732 patients treated with

–Dabigatran (n=207)

–Rivaroxaban (n=472)

–Apixaban (n=53) and

–Severe bleeding

GI bleeding was present in 37% of patients, intracranial in 24%.

In November 2015 we analysed results from 732 mainly elderly patients, (median age: 78) and most with renal dysfunction.

On admission we took the laboratory results on plasma concentration of DOAC (**Figure 2**) (see p. I). This could be determined in 62% (452/732) of cases.

Figure 3 (see p. II) shows the relationship between activated partial thromboplastin time and prothombin time ratio and concentration of dabigatran and rivaroxaban. These results confirm the uselessness of this lab tests in these situations.

Figure 4 (see p. II) shows DOAC plasma concentration depending on time since last dose.

Figure 5 shows plasma concentration in DOAC depending on the time since the last dose in patients with clearance < 60 mL/ min.

Activated or nonactivated prothrombin complex concentrates were administered in 38% (281/732) of patients.

Table 1.

	All N=732
Transfusion n (%)	261 (35.7%)
Packed red blood cells	243 (33.2%)
Platelets	32 (4.4%)
Fresh frozen plasma	70 (9.6%)
PCC	208 (28.4%)
Total dose IU.Kg-1; median (25th-75th)	42.8 (25.0-50.0)
2nd Dose; n (%)	27 (13.0%)
aPCC	73 (10.0%)
Total dose IU.Kg-1; median (25th-75th)	46.0 (38.1-50.0)
2nd Dose; n (%)	5 (6.8%)
Recombinant Factor VIIa	0
Tranexamic acid (%)	34 (4.7%)
Haemodialysis (%)	9 (1.2%)
Mechanical means*	224 (30.7%)
Intervention for haemostasis control	175 (23.9%)
Endoscopy	97 (55.4%)
Surgery	22 (12.6%)
Embolisation	56 (32.0%)

*compression, gauze packing

aPCC activated prothrombin complex concentrate PCC prothrombin complex concentrate

Did the bleeding stop after PCC?

Table 2. Did bleeding stop after PCC?

Yes, completely	42.7%
Yes, partially	39.7%
No	17.7%

It is quite difficult with this method and in these heterogeneous patients to assess the efficacy of PCC. In this study adequacy of haemostasis was assessed by local investigators.

By day 30 mortality was 13.5%, variable according to the bleeding site. Patients were also assessed for suspected major cerebral and cardiovascular events (MACCEs) after the bleeding event (**Table 3**).

Table 3.

	All N=732
MACCE; n (%)	56 (7.6%)
Venous thromboembolism	7 (1.0%)
Ischaemic stroke	10 (1.4%)
Systemic emboli	2 (0.3%)
Myocardial infarction	10 (1.4%)
Pulmonary oedema	18 (2.5%)
Cardiogenic shock	12 (1.6%)
All causes of mortality	
n	99
% [CI 95%]	13.5% [11.0-16.2]
Mortality among patients with: % [CI 95%]	
Intracranial haemorrhage (spontaneous)	28.4% [21.1-36.6]
Head trauma	16.7% [10.0-25.3]
Gastrointestinal bleeding	12.0% [7.8-17.3]

CI confidence interval MACCE major cerebral and cardiovascular events

Conclusion

The GIHP-NACO registry study showed that plasma concentration was positively related to use of PCC. In this cohort, the mortality rates of patients with severe bleeding were similar to those observed for large series treated with DOAC antidotes. Plasma concentration could therefore be important to identify patients for whom the use or an antidote or PCC (if antidotes are not available) could be useful. ■

Conflict of Interest

Pierre Albaladejo has received research support from CSL Behring, LFB, Octapharma and Sanofi. He is on the scientific advisory board of Boehringer Ingelheim, Bayer, BMS-Pfizer and Daiichi-Sankyo and is a consultant for Boehringer Ingelheim, Bayer, BMS-Pfizer, Daiichi-Sankyo, LFB and Sanofi. He has received honoraria from Boehringer Ingelheim, Bayer, BMS-Pfizer, Daiichi-Sankyo, LFB, CSL Behring and Sanofi and travel support from CSL Behring, BBraun, Boehringer Ingelheim, Bayer, BMS-Pfizer.

Abbreviations

DOAC direct oral anticoagulant
FEIBA factor eight inhibitor bypass activity
FFP fresh frozen plasma
MACCE major cerebral and cardiovascular events
PCC prothrombin complex concentrate
PPSB prothrombin-proconvertin-Stuart factor-antihemophilic factor B
rFVIIa recombinant factor VIIa
VKA Vitamin K antagonists

Key Points

- Treat major bleeding in patients receiving DOAC with predetermined approach
- Perform laboratory tests to show plasma concentration
- GIHP-NACO study showed positive relationship between plasma concentration and use of PCC
- Take symptomatic and supportive measures—and time to treat patients with major bleeding
- DOAC antidotes are increasingly available
- PCC or aPCC use differs depending on bleeding sites and plasma concentrations of DOAC.

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Fibrinogen concentrate in elective complex cardiac surgery

A monocentric trial

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Presents the results from a randomised controlled trial which aimed to determine if fibrinogen concentrate infusion reduces intraoperative blood loss in cardiac surgery patients.

Background

Excessive bleeding is a common complication in cardiac surgery, and may result in the need for red blood cell (RBC) transfusion. Intraoperative bleeding during cardiac surgery is often treated with coagulation factor concentrates (CFCs). As yet, however, their efficacy has not been conclusively determined.

Since 1980 our knowledge of damage from transfusion has increased. Risks include infection, effects on the immune system, transfusion-related acute lung injury and risks due to the age of transfused blood (Isbister et al. 2011). Healthcare systems need to also be aware of the associated costs. As doctors it is our challenge and duty to reduce preventable damage from blood transfusion.

Patient blood management

The evidence-based multidisciplinary approach to optimising care of patients who may need transfusion is known as patient blood management (PBM). We know there is considerable variation in perioperative blood transfusion rate. For example, an analysis of 102,470 patients who underwent coronary artery bypass graft surgery at 792 hospitals in the United States found that rates of blood transfusion ranged from 7.8% to 92.8% for red blood cells (Bennett-Guerrero et al. 2010). PBM can also reduce the need for blood transfusions. In cardiac surgery, a study of Jehovah's Witnesses, who refuse blood products, found no difference in morbidity and mortality if patients are evaluated with a multidisciplinary approach to blood management (Moraca et al. 2011).

At Isala Clinics, we have researched patient blood management, including tailor-made transfusion protocols (Bilecen et al. 2014), and the role of point-of-care testing and fibrinogen concentrate (Bilecen et al. 2013). We implemented a specific transfusion protocol for cardiac surgery, and conducted an intervention study to evaluate its effects on transfusion and clinical events (Bilecen et al. 2014). The protocol included giving component therapy and fibrinogen at the end of the schedule. If we measured fibrinogen less than 1g/L we added 2g of extra fibrinogen. If it was more than 1g/L based on the Clauss measurement, we did not give fibrinogen. The cardiac surgery-specific transfusion protocol resulted in fewer patients transfused with RBCs and fresh frozen plasma (FFP) and a lower incidence of myocardial infarction.

Fibrinogen concentrate therapy

We conducted a cohort study to evaluate the effect of fibrinogen concentrate therapy on postoperative blood loss and transfusion and occurrence of clinical events in complex cardiac surgery; 264/1075 patients received fibrinogen concentrate during surgery (Bilecen et al. 2013). There was no reduction in postoperative blood loss and transfusion (intensive care unit [ICU] blood loss: OR 1.02 (0.91-1.14) and ICU transfusion: OR 1.14 (0.83-1.56) and no increase in risk for adverse clinical events. However, the haemostatic effect may have been attenuated by the low doses and relatively late administration of fibrinogen concentrate therapy.

Randomised controlled trial

Therefore we initiated a prospective single-centre, randomised, placebo-controlled, double-blind clinical trial to find out if fibrinogen concentrate infusion dosed to achieve a post-infusion plasma fibrinogen level of at least 2.5 g/L in high-risk elective cardiac surgery patients 18 years or over with intraoperative bleeding reduced intraoperative blood loss (Bilecen et al. 2017).

The primary outcome of the study was intraoperative blood loss measured between intervention and closure of the chest when surgery ended. Secondary outcomes included the measured blood loss at 1, 3, 6,12 and 24 hours after the intervention; the proportion of patients who received transfusion; and number of

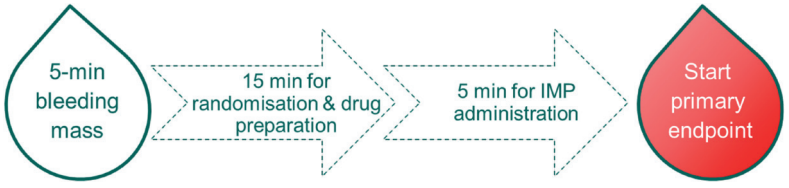

Figure 1.

IMP investigational medicinal product

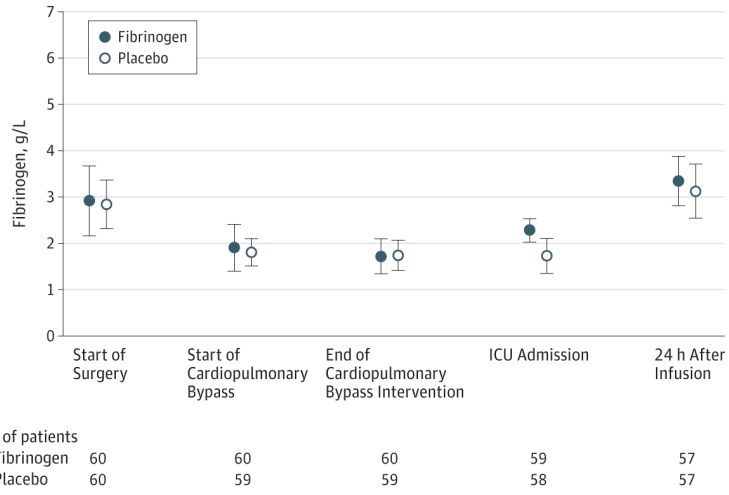

Figure 2. Fibrinogen concentrate dosing

Table 1. Primary, secondary and exploratory study outcomes

	Median (IQR), mL			
	Fibrinogen (n = 58)	Control (n = 57)	Absolute Difference (95% CI)	P Value
Primary Outcome				
Blood loss between intervention and chest closure	50 (29-100)	70 (33-145)	20 (−13 to 35)[a]	.19
Secondary or Exploratory Outcome				
No. of patients	58	59		
Blood loss in the ICU/time interval starting from admission				
0-1 h	70 (35-130)	90 (46-149)		
>1-3 h	80 (50-156)	110 (40-220)		
>3-6 h	100 (54-169)	110 (60-208)		
>6-12 h	110 (80-160)	125 (83-224)		
>12-24 h	130 (80-180)	160 (90-270)		
Cumulative 24-h blood loss	570 (390-730)	690 (400-1090)	120 (−45 to 355)[a]	.047[b]

ICU, intensive care unit IQR, interquartile range. Time point "intervention" is defined as moment of infusion of study medication.
a 95%confidence interval of difference in medians is based on a nonparametric bootstrap procedure (10 000 bootstraps with replacement).
b P value is based on the constructed mixed-model for repeated measurements.

Table 2. Secondary transfusion outcomes

	Fibrinogen (n = 58)	Control (n = 59)
Patients who received transfusion between intervention and chest closure, No. (%)		
Red blood cells	0	3 (5)
Fresh-frozen plasma	0	1 (2)
Platelets	2 (3)	2 (3)
Any transfusion	2 (3)	4 (7)
Patients transfused between intervention and 24 h, thereafter, No. (%)		
Red blood cells	10 (17)	20 (33)
Fresh-frozen plasma	9 (15)	13 (22)
Platelets	9 (15)	13 (22)
Any transfusion	20 (33)	23 (38)
Transfusion units between intervention and 24 h thereafter, median (IQR)		
Red blood cell transfusion units	0 (0-1)	0 (0-4)
Fresh-frozen plasma transfusion units	0 (0-2)	0 (0-4)
Platelets transfusion units	0 (0-1)	0 (0-1)
Any transfusion units	0 (0-2)	0 (0-8)

units of RBCs, FFP or platelet concentrate.

The aim was to achieve surgical haemostasis after heparin reversal. It was the surgeons' decision when to start the 5-minute bleeding time. Once patients had bled for 5 minutes they were entered into the treatment algorithm if they were bleeding >60 mL and <250 mL. The intervention was considered to have started on initiation of infusion of the study medication (**Figure 1**) (see p. V).

Over the four years of the trial, over 700 patients had complex cardiac surgery, of which 40% were eligible for the trial. Of the eligible patients, 43% did not agree to participate; 203 patients agreed to participate, of which 73 (36%) experienced no intraoperative bleeding and 10 were excluded for other reasons. We suggest that the high number of patients that experienced no intraoperative bleeding may be due to the Hawthorne effect—performing differently when being observed. This group of patients had very extensive surgical haemostasis before we started with the 5 minutes bleeding time, much longer than usual. The surgeons may have perceived that they were a better surgeon if they were not included in the trial, and also that after closure of the chest the microvascular bleeding was now the problem for the anaesthesiologist.

The patients were randomised to receive either the placebo or the intervention drug in doses between 60ml and 250ml. The fibrinogen doses were calculated based on plasma fibrinogen levels at the end of cardiopulmonary bypass measured using the Clauss method (**Figure 2**).

Results

Primary outcome

Among patients with intraoperative bleeding who received infusion of fibrinogen concentrate, compared with placebo, there was no significant difference in blood loss measured from the time of the fibrinogen infusion and chest closure (p = 0.19) (**Table 1**).

fibrinogen group
(median, 50 mL; IQR, 29-100 mL)
control group
(median, 70 mL; IQR, 33-145 mL)
absolute difference:
20 mL (95% CI, −13 to 35 mL)

Cumulative 24-hour blood loss was lower in the fibrinogen group compared with placebo (p = 0.047).

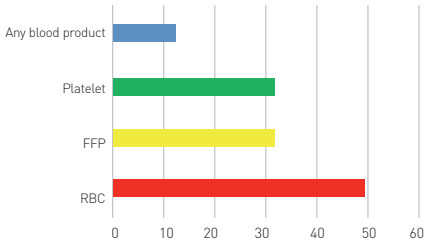

Figure 3. % reduction of transfusion

FFP fresh frozen plasma RBC red blood cells

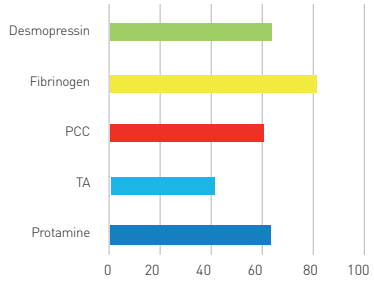

Figure 4. % reduction in procoagulants

PCC prothrombin complex concentrate TA tranexamic acid

Table 3. Procoagulants and antifibrinolytics use during surgery and ICU

	Fibrinogen (n = 60)	Control (n = 60)
During surgery, patients receiving, No. (%):		
Tranexamic acid	59 (98%)	60 (100%)
Desmopressin	42 (70%)	41 (68%)
Prothrombin complex concentrate	5 (8%)	2 (3%)
Recombinant factor VIIa	0 (0%)	0 (0%)
During ICU period, patients receiving, No. (%):		
Protamine	3 (5%)	8 (13%)
Tranexamic acid	9 (15%)	15 (25%)
Desmopressin	3 (5%)	8 (13%)
Prothrombin complex concentrate	4 (7%)	10 (17%)
Fibrinogen concentrate	1 (2%)	6 (10%)
Recombinant factor VIIa	0 (0%)	0 (0%)

Table 4. Clinical adverse events within 30 days

	No. of Events[a]	
	Fibrinogen (n = 60)	Control (n = 60)
In-hospital mortality	2	0
Stroke	4	1
Transient ischaemic attack	0	1
Myocardial infarction	3	1
Renal insufficiency or failure	3	2
Thromboembolism	0	0
Allergic reaction	0	0
Infections	3	2
Rethoracotomy (≤5 d)	4	5

The duration of primary outcome collection was 4.2 minutes (95% CI, 0.4-8.0 minutes) in the fibrinogen group and 8.7 minutes (95% CI, 5.2-12.1 minutes) in the control group.

However, other than these times do suggest these were not the best and fastest surgeons ever. This is why the primary endpoint was different than we expected. We expected that the moment there is a bleeding patient everyone would wait for closure and this would lead to a difference in blood loss in the patient and of course a difference in the intraoperative time factor.

Secondary outcomes

There were fewer patients in the fibrinogen group and fewer units of blood units used (**Table 2**). However, the study was not adequately powered to test the secondary outcomes. The percentage of reduction in transfusion is shown in **Figure 3**.

After surgery, a single patient (2%) in the fibrinogen group and 6 patients (10%) in the control group received additional fibrinogen concentrate. This confounds the effect on overall outcomes.

Procoagulants and antifibrinolytics use is shown in **Table 3**. The percentage of reduction is shown in **Figure 4**.

Clinical adverse events within 30 days

There were more adverse events in the fibrinogen group (**Table 4**). Two patients died, and 4 suffered a stroke. One patient in the control group suffered a stroke, and one a transient ischaemic attack. The trial was not designed to evaluate major adverse cardiac events and there was no screening for embolic risk aortic disease.

Almost 50% (9/19) of adverse events occurred in two patients **(Table 5)** (see p. VIII). Also one stroke occurred in a placebo patient with a fibrinogen level of 0.6g/l.

Transfusion protocol for cardiac surgery

At Isala Clinics we now use the following transfusion protocol **(Figure 5)** (see p. VIII). We conduct viscoelastic tests (ROTEM) to guide haemostatic therapies. Maegele and colleagues have provided a useful haemotherapy algorithm (Maegele et al. 2017).

Conclusion

Fibrinogen is effective after complex cardiac surgery in the bleeding patient. Based on the current trial data, fibrinogen is recommended as a first-line therapy with target plasma level 2.5g/L at the moment there is an idea of microvascular bleeding in these patients. Both visco-elostometry as the conventional Clauss method can be used to determine the level of fibrinogen at the end of bypass surgery and to optimise further treatment.

We have the tools and knowledge now to change transfusion management. But changing transfusion management, as with any change, is a major behavioural process. You need to do this together with your own multidisciplinary group, using a change strategy such as the Kotter model (**https://www.kotterinternational.com/8-steps-process-for-leading-change**). ■

Conflict of Interest

Arno Nierich is the principal investigator for the fibrinogen concentrate trial at Isala Clinics. CSL Behring sponsored the study and donated the bottles of study medication.

Table 5. Data on clinical adverse events, with allocated treatment, infused dose, fibrinogen plasma concentrations and time of event in days after surgery

Participant	Medication	Pre-infusion [fibrinogen g/L][a]	Infusion dose (g)[b]	Post-infusion [fibrinogen g/L][c]	Clinical adverse events						
					Mortality	Stroke	TIA	MI	RI	Infections	Rethoractomy
H-012	fibrinogen	1.6	3	2.4	day +10	day +1		day +1	day +2		day 0
H-161	fibrinogen	0.8	6	1.7	day +5	day +1			day +2		day 0
H-047	placebo	0.5	7	0.6		day 0					
H-140	fibrinogen	1.6	4	2.3		day +1				day +30	
H-155	fibrinogen	2.4	0	2.3		day +6					

MI myocardial infarction RI renal insufficiency or failure TIA transient ischemic attack,
a Plasma fibrinogen concentration at end-CPB.
b Infusion of study medication after removal of cardiopulmonary bypass. For placebo matched number of syringes is infused.
c Plasma fibrinogen concentration at ICU admission.

Key Points

- Implement transfusion management with change strategy
- Multidisciplinary group essential
- Point-of-care and lab monitoring:
  - Part of overcoming the 'blind spot' of coagulation management in operating room and intensive care unit
  - Additional tool in fine-tuning bleeding management
  - Measure fibrinogen level by Clauss as first potential bleeding indication
- Fibrinogen is effective after complex cardiac surgery in the bleeding patient: from rescue medication to first-line therapy with target level 2.5 g/L in the bleeding patient

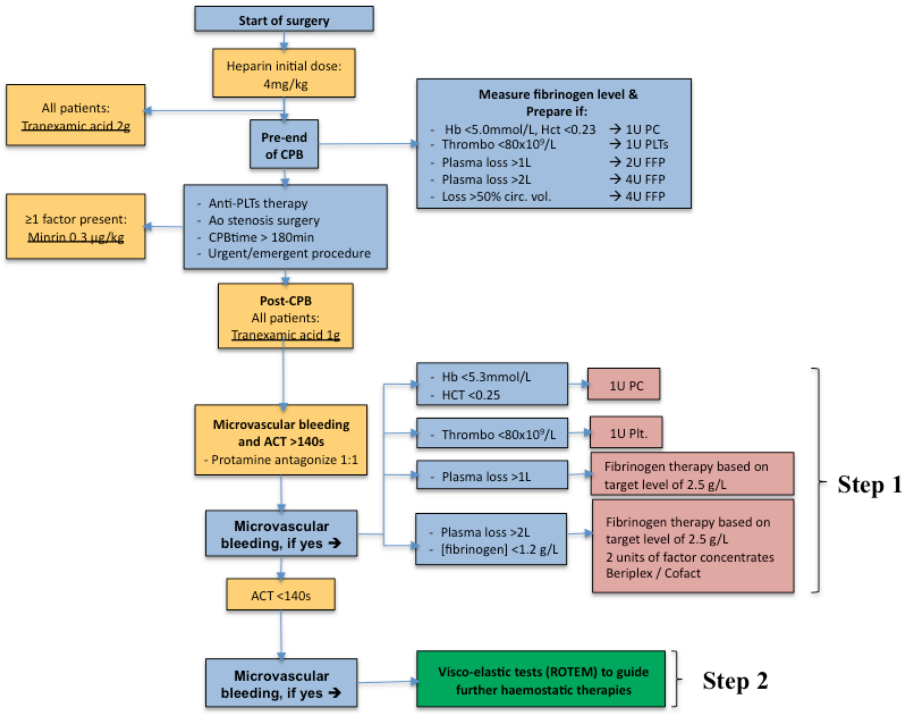

Figure 5. Transfusion protocol for cardiac surgery

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Abbreviations

CFC coagulation factor concentrates
FFP fresh frozen plasma
ICU intensive care unit
PBM patient blood management
RBC red blood cells

Treatment of trauma-induced coagulopathy with factor concentrates versus treatment with fresh frozen plasma

RETIC study

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Presents results of the RETIC study that compared treatment of trauma-induced coagulopathy using coagulation factor concentrates or fresh frozen plasma.

Background

Trauma-induced coagulopathy (TIC) represents a clinical picture resulting from severity of injury, hypoperfusion, blood loss, consumption, dilution and platelet dysfunction. Activation of the protein C system seems to mediate increased fibrinolytic attack. Despite the complex pathophysiology, the clinical picture is quite uniform: low fibrin formation and consequently low clot firmness occur predominantly and are the outcome-related pathologies. In addition, plasmatic test results are more or less impaired, albeit thrombin generation is maintained in the early phase of trauma, and hyperfibrinolysis can be expected in the very severely injured patient.

During the past 10 years coagulation management has gained great importance. Several studies have shown that early and aggressive fresh frozen plasma (FFP) is better than late plasma administration in terms of survival. In addition the evidence that use of coagulation factor concentrates (CF) is an effective alternative has grown. However, only a few study data are available for use of CF and thus both treatments are still recommended by guidelines. The European guideline's recommendation for initial coagulation resuscitation is for either fresh frozen plasma: red blood cell (FFP:RBC) at least 1:2 (evidence grade 1B) or fibrinogen concentrate and RBC (1C) (Rossaint et al. 2016).

RETIC trial

The *Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC)* study focused on treatment of coagulation in major trauma. It was a single-centre, parallel-group, open-label, randomised trial that aimed to compare the efficacy of FFP or CF in reversing TIC, as well as the arising transfusion requirements and development of multiple organ failure (MOF).

The study was terminated early due to institutional review board-mandated, predefined stopping rules; in the plasma arm there was an undesirable harmful effect of massive transfusion. The study received no outside funding. The results are published in *Lancet Haematology* (Innerhofer et al. 2017).

The hypothesis of the study was that the use of CF is superior to FFP for correction of TIC and that this should reduce bleeding and transfusion requirements, and consequently MOF.

The overall primary clinical endpoint was difference in MOF (calculated sample size n=200). The interim analysis was preplanned after 100 included patients.

The main secondary endpoints of the study were:

- transfusion requirements, massive transfusion
- frequency of treatment failure (rescue rate)
- laboratory parameters
- time until reversal of coagulopathy
- other clinical outcome parameters
- post hoc subgroup analysis, analysis adjusted for stratification factors (Injury Severity Score [ISS])

The inclusion criteria for the study were male and female patients ≥ 18–≤ 80 years who had experienced major trauma (ISS >15), who had clinical signs of ongoing bleeding, or who were at risk for significant haemorrhage assessed and judged by the emergency department (ED) team in charge of the patient, and who had the presence of coagulopathy defined by rotational thromboelastometry (ROTEM) —FibTEM assay (10-min value of fibrinogen polymerisation [FibA10] <9 mm) and/or prolonged initia-

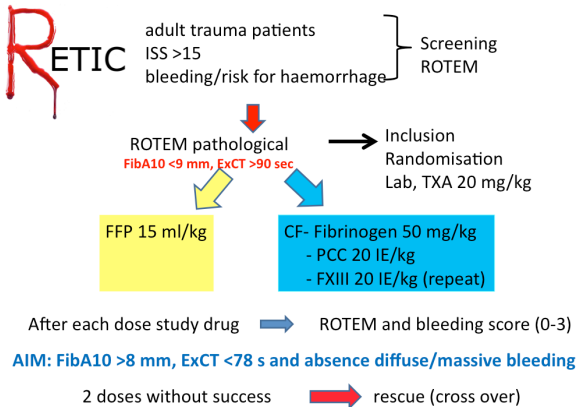


Figure 1.

ExCT Coagulation time of extrinsically activated rotational thromboelastometry assay FibA10 fibrin polymerisation at 10 min FXIII coagulation factor XIII concentrate ISS Injury Severity Score PCC prothrombin complex concentrate ROTEM rotational thromboelastometry TXA tranexamic acid

Table 1. Study population

	CF (n=50)	FFP (n=44)
Age (ys)	43 (27-51)	43 (24-56)
Male sex (n)	38 (76%)	32 (73%)
ISS (pt)	35 (29-42)	30 (24-45)
Brain injury (n)	25 (50%)	21 (48%)
Time to ED (min)	62 (40-90)	57 (44-85)
Systol. BP <90 mmHg (n)	19 (38%)	10 (23%)
Crystalloids (ml)	500 (250-1000)	500 (500-1000)
Colloids (ml)	400 (0-500)	250 (0-500)
BE (mmol/l)	–4.4 (–6 to –2)	–4.2 (–7.8 to –3)
Lactate (mmol/l)	2.2 (1.6-3.2)	2.3 (1.6-3)
Hyperfibrinolysis (n)	4 (8%)	2 (4.5%)
Immediate surgery	44 (88%)	36 (81.8%)

BE base excess BP blood pressure CF coagulation factor concentrate FFP fresh frozen plasma ISS Injury Severity Score

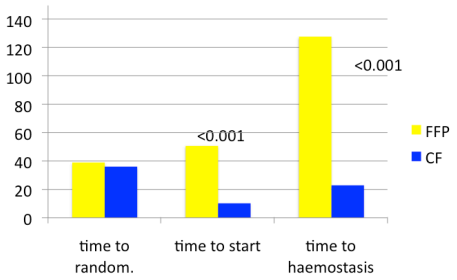
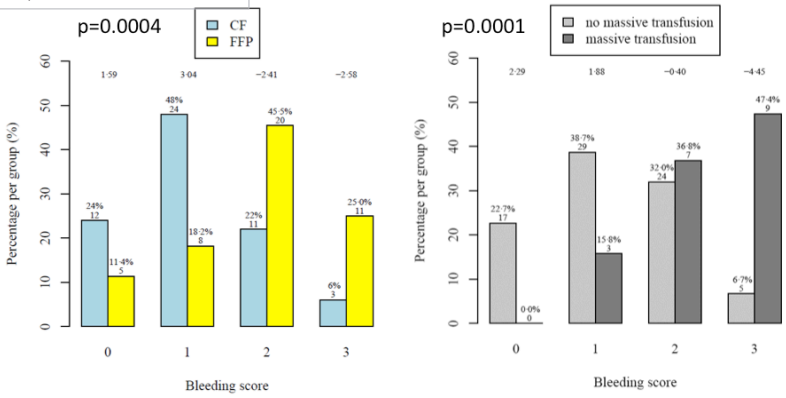


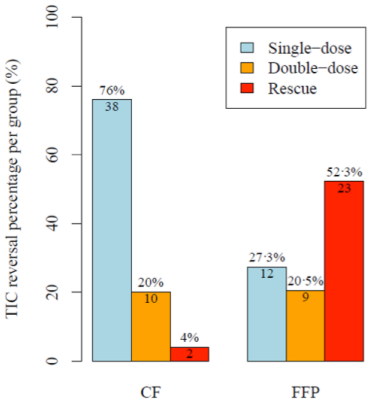
Figure 2. Time intervals

CF coagulation factor concentrate FFP fresh frozen plasma



0 = no significant bleeding; 1 = injury related, clots visible; 2 = diffuse no clots; 3 = massive (>3RBC/h)

Figure 3. Bleeding score after first dose, CF n=50, FFP n=44, CF coagulation factor concentrate FFP fresh frozen plasma



Rescue rate after double-dose
FFP vs CF: **52.3% vs 4%** p<0.001
OR 25.34 (CI 5.47–240.03) **NNT (CF) = 2.07**

Figure 4. Treatment efficacy

CF coagulation factor concentrate CI confidence interval FFP fresh frozen plasma NNT number need to treat OR odds ratio

tion of coagulation in the extrinsically activated ROTEM (ExTEM) assay (coagulation time of ExTEM assay [ExCT] >90 s).

Patients were excluded from the study if they had sustained a lethal injury, received cardiopulmonary resuscitation at the scene, had an isolated brain injury, burn injury, avalanche injury, had received FFP or coagulation factor concentrates before ED admission, were admitted to ED more than 6 hours after the trauma, or had known use of oral anticoagulants, or platelet aggregation inhibitors within 5 days before injury or a known history of severe allergic reaction to plasma products.

Adult trauma patients with severe injury were screened by one of the study team and a ROTEM was performed (**Figure 1**) (see p. IX). If ROTEM was pathological the patient was included. Using closed envelopes the patient was allocated to one of the two groups, a blood sample for detailed coagulation analysis was drawn and all patients received a tranexamic acid bolus. Patients in the plasma group received FFP at a single dose of 15ml/kg, the dose recommended by the European guidelines published in 2010 (the protocol was created in 2011) (Rossaint et al. 2010). As plasma is not a single substance but contains factors for thrombin formation, fibrinogen and also FXIII, we needed to consider this in the CF arm to avoid bias. Patients in the CF group received fibrinogen 50 mg/kg, if indicated also prothrombin complex concentrate (PCC) 20 IE/kg and FXIII 20 IE/kg was administered in patients needing double-dose fibrinogen (repeat).

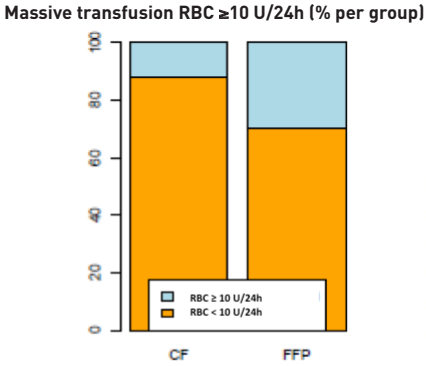
After study drug administration, ROTEM was checked again and the bleeding situation was assessed. Successful therapy was defined as normalised ROTEM and absence of diffuse or massive bleeding. Patients who showed insufficient reversal of TIC received a second dose of the study drug, and if this did not work rescue therapy was started, meaning patients of the CF group received plasma, patients of the plasma group received CF. Each treatment loop consisted of a maximum 4 steps—two times study drugs according to randomisation and one or two times rescue therapy.

Table 1 shows the baseline characteristics of the study population.

The time to start of therapy was significantly different between groups (**Figure 2**). The time to start was longer in the plasma group. This is a clear advantage of using CF as they are immediately available and liquid plasma is not licensed in Austria. The time to haemostatis and normalised ROTEM was significantly longer in the plasma group at about 2 hours. Taking into account the longer time to start of therapy of FFP the difference is still about 1 hour. **Figure 3** shows the bleeding score after first dose.

Patients in the plasma group had more frequently diffuse and massive bleeding after the first study drug administration than patients of the CF group. The bleeding score after first study drug administration was significantly associated with need of massive transfusion.

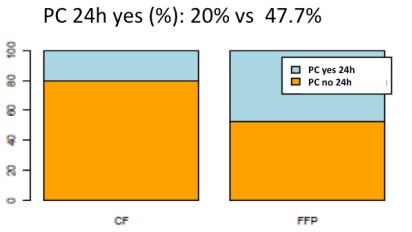
Figure 4 shows the percentage of patients who showed reversal of TIC after a single dose, double dose or need for rescue therapy after having received a double dose of study drugs. There was not only a big difference in success after single dose, but most importantly more than 50% of patients in the plasma group needed



CF vs FFP : MT 12% vs 29.5%
p=0.042; **OR 3.038** (CI 0.0951–10.873)
Log. Regression/ISS/TBI
p=0.0169; **OR 4.2421** (CI1.3630–5.0935)
NNH (FFP) = 5.7

Figure 5. RBC

CF coagulation factor concentrate CI confidence interval FFP fresh frozen plasma ISS Injury Severity Score MT massive transfusion NNH number needed to harm OR odds ratio RBC red blood cells TBI traumatic brain injury



p=0.008; OR 3.599 (CI 1.348541–10.181151)

Figure 6. Platelets

CI confidence interval OR odds ratio PC platelet concentrate

Table 2. Study drugs

	CF (n=50)	FFP (n=44)	p-value
FFP n U	 2 5 (5-5)	 44 14 (10-14)	 N/A N/A
FC n g	 50 (100%) 8 (5-10)	 23 (52.3%) 5 (4.5-8)	 N/A N/A
PCC n IU	 8 (16%) 2000 (1875-3000)	 2 (4.5%) 850 (675-1025)	 0.09 0.046
FXIII (n)	27 (54%)	11 (25%)	0.006

CF coagulation factor concentrate FC fibrinogen concentrate FFP fresh frozen plasma FXIII coagulation factor XIII concentrate PCC prothrombin complex concentrate

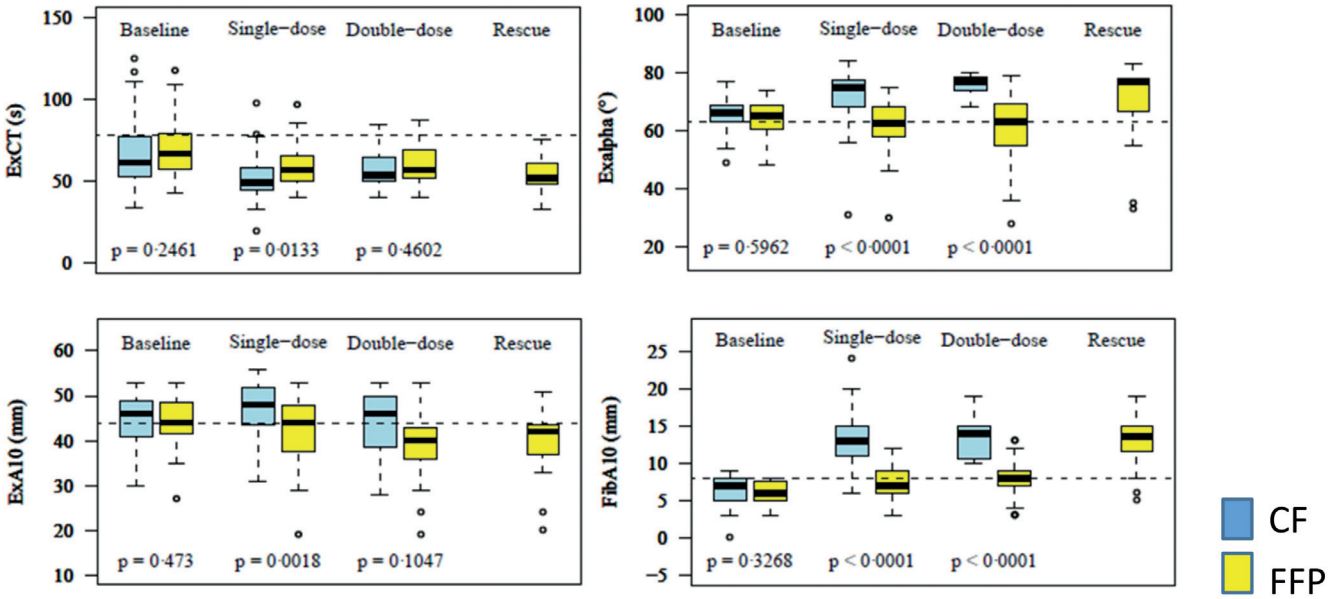


Figure 7. ROTEM parameters

CF coagulation factor concentrate FFP fresh frozen plasma

additional rescue therapy. The odds for receiving rescue were significantly higher for FFP patients and the calculated number needed to treat (NNT) was remarkably low for CF. On average 100 out of 207 patients receiving initial CF treatment will show reversal of TIC, which would have not occurred with initial FFP treatment. **Figure 5** shows RBC transfusion.

The odds for receiving massive transfusion were three-fold higher with plasma. If ISS and brain injury were considered as influencing factors, the odds were four-fold higher with plasma therapy. The calculated NNT was 5.7, meaning that on average 10 out of 57 patients treated initially with FFP need massive transfusion (MT), which would not have occurred with initial CF treatment. We also found a significant difference in numbers of RBC used during the first 24h.

Patients of the plasma group more frequently needed transfusion of platelet concentrates (PC) (**Figure 6**).

Table 2 summarises the dosages of study drugs used in the first 24 hours; important is the finding that patients in the plasma group needed FC after double dose FFP in comparable amounts as did patients receiving FC first-line, meaning nothing had been saved with late fibrinogen concentrate administration. PCC was seldom needed in the CF group; FXIIIc was frequently administered and also needed in the plasma group.

Figure 7 shows the response of ROTEM parameters according to therapy, blue is CF, yellow is plasma. EXCT shortened in both groups, shortest values were reached with CF; Exalpha, EXA10 and FibA10 increased with CF, but remained unchanged or even decreased with plasma.

Baseline CF 50, FFP 44
Single dose CF 50, FFP 44
Double dose CF 12, FFP 32
Rescue FFP 20 (3 patients received rescue at later treatment loops)

Figure 8 (see p. XII) shows levels of FXIII, Hb and platelet count during the first treatment loop.

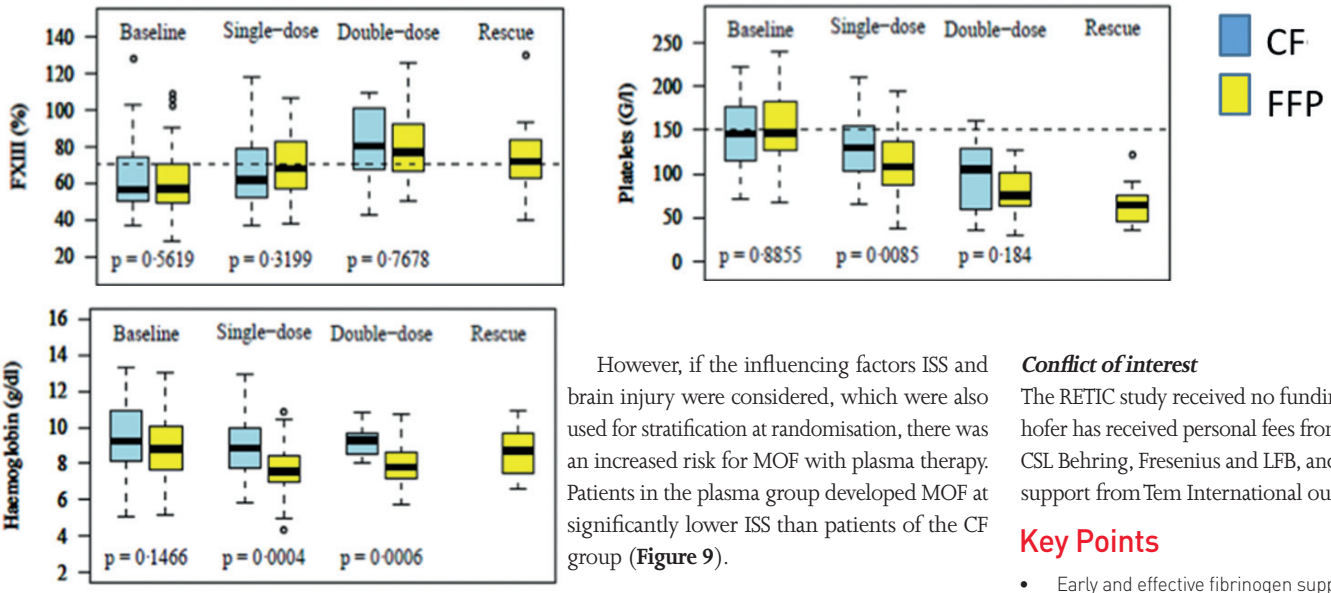


Figure 8. Levels of FXIII, Hb and platelet count during the first treatment loop

CF coagulation factor concentrate FFP fresh frozen plasma Hb haemoglobin FXIII coagulation factor XIII concentrate

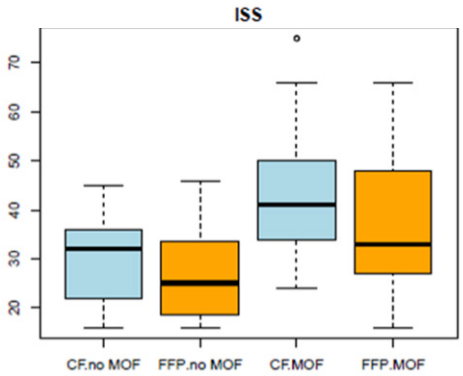


Figure 9. Logistic regression adjusted for stratification factors ISS/TBI: significantly increased risk for MOF with FFP

p = 0.0250, OR 3.1264 (CI 1.1906–8.8756)

CF coagulation factor concentrate FFP fresh frozen plasma ISS Injury Severity Score MOF multi-organ failure TBI traumatic brain injury

FXIII levels were comparable in both groups and at the intended value of 60%. Numbers of platelets and Hb decreased in both groups, lowest values were seen with plasma although these patients received more RBC and PC.

The overall primary clinical endpoint MOF was narrow and not significant with the available limited sample size (the calculated sample size for assessment of MOF was 200 patients) (**Table 3**).

	CF (n=50)	FFP (n=44)	p-value
MOF	25 (50%)	29 (65.9%)	0.1457

Table 3. Multi-organ failure (MOF)

CF coagulation factor concentrate FFP fresh frozen plasma

However, if the influencing factors ISS and brain injury were considered, which were also used for stratification at randomisation, there was an increased risk for MOF with plasma therapy. Patients in the plasma group developed MOF at significantly lower ISS than patients of the CF group (**Figure 9**).

Subgroups	CF only n=48	FFP rescue n=23	FFP only n=21	p-value
MOF	48%	78.3%	52 %	0.0479
	OR 3.839 (CI 1.1323–15.4448), p=0.0209			

Table 4

CF coagulation factor concentrate CI confidence interval FFP fresh frozen plasma OR odds ratio

Finally we also looked at the MOF rate in the 3 subgroups and found a lower risk of MOF in patients receiving first-line CF as compared to those patients receiving first-line plasma and late rescue CF. No difference occurred between the two plasma groups.

Conclusion

Targeted administration of coagulation factor concentrates is more effective than the usual transfusion of fresh plasma in patients with trauma-induced coagulopathy.

First-line administration of CF results in early stop of bleeding, reduced transfusion of all blood components, decreased rate of massive transfusion and decreased risk for MOF. In-hospital mortality was remarkably low with 7.4% and similar in both groups, as was the incidence of thromboembolic events. Thus our treatment concept seems to be quite safe. If you look at the mortality of recent studies including patients with comparable or even lower ISS you see mortality rates of 20 to 35% when transfusion packages are used which contain cryo very late or not at all. Interestingly authors of the last review on the usefulness of fibrinogen concentrate already suggested a probable survival benefit with use of FC (Fominskiy et al. 2016). ■

Conflict of interest

The RETIC study received no funding. Petra Innerhofer has received personal fees from Baxter, Bayer, CSL Behring, Fresenius and LFB, and non-financial support from Tem International outside the study.

Key Points

- Early and effective fibrinogen supplementation important
- Targeted CF-based therapy superior to FFP
- Correction of TIC in 96% with CF, less than 50% with FFP
- Remarkably low NNT with CF (mainly fibrinogen concentrate)
- First-line FFP
  - persisting hypofibrinogenaemia
  - low clot firmness
  - prolonged coagulopathic bleeding
  - increased transfusion of RBC and PC/24 hours
  - increased rate of massive transfusion
  - increased risk of MOF
  - results with continued FFP and without rescue?
- In-hospital mortality rather low with 7.4%

Abbreviations

CF coagulation factor concentrate
ED emergency department
FC fibrinogen concentrate
FFP fresh frozen plasma
FXIII coagulation factor XIII concentrate
Hb Haemoglobin
ISS injury severity score
MOF multiple organ failure
MT massive transfusion
NNT number needed to treat
PC platelet concentrate
PCC prothrombin complex concentrate
RBC red blood cells
ROTEM rotational thromboelastometry
TIC trauma-induced coagulopathy

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