

## **CME** Transfusion of fresh-frozen plasma in critically ill patients with a coagulopathy before invasive procedures: a randomized clinical trial

Marcella C. Müller,<sup>1</sup> M. Sesmu Arbous,<sup>2</sup> Angelique M. Spoelstra-de Man,<sup>3</sup> Roel Vink,<sup>4</sup> Atilla Karakus,<sup>5</sup> Marleen Straat,<sup>1</sup> Jan M. Binnekade,<sup>1</sup> Evert de Jonge,<sup>2</sup> Margreeth B. Vroom,<sup>1</sup> and Nicole P. Juffermans<sup>1</sup>

**BACKGROUND:** Prophylactic use of fresh-frozen plasma (FFP) is common practice in patients with a coagulopathy undergoing an invasive procedure. Evidence that FFP prevents bleeding is lacking, while risks of transfusion-related morbidity after FFP have been well demonstrated. We aimed to assess whether omitting prophylactic FFP transfusion in nonbleeding critically ill patients with a coagulopathy who undergo an intervention is noninferior to a prophylactic transfusion of FFP.

**STUDY DESIGN AND METHODS:** A multicenter randomized open-label trial with blinded endpoint evaluation was performed in critically ill patients with a prolonged international normalized ratio (INR; 1.5-3.0). Patients undergoing placement of a central venous catheter, percutaneous tracheostomy, chest tube, or abscess drainage were eligible. Patients with clinically overt bleeding, thrombocytopenia, or therapeutic use of anticoagulants were excluded. Patients were randomly assigned to omitting or administering a prophylactic transfusion of FFP (12 mL/kg). Outcomes were occurrence of postprocedural bleeding complications, INR correction, and occurrence of lung injury.

**RESULTS:** Due to slow inclusion, the trial was stopped before the predefined target enrollment was reached. Eighty-one patients were randomly assigned, 40 to FFP and 41 to no FFP transfusion. Incidence of bleeding did not differ between groups, with a total of one major and 13 minor bleedings ( $p = 0.08$  for noninferiority). FFP transfusion resulted in a reduction of INR to less than 1.5 in 54% of transfused patients. No differences in lung injury scores were observed.

**CONCLUSION:** In critically ill patients undergoing an invasive procedure, no difference in bleeding complications was found regardless whether FFP was prophylactically administered or not.

**F**resh-frozen plasma (FFP) is effective in correcting multiple clotting factor deficiencies, and transfusion guidelines recommend its use during massive bleeding and such a deficiency.<sup>1,2</sup> In the past decades, use of FFP has grown steadily.<sup>3,4</sup> In addition to the use of FFP in actively bleeding patients, a substantial amount of FFP is transfused prophylactically to nonbleeding patients with a coagulopathy.<sup>5-9</sup> Coagulopathy, defined as prolonged prothrombin time (PT) or international normalized ratio (INR), has a high

**ABBREVIATIONS:** APTT = activated partial thromboplastin time; ICU = intensive care unit; INR = international normalized ratio; PT = prothrombin time; VAP = ventilator-associated pneumonia.

From the <sup>1</sup>Department of Intensive Care Medicine, Academic Medical Center, Amsterdam, the Netherlands; the <sup>2</sup>Department of Intensive Care Medicine, Leiden University Medical Center, Leiden, the Netherlands; the <sup>3</sup>Department of Intensive Care Medicine, VU Medical Center, Amsterdam, the Netherlands; the <sup>4</sup>Department of Intensive Care Medicine, Tergooziekenhuizen, Hilversum, the Netherlands; and the <sup>5</sup>Department of Intensive Care Medicine, Diaconessenhuis, Utrecht, the Netherlands.

*Address reprint requests to:* Marcella C.A. Müller, Department of Intensive Care Medicine, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands; e-mail: m.c.muller@amc.uva.nl.

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prevalence in critically ill patients.<sup>5</sup> Thereby, substantial amounts of FFP are utilized in the intensive care unit (ICU).<sup>8-10</sup>

An important reason for physicians to transfuse FFP is the prevention of bleeding complications in nonbleeding patients with a coagulopathy, in particular in those undergoing an invasive procedure.<sup>8,11</sup> However, currently used diagnostic tests for coagulopathy such as INR and PT poorly represent *in vivo* hemostatic potential. Therefore, PT has limited value in predicting bleeding risk.<sup>12,13</sup> In addition, retrospective studies suggest that commonly performed invasive procedures in the critically ill, such as central venous catheter placement, percutaneous tracheostomy, and thoracocentesis, carry a low bleeding risk.<sup>13-16</sup>

Evidence from randomized controlled trials that support FFP transfusion to correct coagulopathy to reduce risk of bleeding before an invasive procedure is limited.<sup>17,18</sup> On the other hand, FFP transfusion is associated with acute lung injury, which may occur in up to 30% of transfused critically ill patients,<sup>19</sup> prolonging mechanical ventilation and ICU length of stay.<sup>20</sup> Also, an increased infection risk has been reported after FFP transfusion.<sup>21</sup> Thereby, the risk–benefit balance of prophylactic FFP may be limited. Despite the absence of evidence of a benefit, prophylactic FFP transfusion is common practice in the ICU.<sup>8,10,22,23</sup> We conducted a multicenter randomized controlled clinical trial in critically ill patients with a coagulopathy who needed to undergo an invasive procedure. Using noninferiority analysis, we aimed to determine whether FFP transfusion could be safely omitted in these patients.

## MATERIALS AND METHODS

The institutional review board of the Academic Medical Center–University of Amsterdam, Amsterdam, The Netherlands, approved the study protocol. Before entry in the study, written informed consent was obtained from the patient or legal representative in accordance with the Declaration of Helsinki. The study protocol was registered with trial identification numbers NTR2262 and NCT01143909.<sup>24</sup>

### Setting and patients

Consecutive patients of 18 years and older admitted to the intensive care with an INR of at least 1.5 and not more than 3.0 and the need to undergo an invasive procedure were considered eligible. Defined invasive procedures were insertion of a central venous catheter, thoracocentesis, percutaneous tracheotomy, drainage of abscess, or fluid collection. Patients with clinically overt bleeding (defined as either a decrease in hemoglobin [Hb] > 1.6 g/dL or a need for transfusion or hemodynamic insta-

bility due to bleeding at the time of the procedure) or with a thrombocytopenia of not more than  $30 \times 10^9/L$  were excluded from participation. Also, patients were excluded when treated with vitamin K antagonists, activated protein C, abciximab, tirofiban, ticlopidine, or prothrombin complex concentrates. In addition, patients with a history of congenital or acquired coagulation factor deficiency or bleeding diathesis were excluded. Patients treated with low-molecular-weight heparin or heparin in therapeutic dose were eligible if medication was discontinued for an appropriate period. Patients were enrolled at four sites in the Netherlands: two university hospitals (Academic Medical Center, Amsterdam; and Leiden University Medical Center, Leiden) and two large teaching hospitals (Tergooiziekenhuizen, Hilversum; and Diaconessenhuis, Utrecht).

Clinical practices, such as using ultrasound guidance when inserting a central venous catheter or a chest tube, were applied according to each center's specific expertise and routine, to minimize interference of the trial intervention with normal clinical practice. Tracheostomy was performed percutaneously under direct sight using bronchoscopy. Use of low-molecular-weight heparin in a prophylactic dose was standard care in all patients. Selective digestive tract decontamination was part of standard care in three centers. The decision to transfuse red blood cells (RBCs), FFP, or platelets (PLTs) in case of postprocedural bleeding was made by the treating physician in accordance with national guidelines.

### Study design

Since manufacturing a completely matched placebo in full compliance with the current good manufacturing practice standards was considered not possible, a prospective, randomized, open-label, blinded endpoint evaluation (PROBE) design was chosen. Patients admitted to the ICU were prospectively screened between May 2010 and June 2013 for INR prolongation. Patients fulfilling inclusion criteria were randomly assigned to receive or not to receive a single dose of 12 mL/kg FFP.

The randomization procedure was Web-based, using permuted blocks and was stratified by study center and type of invasive procedure. Patients could only be randomized once (e.g., for one procedure). Fresh-frozen quarantine plasma, manufactured by Sanquin, the Dutch National Bloodbank, was used. Transfusion amount was rounded to whole units. After randomization and transfusion or not, the scheduled intervention was carried out and patients were observed for 24 hours.

### Study endpoints

The primary outcome of the study was procedure-related bleeding, occurring within 24 hours after the procedure.

Bleeding was assessed using a tool validated in the critically ill (HEME).<sup>25</sup> Major bleeding was defined as bleeding accompanied by any of the following: a decrease in Hb by more than 2 g/dL in the absence of another cause of bleeding, transfusion of 2 or more units RBCs without an increase in Hb, a decrease in systolic blood pressure by more than 20 mmHg, an increase in heart rate by 20 beats/min or more, or wound-related bleeding requiring an intervention. Minor bleeding was defined as prolonged bleeding at the site of insertion or increase in size of subcutaneous hematoma. The potential bleeding site was assessed by a physician blinded to the intervention who filled out a predefined bleeding score form consisting of blood pressure, heart rate, Hb level, and occurrence of procedure-related bleeding with or without the need for intervention or transfusion. Subsequently this blinded physician assigned a score of major bleeding, minor bleeding, or no bleeding at 1 and 24 hours after the intervention. The effects of FFP on correction of INR and additional transfusion requirements were assessed. Development of lung injury was assessed by calculating the lung injury score 24 hours after the intervention, which includes radiographic infiltrates on chest X-ray, a hypoxemia score ( $\text{PaO}_2/\text{FiO}_2$ ), positive end-expiratory pressure level (cm  $\text{H}_2\text{O}$ ), and respiratory system compliance score when available.<sup>26</sup> Ventilator-associated pneumonia (VAP) was defined as newly diagnosed (infiltrate on chest X-ray and clinical signs of pneumonia), culture proven pneumonia, while on mechanical ventilation.

### Statistical considerations

The sample size and power calculation of this study were based on studies that showed that the occurrence of major bleeding in patients with a coagulopathy undergoing invasive procedures was less than 1%. Group size calculation was focused on demonstrating noninferiority. With a sample size in each group of 198, a one-sided Z test with continuity correction (pooled) achieved 80% power to reject the null hypothesis that the proportion of bleeding patients in the experimental group (no FFP transfusion) was higher, that is, inferior to the proportion in the control group (FFP transfusion) with a margin of 0.03. It was assumed that the expected difference in proportions is zero and the proportion in the control group is 0.01. The one-sided significance level of the test was targeted at 0.05. Therefore, we intended to enroll 200 patients per treatment arm.<sup>24</sup>

### Statistical analysis

Variables are expressed by their mean and standard deviation if normally distributed. If not normally distributed they are expressed by their medians and interquartile ranges. Categorical variables are expressed as number (%).

The primary endpoint of procedure-related major bleeding only occurred once, rendering planned noninferiority analysis impossible. Therefore, a post hoc noninferiority analysis for all types of bleeding complications (major and minor) was performed according to the method of Dunnett and Gent.<sup>27</sup> The null hypothesis stated that the difference between the control treatment (FFP transfusion) and the intervention (no FFP transfusion) equals a delta of 0.03. The alternative hypothesis stated that the difference between the control treatment and the new treatment is smaller than a delta of 0.03. A significant result ( $p \leq 0.05$ ) would indicate that omitting FFP transfusion is noninferior to administering FFP before an intervention. In addition, occurrence of bleeding between both groups was compared by Fisher exact test. Because of the noninferiority design of the trial, both an intention-to-treat analysis and a per-protocol analysis was performed, and results of the per-protocol analysis are reported.

The secondary outcome variables were analyzed using the two-group t test or Mann-Whitney test, simple linear regression, and chi-square test, when appropriate. In case of paired data the paired t-test was used, or in case of not normally distributed data the Wilcoxon signed rank test was used. Correlations were determined by Spearman's rho. In all analyses statistical uncertainties are expressed in 95% confidence limits, with a significance level of 0.05. Statistical analyses were carried out with computer software (R Statistical Computing, Vienna, Austria; <http://www.R-project.org>).

## RESULTS

### Patients and interventions

Owing to slow inclusion, the trial was stopped before the predefined target enrollment was reached. Between May 2010 and June 2013, a total of 13,163 INR values were screened in 6825 patients. A total of 1478 patients had an INR of at least 1.5 and not more than 3.0. Of these, 615 patients did not fulfill inclusion criteria, leaving 263 patients with an INR of at least 1.5 and not more than 3.0 scheduled to undergo a predefined intervention. Of these, 65 patients declined informed consent. An additional 83 patients were missed and 34 patients did not participate due to other reasons, including refusal from treating physicians to include a specific patient (3.8%). This left 81 coagulopathic patients who underwent randomization (Fig. 1). Five patients did not undergo an intervention despite randomization and were therefore excluded from further analysis. The results of the per-protocol analysis are reported. Half of the included patients had sepsis. Prevalence of disseminated intravascular coagulation and liver disease was high (Table 1). Groups were balanced with respect to demographic variables and disease severity scores. However, in patients randomly assigned to the nontransfused group, liver disease was more frequent

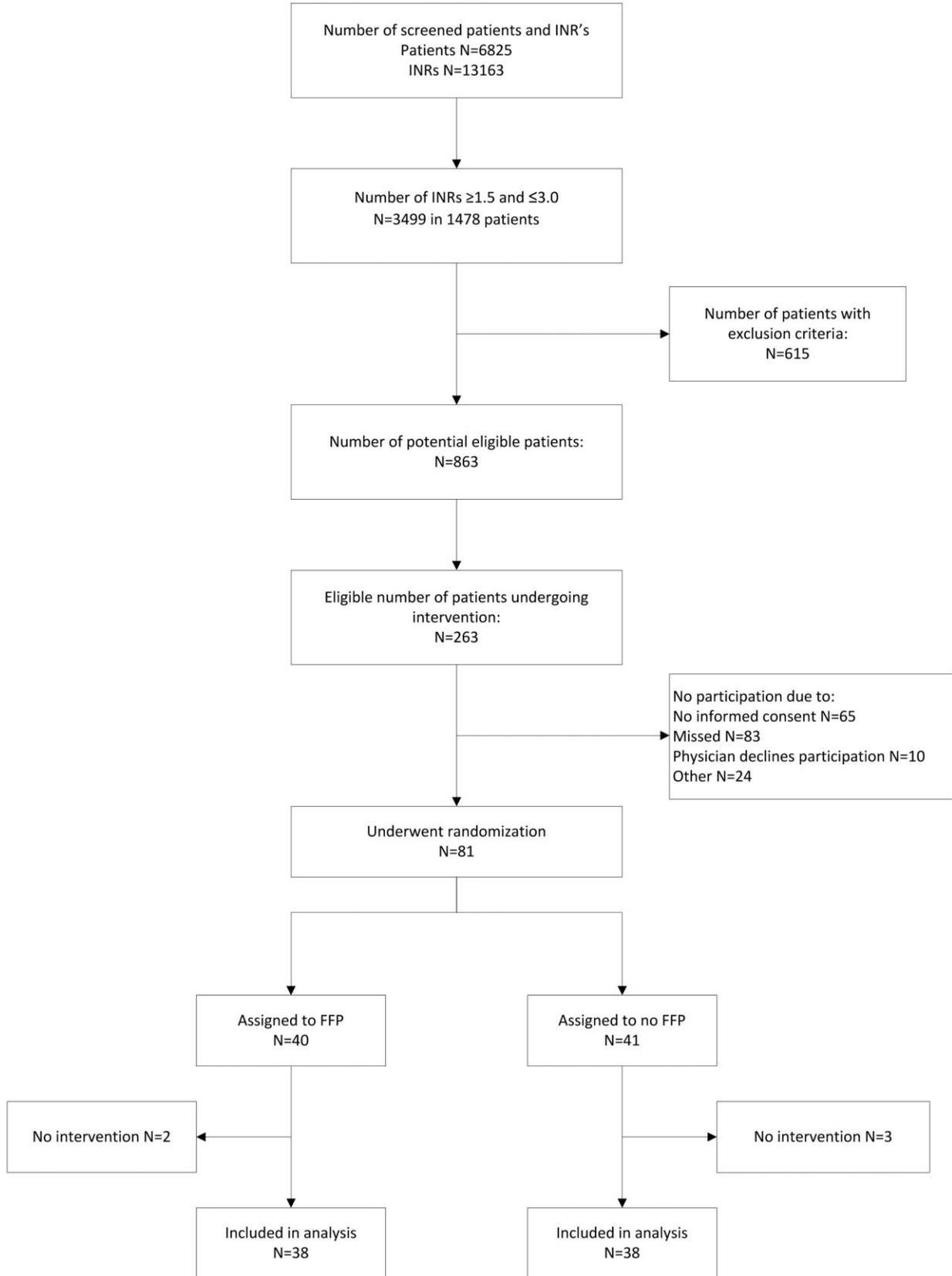


Fig. 1. CONSORT diagram.

**TABLE 1. Patient characteristics\***

	FFP transfusion (n = 38)	No FFP transfusion (n = 38)	p value
<b>General characteristics</b>			
Gender, male	67 (26)	47 (18)	0.09
Age (years)	64 (54-70)	66 (62-72)	0.23
BMI	24 (22-28)	23 (20-26)	0.15
Days admission until intervention	3 (1-8)	2 (1-3)	0.26
APACHE IV score	107 (80-129)	101 (83-126)	0.76
SOFA score	12 (10-14)	12 (10-15)	0.81
<b>Medical history</b>			
Pulmonary disease	13 (5)	10 (4)	0.72
Liver disease	16 (6)	45 (17)	0.006
Cardiac failure	16 (6)	16 (6)	1.00
<b>Medical condition 24 hr before intervention</b>			
Mechanical ventilation	84 (32)	76 (29)	0.52
Sepsis	47 (18)	47 (18)	1.00
Pneumonia	26 (10)	24 (9)	0.89
Disseminated intravascular coagulation	45 (17)	38 (14)	0.54
<b>Baseline measurements</b>			
INR	1.8 (1.5-2.2)	1.9 (1.6-2.2)	0.29
APTT (sec)	43 (38-52)	41 (36-49)	0.35
PLT count ( $\times 10^9/L$ )	92 (52-180)	110 (52-183)	0.94
Hb (g/dL)	9.3 (8.4-10.2)	9.3 (8.4-10.6)	0.79
Lung injury score	2 (1-2.7)	1.3 (0.83-2.3)	0.61
<b>Anticoagulation</b>			
Aspirin	10 (4)	24 (9)	0.11
Clopidogrel	3 (1)	5 (2)	0.54
Aspirin and clopidogrel	0 (0)	5 (2)	0.49
UFH therapeutic dose	10 (4)	18 (7)	0.31
LMWH therapeutic dose	23 (9)	11 (4)	0.14

\* Data are expressed as percent (number) or median (interquartile range).

APACHE = Acute Physiology and Chronic Health Evaluation; BMI = body mass index; LMWH = low-molecular-weight heparin;

SOFA = Sequential Organ Failure Assessment; UFH = unfractionated heparin.

**TABLE 2. Intervention and transfusion characteristics in randomized patients\***

	FFP transfusion (n = 38)	No FFP transfusion (n = 38)	p value
<b>Intervention</b>			
Central venous catheter	76 (29)	76 (29)	0.58
Chest tube	11 (4)	8 (3)	
Tracheotomy	5 (2)	5 (2)	
Abdominal drain	8 (3)	11 (4)	
<b>FFP before intervention</b>			
Units	3 (2-4)	0	
Dose (mL/kg)	12 (10-13)	0	
<b>Transfusions in first 24 hr after intervention</b>			
RBCs (units)	1 (0-2)	1 (0-3)	0.91
FFP (units)	0 (0-1)	2 (0-2)	0.06
PLTs (units)	1 (0-2)	0 (0-1)	0.43

\* Data are expressed as percent (number) or median (interquartile range).

NA = not applicable.

( $p = 0.006$ ). Baseline values of coagulation tests, Hb, and lung injury scores did not differ between the two groups, nor did preprocedural use of anticoagulant medication (Table 1). Central catheter placement was the most frequent intervention (76% in the FFP transfusion and 78% in the nontransfused group; Table 2).

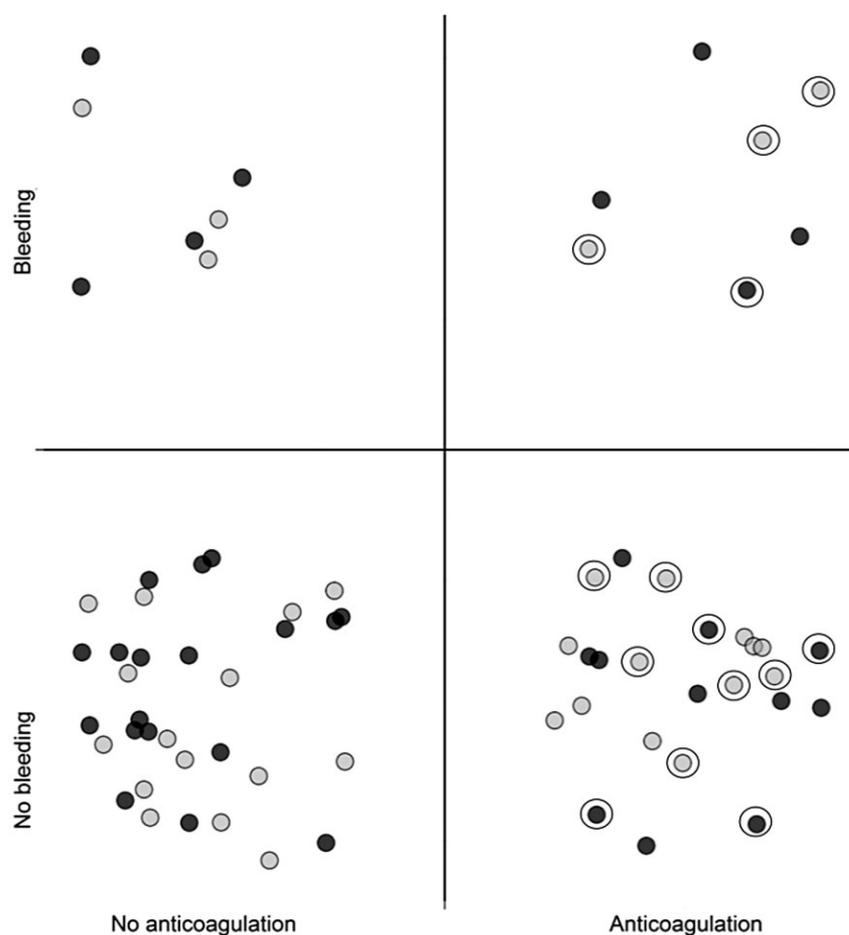
### Occurrence of bleeding

None of the patients experienced a fatal bleeding. Overall, one major and 13 minor bleedings occurred (Table 3). The

**TABLE 3. Bleeding rates in randomized patients**

	FFP transfusion (n = 38)	No FFP transfusion (n = 38)
Fatal bleeding	0	0
Major bleeding	0	1
Minor bleeding	8	5
No bleeding	30	32

\* Data are expressed as number.



**Fig. 2. Occurrence of bleeding complications related to randomization group and use of anticoagulant medication before randomization. Gray dots indicate patients without FFP transfusion before intervention, black dots indicate patients transfused with 12 mL/kg before intervention. Encircled dots indicate patients who received anti-PLT therapy less than 3 days before the intervention.**

major bleeding complication was a hemothorax after ultrasound-guided insertion of a chest drainage system (Pleural Catheter, RM Temena GmbH, Felsberg, Germany) in a patient randomly assigned not to receive FFP transfusion. The patient was treated with 100 mg of aspirin once daily and unfractionated heparin in a dose of 500 IU/hr. The heparin was discontinued more than 3 hours before the procedure. Coagulation tests 1 hour before the intervention showed a PT of 18.9 seconds, an INR of 1.71, activated partial thromboplastin time (APTT) 47 seconds, fibrinogen 2.3 g/L, and a PLT count of  $34 \times 10^9/L$ . Within the first hour after insertion of the chest drainage system 300 mL of blood ran from the drain. In response to this complication the patient was transfused with 3 units of RBCs, 3 units of FFP, and 1 unit of PLTs, which resulted in cessation of the bleeding and stabilization of the patient.

As the primary outcome of major bleeding only occurred once, meaningful statistical analysis was not

possible. Therefore, bleeding data (major and minor bleeding complications) were aggregated into bleeding and no bleeding categories. Occurrence of bleeding did not differ between groups (eight events in the FFP group compared to six in the nontransfused group,  $p = 0.77$ ; Table 3). However, the observed difference in occurrence of bleeding was 4.8% to the detriment of the group transfused with FFP, while a difference of 3% to the detriment of the nontransfused group was allowed. Noninferiority analysis generated a chi-square of 2.05 (df 1,  $p = 0.08$  [one sided]) 1 hour after the intervention and a chi-square of less than 0.01 (df 1,  $p = 0.50$  [one sided]) 24 hours after the intervention.

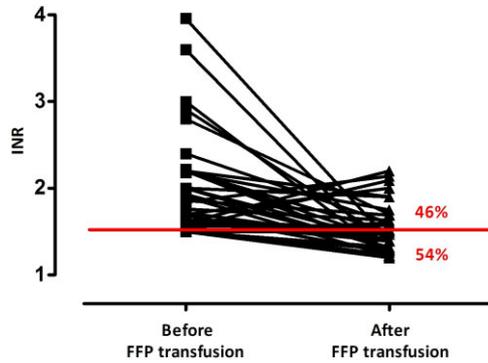
Preprocedural omission of FFP was not associated with increased occurrence of bleeding (relative risk, 1.17; 95% confidence interval [CI], 0.62-2.19;  $p = 0.78$ ). Preprocedural use of anticoagulation (PLT inhibitors, therapeutic use of heparin or low-molecular-weight heparin) was not associated with increased occurrence of bleeding (relative risk, 1.47; 95% CI, 0.55-3.92;  $p = 0.44$ ; Fig. 2). Patients randomly assigned to FFP transfusion received a median of 3 FFP units (IQR, 2-4 units). FFP transfusion before the procedure did not affect transfusion requirements in the first 24 hours after the procedure (Table 2).

### Correction of INR

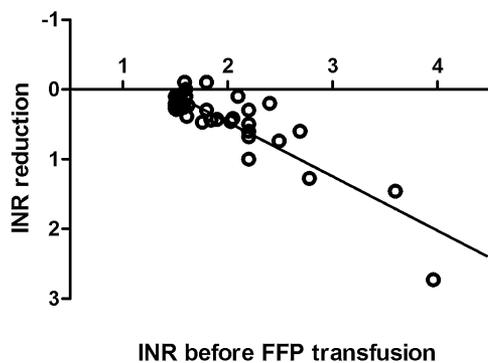
FFP transfusion resulted in a median reduction of INR from 1.8 (IQR, 1.5-2.5) to 1.4 (IQR, 1.3-1.63;  $p < 0.001$ ). However, only 54% of patients had a corrected INR to less than 1.5 after FFP transfusion (Fig. 3). The effect of FFP on INR reduction varied widely. Patients with higher pretransfusion INR values experienced the greatest reduction after FFP transfusion ( $r = 0.68$ ,  $p < 0.01$ ; Figs. 3 and 4).

### Clinical outcome

At baseline, lung injury scores were increased in both groups, with values indicating moderate to severe lung injury, consistent with underlying morbidity of these patients. After the intervention, lung injury score and oxygenation score tended to be lower in the FFP group, but this did not reach statistical significance. Degree of change



**Fig. 3.** Effect of FFP transfusion (12 mL/kg) on correction of INR in 38 patients randomly assigned to the transfusion group. The gray line indicates an INR value of 1.5.



**Fig. 4.** Correlation of INR value before FFP transfusion and magnitude of effect of FFP transfusion.

in lung injury score after 24 hours did not differ between groups. Duration of mechanical ventilation was significantly longer in patients transfused with FFP compared to nontransfused patients ( $p = 0.01$ ). Additional linear regression identified the presence of sepsis and liver disease as important contributors to prolonged duration of mechanical ventilation. Furthermore, the incidence of VAP was significantly higher in the FFP group patients.

ICU length of stay did not differ between both groups. Mortality tended to be higher in the nontransfused group (51% mortality in patients transfused with FFP compared to 71% in those not transfused with FFP before the intervention [ $p = 0.08$ ]; Table 4). Additional linear regression demonstrated that liver disease was the sole predictor for mortality ( $p = 0.056$ ). Hereby, liver disease was a confounder for mortality.

## DISCUSSION

In this multicenter randomized controlled trial, occurrence of bleeding complications after an invasive procedure in critically ill patients with a coagulopathy did not differ between patients with or without a prophylactic FFP

transfusion. Due to limited inclusion, noninferiority of omitting FFP transfusion could not be demonstrated. Post hoc analysis showed a trend toward noninferiority with a 5% higher bleeding rate in the transfused group compared to nontransfused patients. FFP transfusion was associated with prolonged duration of mechanical ventilation and increased VAP rates.

Our study is the first randomized controlled trial on the efficacy of prophylactic FFP transfusion to prevent bleeding in coagulopathic patients undergoing an invasive procedure. Previous studies on prophylactic FFP transfusion reported the effect of FFP on laboratory variables but not on bleeding.<sup>12,28</sup> In this trial, only one major bleeding occurred. Minor bleeding occurred in up to 17% of patients and mostly consisted of prolonged oozing of insertion site or hematoma formation, not requiring any specific therapy or transfusion. Occurrence of minor bleeding is of limited value for clinical practice and most likely clinicians administer FFP to prevent major bleeding complications. From our data it is not possible to determine whether a lack of difference in occurrence of minor bleeding complications also has predictive value for the occurrence of major bleeding complications. However, retrospective studies also showed that the incidence of major bleeding after an invasive procedure in patients with a prolonged INR is less than 1%.<sup>29-31</sup> Low incidence of bleeding has been reported in observational studies in coagulopathic patients receiving central venous catheter placement<sup>32,33</sup> and percutaneous tracheotomy<sup>15</sup> and after thoracocentesis.<sup>14,34</sup> Also, procedure-related bleeding complications were not influenced by the administration of FFP.<sup>14,16</sup> Our data are in line with previous reported observations that invasive procedures can be safely carried out in critically ill patients with a coagulopathy.

Bleeding is a subjective endpoint. We could not blind the transfusion bags and manufacturing a placebo was not considered feasible. Therefore, we have chosen for an observer blinded to intervention safeguarding objectivity. The endpoint evaluation in a PROBE study is as reliable as a double-blind study, provided that the same criteria are applied.<sup>35</sup> In addition, it is shown that results from double-blind, placebo-controlled, and PROBE trials are statistically comparable.<sup>36</sup> The HEME tool used to assess procedure-related relevant bleeding in our trial has been validated for ICU patients, with a high interrater agreement.<sup>25</sup> Another frequently used tool, the World Health Organization bleeding scale, which assesses the presence of petechiae or mucosal bleeding, is validated for patients with cancer but not in the critically ill.<sup>37</sup> A possible disadvantage of the HEME tool is that some items, such as decrease in systolic blood pressure or increase in heart rate, may also occur in the absence of bleeding. However, assessors were asked to consider such physiologic changes only if they occurred in the absence of other causes.<sup>25</sup>

**TABLE 4. Clinical outcomes 24 hours after randomization\***

	FFP transfusion (n = 38)	No FFP transfusion (n = 38)	p value
Lung injury score	2 (0.8-2.5)	1.25 (0.4-2.4)	0.28
P/F ratio	203 (143-308)	248 (180-308)	0.51
VAP	8 (3)	5 (1)	0.001
Mechanical ventilation days	11 (6-16)	3 (2-12)	0.01
SOFA 24 hr after intervention	12 (9-16)	11 (9-14)	0.68
ICU length of stay	12 (6-19)	7 (3-17)	0.13
Overall mortality	51 (19)	71 (27)	0.08

\* Data are expressed as median (interquartile range).

P/F = pO<sub>2</sub> (mmHg)/fraction of inspired oxygen; SOFA = Sequential Organ Failure Assessment.

Although FFP transfusion resulted in a reduction of INR in all patients, only half corrected to an INR of less than 1.5, a value that is a reported trigger for FFP transfusion in clinical practice.<sup>8</sup> In line, most studies show a reduction and not a complete normalization of INR after FFP transfusion.<sup>10,12,19,38</sup> This is probably due to low FFP doses or attempts to correct minimally elevated INR, which is not possible.<sup>28,39</sup> It can be argued that no effect of FFP transfusion was seen in our study due to a low dose. Studies on the dose of FFP to correct INR in ICU patients show conflicting results. In a small cohort of 22 patients, a dose of 33 mL/kg was more effective in achieving target levels of coagulation factors compared to 12 mL/kg.<sup>12</sup> However, in a larger trial in ICU patients, 20 mL/kg did not differ from 12 mL/kg in correction of INR or increasing coagulation factors above a minimum hemostatic threshold.<sup>38</sup> Of note, audits on FFP transfusion show that the dose of prophylactic FFP transfusion used in clinical practice is often less than 10 mL/kg.<sup>9,40</sup> The strength of this study is the use of a fixed dose, which is in line with doses used in common clinical practice.<sup>7,8,10,40,41</sup> Although we cannot exclude that higher doses of FFP may prevent bleeding, we think that underdosing of FFP is unlikely to have contributed to the absence of a difference in bleeding complications between both groups, because there was no trend toward efficacy of FFP.

In line with previous reports, the effect of FFP transfusion on INR decrease correlated with pretransfusion INR.<sup>12,28</sup> In the current study, the lower INR boundary was chosen in line with clinical practice, in which an INR of at least 1.5 is frequently reported to be a transfusion trigger,<sup>6,8</sup> in particular when an intervention is scheduled.<sup>40</sup> We chose an upper limit of an INR of not more than 3.0 to prevent noncompliance by participating physicians.<sup>11</sup>

In recent years, many reports have been published on the adverse effects of FFP. FFP transfusion is an independent risk factor for new onset of acute lung injury,<sup>42-45</sup> in particular in patients who are mechanically ventilated.<sup>46</sup> Furthermore, studies consistently report an association between FFP and increased length of ICU stay.<sup>6,45,46</sup> We did not confirm an association between FFP and lung injury, probably due to low numbers of patients. Of note, oxygen-

ation tended to be worse and duration of mechanical ventilation was prolonged in patients transfused with FFP, associated with an increased incidence of VAP in the transfused group. This observation is consistent with reports in trauma and nontrauma patients, where transfusion of FFP has been shown to be independently associated with infection and pneumonia.<sup>21,47</sup> However, in our cohort duration of mechanical ventilation was affected by the presence of sepsis or liver disease, hereby impeding conclusions about the association between FFP and duration of mechanical ventilation. Whether FFP transfusion indeed can induce transfusion-related immunomodulation is, however, under debate.<sup>48,49</sup>

The major limitation of our trial is that we stopped early due to slow inclusion. Despite the addition of extra recruitment sites, we were only able to randomize 20% of the targeted patient number. Several factors contributed to this disappointing inclusion rate. First, there is a small window of opportunity to include patients. Placement of a central venous catheter may be an urgent procedure in critically ill patients, which does not allow postponing the intervention until informed consent is obtained. This accounted for a 20% loss of potentially eligible patients. Second, despite the fact that certified ICU staff physicians requested informed consent, denial rate was high. Third, treating physicians were at times reluctant to randomize patients for the trial. The reasons were bidirectional: physicians who wanted to correct coagulopathy before the invasive procedure did not want to take the risk of randomization to no FFP, and on the other hand physicians who felt no need for FFP transfusion did not want to risk having to administer FFP. Therefore, despite the expressed need for trials on the use of FFP in critically ill patients with a coagulopathy, preferences of treating physicians about the use of FFP were major constraints to the conduct of a successful clinical trial. We feel that future trials on the efficacy of FFP may not be feasible to conduct, at least in the Netherlands, and that further knowledge on the efficacy of FFP should be gathered from prospective cohort studies or retrospective studies.

Another limitation of our study is the randomization imbalance resulting in a higher proportion of patients with liver disease in the no FFP group. As liver disease

influenced mortality, it also affected duration of mechanical ventilation. Of note, the combined outcome of major and minor bleeding was assessed within 24 hours; therefore, these outcomes are less likely to be affected by the presence or absence of liver disease. Despite disappointing inclusion rates, our study is the largest randomized trial to date on the effectiveness of FFP to prevent bleeding in critically ill patients with a coagulopathy and we believe that results are of interest to any physician involved in performing invasive procedures.

In conclusion, the effect of FFP on major bleeding complications could not be assessed due to low inclusion rate and low incidence of major bleeding complications in critically ill patients with a coagulopathy undergoing an invasive procedure. The combined outcome of major and minor bleeding complications did not differ between patients with or without FFP transfusion. A dose of 12 mL/kg of FFP only partially corrected INR.

#### CONFLICT OF INTEREST

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