OBSERVATIONAL STUDY

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Plasma Transfusion and Procoagulant Product Administration in Extracorporeal Membrane Oxygenation: A Secondary Analysis of an International Observational Study on Current Practices

Maite M.T. van Haeren, MD[1]
Senta Jorinde Raasveld, MD[1]
Mina Karami, MD, PhD[2]
Dinis Dos Reis Miranda, MD, PhD[3]
Loes Mandigers, MD[3,4]
Dieter F. Dauwe, MD, PhD[5]
Erwin De Troy, MD[5]
Federico Pappalardo, MD, PhD[6]
Evgeny Fominskiy, MD, PhD[7]
Walter M. van den Bergh, MD, PhD[8]
Annemieke Oude Lansink-Hartgring, MD, PhD[8]
Franciska van der Velde, MD[9]
Jacinta J. Maas, MD, PhD[9]
Pablo van de Berg, MD, PhD[10]
Maarten de Haan, ECCP[11]
Dirk W. Donker, MD, PhD[12,13]
Christiaan L. Meuwese, MD, PhD[3]
Fabio Silvio Taccone, MD, PhD[14]
Lorenzo Peluso, MD[14]

OBJECTIVES: To achieve optimal hemostatic balance in patients on extracorporeal membrane oxygenation (ECMO), a liberal transfusion practice is currently applied despite clear evidence. We aimed to give an overview of the current use of plasma, fibrinogen concentrate, tranexamic acid (TXA), and prothrombin complex concentrate (PCC) in patients on ECMO.

DESIGN: A prespecified subanalysis of a multicenter retrospective study. Venovenous (VV)-ECMO and venoarterial (VA)-ECMO are analyzed as separate populations, comparing patients with and without bleeding and with and without thrombotic complications.

SETTING: Sixteen international ICUs.

PATIENTS: Adult patients on VA-ECMO or VV-ECMO.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Of 420 VA-ECMO patients, 59% ($n = 247$) received plasma, 20% ($n = 82$) received fibrinogen concentrate, 17% ($n = 70$) received TXA, and 7% of patients ($n = 28$) received PCC. Fifty percent of patients ($n = 208$) suffered bleeding complications and 27% ($n = 112$) suffered thrombotic complications. More patients with bleeding complications than patients without bleeding complications received plasma (77% vs. 41%, $p < 0.001$), fibrinogen concentrate (28% vs 11%, $p < 0.001$), and TXA (23% vs 10%, $p < 0.001$). More patients with than without thrombotic complications received TXA (24% vs 14%, $p = 0.02$, odds ratio 1.75) in VA-ECMO, where no difference was seen in VV-ECMO. Of 205 VV-ECMO patients, 40% ($n = 81$) received plasma, 6% ($n = 12$) fibrinogen concentrate, 7% ($n = 14$) TXA, and 5% ($n = 10$) PCC. Thirty-nine percent ($n = 80$) of VV-ECMO patients suffered bleeding complications and 23% ($n = 48$) of patients suffered thrombotic complications. More patients with than without bleeding complications received plasma (58% vs 28%, $p < 0.001$), fibrinogen concentrate (13% vs 2%, $p < 0.01$), and TXA (11% vs 2%, $p < 0.01$).

CONCLUSIONS: The majority of patients on ECMO receive transfusions of plasma, procoagulant products, or antifibrinolytics. In a significant part of the plasma transfused patients, this was in the absence of bleeding or prolonged international normalized ratio. This poses the question if these plasma transfusions were administered for another indication or could have been avoided.

KEY WORDS: blood coagulation factors; coagulants; extracorporeal membrane oxygenation; fibrinogen; plasma; transfusion

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Roberto Lorusso, MD, PhD[15,16]
Thijs S.R. Delnoij, MD[16,17]
Erik Scholten, MD[18]
Martijn Overmars, MD[18]
Višnja Ivancan, MD, PhD[19]
Robert Bojčić, MD[19]
Jesse de Metz, MD, PhD[20]
Bas van den Bogaard, MD, PhD[20]
Martin de Bakker, MB, BCh, BAO[21]
Benjamin Reddi, MBChB, PhD[21]
Greet Hermans, MD, PhD[22,23]
Lars Mikael Broman, MD, PhD[24,25]
José P.S. Henriques, MD, PhD[2]
Jimmy Schenk, PhD[1,26,27]
Alexander P.J. Vlaar, MD, PhD[1]
Marcella C.A. Müller, MD, PhD[1]

KEY POINTS

Question: What are the current practices in plasma transfusions, procoagulant products, and antifibrinolytic administrations in patients receiving VA-ECMO or VV-ECMO?

Findings: The majority of patients receive transfusions of plasma, procoagulant products, or antifibrinolytics. In a significant part of the plasma transfused patients, this was in the absence of bleeding or prolonged international normalized ratio.

Meanings: The findings of this study poses the question of what the indications for plasma transfusions in ECMO patients are and if plasma transfusions could possibly be avoided, which needs to be further investigated in prospective studies.

Extracorporeal membrane oxygenation (ECMO) is a potential life-saving supportive therapy in severe cardiac or respiratory failure. The two most commonly used modes consist of venovenous ECMO (VV-ECMO) for respiratory failure and veno-arterial ECMO (VA-ECMO) for cardiac or circulatory failure (1).

Achieving the optimal hemostatic balance in patients on ECMO is challenging. On the one hand, as the blood of the patient is exposed to artificial material, it induces a hypercoagulable state, which can lead to mechanical failure (2), and thrombotic complications in up to 10% (3). On the other hand, enhanced fibrinolysis, consumption of platelets and coagulation factors, and acquired von Willebrand disease (4, 5), together with the use of anticoagulant medication, create a hypocoagulable state which can result in major bleeding, occurring in up to 30% of the ECMO patients (2, 3, 6).

Hypocoagulability accompanied by bleeding can be treated in several ways. In addition to red blood cells (RBC) and platelets, plasma, fibrinogen concentrate, prothrombin complex concentrate (PCC), and other coagulation factors and antifibrinolytics can be administered. However, little is known about the daily practice of the correction of coagulopathy in patients on ECMO. Larger studies on this topic are available in general critically ill ICU patients (7), surgical or trauma patients (8, 9), and cardiac surgery patients (10–15). Most data on ECMO patients on the use of plasma and procoagulant products result from pediatric (16) or bleeding adult patients on ECMO (17). Studies on plasma transfusion and administration of other procoagulant products in the adult ECMO population, specifically in nonbleeding patients, are scarce.

The aim of this study was to create an overview of the current use of plasma and procoagulant products in patients receiving support with VA-ECMO and VV-ECMO. In addition, we aimed to assess differences between patients with and without a bleeding complication, and with and without a thrombotic complication.

MATERIALS AND METHODS

Study Design

This was a prespecified subanalysis of an international, multicenter observational cohort study that included patients receiving ECMO in 16 ICUs (**Supplementary S1**, http://links.lww.com/CCX/B229). The study was approved by the Amsterdam University Medical Center institutional review board (AMC, W19_222 no. 19.267), followed by local approvals, and was registered at the Netherlands Trial Register (NL8413, date

of registration February 2, 2020). This study involving human participants was in accordance with the ethical standards of the institutional and national research committee, and with the 1975 Helsinki Declaration. The study consisted of retrospective data collection using patient records, combined with a survey on local transfusion guidelines and anticoagulation strategy (**Supplementary S2**, http://links.lww.com/CCX/B229). This analysis adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Study Population

Eligibility criteria consisted of adult patients who received any mode of ECMO (including extracorporeal cardiopulmonary resuscitation) between January 1, 2018, and July 1, 2019, for at least 24 hours. For the current analyses, we excluded patients receiving either triple cannulation configurations or extracorporeal CO_2 removal, and patients with missing data on whether they had suffered a bleeding or thrombotic event during ECMO.

Data Collection

A full list of collected variables can be shown in **Supplementary materials** (**Supplement S3**, http://links.lww.com/CCX/B229). Laboratory values and transfusion parameters were collected daily as long as the patient was supported by ECMO, up to a maximum of 28 days. Data on plasma transfusion, administration of fibrinogen concentrate (both fibrinogen concentrate and cryoprecipitate), PCC (both three-factor and four-factor concentrates), and tranexamic acid (TXA) were collected.

A bleeding event was defined according to the Extracorporeal Life Support Organization [ELSO] definitions: bleeding that led to 1) surgical exploration or intervention by an interventional radiologist or 2) required immediate transfusion of greater than 2 RBC units due to a sudden fall in hemoglobin greater than 1 mmol/L, new hemodynamic instability or overt bleeding. Thrombotic events were divided into arterial, venous, and mechanical thrombosis, in line with the ELSO data registry. Thrombotic events included arterial thrombosis resulting in "stroke," "leg ischemia," or "other," venous thrombosis in "upper extremity," "lower extremity," or "other," and mechanical thrombosis in the cannula, pump, or oxygenator. For the comparison between patients with and without a bleeding complication, one or more bleeding events allocated a patient to a "bleeding patient." For the comparison of a patient with or without a thrombotic complication, any of the abovementioned thrombotic events allocated a patient to a "patient with a thrombotic complication."

Outcomes

The primary objective was to give an overview of the use of plasma, fibrinogen concentrate, PCC, and TXA. VA-ECMO- and VV-ECMO-supported patients were analyzed separately as two different populations and were not compared. The use of these products was reported in the total VA-ECMO or VV-ECMO population and further compared in patients with or without a bleeding complication and with or without a thrombotic complication. The primary outcomes were the proportion of patients receiving the abovementioned products; the number of days on which the products were administered; the amount of product per day the product was administered; the total amount of administered products for the duration of the ECMO run.

Secondary objectives included an overview of patient outcomes per ECMO mode and an overview of adherence to the ELSO guideline (18), using thresholds of laboratory values (international normalized ratio [INR], and fibrinogen) in bleeding and nonbleeding patients per ECMO mode.

Statistical Analysis

All statistical analyses were performed in R with R studio interface (version 4.0.3, R Foundation for Statistical Computing, Vienna, Austria) (19). All continuous variables were non-normally distributed and presented as median (first - third quartile). Categorical variables were reported as counts (%). Data were missing not at random for pre-ECMO laboratory values, with high correlation between missing laboratory values, therefore no method for imputing missing data was performed. Subgroup analyses were performed to compare patients with or without a bleeding complication and with or without a thrombotic complication per ECMO mode. Differences were reported as estimated median differences with 95% CIs estimated using the Hodges-Lehmann method. Differences were tested for significance by the Wilcoxon rank sum test

on continuous variables and a Chi-square test on categorical variables. The association between bleeding or thrombosis and receiving plasma and procoagulant products was assessed by performing exploratory multivariable logistic regression analyses, with ECMO run duration as a covariate to correct for, as longer ECMO run duration was deemed likely to affect the risk of receiving transfusion, regardless of bleeding or thrombotic complication. Results were portrayed with odds ratios (OR) and 95% CIs. Tests were two-sided with a *p* value considered significant of less than 0.05.

RESULTS

Population

Six hundred forty-five patients were enrolled for data collection, of whom 625 were eligible for inclusion. Reasons for exclusion are given in Supplementary materials (**Supplementary S4**, http://links.lww.com/CCX/B229). A total of 420 patients received VA-ECMO and 205 received VV-ECMO. Patient demographics are shown in **Supplementary S5** (http://links.lww.com/CCX/B229). The main reason to initiate VA-ECMO was myocardial infarction (*n* = 117) or postcardiotomy (*n* = 113). In VV-ECMO patients, pneumonia (*n* = 72) and acute respiratory distress syndrome (*n* = 63) were the most frequent indications.

Questionnaire on Employed Transfusion Thresholds, Type of Products, and Anticoagulation Strategy

The questionnaire on thresholds for plasma, PCC, and fibrinogen administration showed a large variability between participating centers, with thresholds for INR varying from 1.5 to 2.0 and for fibrinogen from 1.0 to 2.0 g/L. Thresholds were mostly defined for bleeding patients and did not differ between VA-ECMO or VV-ECMO patients in any of the participating centers (**Supplementary S2*B***, http://links.lww.com/CCX/B229). For plasma transfusions, half of the centers used fresh frozen plasma, and half used pooled plasma. For fibrinogen suppletion and PCC administration, 12 of 16 centers used fibrinogen concentrate and four-factor concentrate (Supplementary S2*B*, http://links.lww.com/CCX/B229). All but one center used unfractionated heparin as anticoagulation. All but one center monitored their anticoagulation with activated partial thromboplastin time (aPTT) with lower thresholds ranging from 40 to 60 seconds and upper thresholds ranging from 50 to 90 seconds. Three centers additionally monitored anti-Xa levels, and one center additionally performed viscoelastic testing (thromboelastometry [ROTEM], Werfen Benelux, Breda, The Netherlands). Five centers had different ranges for VA-ECMO and VV-ECMO (Supplementary S2*C*, http://links.lww.com/CCX/B229).

Plasma and Procoagulant Product Use in VA-ECMO

Of the 420 patients receiving VA-ECMO, more than half of the patients (*n* = 247, 59%) received one or more plasma transfusions (**Table 1**). Transfused patients received a total of 7 (3–13) plasma units during their ECMO run, equivalent to 21 (10–43) mL/kg of body weight. Per day, when a transfusion was administered, they received 4 (2–6) plasma units (equivalent to 12 [7–20] mL/kg). Most plasma transfusions were given in the first 3 days of ECMO (**Supplementary S6**, http://links.lww.com/CCX/B229). Fibrinogen concentrate, TXA, and PCC were less frequently administered, respectively, in 20% (*n* = 82), 17% (*n* = 70), and 7% (*n* = 28) of the patients (Table 1).

Half of the VA-ECMO patients suffered a bleeding complication (50%, *n* = 208, **Table 2**). These patients more often received plasma, fibrinogen concentrate, and TXA compared to nonbleeding patients. Of note, of the nonbleeding VA-ECMO patients, 41% (*n* = 87) received one or more plasma transfusions during their ECMO support. However, bleeding patients received substantially more plasma units than nonbleeding patients: 9 (4–16) versus 4 (2–8) units ($p < 0.001$, Table 2). Compared with non bleeding patients, bleeding patients had significantly higher odds of receiving plasma (OR 4.47; 95% CI, 2.93–6.91; $p < 0.001$), fibrinogen concentrate (OR 3.50; 95% CI, 2.07–6.10; $p < 0.001$), and TXA (OR 2.45; 95% CI, 1.43–4.31; $p = 0.002$, **Fig. 1** and **Supplementary S7**, http://links.lww.com/CCX/B229). We observed a statistically significantly higher proportion of bleeding patients in postcardiotomy VA-ECMO patients versus other VA-ECMO indications ("myocardial infarction" or "other," **Supplementary S8**, http://links.lww.com/CCX/B229). After correcting for ECMO indication in a post hoc regression, bleeding patients remained

TABLE 1.
Plasma and Procoagulant Product Use Per Extracorporeal Membrane Oxygenation Mode

Variable	Total, *n* = 625	VA-ECMO, *n* = 420	VV-ECMO, *n* = 205
Plasma			
Received plasma, *n* (%)	328 (53)	247 (59)	81 (40)
Total amount of plasma, units (median [IQR])	6 (3–12)	7 (3–13)	5 (3–8)
Total amount of plasma, mL/kg (median [IQR])	20 (10–40)	21 (10–43)	17 (10–34)
Days plasma received (median [IQR])	2 (1–3)	2 (1–3)	1 (1–3)
Plasma per administered day, units(median [IQR])	3 (2–5)	4 (2–6)	3 (2–4)
Plasma per administered day, mL/kg (median [IQR])	10 (6–18)	12 (7–20)	9 (6–17)
Fibrinogen concentrate			
Received fibrinogen, *n* (%)	94 (15)	82 (20)	12 (6)
Total amount of fibrinogen, g (median [IQR])	2.5 (2.0–4.4)	3.0 (2.0–4.9)	2.0 (1.0–3.3)
Days fibrinogen received (median [IQR])	1 (1–1)	1 (1–1)	1 (1–1)
Fibrinogen per administered day, g (median [IQR])	2.0 (2.0–4.0)	2.0 (2.0–4.0)	2.0 (1.0–3.3)
TXA			
Received TXA, *n* (%)	84 (13)	70 (17)	14 (7)
Total amount of TXA, g (median [IQR])	2.0 (1.0–3.0)	2.0 (1.5–3.0)	2.0 (1.0–2.0)
Days of TXA (median [IQR])	1 (1–1)	1 (1–1)	1 (1–1)
TXA per administered day, g (median [IQR])	2.0 (1.0–2.0)	2.0 (1.0–2.0)	2.0 (1.0–2.0)
PCC			
Received PCC, *n* (%)	38 (6)	28 (7)	10 (5)
Total amount of PCC, IU (median [IQR])	1500 (750–2,500)	1,500 (500–2,625)	2,500 (1,000–2,500)
Days PCC received (median [IQR])	1 (1–1)	1 (1–1)	1 (1–1)
PCC per administered day, IU (median [IQR])	1,500 (750–2,500)	1,500 (500–2,500)	2,250 (1,000–2,500)

ECMO = extracorporeal membrane oxygenation, IU = International Unit, IQR = interquartile range, PCC = prothrombin complex concentrate, TXA = tranexamic acid, VA = venoarterial, VV = venovenous.
Total amount of products, days of products received and product per administered day are all calculated in only the patients that received the said product.

more likely to receive products (**Supplementary S9**, http://links.lww.com/CCX/B229).

One or more thrombotic events occurred in 27% (*n* = 112) of patients supported by VA-ECMO (**Table 3**). TXA was given in a larger proportion of patients that developed thrombotic complications compared to those who did not (24% vs 14%, $p = 0.02$). No differences in frequency or dosages of the other products were seen between patients with and without thrombotic complications (Table 3). Compared with patients without a thrombotic complication, patients with a thrombotic complication had significantly higher odds of receiving or having received TXA (OR 1.75; 95% CI, 1.00–3.04; $p = 0.048$, Fig. 1 and Supplementary S7, http://links.lww.com/CCX/B229).

Plasma and Procoagulant Product Use in VV-ECMO

Of the 205 VV-ECMO patients, 40% of the patients (*n* = 81) received one or more plasma transfusions (Table 1) during their ECMO runs. Patients received 5 (3–8) plasma units in total, equivalent to 17 (10–34) mL/kg of bodyweight. They received 3 units (2–4) per administered day (equivalent to 9 [6–17] mL/kg bodyweight). Most plasma transfusions were administered on the first 2 days of ECMO (Supplementary S6, http://links.lww.com/CCX/B229). Fibrinogen concentrate, TXA, and PCC were all less frequently given, respectively, in 6% (*n* = 12), 7% (*n* = 14), and 5% (*n* = 10) of the patients (Table 1).

TABLE 2.
Plasma and Procoagulant Product Use in Bleeding and Nonbleeding Patients

Variable	VA-ECMO			VV-ECMO		
	Bleeding, *n* = 208 (50%)	Nonbleeding, *n* = 212 (50%)	Estimated Difference + 95% CI	Bleeding, *n* = 80 (39%)	Nonbleeding, *n* = 125 (61%)	Estimated Difference + 95% CI
Plasma						
Plasma received, *n* (%)	160 (77)	87 (41)	36 (27–45)[a]	46 (58)	35 (28)	30 (15–44)[a]
Total amount of plasma, units (median [IQR])	9 (4–16)	4 (2–8)	4 (2–6)[a]	6 (3–11)	4 (3–7)	1 (0–3)
Total amount of plasma, mL/kg (median [IQR])	28 (13–58)	15 (7–26)	12 (7–18)[a]	19 (10–40)	12 (9–26)	4 (–2–10)
Days plasma received (median [IQR])	2 (1–3)	1 (1–2)	1 (0–1)[a]	1 (1–3)	1 (1–3)	0 (0–0)
Plasma per administered day, units (median [IQR])	4 (3–7)	3 (2–5)	1 (0–2)[b]	3 (2–5)	2 (2–4)	0 (0–1)
Plasma per administered day, mL/kg (median [IQR])	12 (8–23)	10 (6–16)	3 (0–5)[c]	10 (7–17)	8 (4–12)	1 (–2–4)
Fibrinogen concentrate						
Fibrinogen received, *n* (%)	59 (28)	23 (11)	17 (10–25)[a]	10 (13)	2 (2)	11 (2–20)[b]
Total amount of fibrinogen, g (median [IQR])	2.0 (2.0–6.0)	4.0 (2.0–4.1)	0 (–1–1)	2.0 (1.0–2.8)	3.6 (2.8–4.4)	–1 (–4.2–8.0)
Days fibrinogen received (median [IQR])	1 (1–2)	1 (1–1)	0 (0–0)	1 (1–1)	1 (1–1)	0 (0–0)
Fibrinogen per administered day, g (median [IQR])	2.0 (2.0–4.0)	2.5 (2.0–4.0)	0 (–1–0.5)	2.0 (1.0–2.8)	3.6 (2.8–4.4)	–1 (–4.2–8.0)
TXA						
TXA received, *n* (%)	48 (23)	22 (10)	13 (5–20)[a]	11 (14)	3 (2)	12 (2–20)[b]
Total amount of TXA, g (median [IQR])	2.0 (1.5–4.0)	2.0 (1.1–2.0)	0 (0–10.0)	2.0 (1.5–2.5)	1.0 (1.0–1.5)	1.0 (0–2.0)
Days TXA received (median [IQR])	1 (1–1)	1 (1–1)	0 (0–0)	1 (1–1)	1 (1–1)	0 (0–1)
TXA per administered day, g (median [IQR])	2.0 (1.0–2.0)	1.8 (1.0–2.0)	0 (0–0.7)	2.0 (1.3–2.0)	1.0 (1.0–1.5)	0.5 (–0.5–1.0)

(*Continued*)

TABLE 2. (*Continued*)

Plasma and Procoagulant Product Use in Bleeding and Nonbleeding Patients

Variable	VA-ECMO			VV-ECMO		
	Bleeding, *n* = 208 (50%)	Nonbleeding, *n* = 212 (50%)	Estimated Difference + 95% CI	Bleeding, *n* = 80 (39%)	Nonbleeding, *n* = 125 (61%)	Estimated Difference + 95% CI
PCC						
PCC received, *n* (%)	17 (8)	11 (5)	3 (−2–8)	6 (8)	4 (3)	5 (−3–12)
Total amount of PCC, IU (median [IQR])	1,500 (750–3,000)	1,500 (500–2,250)	250 (−500–2,000)	2,500 (2,500–3,325)	875 (688–1,375)	1,634 (0–3,100)
Days PCC received (median [IQR])	1 (1–1)	1 (1–1)	0 (0–0)	1 (1–1)	1 (1–1)	0 (0–1)
PCC per administered day, IU (median [IQR])	1,500 (750–2,500)	1,500 (500–2,250)	250 (−700–1,500)	2,500 (2,125–2,500)	875 (688–1,375)	1,500 (0–2,600)

ECMO = extracorporeal membrane oxygenation, IU = International Unit, IQR = interquartile range, PCC = prothrombin complex concentrate, TXA = tranexamic acid, VA = venoarterial, VV = venovenous.

[a]$p < 0.001$.

[b]$p < 0.01$.

[c]$p < 0.05$.

Total amount of product, days of products received and product per administered day are calculated in only the patients that received the said product; estimated difference + 95% CIs are calculated by Hodges-Lehman.

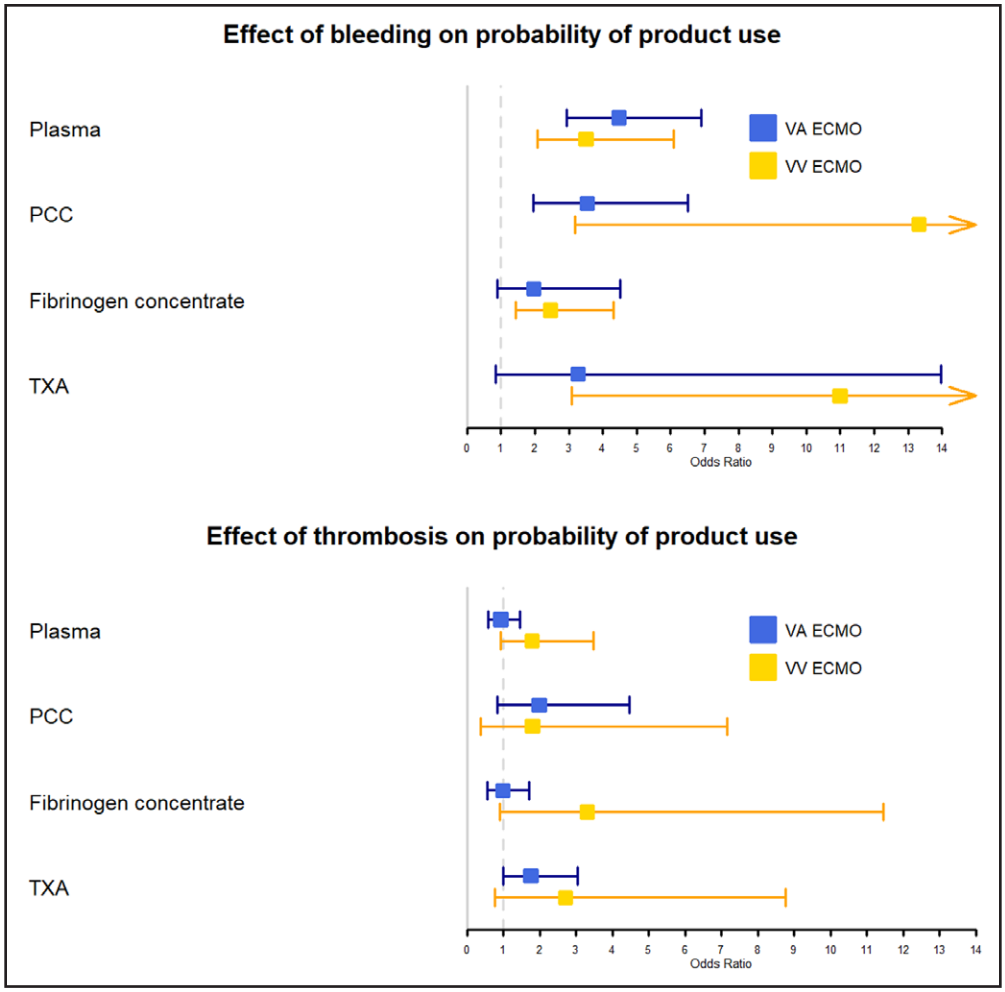

Figure 1. Regression analyses—effect of bleeding and thrombosis on product use. The odds ratios are presented with 95% CIs and corrected for duration on extracorporeal membrane oxygenation (ECMO). VA = venoarterial, VV = venovenous, PCC = prothrombin complex concentrate, TXA = tranexamic acid.

Of the VV-ECMO patients, 39% (n = 80) suffered a bleeding complication (Table 2). A larger proportion of the bleeding patients compared with the nonbleeding patients received plasma, fibrinogen concentrate, and TXA. However, 28% (n = 35) of the nonbleeding patients also received plasma transfusions. In patients receiving plasma, fibrinogen concentrate, and TXA, no differences in dosages were seen between bleeding and nonbleeding patients (Table 2). Compared with nonbleeding patients, bleeding patients had significantly higher odds of receiving plasma (OR 3.54; 95% CI, 1.96–6.51; $p < 0.001$), fibrinogen concentrate (OR 13.32; 95% CI, 3.17–91.48; $p = 0.002$), and TXA (OR 10.99; 95% CI, 3.08–52.20; $p < 0.001$, Fig. 1 and Supplementary S7, http://links.lww.com/CCX/B229).

A thrombotic event occurred in 23% (n = 48) of the VV-ECMO patients (Table 3). No differences between patients with a thrombotic complication to those without a thrombotic complication in VV-ECMO were seen in plasma or procoagulant product use (Table 3, Fig. 1, and Supplementary S7, http://links.lww.com/CCX/B229).

Patient Outcomes

Sixty-one percent (n = 258) of the VA-ECMO patients were successfully weaned, after which 47 patients deceased, leading to an overall survival of 50% (n = 211). The most common complications were bleeding (50%, n = 208), need for renal replacement therapy (RRT, 37%, n = 155), and infection (29%, n = 121) Of the thrombotic complications, leg ischemia was the most common (9%, n = 40) (**Supplementary S10**, http://links.lww.com/CCX/B229).

Of the VV-ECMO patients, 68% (n = 139) were successfully weaned, after which 14 patients deceased, leading to an overall survival of 62% (n = 126). The most common complications were infection (45%, n = 92), need for RRT (42%, n = 87), and bleeding (39%, n = 80). Of the thrombotic complications, thrombi in the oxygenator were the most common (11%, n = 22) (Supplementary S10, http://links.lww.com/CCX/B229).

Fifteen percent of VA-ECMO (n = 63) and 12% of VV-ECMO (n = 24) suffered both a thrombotic and a bleeding complication during their ECMO run.

ELSO Guideline Adherence Using Laboratory Values

In patients who suffered a bleeding complication, the INR was greater than 1.5 in 39% of the plasma

TABLE 3.

Plasma and Procoagulant Product Use in Patients With and Without Thrombotic Complications

Variable	VA-ECMO			VV-ECMO		
	Thrombotic Complications, *n* = 112 (27%)	No Thrombotic Complications, *n* = 308 (73%)	Estimated Difference + 95% CI	Thrombotic Complications, *n* = 48 (23%)	No Thrombotic Complications, *n* = 157 (77%)	Estimated Difference + 95% CI
Plasma						
Plasma received, *n* (%)	68 (61)	179 (58)	3 (−8 to 14)	24 (50)	57 (36)	14 (−4 to 31)
Total amount of plasma, units (median [IQR])	8 (3 to 14)	7 (3 to 12)	0 (−1 to 2)	7 (4 to 11)	5 (3 to 8)	2 (0 to 40)
Total amount of plasma, mL/kg (median [IQR])	20 (9 to 55)	24 (10 to 42)	0 (−5 to 5)	22 (10 to 40)	14 (10 to 26)	6 (−3 to 16)
Days plasma received (median [IQR])	2 (1 to 3)	2 (1 to 2)	0 (0 to 1)	2 (1 to 3)	1 (1 to 3)	0 (0 to 1)
Plasma per administered day, units (median [IQR])	3 (2 to 5)	4 (2 to 6)	0 (−1 to 0)	3 (2 to 4)	3 (2 to 4)	0 (−1 to 1)
Plasma per administered day, mL/kg (median [IQR])	10 (6 to 18)	12 (7 to 20)	−1 (−4 to 1)	9 (6 to 16)	10 (6 to 17)	0 (−3 to 3)
Fibrinogen concentrate						
Fibrinogen received, *n* (%)	21 (19)	61 (20)	1 (−10 to 8)	5 (10)	7 (5)	5 (−5 to 17)
Total amount of fibrinogen, g (median [IQR])	3.0 (2.0 to 11.0)	3.0 (2.0 to 4.0)	1.0 (0 to 20)	2.0 (2.0 to 4.0)	2.0 (1.0 to 2.5)	1.0 (−1 to 7)
Days fibrinogen received (median [IQR])	1 (1 to 2)	1 (1 to 1)	0 (0 to 0)	1 (1 to 1)	1 (1 to 1)	0 (0 to 0)
Fibrinogen per administered day, g (median [IQR])	2.0 (1.5 to 4.7)	2.0 (2.0 to 4.0)	0 (−0.5 to 1.0)	2.0 (2.0 to 4.0)	2.0 (1.0 to 2.5)	1.0 (−1 to 7)
TXA						
TXA received, *n* (%)	27 (24)	43 (14)	10 (1 to 20)[a]	5 (10)	9 (6)	4 (−6 to 15)
Total amount of TXA, g (median [IQR])	2.0 (1.5 to 4.0)	2.0 (1.3 to 2.5)	0 (0 to 10.0)	3.0 (1.0 to 3.0)	2.0 (1.0 to 2.0)	1.0 (−1.0 to 2.0)
Days TXA received (median [IQR])	1 (1 to 2)	1 (1 to 1)	0 (0 to 0)	1 (1 to 2)	1 (1 to 1)	0 (0 to 1)
TXA per administered day, g (median [IQR])	2.0 (1.5 to 2.0)	2.0 (1.0 to 2.0)	0 (0 to 0.5)	1.5 (1.0 to 2.0)	2.0 (1.0 to 2.0)	0 (−1.0 to 1.0)

(*Continued*)

TABLE 3. (*Continued*)

Plasma and Procoagulant Product Use in Patients With and Without Thrombotic Complications

Variable	VA-ECMO			VV-ECMO		
	Thrombotic Complications, *n* = 112 (27%)	No Thrombotic Complications, *n* = 308 (73%)	Estimated Difference + 95% CI	Thrombotic Complications, *n* = 48 (23%)	No Thrombotic Complications, *n* = 157 (77%)	Estimated Difference + 95% CI
PCC						
PCC received, *n* (%)	10 (9)	18 (6)	3 (–3 to 10)	3 (6)	7 (5)	1 (–7 to 11)
Total amount of PCC, IU (median [IQR])	1,750 (1,125 to 4,750)	1,250 (500 to 2,500)	661 (–500 to 3,000)	2,500 (1,625 to 3,050)	2,500 (1,000 to 2,500)	0 (–1,750 to 2,600)
Days PCC received (median [IQR])	1 (1 to 1)	1 (1 to 1)	0 (0 to 0)	1 (1 to 1)	1 (1 to 1)	0 (–1 to 0)
PCC per administered day, IU (median [IQR])	1,750 (1,125 to 4,750)	1,250 (500 to 2,375)	750 (–500 to 3,500)	2,500 (1,625 to 3,050)	2,000 (1,000 to 2,500)	500 (–1,750 to 2,600)

ECMO = extracorporeal membrane oxygenation, IU = International Unit, IQR = interquartile range, PCC = prothrombin complex concentrate, TXA = tranexamic acid, VA = venoarterial, VV = venovenous.

[a]*p* was 0.02.

Total amount of product, days of products received and product per administered day are calculated in only the patients that received the said product; estimated difference + 95% CIs are calculated by Hodges-Lehman.

transfusions in VA-ECMO and in 41% of the plasma transfusions in VV-ECMO. In patients on VA-ECMO, 10% (14 of 135) of plasma transfusions were given to nonbleeding patients with an INR greater than 3.0. For plasma transfusions in VV-ECMO, 11% (7 of 66) were given to nonbleeding patients with an INR greater than 3.0. Of the 34 times fibrinogen concentrate was administered in nonbleeding VA-ECMO patients, in 11 patients (32%) the fibrinogen level was less than 1.0 g/L. In VV-ECMO, 2 of 2 (100%) fibrinogen concentrate administrations in nonbleeding patients were given to patients with a fibrinogen level of less than 1.0 g/L (**Supplementary S11**, http://links.lww.com/CCX/B229).

DISCUSSION

This is the first large multicenter study on current practices of the use of plasma and other procoagulant products in adult ECMO patients. We observed that 59% of VA-ECMO and 40% of VV-ECMO patients received plasma transfusions and that a substantial amount of these patients received plasma in the absence of bleeding. Furthermore, nearly all plasma transfusions in nonbleeding VA-ECMO and VV-ECMO patients were administered to patients with an INR less than 3.0. Other procoagulant products (PCC, fibrinogen concentrate, TXA) were less frequently administered compared to plasma. Overall, patients with bleeding complications more often received plasma, fibrinogen concentrate, and TXA compared with nonbleeding patients. In VA-ECMO, a larger proportion of patients with than without thrombotic complications received TXA.

Plasma

The number of patients transfused with plasma despite the presence of bleeding is in line with those in the general critically ill population; previous studies showed that a third of the plasma transfusions are given to critically ill patients who are not bleeding (7, 20). However, it has been demonstrated that administrating plasma to nonbleeding critically ill patients for correction of coagulopathy is not effective in inducing a more procoagulant state (21–23) and fails to reduce the occurrence of bleeding complications (7, 24, 25). Furthermore, plasma transfusions in critically ill are potentially harmful with adverse reactions such as transfusion-related acute lung injury and transfusion-associated cardiac overload (26). These potentially harmful events could also occur in ECMO patients, indeed plasma transfusions have been associated with mortality in adult ECMO studies (17, 27).

The actual ELSO guidelines from 2021 recommend an INR threshold of 3.0 for plasma transfusion in nonbleeding ECMO patients (18). In our study, only a minority of plasma transfusions were administered in accordance with this guideline. This observation poses the question of whether these plasma transfusions in ECMO patients without bleeding were administered for another indication or could have been avoided, hereby diminishing transfusion-related side effects that possibly negatively impact patients' outcomes. However, the data collection of this study was performed in 2018–2019. The ELSO guideline from 2017 (28) stated that fibrinogen levels should be maintained at a normal range and INR thresholds were not mentioned, both could partly explain the liberal use of plasma transfusions in our study. Furthermore, plasma transfusion to replenish antithrombin can be a contributing factor to the substantial use of plasma in this population (29). For future studies it would increase our knowledge of the indication and effectiveness of plasma transfusions to collect data on heparin dosages and antithrombin III levels in the case plasma transfusions are given for replenishing antithrombin.

Other Procoagulant Products

Both fibrinogen and PCC were infrequently administered to patients on ECMO. Although there are studies in cardiac surgery that show the beneficial effects of fibrinogen concentrate and PCC on blood product use (9–12, 30–36), there are no studies on the effectiveness and safety of fibrinogen or PCC administration to prevent or treat bleeding in adult ECMO patients. Our data are too limited to draw any conclusions on the safety or effectiveness of fibrinogen and PCC administration in the ECMO population.

Our data show that more patients with than without a thrombotic complication on VA-ECMO received TXA. This raises the question if administering TXA is safe in VA-ECMO patients. Antifibrinolytics reduce postoperative blood loss and/or RBC transfusions in cardiac surgery (14, 15, 37), and also have been shown to be possibly effective in bleeding control in adults (38–40) and in children (41) on ECMO. However, antifibrinolytics have also been linked to thrombotic

complications, but data are scarce and inconsistent. A small study in adult VA-ECMO patients found an association of aprotinin with intracardiac thrombus formation, but not with TXA administration (42). Another study in adult ECMO patients showed that antifibrinolytic administration to treat bleeding complications did not affect circuit survival (43). However, TXA was associated with the occurrence of thrombi in the circuit in pediatric ECMO patients (44). Unfortunately, the timing of the thrombotic event in our study was not registered, therefore causality with TXA administration cannot be assessed.

Hemorrhage and Thrombosis

Fourteen percent of the studied patients suffered both a thrombotic and a bleeding complication during their ECMO run, underlining the complex balance between hemostasis and thrombosis. It is important to note that the complication "leg ischemia" may also be related to the size of the arterial cannula and the presence or absence of a distal reperfusion cannula; however, in this study leg ischemia was specified as leg ischemia due to arterial thrombosis.

A possible contributing factor to the complex balance of hemostasis and thrombosis is the difficult monitoring of the coagulation status. The currently used tests do not reflect in vivo coagulation status and are not predictive of bleeding or thrombosis (18). Monitoring with aPTT is currently the most applied strategy; however, aPTT values are highly variable and influenced by many factors (45). Furthermore, aPTT values and ranges differ greatly between laboratories (46), complicating comparisons between different centers. Anti-Xa monitoring has been proposed as a superior alternative for monitoring the heparin effect; however, it does not take into account other coagulation parameters that could be of clinical importance (47) and is not widely available (48). Lastly, viscoelastic testing (thromboelastography or ROTEM) has been gaining interest to monitor coagulation status, as it provides information on initiation and propagation of coagulation, amount of fibrinolysis, and heparin effect all in one test that is bedside available. Although its use is increasing in pediatric ECMO, for example, it is not yet widely available (49). Of the 16 participating centers, three centers were monitored additionally with anti-Xa and only one center with ROTEM.

Another possible contributing factor to the complex balance of hemostasis and thrombosis is the interaction between infection and coagulation. Our results show that infection is a very common complication in both VA-ECMO and VV-ECMO. This might further contribute to endothelial activation and coagulopathy and hereby dynamically affecting patients' coagulant status. Although many studies in ECMO and general ICU patients report the incidence of bleeding and thrombotic complications, reporting of the incidence of both bleeding and thrombotic complications occurring in the same patients is often lacking, making it difficult to compare our results.

Strengths and Limitations

To our knowledge, this is the first large multicenter study in adult ECMO patients on the use of plasma and procoagulant products in both VA-ECMO and VV-ECMO. An important limitation is the lack of data on the timing of bleeding and thrombotic events, making interpretations of causality impossible. Also, no indications for transfusions were collected. Lastly, due to this investigation's retrospective observational design, it includes downsides such as unmeasured confounding. As a result, associations assessed in multivariable regression analyses in Figure 1 and Supplementary S6, S7 and S9 (http://links.lww.com/CCX/B229) should be interpreted as exploratory.

CONCLUSIONS

The majority of adult patients on ECMO receive a transfusion of plasma or procoagulant products. In a significant proportion of the plasma transfused patients, this was in the absence of bleeding or prolonged INR. This observation poses the question of whether these plasma transfusions in ECMO patients without bleeding were administered for another indication or could have been avoided.

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1 *Department of Critical Care, Amsterdam University Medical Centers, location Academic Medical Centers, Amsterdam, the Netherlands.*

2 *Department of Cardiology, Amsterdam University Medical Centers, location Academic Medical Centers, Amsterdam, the Netherlands.*

3 *Adult Intensive Care Unit, Erasmus University Medical Center, Rotterdam, the Netherlands.*

4 *Department of Cardiology, Catharina Hospital Eindhoven, Eindhoven, The Netherlands.*

5 *Department of Intensive Care Medicine, Surgical Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium.*

6 *Cardiothoracic and Vascular Anesthesia and Intensive Care, AO SS Antonio e Biagio e Cesare Arrigo, Allesandria, Italy.*

7 *Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy.*

8 *Department of Critical Care, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands.*

9 *Adult Intensive Care Unit, Leiden University Medical Center, Leiden, the Netherlands.*

10 *Adult Intensive Care Unit, Catharina Hospital Eindhoven, Eindhoven, the Netherlands.*

11 *Department of Extracorporeal Circulation, Catharina hospital Eindhoven, the Netherlands.*

12 *Intensive Care Center, University Medical Center Utrecht (UMCU), Utrecht, the Netherlands.*

13 *Cardiovascular and Respiratory Physiology Group, TechMed Centre, University of Twente, Enschede, the Netherlands.*

14 *Department of Intensive Care, Université Libre de Bruxelles, Hôpital Erasme Bruxelles, Brussels, Belgium.*

15 *Cardiothoracic Surgery, Heart and Vascular Center, Maastricht University Medical Center, Maastricht, the Netherlands.*

16 *Department of Intensive Care, Maastricht University Medical Center, Maastricht, the Netherlands.*

17 *Department of Cardiology, Maastricht University Medical Center, Maastricht, the Netherlands.*

18 *Department of Intensive Care, St. Antonius Hospital, Nieuwegein, the Netherlands.*

19 *Department of Anesthesia and Intensive care, University Hospital Centre Zagreb, Zagreb, Croatia.*

20 *Department of Intensive Care, OLVG, Amsterdam, the Netherlands.*

21 *Department of Critical Care, Royal Adelaide Hospital, Adelaide, Australia.*

22 *Medical Intensive Care Unit, Department of General Internal Medicine, University Hospitals Leuven, Leuven, Belgium.*

23 *Laboratory of Intensive Care Medicine, Department of Cellular and Molecular Medicine, KU Leuven, Leuven, Belgium.*

24 *Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden.*

25 *ECMO Centre Karolinska, Pediatric Perioperative Medicine and Intensive Care, Karolinska University Hospital, Stockholm, Sweden.*

26 *Department of Epidemiology and Data Science, Amsterdam University Medical Centre, location AMC, Amsterdam Public Health, University of Amsterdam, Amsterdam, The Netherlands.*

27 *Department of Anesthesiology, Amsterdam University Medical Centre, University of Amsterdam, Amsterdam Cardiovascular Sciences, Amsterdam, the Netherlands.*

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For information regarding this article, E-mail: a.p.vlaar@amsterdamumc.nl

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