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Original Research

Effect of Initial Anticoagulation Targets on Bleeding and Thrombotic Complications for Patients With Acute Respiratory Distress Syndrome Receiving Extracorporeal Membrane Oxygenation

Jessica L. Cercone, PharmD[*],
Shawn J. Kram, PharmD, BCPS, BCCCP[†],
Morgan A. Trammel, PharmD, BCCCP[†], Craig R. Rackley, MD[‡],
Hui-Jie Lee, PhD[§], James Merchant Jr., MB[§],
Bridgette L. Kram, PharmD, BCPS, BCCCP, FCCM[†,1]

[*]*Department of Pharmacy, University of Maryland Medical Center, Baltimore, MD*
[†]*Department of Pharmacy, Duke University Hospital, Durham, NC*
[‡]*Department of Medicine, Duke University Hospital, Durham, NC*
[§]*Office of Biostatistics and Bioinformatics, Duke University Hospital, Durham, NC*

Objective: To evaluate the effect of anticoagulation targets and intensity on bleeding events, thrombotic events, and transfusion requirements in patients with acute respiratory distress syndrome (ARDS) receiving venovenous extracorporeal membrane oxygenation (ECMO) and continuous-infusion heparin.
Design: A retrospective cohort study.
Setting: At a single-center, large academic medical center.
Participants: One hundred thirty-six critically ill patients.
Interventions: The following three therapeutic targets were implemented over time and evaluated: (1) no protocol (September 2013-August 2016): no standardized anticoagulation protocol or transfusion thresholds; (2) <50 seconds (September 2016-January 2018): standardized activated partial thromboplastin time (aPTT) goal of <50 seconds, maximum heparin infusion rate of 1,200 units/h, transfusion threshold of hemoglobin (Hgb) <8 g/dL; and (3) 40-to-50 seconds (February 2018-December 2019): aPTT goal of 40-to-50 sec, no maximum heparin infusion rate, transfusion threshold of Hgb <7 g/dL.
Measurements and Main Results: Continuous variables were compared using the Kruskal-Wallis test, and categorical variables were compared using Fisher exact tests. The primary endpoint, an incidence of at least 1 bleeding event, was highest in the no-protocol group though not statistically different among groups (39.3% *v* 26.7% *v* 34%, p = 0.5). Thrombotic complications were similar. The median units of packed red blood cells transfused were highest in the no-protocol group (3 *v* 2 *v* 0.5, p < 0.001).
Conclusion: Anticoagulation protocols standardizing aPTT goals to <50 or 40-to-50 seconds may be a reasonable strategy for patients receiving venovenous ECMO for ARDS. More restrictive hemoglobin transfusion thresholds, in combination with lower aPTT targets, may be associated with a reduction in transfusion requirements.

Key Words: ECMO; heparin; activated partial thromboplastin time; ARDS; transfusion

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[1]*Address correspondence to* Bridgette L. Kram, PharmD, BCPS, BCCCP, FCCM Department of Pharmacy, Duke University Hospital, DUMC Box 3089, Durham, NC 27710.
E-mail address: bridgette.kram@duke.edu (B.L. Kram).

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ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS) is associated with significant morbidity and in-hospital mortality rates ranging from 34%-to-46%.[1,2] The management of ARDS includes low-tidal-volume ventilation, prone positioning, judicious fluid management, and, in select patients, neuromuscular blocking agents.[3] The use of extracorporeal membrane oxygenation (ECMO) in adult patients has risen steadily since 2009.[4] Venovenous (VV) ECMO serves as rescue therapy for patients with refractory ARDS when conventional therapies fail to adequately support oxygenation and/or ventilation.[3,5,6]

The complications of ECMO primarily are related to bleeding or thromboembolism.[7,8] Introduction of the ECMO circuit into the circulatory system results in an inflammatory and hypercoagulable response. To balance this pro-thrombotic state, a reduction in coagulation factors may induce bleeding disorders after cannulation.[7-9] Systemic anticoagulation is administered routinely to prevent ECMO circuit thromboses.[10] Bleeding is the most common complication of ECMO, with rates estimated between 29.3% and 60%.[2,6,9,11] Bleeding complications may include intracranial hemorrhage, pulmonary hemorrhage, surgical site bleeding, and gastrointestinal bleeding.[4,8,9] A higher severity of illness, activated partial thromboplastin time (aPTT) levels higher than goal on systemic anticoagulation, and initiation of ECMO in post-surgical patients have been identified as risk factors for bleeding.[9] Bleeding complications have been associated independently with reduced survival.[9] Neurologic events, such as ischemic stroke and intracranial hemorrhage, are associated with increased mortality among patients receiving ECMO.[12-15] Thrombotic complications, including both within the circuit (eg, oxygenator thrombosis) and the patient (eg, venous thromboembolism), occur frequently in patients supported with ECMO.[16] Thus, the risk of bleeding and thrombotic complications must be balanced when using systemic anticoagulation.

Due to a lack of data supporting standardized anticoagulant goals and monitoring, anticoagulant laboratory targets during ECMO are variable and may include aPTT, activated clotting time, thromboelastography, and anti-Xa levels.[16,17] The accompanying inflammatory response to the device itself may complicate anticoagulant titration to laboratory targets due to a diminished sensitivity of aPTT to unfractionated heparin.[10] Previous studies evaluating anticoagulation targets in patients receiving VV ECMO were limited by small sample sizes and heterogenous cohorts inclusive of venoarterial (VA) ECMO, which carries a different risk profile for both bleeding and thrombosis.[11,16,18-20] The purpose of this study was to evaluate the association of different initial anticoagulation targets and intensity with bleeding and thrombotic events in patients receiving VV ECMO for ARDS.

Material and Methods

Design and Setting

This retrospective, observational cohort study was conducted at a large tertiary and quaternary care academic medical center. Patients ≥18 years of age were included if they received VV ECMO in the medical intensive care unit for ARDS from September 1, 2013, to December 31, 2019. Included patients received continuous infusion heparin and aPTT monitoring, with at least 2 consecutive aPTTs. Patients were excluded if they received ECMO as a bridge to lung transplant, received ECMO for <24 hours, were placed on ECMO >24 hours at an outside hospital prior to admission to the authors' institution, received ECMO for more than 30 days, were initially anticoagulated with a direct thrombin inhibitor, or had an additional indication for anticoagulation at the time of cannulation (eg, pulmonary embolism or atrial fibrillation). This study was Institutional Review Board-approved with a waiver of informed consent.

Although continuous-infusion heparin has remained the standard anticoagulant during the study period, therapeutic targets have changed over time at the authors' institution. From January 2009 to August 2016, aPTT goals were not standardized and were selected at the discretion of the multidisciplinary team. In September 2016, anticoagulation goals were standardized to an aPTT <50 seconds, with a maximum heparin infusion rate of 1,200 units/h. Additional hematologic targets also were standardized and included hemoglobin ≥8 g/dL, platelets ≥75 × 10^9/L, fibrinogen ≥100 mg/dL, international normalized ratio <2, and antithrombin III >60% if heparin-resistant. Heparin resistance was defined as a heparin rate ≥35 units/kg/h with or without achieving therapeutic targets or clot formation. In February 2018, the ECMO protocol was amended to target a standardized aPTT goal of 40-to-50 seconds, with no maximum heparin infusion rate. Hematologic targets were revised based on the best available evidence and institutional experience to target hemoglobin ≥7 g/dL, platelets ≥50 × 10^9/L, fibrinogen ≥100 mg/dL, international normalized ratio <2, and the antithrombin III was removed. The aPTT of 40 seconds for the lower target goal was added to provide clarification and consistency for providers. During the entire study period, nursing staff collected aPTTs every 6 hours while the patient was receiving heparin. Samples suspected of contamination were redrawn at the discretion of the treating team. The normal reference range for aPTT values at the authors' institution is 26.8-to-37.1 seconds. CardioHelp (Maquet/Getinge; Rastatt, Germany) and Rotaflow with a Quadrox-D membrane oxygenator (Maquet/Getinge; Rastatt, Germany), with both Bioline and Softline circuit surface coating, were used during the study period.

Measures

The primary endpoint was the occurrence of any bleeding event while receiving continuous-infusion heparin for VV ECMO at the initial aPTT goal ordered after cannulation during the evaluation period. This evaluation period was defined as the time from heparin infusion initiation while on ECMO until 1one of the following occurred:

discontinuation of ECMO therapy, change in aPTT goal, discontinuation of heparin for greater than 48 hours, switch to a direct thrombin inhibitor, or death. A bleeding event was defined as a hemoglobin drop of ≥2 g/dL in 24 hours, transfusion of more than 3 units of packed red blood cells (pRBCs) in 24 hours, or intracerebral hemorrhage (ICH) identified by computed tomography or magnetic resonance imaging findings.[17] Patients were classified into the following 3 groups based on the time period of ECMO cannulation and the aPTT goal confirmed in the initial heparin order: (1) no protocol (September 2013-August 2016), (2) aPTT < 50 sec (September 2016-January 2018), (3) aPTT 40-to-50 seconds (February 2018-December 2019).

Secondary endpoints included the occurrence of any thrombotic event, blood product administration, time to first bleeding event, time to first thrombotic event, and process indicators, including the proportion of aPTT values above, below, and at goal while receiving heparin. Thrombotic events were defined as imaging-confirmed deep vein thrombosis, pulmonary embolism, ischemic stroke, or clot formation requiring an ECMO circuit change.[17] To exclude events attributable to the cannulation procedure, time to first bleeding or thrombotic event was calculated from the time the heparin infusion was initiated. Additional secondary endpoints included the duration of mechanical ventilation, duration of ECMO cannulation, length of stay, and mortality.

The primary endpoint and all secondary endpoints, except thrombotic events, were collected during the evaluation period. Thrombotic events were collected for the duration of hospitalization.[21,22] Collection of aPTT values began after a 6-hour washout period following heparin bolus administration during cannulation.

Data Collection

Patients meeting the inclusion criteria were identified by an institutional data repository, from which demographics, hospitalization data, ECMO-specific data, and blood product administration were obtained. Heparin infusion rates and aPTT values were collected by manual chart review. Data were managed by REDCap electronic data capture tool.[23]

Statistical Analysis

Descriptive statistics were used to summarize patient demographics and clinical characteristics among the 3 groups. Continuous variables were compared using the Kruskal-Wallis test, and categorical variables were compared using the Fisher exact test. For the primary endpoint, the proportion of patients with at least 1 bleeding event for each intervention group was estimated with the exact binomial 95% confidence interval (CI) using the Clopper-Pearson method. The mean aPTT values and heparin infusion rates while on ECMO were calculated for each patient, and boxplots were used for visualizing the distribution among groups. The proportion of time aPTT values were below, above, or at goal were assessed for each patient based on their anticoagulation targets; then the median was aggregated for each group. To summarize and evaluate this endpoint in the no-protocol group, actual aPTT goals documented in the heparin order were used for these patients.

A sensitivity analysis was repeated for the primary and secondary endpoints using the actual aPTT goals specified in the heparin order for patients in the no-protocol group. Patients were reassigned into the following 3 groups based on the intensity of the aPTT goal range selected: (1) low-intensity (<50, 40-50, 30-40 seconds), (2) moderate-intensity (40-60 or 45-55 seconds), (3) and high-intensity (50-70, 50-80, 60-80 seconds).

To account for differences in baseline characteristics that may confound the results, a post hoc logistic regression was performed for both the main analysis and sensitivity analysis using age, sex, duration of the evaluation period, duration of ECMO cannulation, and aPTT goals as covariates based on differences identified in univariate analysis. All statistical tests were 2-sided and assessed at an alpha = 0.05 without accounting for multiple testing using R 4.0.0 (R Core Team, Vienna, Austria).

Results

A total of 136 patients met the inclusion criteria, with 56 patients (41%) included prior to standardized aPTT goals (no protocol), 30 patients (22%) with an initial aPTT goal <50 sec, and 50 patients (37%) with an initial aPTT goal 40-to-50 seconds group (Fig 1). In the no-protocol group, the initial aPTT goal prescribed varied (40-60 seconds [n = 28], 60-80 seconds [n = 18], 40-50 seconds [n = 5], 50-70 [n = 2], 30-40 seconds [n = 1], 45-55 seconds [n = 1], 50-80 [n = 1]). Baseline characteristics are outlined in Table 1. Patients in the no-protocol group were more likely to be men, with a longer duration of mechanical ventilation prior to ECMO cannulation. A change in aPTT goal occurred more frequently in the no-protocol group and primarily was attributed to a bleeding event. In the study cohort, concomitant administration of antiplatelet medications was infrequent—5 patients (3.7%) received aspirin monotherapy, and 1 patient (0.7%) received both aspirin and clopidogrel. Four patients (2.9%) received antithrombin III, and 1 patient (0.7%) received protamine. Laboratory-confirmed heparin-induced thrombocytopenia was observed in 3 patients in the study cohort. In addition to clinical criteria, 1 patient was diagnosed by platelet factor 4 assay alone, whereas the other 2 were confirmed by serotonin release assay.

In all groups, the median intravenous bolus dose of heparin administered during the cannulation procedure was 5,000 units. The average heparin infusion rates and aPTT values per patient are summarized in Figure 2, and were higher in the no-protocol group compared to the <50 seconds and 40-50 seconds groups ($p < 0.001$ for both Fig 2, A and B).

Primary and secondary endpoints are summarized in Table 2. Overall, 47 patients (34.6%) had at least 1 bleeding event during the evaluationble period. The incidence of a bleeding event was highest in the no-protocol group (39.3%, 95% CI 28.3-51.1), followed by the 40-50 sec group (34%, 95% CI 23-46.5), and was lowest in the <50 seconds group (26.7%, 95% CI 14-43); however, the difference was not statistically

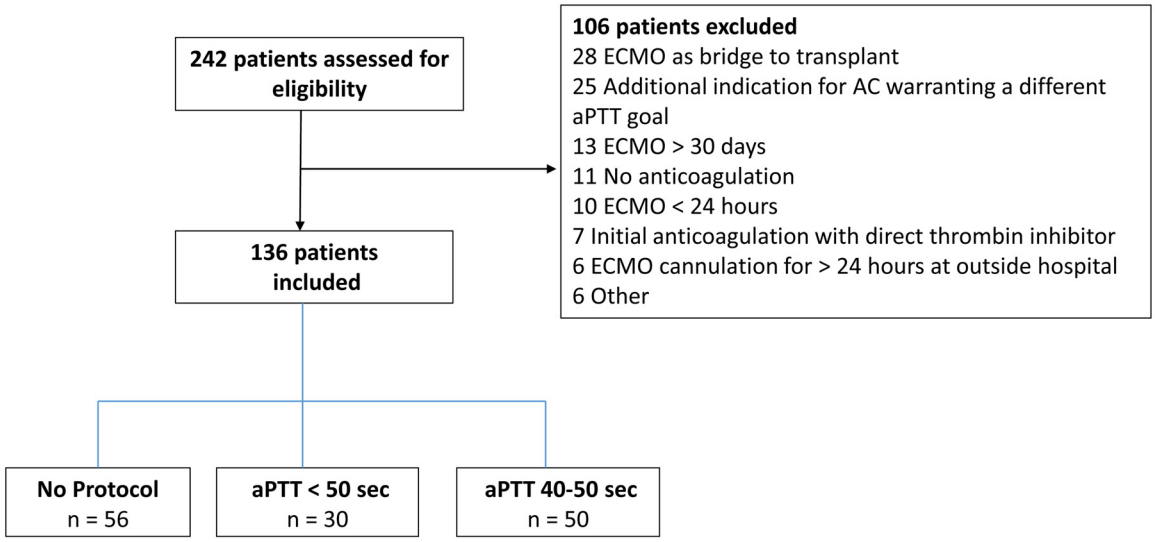


Fig 1. Study enrollment. AC, anticoagulation; aPTT, activated partial thromboplastin time; ECMO, extracorporeal membrane oxygenation.

Table 1
Baseline Characteristics

Baseline Characteristic	No Protocol (n = 56)	<50 Seconds (n = 30)	40-50 Seconds (n = 50)	p
Age, median (IQR), y	45 (32.8-53)	39.5 (28.2-48.5)	43 (35-49)	0.36
Female sex, n (%)	20 (36)	17 (57)	32 (64)	0.011
Race, n (%):				0.76
White	35 (63)	19 (63)	28 (56)	
African American	18 (32)	8 (27)	16 (32)	
Other races	3 (5)	3 (10)	6 (12)	
Weight, median (IQR), kg	100 (74.8-121.2)	88.5 (64.2-119)	89 (72.2-110.2)	0.32
BMI, median (IQR), kg/m^2	32.7 (25.1-38.9)	33.8 (26-42.1)	31.2 (27.1-41.5)	0.98
Immunocompromised, n (%)*	11 (19.6)	5 (16.7)	8 (16)	0.96
SOFA score, median (IQR)†	9 (7-11.2)	10.5 (8-14)	10 (8-11.8)	0.21
RESP score, median (IQR)‡	3 (1-5)	5 (3.2-7)	3 (0.2-6.8)	0.05
Hemoglobin, g/dL	10 (9.9-10.1)	9.7 (9.1-10)	9.4 (8.4-11.4)	0.59
Duration of mechanical ventilation prior to ECMO cannulation,, n (%), d	3 (1-6)	1 (0-2)	1 (0-3)	0.023
ECMO cannulation at outside hospital, n (%)	24 (43)	10 (33)	33 (66)	0.008
Initial heparin infusion rate, median (IQR):				
units/h	1,100 (975-1,500)	800 (700-1,075)	1,000 (712.5-1,200)	<0.001
units/kg/h	11.8 (9.8-14.8)	8.8 (7.9-10.4)	11 (8.3-13.7)	0.004
Evaluable period duration, median (IQR), d§	6.6 (5-9.9)	4 (2-6.6)	3 (2-4.3)	<0.001
Change in aPTT goal, n (%):				0.002
Due to bleeding event‖	12 (21)	1 (3)	6 (12)	
Due to thrombotic event‖	10 (83)	1 (100)	0	
Other reasons	2 (17)	0	4 (67)	
	0	0	2 (33)	
Reason for heparin discontinuation, n (%):				0.64
ECMO decannulation	33 (59)	20 (67)	36 (72)	
Bleeding concern	17 (30)	7 (23)	11 (22)	
Switch to DTI	6 (11)	3 (10)	3 (6)	

NOTE: Data reported as median (IQR) or n (%).

Abbreviations: aPTT, activated partial thromboplastin time; BMI, body mass index; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; DTI, direct thrombin inhibitor; RESP, respiratory ECMO survival prediction; SOFA, sequential organ failure assessment.

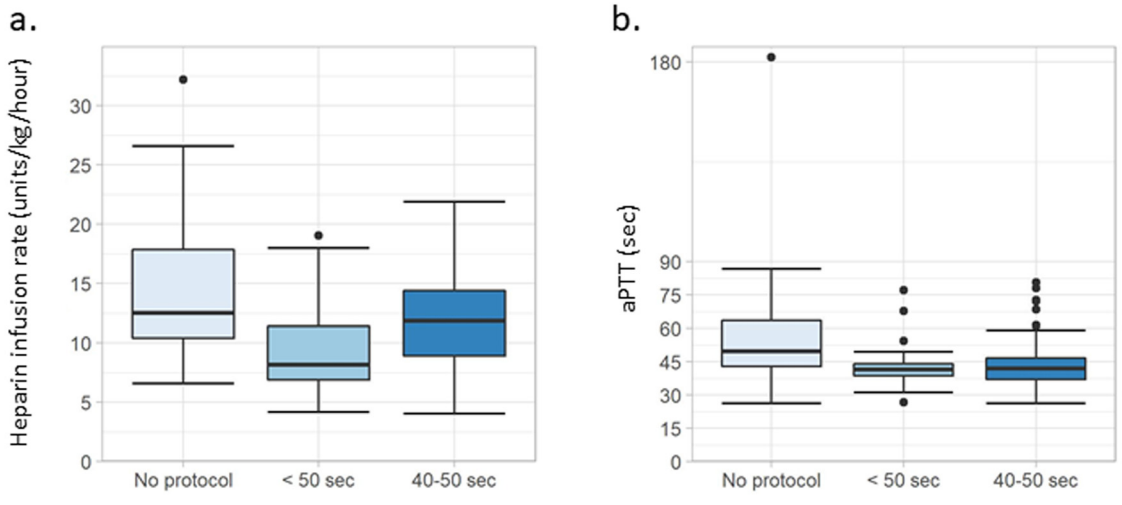
* One patient in the 40-50 sec group had unknown immunocompromised status.

† Four patients in the 40-50 sec group had missing values.

‡ Four patients in the no protocol group and 4 patients in the <50 sec group had missing values.

§ Defined as the time from heparin infusion initiation following ECMO cannulation until one of the following occurred: discontinuation of ECMO therapy, change in aPTT goal, discontinuation of heparin for greater than 48 hours, switch to a direct thrombin inhibitor, or death.

‖ Of patients with a change in aPTT goal.



Median	12.5	8.2	11.9
IQR	10.4-17.8	6.9-11.4	8.9-21.9

Median	49.8	41.5	41.9
IQR	42.7-63.4	38.5-44	37-46.6

Fig 2. Anticoagulant rates and therapeutic targets. (A) heparin infusion rates. (B) aPTT. aPTT, activated partial thromboplastin times; IQR, interquartile range.

significant (p = 0.5). In patients who experienced a bleeding event, the median time to the first event was fewer than 48 hours in all groups (no protocol: 44 hours [interquartile range (IQR) 8.6-140.5]; <50 seconds: 23.3 hours [IQR 16.6-34.5]; 40-50 seconds: 23 hours [IQR 17.8-54.6]). Thirty-nine patients (28.7%) had at least 1 thrombotic event, and the incidence was similar among groups. In patients who experienced a thrombotic event, the median time to the first thrombotic event was 230.8 hours (IQR 179.9-265.9) in the no-protocol group, 305 hours (IQR 257-394.5) in the <50 seconds group, and 174.7 hours (104.8-205.9) in the 40-50 seconds group. The median units of pRBCs transfused were highest in the no-protocol group (p < 0.001). Notably, 43 patients (30.8%) in the cohort received >3 units of pRBCs during the study evaluatble period. Of these 43 patients, the characterization of a bleeding event due to transfusion of >3 units within 24 hours was observed for 8 of 27 patients (30%) in the no-protocol group, 2 of 9 patients (22%) in the <50 seconds group, and 3 of 7 patients (43%) in the 40-to-50 seconds group. Blood product administration for the duration of ECMO cannulation is reported in Supplemental Table 1.

Results of the sensitivity analysis are summarized in Table 3. The incidence of at least one 1 event was not statistically different in the low-intensity, medium-intensity, and high-intensity groups (32.6% [95% CI 24.2-41.8]; 31% [95% CI 17.2-47.9]; 47.6% (95% CI 28.6-67.2), p = 0.39]. The incidence of a thrombotic event was similar among groups. Patients in the moderate-intensity and high-intensity groups received more pRBCs compared to the low-intensity group. Demographic and anticoagulation data for the sensitivity analysis are reported in Supplemental Table 2.

In the multivariate logistic regression analysis (Table 4), after accounting for age, sex, duration of evaluable period, and the duration of ECMO cannulation, the odds of at least 1 bleeding event in the <50 seconds group were 51% lower (odds ratio 0.49, 95% CI 0.16-1.4), and for the 40-to-50 seconds group was 33% lower (odds ratio 0.67, 95% CI 0.25-1.75) than the no-protocol group; however, the difference was not statistically different.

Discussion

Among patients with ARDS receiving VV ECMO, a clinically meaningful though not statistically significant reduction in the rate of bleeding events was observed after standardizing aPTT to <50 seconds or 40-to-50 seconds. The incidence of at least 1 thrombotic event during ECMO cannulation was similar among the 3 groups. Standardized aPTT goals resulted in reduced aPTT variability and overall heparin exposure. In both the main analysis and sensitivity analysis, lower aPTT goals, coupled with standardized transfusion thresholds, were associated with a reduction in pRBC transfusions. Similar to other recent retrospective evaluations, the present study's endpoints reflected an overall improvement in outcomes for patients with ARDS receiving VV ECMO, as observed by reductions in length of stay, mortality, duration of mechanical ventilation, and duration of ECMO over time.[24,25]

Though the Extracorporeal Life Support Organization guidelines do not endorse a standardized anticoagulation approach for patients receiving ECMO, several studies have evaluated the effect of aPTT targets on outcomes.[17] A systematic review evaluated bleeding and thrombotic events when comparing aPTT targets of <60 or >60 seconds. In 5 studies with an aPTT target of >60 seconds, a 56% rate of bleeding and a 7% rate of thrombosis were reported. In contrast, 3 studies with an aPTT target <60 seconds found a lower incidence of bleeding (8%) and a higher rate of thrombosis (32%).[16] In a registry review of 192 patients who received VV ECMO, a

Table 2
Endpoints

Endpoint	No Protocol (n = 56)	<50 s (n = 30)	40-50 s (n = 50)	p
Bleeding events, (%)[*,†];	22 (39)	8 (27)	17 (34)	0.50
Intracerebral hemorrhage	6 (11)	3 (10)	5 (10)	
Hemoglobin drop ≥2 g/dL in 24 h	12 (21)	7 (23)	10 (20)	
>3 units pRBC transfused in 24 h	9 (16)	2 (7)	3 (6)	
Thrombotic events, n (%)[*,‡]:	16 (29)	9 (30)	14 (28)	0.98
Deep vein thrombosis	11 (20)	4 (13)	9 (18)	
Pulmonary embolism	0	1 (3)	3 (6)	
Stroke	0	1 (3)	1 (2)	
ECMO circuit clot	9 (16)	3 (10)	3 (6)	
Blood product administration, median % (IQR)[†]:				
Packed red blood cells, units	3 (2-5)	2 (0.2-4)	0.5 (0-2.8)	<0.001
Fresh frozen plasma, units	0 (0-1)	0 (0-0)	0 (0-0)	0.002
Platelets, packs	0 (0-2)	0 (0-1)	0 (0-0)	0.12
Cryoprecipitate, units	0 (0-0)	0 (0-0)	0 (0-0)	0.13
Proportion of aPTT values, median % (IQR)[†,§]:				
At goal	53.3 (40-62.2)	86.3 (78.3-100)	31 (1.9-49.3)	<0.001
Above goal	11.1 (3.2-23.2)	13.7 (0-21.7)	8.5 (0-32.9)	0.65
Below goal	31.4 (21.1-42.1)	–	50 (16-73.6)	<0.001
Duration of ECMO cannulation, median % (IQR), d	12.5 (7.8-17)	6.5 (3-10.8)	4 (3-6.8)	<0.001
Duration of mechanical ventilation, median % (IQR), d	25 (21-34)	15 (8.5-28.2)	11 (7.5-23.5)	<0.001
ICU length of stay, median % (IQR), d	23.5 (15.8-30.2)	18 (9.2-29.5)	12.5 (8-20)	0.005
Hospital length of stay, median % (IQR), d	27.5 (18.8-39.5)	23 (13.2-40.5)	19.5 (11-35)	0.29
ICU mortality, n (%)	20 (36)	5 (17)	12 (24)	0.15
Hospital mortality, n (%)	21 (38)	7 (23)	13 (26)	0.29

NOTE: Data reported as median (interquartile range) or n (%), unless otherwise specified
Abbreviations: aPTT, activated partial thromboplastin time; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; pRBC, packed red blood cells.

* Number of patients with at least 1 bleeding or thrombotic event. Patients could encounter multiple bleeding or thrombotic events, and thus the sum of different types of bleeding or thrombotic events can be more than the total number of patients with bleeding or thrombotic events.

† During the evaluation period, defined as the time from heparin infusion initiation following ECMO cannulation until 1 of the following occurred: discontinuation of ECMO therapy, change in aPTT goal, discontinuation of heparin for greater than 48 hours, switch to a direct thrombin inhibitor, or death.

‡ During ECMO cannulation

§ All aPTT values during the evaluable period were collected and determined if they were below, above, or at goal. The proportion of time aPTT values were below, above, or at goal were assessed for each patient based on the anticoagulation goal ordered for the individual patient in their heparin order.

mean aPTT >53 seconds was associated with more pRBC transfusions without a difference in oxygenator changes.[19] In a randomized, unblinded study (n = 32), Aubron et al compared low-dose (aPTT < 45 seconds) and therapeutic heparin (aPTT 50-70 seconds). Patients receiving therapeutic anticoagulation received more units of heparin per day, achieved higher mean aPTT values, and were more likely to receive at least 1 unit of pRBCs. No differences in the rates of bleeding and thrombosis were observed in this pilot study. Notably, this study included both VA ECMO and VV ECMO and crossover between groups, thus limiting extrapolation to a homogenous VV ECMO cohort.[18] Deatrick et al compared heparin using aPTT titration (goal 45-55 seconds) to weight-based dosing (10 units/kg/h) without titration, and found that the titration arm had a higher median aPTT (48 *v* 38 seconds) but reported no differences in transfusion requirements, bleeding, or need for circuit changes.[20] Despite minor differences in bleeding definitions and transfusion thresholds, these studies aligned with the authors' findings and supported that ECMO centers define a maximum aPTT target to mitigate the bleeding risk.

The rates and timing of bleeding events in the present study were comparable to those reported in other ECMO centers.[2,11,16,18] In an observational cohort of patients receiving VV ECMO, bleeding was observed in 41.4% of patients when targeting aPTT goal of 40-to-50 seconds, and a transfusion of pRBCs was independently associated with mortality.[11] In a retrospective cohort of patients receiving VV ECMO, ICH occurred in 11% of included patients, with a median of 4 days after ECMO cannulation.[15] Heparin was titrated to a goal aPTT of 50-to-75 seconds in this study, though anticoagulation intensity was not evaluated as a risk factor for ICH. Aubron et al reported a median time to the first bleeding event of 4 days, with a previous day aPTT >70 seconds as a risk factor independently associated with bleeding in a mixed cohort of VA ECMO and VV ECMO.[9]

This study had limitations related to the retrospective design. Bleeding endpoints were evaluated while the patient was receiving heparin at a pre-specified aPTT goal; therefore, the rates of bleeding reflected only the initial aPTT goal during the evaluation period and may have underestimated bleeding that occurred during the entire ECMO course if a change in

Table 3
Sensitivity Analysis

Endpoint	Low-Intensity (n = 86)	Moderate-Intensity (n = 29)	High-Intensity (n = 21)	p
Bleeding event*,†:	28 (33)	9 (31)	10 (48)	0.4
Intracerebral hemorrhage	9 (11)	3 (10)	2 (10)	
Hemoglobin drop ≥2 g/dL in 24 hours	18 (21)	6 (21)	5 (24)	
>3 units pRBC transfused in 24 hours	7 (8)	2 (7)	5 (24)	
Thrombotic event, n (%)*,‡:	24 (28)	7 (24.1)	8 (38)	0.52
Deep vein thrombosis	14 (16)	5 (17.2)	5 (24)	
Pulmonary embolism	4 (5)	0	0	
Stroke	2 (2)	0	0	
ECMO circuit clot	6 (7)	4 (13.8)	5 (24)	
Blood product administration†:				
Packed red blood cells, units	1 (0-3)	3 (1-5)	5 (2-7)	<0.001
Fresh frozen plasma, units	0 (0-0)	0 (0-1)	1 (0-2)	<0.001
Platelets, packs	0 (0-1)	0 (0-3)	0 (0-2)	0.65
Cryoprecipitate, units	0 (0-0)	0 (0-0)	0 (0-0)	0.19
aPTT values, median % (IQR)†,§:				
At goal	50 (20-83.3)	53.3 (44-63.2)	50 (39.1-61.5)	0.98
Above goal	11.1 (0-31.5)	5.6 (0-20)	18.2 (5-24.1)	0.41
Below goal	14.7 (0-52.9)	31.6 (21.1-46.7)	30.8 (22.2-40.6)	0.56
Duration of ECMO cannulation, median (IQR), d	5 (3-10)	13 (7-18)	11 (9-15)	<0.001
Duration of mechanical ventilation, median (IQR), d	13 (8-26.8)	23.5 (18-31.2)	17.5 (9-29.2)	0.013
ICU length of stay, median (IQR), d	15 (9-26)	17 (14-27)	25 (19-37)	0.015
Hospital length of stay, median (IQR), d	22 (12-39)	27 (17-33)	47.5 (60.7)	0.062
ICU mortality, n (%)	19 (22)	13 (45)	5 (24)	0.063
Hospital mortality, n (%)	22 (26)	13 (45)	6 (29)	0.15

NOTE: Data reported as median (interquartile range) or n (%) unless otherwise specified. Low-intensity represents <50, 40-50, or 30-40 seconds, moderate-intensity represents 40-60 or 45-55 seconds, and high-intensity represents 50-70, 50-80, or 60-80 seconds).
Abbreviations: aPTT, activated partial thromboplastin time; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; pRBC, packed red blood cells.
* Number of patients with at least 1 bleeding or thrombotic event. Patients could encounter multiple bleeding or thrombotic events and thus the sum of different types of bleeding and/or thrombotic events can be more than the total number of patients with bleeding and/or thrombotic events.
† During evaluable period, defined as the time from heparin infusion initiation following ECMO cannulation until one of the following occurred: discontinuation of ECMO therapy, change in aPTT goal, discontinuation of heparin for greater than 48 hours, switch to a direct thrombin inhibitor, or death.
‡ During ECMO cannulation.
§ All aPTT values during the evaluable period were collected and determined if they were below, above or at goal. The proportions of times aPTT values were below, above, or at goal were assessed for each patient based on the anticoagulation goal ordered for the individual patient in their heparin order.

aPTT goal occurred. The patient population was restricted to VV ECMO and may not be generalizable to patients on VA ECMO. While there was no standard transfusion protocol prior to 2016, patients typically were transfused to target hemoglobin of 8-to-10 g/dL. Therefore, the primary endpoint had the potential to be confounded by the implementation of lower transfusion thresholds during the study period; however, the proportion of patients with a bleeding event characterized by receipt of >3 units of pRBCs within 24 hours was low in the no-protocol group and highest in the 40-50 seconds group.

The strengths of this study were numerous. Objective criteria were utilized to define clinically significant major bleeding. By evaluating bleeding events only after heparin initiation and aPTT values after a 6-hour washout period, any bleeding event

Table 4
Multivariate Logistic Regression Analysis for at Least 1 Bleeding Event

Main Analysis	Adjusted OR (95% CI)	Sensitivity Analysis	Adjusted OR (95% CI)
Goal aPTT:	Reference	Goal aPTT:	Reference
No protocol	0.49 (0.16-1.4)	Low-intensity	0.96 (0.34-2.61)
<50 s	0.67 (0.25-1.75)	Moderate-intensity	2.03 (0.72-5.78)
40-50 s		High-intensity	
Age, 1-y	1 (0.97-1.03)	Age, 1-year	1 (0.97-1.03)
Male	0.58 (0.27-1.22)	Male	0.61 (0.29-1.28)
Duration of evaluation period*	0.98 (0.88-1.09)	Duration of evaluation period*	0.99 (0.89-1.10)
Duration of ECMO cannulation	1.01 (0.94-1.08)	Duration of ECMO cannulation	1.02 (0.95-1.09)

Abbreviations: aPTT, activated partial thromboplastin time; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; OR, odds ratio.
* Defined as the time from heparin infusion initiation following ECMO cannulation until one of the following occurred: discontinuation of ECMO therapy, change in aPTT goal, discontinuation of heparin for greater than 48 hours, switch to a direct thrombin inhibitor, or death.

or elevated aPTT due to the cannulation procedure itself was excluded. Bleeding outcomes and aPTT values reported in this study were correlated with the pre-specified aPTT goal because the study was designed to cease data collection upon a change in aPTT goal, discontinuation of heparin, or decannulation. Additionally, the 3 groups had a similar proportion of aPTT values above goal, so the authors did not suspect the times outside of the therapeutic range to be a cause of differences in rates of bleeding. From an operational standpoint, targeting an aPTT of 40-to-50 seconds may be advantageous, as it defines explicit instructions for nursing and providers when titrating heparin infusions.

Conclusions

Among patients with ARDS receiving VV ECMO, a clinically meaningful, though not statistically significant reduction in the rate of bleeding events, was observed after standardizing the aPTT goal to <50 seconds or 40-to-50 seconds. Lower aPTT targets and restrictive transfusion thresholds pursuant to a protocol may reduce the need for pRBC transfusion. Anticoagulation protocols targeting lower aPTT goals of <50 seconds or 40-to-50 seconds may be a reasonable strategy for patients receiving VV ECMO for ARDS.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Conflict of Interest

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2022.05.012.

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