Comparison of Bivalirudin Versus Heparin for Maintenance Systemic Anticoagulation During Adult and Pediatric Extracorporeal Membrane Oxygenation

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OBJECTIVES: To provide a comparative analysis of conventional heparin- versus bivalirudin-based systemic anticoagulation in adult and pediatric patients supported on extracorporeal membrane oxygenation.

DESIGN: Retrospective chart review study of adult and pediatric patients receiving extracorporeal membrane oxygenation from January 1, 2014, to October 1, 2019.

SETTING: A large, high-volume tertiary referral adult and pediatric extracorporeal membrane oxygenation center.

PATIENTS: Four hundred twenty-four individuals requiring extracorporeal membrane oxygenation support and systemically anticoagulated with either unfractionated heparin (223 adult and 65 pediatric patients) or bivalirudin (110 adult and 24 pediatric patients) were included.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Digital data abstraction was used to retrospectively collect patient details. The majority of both groups were cannulated centrally (67%), and the extracorporeal membrane oxygenation type was predominantly venoarterial (84%). The adult bivalirudin group had a greater occurrence of heparin-induced thrombocytopenia (12% vs 1%; $p < 0.01$) and was more likely to require postcardiotomy extracorporeal membrane oxygenation (36% vs 55%; $p < 0.01$). There were no statistical differences between the groups in regards to age, sex, and extracorporeal membrane oxygenation initiation location. The main finding was a reduced mortality in the adult bivalirudin group (odds ratio, 0.39; $p < 0.01$), whereas no difference was noted in the pediatric group. A significant reduction in the composite transfusion requirement in the first 24 hours was noted in the pediatric bivaluridin group with an odds ratio of 0.28 ($p = 0.02$). Groups did not differ in regard to laboratories per day, anticoagulant dose adjustments, or ischemic complications.

CONCLUSIONS: When compared with heparin-based systemic anticoagulation, bivalirudin demonstrated feasibility and safety as established by the absence of increases in identifiable adverse outcomes while manifesting substantial improvements in hospital mortality in adult patients. Further studies are necessary to corroborate these findings and further elucidate the role of bivalirudin during extracorporeal membrane oxygenation support.

KEY WORDS: anticoagulation; bivalirudin; direct thrombin inhibitors; extracorporeal; extracorporeal membrane oxygenation; heparin

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In extracorporeal membrane oxygenation (ECMO), the extensive foreign material surface area present within the ECMO circuit (membrane oxygenator, pump, and tubing) necessitates systemic anticoagulation to avoid thromboembolic and hemorrhagic complications, which challenges ECMO runs in 10–30% of cases (1). The extended duration of exposure to artificial surfaces requires a carefully calibrated anticoagulation strategy that weighs the need for anticoagulation to prevent thrombus deposition concurrently against the requirement for avoidance of hemorrhage, both of which are associated with adverse outcomes (2).

Unfractionated heparin (UFH) is the historical mainstay for systemic anticoagulation in ECMO due to its expeditious onset of action, ubiquitous availability, prescriber familiarity, and the ability to antagonize its effect with protamine. However, it may not be the ideal agent due to inherent limitations that include the requirement for the cofactor antithrombin that, while essential for producing its clinical action, also predisposes to fluctuations in dose sensitivity (3). Other drawbacks of UFH involve the complete inaction on clot-bound thrombin excluding efficacy at sites of preexisting thrombotic deposition and heparin-induced thrombocytopenia (HIT) that occurs in both its nonimmune (type 1) form and its immune-mediated (type 2) manifestation triggered by the antigenic nature of heparin (4). In children, quantitative deficiencies in zymogen precursor proteins resulting from liver immaturity may further complicate the pro and anticoagulant aspects of the coagulation cascade (5, 6).

The emergence of direct thrombin inhibitors (DTIs) offered clinicians an avenue to exert necessary anticoagulation in select patients demonstrating intolerance to heparin (HIT or resistance to heparin). This drug class produces transient inhibition of thrombin to down-regulate the cleavage of fibrinogen into its active form (7). The clinical action of DTIs is mediated directly through the binding to thrombin and as such does not require a cofactor such as antithrombin. Importantly, DTIs have the ability to bind to both soluble thrombin and fibrin-bound thrombin thereby providing a potential advantage over UFH by facilitating abatement of further propagation at the site of existing thrombus (8). Other reported desirable aspects of DTIs include a predictable anticoagulant effect due to absence of binding to other plasma proteins, activity against thrombin-mediated platelet activation (antiplatelet effect), and the absence of immune-mediated thrombocytopenia with low rates of thrombocytopenia (7, 9, 10).

Bivalirudin, a member of the DTI drug class, offers the potential to supersede heparin for several reasons. Bivalirudin binds reversibly to thrombin yielding transient inhibition and reversibility of anticoagulation effect that may contribute to its reduced hemorrhagic risk and enhanced safety profile (7). It offers an immediate onset of action and a short half-life of 25 minutes with clearance provided primarily by proteolytic cleavage (11). Like other DTIs, bivalirudin inhibits circulating and clot-bound thrombin while simultaneously affording the absence of nonimmune and immune-mediated thrombocytopenia. Over the past decade, increased use of bivalirudin during ECMO has resulted in an expanding body of evidence demonstrating the safety and suggesting potential superiority of bivalirudin in achieving harmony between thrombosis and hemorrhage. With this in mind, in November 2017, our center transitioned to using bivalirudin as our first-line agent for systemic anticoagulation in adult and pediatric ECMO. The objective of this study is to provide a retrospective cohort comparative analysis of adult and pediatric patients supported on ECMO receiving the systemic administration of conventional UFH versus bivaluridin-based anticoagulation.

MATERIALS AND METHODS

This study was performed at a large Midwestern tertiary referral high-volume adult and pediatric ECMO center. The study was approved by the Institutional Review Board (IRB) (Study ID 17-003518), and the requirement for individual informed consent was waived by the IRB. We excluded patients who refused use of medical records in research under Minnesota laws (Statute 144.295). Patients were identified retrospectively from the electronic records of our ECMO program database. Patients who were receiving heparin or bivaluridin as a continuous infusion from January 1, 2014, to October 1, 2019, were evaluated for enrollment. Pediatric was defined as neonates extending up to age less than 18 years, whereas adult was defined as age equal or greater than 18 years. Patients who died within the first 6 hours of ECMO initiation were excluded.

Data abstraction was accomplished using a combination of high-fidelity electronic data abstraction and manual (chart review) methods with the patient's

electronic health record being the source of all data collected. A detailed description of the data collection is provided in the **Supplemental Materials and Methods** (http://links.lww.com/CCM/G354).

Materials

ECMO support was provided by a CardioHelp system (Getinge, Gothenburg, Sweden) using an HLS Set Advanced coupled to a QUADROX-iD oxygenator (Maquet, Rastatt, Germany). All extracorporeal aspects of the circuit were biocompatible coated (CardioHelp and QUADROS iD; Bioline, Maquet Cardiopulmonary AG, Hirrlingen, Germany; and tubing [Carmeda; Medtronic, Minneapolis, MN]). Importantly, no programmatic changes to circuit components were made during the study period. Barring established contraindications to its use, the pharmacologic agent selected was determined at the discretion of the critical care physician in conjunction with the cannulating proceduralist. Detailed description of anticoagulant agent selection, titration, laboratory testing, and blood product administration in adult and pediatric ECMO patients is provided in the Supplemental Materials and Methods (http://links.lww.com/CCM/G354). Bivalirudin titration tables are provided as **Supplemental Table 2** (http://links.lww.com/CCM/G356).

Statistical Analysis

Patient and ECMO characteristic are presented as number (percentage) according to age group and initial treatment medication. Characteristics are compared using Kruskal-Wallis tests for continuous variables and Pearson chi-square tests for categorical variables. Outcomes are presented according to age group and initial treatment medication as number (percentage) for categorical outcomes and median (25th, 75th percentile) for continuous outcomes. ECMO-free days was calculated as the number of days alive and off ECMO over the 14 days following ECMO initiation. Similarly, hospital-free days were defined according to number of days alive and out of hospital over the 35 days following ECMO initiation. Dose changes and activated partial thromboplastin time (aPTT) laboratories per day were defined as the total count of the given laboratory during the entire ECMO period divided by the total days in the ECMO period. The effect of bivalirudin was assessed using multivariable logistic or linear regression models as appropriate. All models were adjusted for variables prespecified prior to analysis based on available data and investigator expertise, including age, cannulation approach (aortic vs peripheral), ECMO type, and year of ECMO. The ECMO cannulation year was included to attempt to adjust for unmeasured changes in our centers ECMO practice changing during the study period. The effect of bivalirudin was estimated for pediatric patients and for adult patients, and estimates with associated 95% confidence limits were presented. Odds ratios (ORs) are presented for binary endpoints, and effect estimates are presented for continuous endpoints. A landmark analysis subset to those patients alive and on ECMO at 24 hours was used to assess the association between bivalirudin and transfusion requirement from day 2 through first week on ECMO. Variance stabilizing log-transformations were applied when residuals did not meet model assumptions.

For patients receiving bivalirudin, aPTT and kaolin thromboelastography R-time values were plotted according to time on ECMO at laboratory draw along with a locally estimated scatter plot smoothing (LOESS) line. The correlation coefficient between aPTT and kaolin thromboelastography R-time accounting for multiple observations per subject was estimated using the method proposed by Bland and Altman (12). Only aPTT and kaolin thromboelastography R-time values measured within approximately 1 hour of each other were considered when estimating the correlation statistic.

Statistical tests were interpreted using the 0.05 alpha level; p value of less than 0.05 was considered statistically significant. The primary outcome is mortality; secondary outcomes included ECMO-free days and hospital-free days. aPTT laboratories per day, anticoagulant agent dose changes per day, ischemic complications, or the requirement for an additional run of ECMO were also analyzed. No adjustment was made for multiple comparisons for multiple endpoints assessed. All analysis was performed using SAS 9.4 software (SAS Institute, Cary, NC). Power calculation was performed posteriori as provided in Supplemental Materials and Methods (http://links.lww.com/CCM/G354). The study complies with the Strengthening the Reporting of Observational Studies in Epidemiology reporting requirements for observational studies (**Supplemental Table 1**, http://links.lww.com/CCM/G355) (13).

RESULTS

Patient Characteristics

Four hundred twenty-two subjects meeting inclusion criteria were included in the study. Of these, 288 subjects received UFH (223 adult and 65 pediatric), and 134 subjects (110 adult and 24 pediatric) received bivalirudin as the primary systemic anticoagulant as depicted in the flow diagram (**Fig. 1**). Patient demographics are depicted in **Table 1**. The main difference lies in the incidence of HIT identified prior to systemic anticoagulant selection that was greater in the adult bivalirudin group (12% vs 1%, $p < 0.01$). Additionally, the requirement for continuous renal replacement therapy while on ECMO and postcardiotomy as the indication for ECMO was greater in the adult bivalirudin group. There was no statistical differences between the groups in regards to age, sex, Charlson score (adults only), heparin bolus at ECMO initiation, and ECMO initiation location or configuration type.

ECMO Characteristics

Although the majority of both anticoagulation strategy groups were cannulated centrally, the pediatric bivalirudin group was more likely to have been cannulated peripherally (42 % vs 18%; $p = 0.02$), whereas the inverse was true for the adult bivalirudin group who were more likely to have received aortic cannulation (76% vs 60%; $p < 0.01$), as found in Table 1.

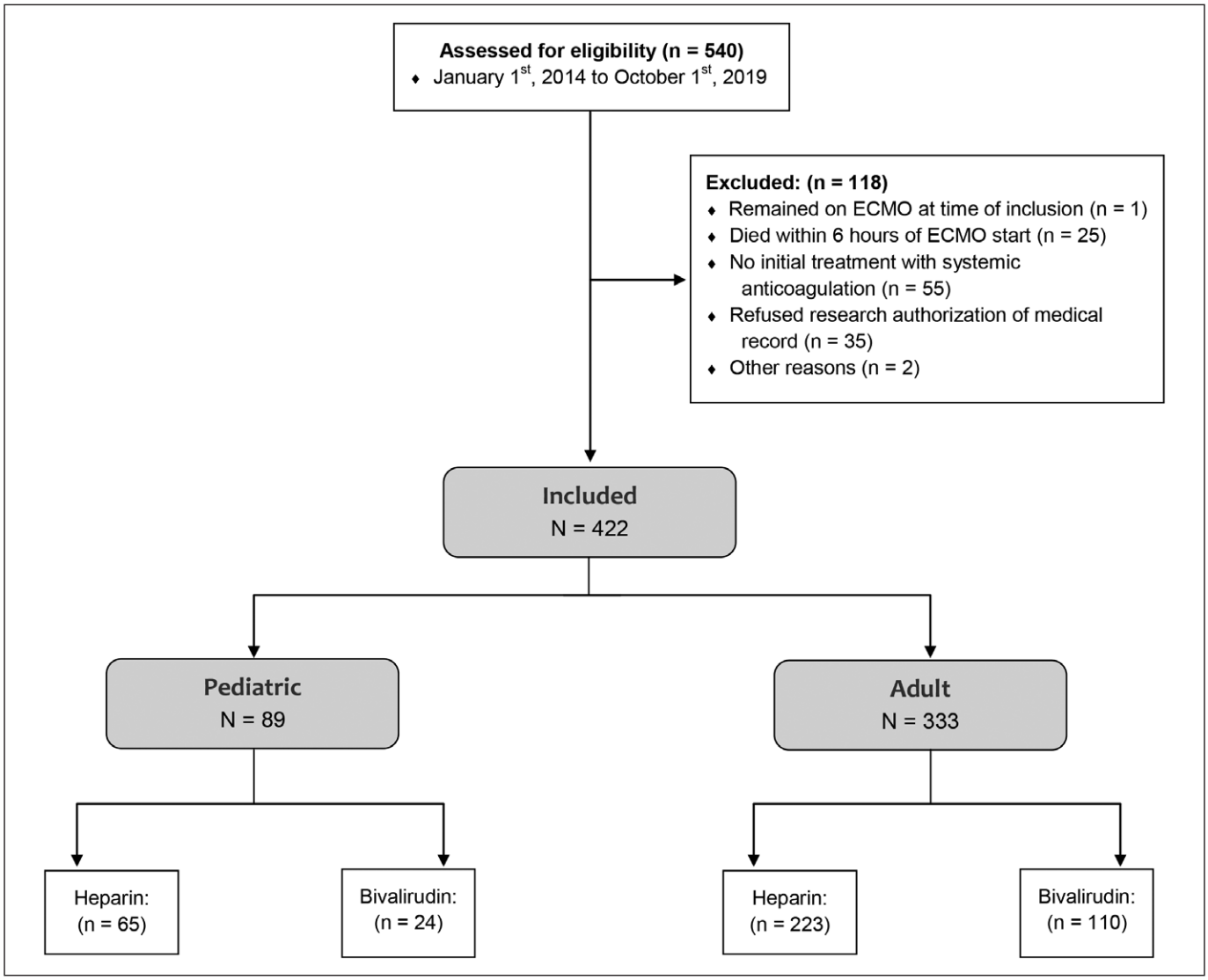

Figure 1. Flow diagram of patient inclusion in this retrospective cohort study between January 1, 2014 and October 1, 2019. ECMO = extracorporeal membrane oxygenation.

TABLE 1.

Patient Characteristics and Extracorporeal Membrane Oxygenation Cannulation Details According to Initial Treatment Plan[a]

Variable	Pediatric			Adult		
	Heparin (*n* = 65)	Bivalirudin (*n* = 24)	*P*	Heparin (*n* = 223)	Bivalirudin (*n* = 110)	*p*
Age group, yr, *n* (%)			0.21			0.75
< 1	42 (65)	11 (46)		0 (0)	0 (0)	
1–4	12 (18)	8 (33)		0 (0)	0 (0)	
5–17	11 (17)	5 (21)		0 (0)	0 (0)	
18–34	0 (0)	0 (0)		32 (14)	14 (13)	
34–49	0 (0)	0 (0)		37 (17)	20 (18)	
50–64	0 (0)	0 (0)		77 (35)	36 (33)	
65+	0 (0)	0 (0)		77 (35)	40 (36)	
Sex, *n* (%)			0.98			0.51
Female	30 (46)	11 (46)		75 (34)	41 (37)	
Male	35 (54)	13 (54)		148 (66)	69 (63)	
Charlson score (age 18+), median (25th, 75th percentile)	NA	NA	NA	4 (2, 6)	4 (2, 7)	0.67
Heparin-induced thrombocytopenia[b], *n* (%)	1 (2)	0 (0)	0.54	2 (1)	13 (12)	< 0.01
Concurrent continuous renal replacement therapy while on ECMO, *n* (%)			0.35			0.03
No	48 (74)	20 (83)		143 (64)	57 (52)	
Yes	17 (26)	4 (17)		80 (36)	53 (48)	
Admitted on ECMO, *n* (%)	6 (9)	2 (8)	0.90	30 (13)	15 (14)	0.96
ECMO indication, *n* (%)			0.27			< 0.01
Post cardiotomy	18 (28)	3 (13)		81 (36)	60 (55)	
Cardiac	18 (28)	6 (25)		55 (25)	21 (19)	
Respiratory	13 (20)	9 (38)		46 (21)	18 (16)	
Extracorporeal cardiopulmonary resuscitation	16 (25)	6 (25)		39 (17)	8 (7)	
Post transplant	0 (0)	0 (0)		2 (1)	3 (3)	
Heparin bolus, U/kg ×1,000; *n* = 64/257, median (25th, 75th percentile)	0.8 (0.3, 2.5)	1.0 (0.3, 3.0)	0.64	7 (5, 10)	10 (5, 10)	0.09

(*Continued*)

TABLE 1. (*Continued*)
Patient Characteristics and Extracorporeal Membrane Oxygenation Cannulation Details According to Initial Treatment Plan[a]

Variable	Pediatric			Adult		
	Heparin (*n* = 65)	Bivalirudin (*n* = 24)	*P*	Heparin (*n* = 223)	Bivalirudin (*n* = 110)	*p*
Location of cannulation, *n* (%)			0.02			< 0.01
Aortic	53 (82)	14 (58)		133 (60)	84 (76)	
Peripheral	12 (18)	10 (42)		90 (40)	26 (24)	
ECMO type, *n* (%)			0.12			0.64
Venoarterial	61 (94)	20 (83)		184 (83)	93 (85)	
Venovenous	4 (6)	4 (17)		39 (17)	17 (15)	

ECMO = extracorporeal membrane oxygenation, NA = not available.

[a]*p* values are Kruskal-Wallis tests for continuous variables and Pearson's χ^2 tests for categorical variables. Age is presented in categories but compared with Kruskal-Wallis tests.

[b]Known or suspected heparin-induced thrombocytopenia prior to initiation of systemic anticoagulation.

Outcomes

The composite circuit intervention rate and oxygenator/pump change-out rate failed to reach statistical significance in both adults (OR, 0.4; $p = 0.07$) and pediatrics (OR, 0.95; $p = 0.93$), as provided in **Table 2**. The ischemic complication rate ranged from 12% (adult bivalirudin) to 22% (pediatric UHF). Although only minor differences were identified in regard to individual allogeneic blood product transfusion in the first 24 hours and extending out to 7 days as seen in **Table 3**, there was a significant reduction in the composite transfusion requirement in the first 24 hours in the pediatric bivaluridin group with an odds ratio of 0.28 ($p = 0.02$).

As shown in **Table 4**, in multivariate analysis, hospital mortality was lower in the adult bivaluridin groups (OR, 0.39; $p < 0.01$) but failed to reach statistical significance in the pediatric bivaluridin group (OR, 0.56; $p = 0.24$). However, hospital-free days as defined as time alive and out of the hospital in the first 35 days was lower in the pediatric bivalirudin group with an estimated conditional mean difference of 4.2 days ($p = 0.03$). No differences were identified between groups in regard to aPTT laboratories per day, anticoagulant agent dose changes per day, ischemic complications, or the requirement for an additional run of ECMO.

To compare the correlation between aPTT and kaolin thromboelastography (KTEG) reaction time (R-time) between anticoagulant groups, aPTT was plotted against KTEG R-time with a LOESS curve generated for adult and pediatric ECMO patients receiving UFH and bivalirudin (**Supplemental Fig. 1**, http://links.lww.com/CCM/G357 and **Supplemental Fig. 2**, http://links.lww.com/CCM/G358 [**legend**, http://links.lww.com/CCM/G359]) with all subgroups found to have similar correlation coefficients.

DISCUSSION

Although the use of nonheparin anticoagulants remains atypical during ECMO, DTIs have been used when UFH is contraindicated, and a growing body of evidence exists to support both its safety and potential clinical superiority (14–25). Compared with other DTIs, bivalirudin offers a short half-life with limited reliance on organ function for clearance (26). The combination of these features supports the potential role for bivalirudin in ECMO where thrombus deposition is relatively common (10–33% according to registry data) (2, 27), plasma concentrations of antithrombin fluctuate substantially (3), and anticoagulation exposure is frequently prolonged. This study presents the largest cohort to date of adult and pediatric patients

TABLE 2.
Extracorporeal Membrane Oxygenation and Hospital Outcomes According to Initial Treatment Plan[a]

Variable	Pediatric (*N* = 89)			Adult (*N* = 333)		
	Heparin (*n* = 65)	Bivalirudin (*n* = 24)	*p*	Heparin (*n* = 223)	Bivalirudin (*n* = 110)	*p*
ECMO duration, d, median (25th, 75th percentile)	7.2 (4.2, 18.6)	5.3 (2.7, 13.8)	0.19	5.1 (2.9, 10.2)	4.7 (2.8, 8.8)	0.51
ECMO-free days (14 d), median (25th, 75th percentile)	5.1 (0, 9.1)	8.7 (0.5, 11.3)	0.10	8.5 (2.9, 11.1)	9.3 (4.7, 11.1)	0.29
Anticoagulant dose changes per day[b], median (25th, 75th percentile)	1.5 (0.9, 2.1)	1.4 (0.7, 1.9)	0.36	1.2 (0.7, 1.7)	1.1 (0.5, 1.5)	0.03
aPTT laboratories per day[b], median (25th, 75th percentile)	4.6 (3.2, 5.2)	4.5 (3.6, 4.9)	0.81	4.9 (4.1, 6.0)	5.1 (4.2, 5.9)	0.83
Oxygenator/pump change out, *n* (%)	4 (6)	3 (13)	0.38[d]	12 (5)	4 (4)	0.48
Other circuit interventions, *n* (%)	30 (46)	8 (33)	0.28	44 (20)	6 (5)	< 0.01
Required additional *n* (%)	11 (17)	5 (21)	0.76[d]	20 (9)	8 (7)	0.60
Hospital length of stay following ECMO start, d, median (25th, 75th percentile)	35.8 (16.0, 72.9)	23.3 (12.8, 54.9)	0.41	17.7 (9.3, 37.5)	21.5 (10.1, 47.0)	0.26
Hospital mortality, *n* (%)	37 (57)	10 (42)	0.20	118 (53)	42 (38)	0.01
Any ischemic complication, *n* (%)	14 (22)	3 (13)	0.54[d]	38 (17)	13 (12)	0.21
Stroke	11 (17)	3 (13)	0.75[d]	18 (8)	4 (4)	0.13
Seep vein thrombosis	6 (9)	0 (0)	0.19[d]	15 (7)	6 (5)	0.65
Pulmonary embolism	0 (0)	0 (0)	1.00	5 (2)	2 (2)	1.00[d]
Myocardial infarction	0 (0)	0 (0)	1.00	3 (1)	0 (0)	0.55[d]
Mesenteric ischemia	0 (0)	0 (0)	1.00	2 (1)	2 (2)	0.60[d]
ECMO laboratory values[c], median (25th, 75th percentile)						
Platelets, $\times 10^3$ per μL	64 (54, 86)	76 (60, 108)	0.11	84 (67, 112)	84 (68, 107)	0.92
Fibrinogen, mg/dL; *n* = 89/332	230 (169, 265)	214 (176, 275)	1.00	326 (239, 424)	280 (225, 361)	0.04
aPTT, seconds; *n* = 88/333	79 (66, 88)	79 (71, 90)	0.59	54 (48, 62)	57 (49, 64)	0.16
Oxyhemoglobin, mg/dL; *n* = 86/324	39 (28, 67)	42 (32, 67)	0.98	20 (14, 31)	18 (13, 27)	0.06
Antithrombin level laboratories per day[b]	0.6 (0.2, 0.9)	0.5 (0.2, 0.7)	0.32	0.8 (0.3, 1.0)	0.1 (0.0, 0.3)	< 0.01

ECMO = extracorporeal membrane oxygenation, aPTT = activated partial thromboplastin time.

[a]Continuous variables are compared using Wilcoxon rank-sum tests and categorical variables are compared using Pearson's χ^2 tests unless indicated. When not all data are available for a given variable, numbers with available information are reported for both pediatric and adult patient groups.

[b]Dose changes and laboratories per day are calculated over the entire ECMO run.

[c]Laboratory values are averaged over the entire ECMO run, so that each patient has an "average" value, and those average values are summarized in the table.

[d]Fisher exact test.

supported on ECMO where bivalirudin was used as the primary anticoagulant.

The main finding of this study is that bivalirudin is effective and feasible in providing the necessary systemic anticoagulation intensity for both adult and pediatric ECMO patients. We report a hospital mortality for pediatrics of 53% and for adults of 48% in a population of largely venoarterial ECMO (85%) which compares favorably with that as detailed from national registries (27). Importantly, the mortality was found to be lower in adults receiving bivalirudin with an adjusted OR of 0.39 ($p < 0.01$). These results are even more impressive when considering that the adult bivaluridin group was more likely to have a postcardiotomy requirement for ECMO which has been associated with worse survival (28). The increased requirement for continuous renal replacement therapy in the adult postcardiotomy group may have been secondary to the greater prevalence of postcardiotomy ECMO which carries an increased risk for acute kidney injury with a reported prevalence as high as 85% while also portending a worse prognosis (29). The rate of HIT was markedly greater in the adult bivalirudin group which is explained by the fact that patients with known or suspected HIT preferentially received bivalirudin.

Although the reduced in hospital mortality rate in the bivalirudin group is encouraging, the rational for this improved survival remains elusive in the remainder of the data where no difference was found in regards to blood loss, transfusion, or composite ischemic complications. A possible explanation for the reduced mortality seen in the bivalirudin group that was not specifically explored in our study exists in the critical interplay between the innate immune system and platelets that takes place at the site of endothelial lesions with modulation (up-regulation) occurring due to thrombin effect. The endothelium, including that present in alveolar capillaries, is directly affected by thrombin in two important ways: 1) via the cleavage of fibrinogen to active fibrin yielding diffuse alveolar and interstitial fibrin deposition (i.e., microthrombi) and 2) through the direct activation of platelets that accumulate where endothelial lesions are present with subsequent interaction with innate immune cells (30). Importantly, the interplay between platelets and neutrophils occurring at these sites is regulated by coagulation and inflammatory mediators, which is a concept termed immunothrombosis (31, 32). By directly abating the action of thrombin in circulating and clot-bound sites, DTIs may impede this pathway thereby retarding a humoral regulatory process that is perturbed in settings of acute inflammation with resultant mitigation of potential deleterious downstream effects. In this way, bivalirudin offers a potential route to down-regulate the secondary hemostatic cascade while concurrently interrupting the interaction with the innate immune system. Admittedly, our data did not demonstrate a significant difference in macrovascular thrombotic events. However, due to our limited ability to detect microthrombi, it remains possible, albeit unproven, that bivalirudin may have negatively impacted the generation of subclinical thrombotic deposition and secondarily immunothrombosis.

It is worth noting that our study did not identify any difference in dose adjustments per day or laboratory monitoring frequency between the UFH and bivalirudin groups. This differs from prior reports where a reduction in aPTT variation facilitated fewer dose adjustments and reduced aPTT testing frequency (20, 21). The establishment of a robust UFH dosing protocol, as described in the Supplemental Materials and Methods (http://links.lww.com/CCM/G354), relying on an integrated multiassay titration approach prior to the adoption of bivalirudin into our centers practice warrants consideration as it may have 1) reduced the dose adjustments per day in the heparin cohort and 2) decreased the requirement for aPTT laboratories per day as alternative assays were concurrently used (anti-Xa and thromboelastography). Unfortunately, due to limitations in our centers electronic health record, we were unable to determine individual patients target aPTT retrospectively and as such are unable to report on time to therapeutic range and time within therapeutic range. Recent studies have demonstrated an advantage with bivalirudin in these important metrics (14, 17).

The pediatric bivalirudin group in our study did have a reduction in blood product transfusion in the first 24 hours, but this did not persist in subsequent temporal cohorts. Although quite different in study design, a recent report by Machado et al (33) of 32 consecutive pediatric ECMO patients (14 heparin and 18 bivalirudin patients) also found no difference in blood product utilization between groups. Additionally, our study found no difference was found in regard to ischemic complications, which is also similar prior reports (14).

TABLE 3.

Operating Room Blood Loss and ICU Transfusion Requirement According to Initial Treatment Plan[a]*

Variable	Pediatric (*N* = 89)			Adult (*N* = 333)		
	Heparin (*n* = 65)	Bivalirudin (*n* = 24)	*p*	Heparin (*n* = 223)	Bivalirudin (*n* = 110)	*p*
Operating room blood loss (estimated blood loss, drain, and chest tube output), mL; *n* = 63/267, median (25th, 75th percentile)	79 (31, 407)	127 (57, 340)	0.84	924 (115, 3,467)	1,600 (310, 3,445)	0.13
Any transfusion during first 24 hr on extracorporeal membrane oxygenation, *n* (%)	52 (80)	12 (50)	< 0.01	177 (79)	88 (80)	0.89
Any RBCs, *n* (%)	33 (51)	9 (38)	0.27	169 (76)	84 (76)	0.91
RBCs, U; *n* = 42/253, median (25th, 75th percentile)	2 (1, 3)	2 (1, 3)	0.76	4 (2, 7)	5 (2, 9)	0.19
Any platelets, *n* (%)	30 (46)	10 (42)	0.71	119 (53)	66 (60)	0.25
Platelets, U; *n* = 40/185, median (25th, 75th percentile)	1 (1, 2)	1 (1, 2)	0.86	3 (1, 4)	3 (2, 5)	0.09
Any plasma, *n* (%)	36 (55)	8 (33)	0.07	112 (50)	63 (57)	0.23
Plasma, U; *n* = 44/175, median (25th, 75th percentile)	1 (1, 3)	1 (1, 3)	0.47	3 (2, 5)	4 (2, 6)	0.03
Any cryoprecipitate, *n* (%)	24 (37)	8 (33%	0.75	79 (35)	52 (47)	0.04
Cryoprecipitate, U; *n* = 32/131, median (25th, 75th percentile)	1 (1, 2)	1 (1, 2)	0.89	2 (1, 3)	3 (2, 5)	< 0.01
Any transfusion 24 hr to 7 d[b]	60 (94)	20 (83)	0.38[c]	194 (87)	94 (85)	0.68
Any RBCs; *n* = 87/324[b], *n* (%)	60 (94)	19 (79)	0.20[c]	191 (86)	92 (84)	0.60
RBCs, U; *n* = 79/283[b], median (25th, 75th percentile)	5 (2, 15)	3 (1, 11)	0.15	7 (3, 14)	5 (2, 12)	0.21
Any platelets; *n* = 87/324[b], *n* (%)	47 (74)	13 (54)	0.13	126 (57)	59 (54)	0.62
Platelets, Units; *n* = 60/185[b], median (25th, 75th percentile)	6 (2, 13)	3 (1, 6)	0.04	3 (1, 7)	2 (1, 6)	0.42
Any plasma; *n* = 87/324[b], *n* (%)	34 (53)	9 (38)	0.25	78 (35)	36 (33)	0.68
Plasma, U; *n* = 43/114[b], median (25th, 75th percentile)	2 (1, 4)	3 (2, 6)	0.19	2 (1, 4)	2 (2, 4)	0.79
Any cryoprecipitate; *n* = 87/324[b], *n* (%)	24 (38)	6 (25)	0.32	26 (12)	21 (19)	0.07
Cryoprecipitate, U; *n* = 30/47[b], median (25th, 75th percentile)	2 (1, 4)	1 (1, 2)	0.15	2 (1, 3)	2 (2, 3)	0.75

[a]Continuous variables are compared using Wilcoxon rank-sum tests and categorical variables are compared using Pearson's χ^2 tests unless indicated. When not all data are available for a given variable, numbers with available information are reported for both pediatric and adult patient groups.

[b]Includes only patients alive and on extracorporeal membrane oxygenation at 24 hr.

[c]Fisher exact test.

TABLE 4.
Summary of Multivariable Analysis[a]

Variable	Pediatric		Adult	
	Bivalirudin Estimate (95% CI)	*p*	Bivalirudin Estimate (95% CI)	*p*
Hospital mortality	0.56 (0.21–1.49)	0.24	0.39 (0.23–0.68)	< 0.01
ECMO-free days (14 d)[d]	1.9 (–0.2 to 3.9)	0.07	0.7 (–0.4 to 1.9)	0.20
Hospital-free days (35 d)[d]	4.2 (0.4–8.1)	0.03	2.0 (–0.1 to 4.1)	0.07
Anticoagulant dose changes per day[b]	0.75 (0.47–1.19)	0.23	0.81 (0.63–1.04)	0.11
Activated partial thromboplastin time, laboratories per day	0.36 (–0.40 to 1.11)	0.35	0.20 (–0.22 to 0.61)	0.35
Any transfusion during first 24 hr on ECMO	0.28 (0.10–0.81)	0.02	0.69 (0.35–1.38)	0.30
Any transfusion day 2 through first week on ECMO[c]	0.46 (0.09–2.38)	0.36	0.69 (0.30–1.63)	0.40
Other circuit interventions	0.95 (0.34–2.69)	0.93	0.40 (0.15–1.07)	0.07
Any ischemic complication	0.62 (0.16–2.44)	0.49	0.72 (0.33–1.54)	0.40
Required additional run on ECMO	1.89 (0.54–6.64)	0.32	0.92 (0.35–2.44)	0.87

ECMO = extracorporeal membrane oxygenation.

[a]Continuous and categorical outcomes were modeled using multiple linear and logistic regression respectively. All models were adjusted for age, aortic vs peripheral cannulation, venoarterial vs venovenous ECMO, and year of ECMO. Different effect estimates were allowed for age according to pediatric status (i.e., models included the age by pediatric flag interaction). In addition, we included the treatment by pediatric flag interaction to obtain the age group–specific estimates for the effect of bivalirudin. Estimates are odds ratios for categorical endpoints and reflect the estimated increase in odds of the given event associated with initial treatment of bivalirudin.

[b]Values were modeled on the log scale to stabilize variance in the residuals. Estimates are for the multiplicative increase in geometric mean associated with bivalirudin.

[c]Analysis excludes patients who died or were weaned from ECMO prior to 6 hr.

[d]Estimates for ECMO and hospital-free days are for the conditional increase in mean-free days associated with initial treatment of bivalirudin from the linear regression model (i.e., more positive values reflect improved outcome).

Last, a crude analysis comparing the association between aPTT and KTEG R-time found a moderate correlation which is similar to a recent report of moderate correlation between rotational thromboelastometry (ROTEM) intrinsic coagulation pathway and aPTT (34). The correlation between KTEG R-time in ECMO patients' anticoagulated with heparin has been previously reported to also be of moderate correlation (35). Although related viscoelastic assays, thromboelastography and ROTEM have important functional differences, and it is reassuring that our findings uphold prior reports despite the distinct nature of the laboratory assays.

Despite the gradual accumulation of more robust data, the experience with bivalirudin remains limited in both adult and pediatric ECMO populations. Our findings, including that of reduced mortality associated with bivalirudin in adult ECMO patients, require future randomized prospective multicenter studies for validation. Such future efforts should ideally employ methods to systematically gather data with an improved granularity and fidelity ideally while providing a robust pharmacoeconomic analysis, to elucidate the potential role in the general ECMO population. Further, future studies should explore in additional detail the role for alternative laboratory testing schema, such as viscoelastic and DTI specific assays. Last, the interplay between thrombosis and the innate immune system would benefit from additional illumination.

LIMITATIONS

We concede the presence of several limitations that are relevant to this study. The single-center retrospective, nonrandomized nature of the study along with the modest sample size tempers the interpretation of our findings and limits its generalizability. There exists potential temporal bias as a portion of the UFH subjects received ECMO between 2014 and 2016 prior to the establishment of bivalirudin as an alternate first-line agent. Given the rapidity of the evolution of technology and experience, the introduction of potential temporal bias necessitates caution with interpretation of study results. It should be noted that temporal bias has, in part, been mitigated by the absence of major changes made in the study interval in regard to the ECMO circuit employed (pump, oxygenator, and tubing), staffing model, cannulation approach, or ECMO volume and further by inclusion of year of cannulation in the regression analysis.

CONCLUSIONS

In the largest study to date comparing DTIs with conventional UHF-based systemic anticoagulation strategy during ECMO, bivalirudin manifested superiority in the most essential clinical outcome: survival. Our study demonstrated the feasibility and safety of bivalirudin in this population as established by the absence of increases in identifiable adverse outcomes with improved hospital mortality in the adult population. Further studies are necessary to corroborate these findings and further elucidate the role of bivalirudin during ECMO support.

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