American Journal of Cardiovascular Drugs (2021) 21:395–409
https://doi.org/10.1007/s40256-020-00450-w

REVIEW ARTICLE

A Review of Bivalirudin for Pediatric and Adult Mechanical Circulatory Support

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Accepted: 30 October 2020 / Published online: 10 November 2020

Abstract

As the use of mechanical circulatory support has increased in volume and complexity, anticoagulation remains an intricate component of a patient's pharmacotherapy plan. Traditionally, heparin has been the primary anticoagulant utilized because of its ease of titration and familiarity of use. More recently, bivalirudin, a direct thrombin inhibitor, has attracted attention as a potential alternative to traditional therapy. While labeled for use in percutaneous coronary interventions, it is utilized off-label for heparin-induced thrombocytopenia and mechanical circulatory support. A literature search identified ten studies in which bivalirudin was used in extracorporeal membrane oxygenation and five studies in which it was used in ventricular assist devices. The purpose of this review was to summarize the currently available literature for bivalirudin use for mechanical circulatory support in both adult and pediatric patients.

Key Points

The use of mechanical circulatory support for children and adults has increased in volume and complexity, prompting exploration of alternative anticoagulation options.

Increasing data for bivalirudin during mechanical circulatory support suggests an opportunity for use as an alternative anticoagulant to heparin.

1 Introduction

In recent years, the prevalence of heart failure has steadily increased in both children and adults, though due to differing etiologies. As such, and due to extensive technological advances in device therapy, the use of mechanical circulatory support (MCS) across both patient populations has expanded [1]. In patients with cardiovascular disorders, including congenital heart disease in pediatrics, MCS is often utilized when conventional therapy fails. Extracorporeal membrane oxygenation (ECMO) is useful in patients who require short-term cardiac and/or respiratory support, as it provides complete cardiopulmonary bypass [1, 2]. Meanwhile, ventricular assist devices (VADs) have served a variety of uses in patients with heart failure, including long-term use as bridging to transplantation or "destination therapy" in many adults. Although MCS devices have proven successful in improving quality of life and survival rates in critically ill patients, such therapy is not without complications [1].

One of the most difficult aspects to manage in the operation of MCS is a balance between the need for anticoagulation with an increased risk of bleeding, a significant adverse effect estimated to occur in up to 60% of patients [3]. Per extracorporeal life support organization (ELSO) 2017 guidelines, unfractionated heparin (UFH) was the primary anticoagulant described for use in MCS due to ease of titration and monitoring, low cost, and familiarity of use [4–6]. However, well-known complications of heparin therapy,

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including heparin-induced thrombocytopenia (HIT) and heparin resistance, may require alternative anticoagulation methods in certain patients [4, 7].

Bivalirudin, a direct thrombin inhibitor (DTI), has emerged recently as an alternative therapy for patients requiring use of ECMO or VAD in which heparin is not ideal. As a DTI, bivalirudin does not require the presence of antithrombin. Instead, the drug binds simultaneously to the active catalytic site of thrombin and the substrate recognition site on both circulating and clot-bound thrombin to provide its anticoagulant effect [6, 7]. After intravenous administration, bivalirudin reaches peak plasma concentrations in approximately 2 minutes. Combined with its short half-life of 25–30 min in patients with normal renal function (estimated glomerular filtration rate [eGFR] > 60 mL/min), the pharmacokinetics of bivalirudin make it advantageous for titration or discontinuation purposes [8]. Monitoring of drug effect is most often performed through evaluation of activated partial thromboplastin time (aPTT), though activated clotting time (ACT) and reaction times at thromboelastography (TEG) may also be used [4]. Dose adjustment may be necessary to maintain the anticoagulation targets within range. Although such targets vary across populations and are generally center specific, aPTT is frequently utilized, and the goal range is typically 1.5–2 times the normal value for the majority of patients [1, 7]. While an in-depth comparison between bivalirudin and heparin is outside of the scope of this review, particularly given the lack of prospective comparative studies, it is vital to understand the differences between these agents. Table 1 outlines the important pharmacotherapeutic characteristics of the medications. There is some hesitation in using DTIs because of the lack of published literature and an available reversal agent. The high medication acquisition cost of bivalirudin has been another deterrent to its regular use, although studies have shown an overall reduction in total costs when including equipment changes, laboratory testing, and blood products [9, 10]. The purpose of this review is to summarize the available literature for bivalirudin during MCS in adult and pediatric patients.

2 Methods

Literature for this review was obtained through a PubMed database query using the following terms: bivalirudin, angiomax, direct thrombin inhibitor, anticoagulation, extracorporeal membrane oxygenation, extracorporeal life support, biventricular assist device, and ventricular assist device. Combinations of these terms were searched paired with the terms pediatric, children, and adult. Additional articles were identified by a review of the reference lists of the identified articles. Articles describing the clinical usage of bivalirudin in the human population were included. Studies not published in English were excluded.

3 Results

In total, 20 studies were identified for inclusion in this review. For ECMO, nine retrospective observational analyses and five case reports were included, whereas five retrospective studies and one case report were included for VADs. No prospective studies were identified. The studies included are summarized in Tables 2 and 3.

3.1 Bivalirudin Use in Adults Receiving Extracorporeal Membrane Oxygenation (ECMO)

Although bivalirudin use in adult patients requiring ECMO has grown steadily, key aspects of drug therapy, such as established dosing and duration of use, remain unclear. Dosing strategies, including utilization of loading doses

Table 1 Medication details

	Heparin [31]	Bivalirudin [32]
Mechanism of action	Potentiates the activity of antithrombin III to inactivate thrombin	Reversible direct thrombin inhibitor
Half-life	1.5 h[a]	Normal renal function: 25 min Severe renal impairment: 57 min
Metabolism/elimination	Depolymerization and desulphation via the reticuloendothelial system in the liver and spleen; some renal elimination	Proteolytic cleavage; excreted 20% in urine
Monitoring	aPTT; anti-factor Xa activity; ACT	aPTT; ACT
Complications (noted >10%)	HIT; heparin resistance	Hypotension, pain, headache, back pain
Reversal [33, 34]	Protamine	Factor VII; hemofiltration
Cost per day ($US) [10]	6	303

ACT activated clotting time, *aPTT* activated partial thromboplastin time, *HIT* heparin-induced thrombocytopenia

[a]Dependent on obesity, renal function, presence of pulmonary embolism, and infections

Table 2 Review of literature in patients receiving extracorporeal membrane oxygenation (ECMO)

Study	Sample size and population	Study design	Anticoagulant dose and therapeutic targets	ECMO run time	Outcomes
Berei et al. [11]	72 adult pts receiving ECMO due to cardiogenic shock (71%), septic shock (15%), respiratory issues (5.5%), and mixed indications (8.5%); 28 pts received heparin (26 on VA ECMO, 2 on VV ECMO); 44 pts received bivalirudin (40 on VA ECMO, 4 on VV ECMO)	Retrospective case–control	Heparin bolus of 80 units/kg at time of cannulation; no bivalirudin bolus, initial infusion rate of 0.04 mg/kg/h, maintenance dose not reported; target aPTT of either low-intensity (45–65 s) or high-intensity (60–80 s) protocol	156.9 h, mean	Heparin group had higher rates of pt thrombosis (85.7 vs. 80.0%) and pump thrombosis events (14.3 vs. 10.0%), although not statistically significant; bivalirudin group had higher rate of major bleeding (45.5 vs. 25.0%), whereas the heparin group had higher rates of minor bleeding (25.0 vs. 22.7%), although not statistically significant; no clinically significant advantage of bivalirudin was demonstrated
Kaseer et al. [13]	52 adult pts on ECMO; 33 pts received heparin (11 on VV ECMO, 22 on VA ECMO); 19 pts received bivalirudin (13 on VV ECMO, 6 on VA ECMO)	Retrospective observational study	Median initial bivalirudin dose 0.1 mg/kg/h; targets varied (aPTT 50–70 s; aPTT 60–90 s)	Median 10 days (range 3–70)	No difference in composite thrombotic complications or bleeding. No difference in 30-day mortality. No difference in hepatic or renal impairment. Higher percent time of therapeutic aPTT with bivalirudin (85.7 vs. 50%, $p = 0.007$)
Pieri et al. [4]	20 adult pts on ECMO for at least 24-h duration; 10 pts received bivalirudin (5 on VV ECMO, 5 on VA ECMO); 10 pts received heparin (5 on VV ECMO, 5 on VA ECMO)	Retrospective case–control	No bivalirudin bolus; initial infusion rate of 0.025 mg/kg/h, median maintenance dose of 0.028 mg/kg/h; target aPTT of 45–60 s (ideal target of 52.5 s)	8 days, median (4.5 days in heparin group)	Heparin group had significantly more incidents of aPTT variations >20% than bivalirudin group (52 vs. 24). Heparin group had higher rates of aPTT >80 s (6 vs. 3 episodes), major bleeding events (2 vs. 0), minor bleeding events (4 vs. 3), pt thrombus events (2 vs. 1), circuit thrombus events (1 vs. 0), and deaths (5 vs. 4), although no adverse events were statistically significant

Table 2 (continued)

Study	Sample size and population	Study design	Anticoagulant dose and therapeutic targets	ECMO run time	Outcomes
Ranucci et al. [9]	21 pts (12 adults, 9 children) undergoing postcardiotomy VA ECMO; 13 pts received bivalirudin (5 pediatric), 8 pts received heparin (5 pediatric)	Retrospective case–control	No bivalirudin bolus; initial infusion rate of 0.03–0.05 mg/kg/h, average maintenance dose of 0.05-0.1 mg/kg/h; target aPTT of 50–80 s ; target ACT of 160–180 s	Mean 143 h	Bivalirudin group had significantly longer ACT and aPTT values maintained within required range; bivalirudin group had significantly lower bleeding during ECMO, with significantly lower need for FFP and platelet concentrate; bivalirudin group had lower requirement for pRBCs, but not statistically significant; no difference in rate of thromboembolic events between groups (2 with heparin, 1 with bivalirudin)
Netley et al. [12]	11 adult pts (4 on VA ECMO, 6 on VV ECMO, and 1 transition from VV to VA ECMO); ECMO use due to indication of ARDS ($n = 8$) or cardiac arrest ($n = 3$)	Retrospective analysis	No bivalirudin bolus; initial infusion rate of 0.15 mg/kg/h; protocol-based adjustments dependent on CrCl; target aPTT of 40–60, 50–70, or 60–80 s depending on provider preference	Mean 9.9 days	Average of 66.3% of time spent within therapeutic aPTT target range (range 30–90%); significant bleeding occurred in 8 pts (72.7%); no pts required discontinuation of ECMO due to obstruction
Brown et al. [30]	15 pts on both heparin and bivalirudin during different times during ECMO	Retrospective analysis	Not described	Mean 14.6 days	Lower bleeding and thrombotic events with bivalirudin vs. heparin, 0.06 events/ECMO day on bivalirudin vs. 0.35 events/ECMO day on heparin, $p = 0.0125$
Koster et al. [15]	40-year-old female with confirmed HIT on VA ECMO therapy as bridge to RVAD implantation	Case report	Bivalirudin bolus of 0.5 mg/kg, followed by continuous infusion of 0.5 mg/kg/h (total infusion duration < 48 h); target ACT of 200–250 s	8 days (< 48 h on bivalirudin)	Authors report low perioperative blood loss (1250 mL), moderate transfusion requirements (4 units of pRBCs, 6 units FFP, 1 platelet concentrate), and short chest closure time (90 min); major bleeding or thrombus events not reported; at 8 days, pt received RVAD with additional bivalirudin bolus and infusion rate up to 1 mg/kg/h; after RVAD implantation, anticoagulation maintained with argatroban

Table 2 (continued)

Study	Sample size and population	Study design	Anticoagulant dose and therapeutic targets	ECMO run time	Outcomes
Jyoti et al. [14]	54-year-old male pt on VV ECMO with documented heparin resistance due to antithrombin III deficiency	Case report	No bivalirudin bolus; initial infusion rate of 0.6 mg/kg/h, average maintenance dose of 0.1–0.2 mg/kg/h; target ACT of 200–220 s	23 days (2 days on heparin, 21 days on bivalirudin)	No requirement for supplemental boluses to maintain target ACT; no bleeding events or thrombotic complications occurred for duration of therapy; no requirement for platelet transfusion, but 175 mL/day of pRBCs needed to maintain hemoglobin above 80 g/dL
Hamzah et al. [10]	32 pediatric pts (3 on VV ECMO, 29 on VA ECMO); 16 pts received bivalirudin (3 on VV ECMO, 13 on VA ECMO); 16 pts received heparin (16 on VA ECMO)	Retrospective case series	Heparin bolus at 50–100 units/kg at cannulation. Bivalirudin 0.3 mg/kg/h; if CrCl <60 mL/min, 0.15 mg/kg/h	106 h (range 32–419)	Shorter time to goal therapeutic anticoagulation levels with bivalirudin, 11 vs. 29 h, $p = 0.01$. Lower significant bleeding events per 10 days of ECMO support with bivalirudin, $p = 0.002$. Lower rates of pRBCs and FFP replacements with bivalirudin. Total cost of therapy less with bivalirudin ($US1184 vs. 494 per day; $p = 0.03$)
Nagle et al. [7]	12 pediatric pts (3 on VV ECMO, 9 on VA ECMO); use on ECMO due to heparin resistance ($n = 5$), unstable ACTs ($n = 4$), clotting on heparin ($n = 2$), and HIT ($n = 1$)	Retrospective case series	Four pts received bolus dose, median bolus of 0.1 mg/kg (range 0.04–0.14); initial infusion rate of 0.05–0.3 mg/kg/h, median maintenance dose of 0.16 mg/kg/h (range 0.045–0.48); target aPTT not specified	226 h, median (median 92 h on bivalirudin)	Average percentage of time spent within goal aPTT range was 47.5%; no incidence of intracranial hemorrhage, 2 incidences of hemorrhage from chest tubes; rate of survival to ECMO decannulation was 66%; rate of survival to hospital discharge was 42%
Campbell et al. [20]	15 pediatric pts (1 on VV ECMO, 14 on VA ECMO); also included 19 VAD pts in outcomes	Retrospective analysis	Initial median (IQR) infusion rate of 0.1 (0.05–0.18) mg/kg/h; average infusion rate 0.28 (0.2–0.5) mg/kg/h; maximum median (IQR) infusion rate 0.44 (0.22–0.66) mg/kg/h; target aPTT 60 – 90 s	Median 5.5 days	Average percentage of time spent within goal aPTT range was 55%; lower average and maximum dose compared with pts on VADs; similar initial dose used
Ezetendu et al. [17]	2-month-old, full-term infant with RSV and respiratory distress placed on VA ECMO; course complicated by hemolysis and hyperbilirubinemia	Case report	No bivalirudin bolus; initial infusion rate of 0.3 mg/kg/h; maintenance dose range of 0.2–1 mg/kg/h; target aPTT 60–80 s	5 days (3.5 days on bivalirudin)	Heparin anti-Xa assay inaccurate due to hyperbilirubinemia; upon switch to bivalirudin, therapeutic aPTT goals achieved without complications, bleeding, or clot formation in ECMO circuit

Table 2 (continued)

Study	Sample size and population	Study design	Anticoagulant dose and therapeutic targets	ECMO run time	Outcomes
Preston et al. [18]	8-year-old child on VV ECMO for bridge to lung transplantation developed HIT; plasma exchange performed due to allosensitization	Case report	Four bivalirudin boluses given over both plasma exchanges, ranged from 0.75 to 1.6 mg/kg; maintenance infusion rate 1.2–1.8 mg/kg/h; target aPTT 60–80 s	92 days	Authors reported no circuit thrombus events no clinical concern for bleeding; more consistency in aPTT values with FFP exchange rather than with a 50:50 mixture of FFP with albumin 25%
Pollak et al. [19]	5-day-old newborn female with congenital diaphragmatic hernia placed on VA ECMO; diagnosis of HIT	Case report	Bivalirudin bolus of 0.4 mg/kg; initial infusion rate of 0.15 mg/kg/h; maintenance dose range of 0.06–0.17 mg/kg/h. Infusion increased to 1.6 mg/kg/h due to pt deterioration. Target ACT of 180–200 s	21 days (15 days on bivalirudin)	Pt underwent bedside diaphragmatic hernia repair after 7 days; no significant bleeding during surgery and no disturbances to ECMO support. Postoperatively, pt developed renal and hepatic failure and coagulopathy; 7 days postoperatively, pt died after termination of ECMO support. Ten platelet transfusions required over 21 days of support (4 on heparin, 6 on bivalirudin)

ACT activated clotting time, *aPTT* activated partial thromboplastin time, *ARDS* acute respiratory distress syndrome, *CrCl* creatinine clearance, *FFP* fresh frozen plasma, *HIT* heparin-induced thrombocytopenia, *IQR* int erquartile range, *pRBC* packed red blood cells, *pt(s)* patient(s), *RSV* respiratory syncytial virus, *RVAD* right ventricular assist device, *VA* veno us arterial, *VAD* ventricular assist device, *VV* veno-venous

Table 3 Review of literature in patients with ventricular assist devices (VAD)

Study	Sample size and population	Study design	Anticoagulant dose and therapeutic targets	Outcomes
Ljajikj et al. [24]	57 adult pts undergoing LVAD implantation on ECLS; 21 pts with HIT received bivalirudin; 36 non-HIT pts received heparin	Retrospective case–control	In pts with ACT <160 s, bivalirudin bolus of 0.5 mg/kg, followed by infusion of 0.5 mg/kg/h. In pts with ACT >160 s, bivalirudin bolus of 0.25 mg/kg, followed by infusion of 0.25 mg/kg/h. Target ACT of 180–220 s	Bivalirudin group had non-significantly higher rate of re-thoracotomy and non-significantly lower rates of delayed chest closure, stroke, intracranial bleeding, 30-day mortality, and 1-year mortality; PS matched analysis revealed no differences in significant outcomes
Pieri et al. [26]	12 adult pts undergoing LVAD placement; 10 pts due to dilated cardiomyopathy, 2 pts due to cardiogenic shock	Retrospective case series	No bivalirudin bolus reported; initial infusion rate 0.025 mg/kg/h; maintenance infusion rate of 0.04 mg/kg/h; target aPTT of 45–60 s	No thromboembolic or major bleeding complications; no VAD-related complications or hemolysis recorded; two episodes of minor bleeding from chest tubes that subsided after reduction or suspension of bivalirudin infusion; RBC transfusions required in 6 pts, FFP transfusion required in 1 pt; no platelet transfusions required; all pts survived to hospital discharge and 1 year; one pt died due to sepsis after 1.5 years of support
Bates et al. [25]	14 long-term VAD pts (9 adults, 5 pediatric) with 17 episodes of bivalirudin therapy; 13 episodes due to suspected or confirmed pump thrombosis, 1 episode due to HIT, 1 episode due to coagulopathy on UFH, 1 episode due to acute kidney injury, and 1 episode due to heparin resistance	Retrospective case series	No bivalirudin bolus reported; initial infusion rate 0.3 mg/kg/h; no maintenance dose reported; target aPTT of 70–90 or 80–100 s	Complications on bivalirudin: suspected pump thrombosis ($n = 2$); VAP ($n = 2$); major bleed, SDH secondary to fall ($n = 1$); GI bleeding ($n = 2$); hemorrhoids ($n = 1$). Outcome following discontinuation of bivalirudin: discharge on warfarin ($n = 8$); death ($n = 4$); transplant ($n = 3$); pump replaced ($n = 2$). No pt deaths directly related to bivalirudin; no reports of reaction to bivalirudin infusion or development of end-organ dysfunction
VanderPluym et al. [28]	43 pediatric pts on DTI for duration of VAD support (39 on bivalirudin); LVAD, $n = 28$; RVAD, $n = 2$; BiVAD, $n = 13$	Retrospective case series	No bivalirudin bolus reported; median initial infusion rate 0.3 mg/kg/h (range 0.1–1.4); median maximum dose 1.0 mg/kg/h (range 0.1–3.9). Target aPTT variable (range 50–100 s)	Major bleeding events occurred in 7 pts with 8 overall bleeding events (6 pts on bivalirudin, 1 on argatroban); all pts were on antiplatelet agent at time of bleeding event. Pump thrombosis event rate of 5.7 per 1000 pt days of support; neurologic event rate of 2.1 per 1000 pt days of support on bivalirudin
Campbell et al. [20]	19 pediatric pts on bivalirudin for VAD (9 pts with BiVAD, 5 pts with LVAD, 5 pts with RVAD)	Retrospective analysis	Initial median (IQR) infusion rate 0.1 (0.1–0.2) mg/kg/h; average infusion rate 0.4 (0.31–1) mg/kg/h; maximum median (IQR) infusion rate of 0.7 (0.41–1.2) mg/kg/h; target aPTT 60–90 s	Average percentage of time spent within goal aPTT range was 67.4%; higher average and maximum dose vs. pts on ECMO; similar initial dose used

Table 3 (continued)

Study	Sample size and population	Study design	Anticoagulant dose and therapeutic targets	Outcomes
Medar et al. [29]	11-month-old girl with dilated cardiomyopathy utilizing LVAD as bridge to transplant (122 days of support)	Case report	No bivalirudin bolus reported; initial infusion rate 0.15 mg/kg/h; maintenance rate ranged from 0.15 to 2.3 mg/kg/h; target aPTT 60–90 s	No evidence of thrombus or need for pump change; no significant bleeding intraoperatively or postoperatively. Pt discharged home on postoperative day 15

ACT activated clotting time, *aPTT* activated partial thromboplastin time, *BiVAD* biventricular assist device, *DTI* direct thrombin inhibitor, *ECLS* extracorporeal life support, *ECMO* extracorporeal membrane oxygenation, *FFP* fresh frozen plasma, *GI* gastrointestinal, *HIT* heparin-induced thrombocytopenia, *LVAD* left ventricular assist device, *PS* propensity score, *pt(s)* patient(s), *RBC* red blood cells, *RVAD* right ventricular assist device, *SDH* subdural hematoma, *UFH* unfractionated heparin, *VAD* ventricular assist device, *VAP* ventilator-associated pneumonia

and initial infusion rate, are largely dependent upon center-specific monitoring parameters and anticoagulation targets.

3.1.1 Dosing Strategies

In the largest study of adults examined, bivalirudin was initiated without a bolus as a continuous infusion of 0.04 mg/kg/h and titrated to maintain a pre-specified target aPTT range of either low intensity (45–65 s) or high intensity (60–80 s). The study was performed retrospectively, and average dosing requirements necessary to maintain anticoagulation targets were not reported [11]. Initial bivalirudin doses, maintenance rates, and important outcomes are shown in Table 2.

Two comparable studies that also did not use loading doses reported similar initial infusion rates, ranging from 0.025 to 0.05 mg/kg/h. The average rate of bivalirudin required to maintain pre-specified anticoagulation targets differed between the studies, varying from 0.028 to 0.1 mg/kg/h [4, 9]. In an additional retrospective study of 11 adult patients by Netley et al. [12], bivalirudin was initiated at a rate of 2.5 mcg/kg/min (0.15 mg/kg/h), and dose adjustment was guided by a pre-specified protocol. Despite the widely varied population characteristics, patients remained within their defined therapeutic aPTT target range for the majority of the time (66.3%), demonstrating the efficacy of a standardized protocol for bivalirudin dose adjustment across a diverse population [12]. Similarly, Kaseer et al. [13] started bivalirudin at a median dose of 0.1 mg/kg/h and reported a higher time in therapeutic range (aPTT) versus heparin therapy (50% in the heparin group vs. 85.7% in the bivalirudin group; $p = 0.007$). In another retrospective case report, by Jyoti et al. [14], no loading dose was utilized, and bivalirudin was initiated at a rate of 0.6 mg/kg/h then titrated according to ACT and aPTT goals. The average dose required to maintain a target ACT of 200–220 s was 0.1–0.2 mg/kg/h, and no supplemental boluses were required [14]. Finally, in the only identified retrospective adult case report to utilize a loading dose, Koster et al. [15] reported on the initiation of bivalirudin as a heparin alternative in the incidence of HIT. In this case, bivalirudin was initiated as a 0.5 mg/kg bolus followed by a continuous infusion of 0.5 mg/kg/h to maintain an ACT of 200–220 s [15].

In regard to dosing of bivalirudin, it is clear that initial and maintenance infusion rates varied significantly between studies, even when targeting similar aPTT and ACT targets. For example, in the retrospective case reports presented by Jyoti et al. [14] and Koster et al. [15], ACT targets for therapy were similar at 200–220 s; still, infusion rates differed significantly. Additionally, Koster et al. [15] reported that a higher infusion rate of 0.5 mg/kg/h was necessary to maintain therapeutic ACT goals, even with the addition of a loading dose. In such cases, it is likely that patient-specific

metabolism and clearance of bivalirudin plays a large role. In patients with unimpaired renal function, approximately 20% of the drug is cleared via the kidneys, and the remainder is cleared via proteolytic cleavage [6]. Therefore, although only a small percentage undergoes renal clearance, patients with differing renal function are likely to require various dose adjustments to maintain the same anticoagulation targets. Furthermore, Pieri et al. [4] demonstrated that, in patients with acute renal failure receiving continuous veno-venous hemofiltration (CVVH), higher doses of bivalirudin were necessary to maintain similar aPTT goals as those not receiving CVVH. As such, interpatient variability and differing renal function plays a large role in the dosing strategy of bivalirudin and should be considered when determining initial dose [4]. It may be reasonable, therefore, to initiate bivalirudin infusion at the lower end of dosing and titrate upwards to maintain pre-specified anticoagulation targets.

When contemplating the use of a loading dose in bivalirudin therapy, several factors should be considered. First, only one study utilized a loading dose. In the remaining six studies discussed, therapeutic aPTT and ACT targets were reached rather quickly without need for an initial bolus. In one study, eight of eleven adult patients (72.7%) reached their pre-specified target aPTT within 14 h following the start of the infusion, and all 11 patients reached target aPTT within the first 24 h of therapy [12]. Taking into account the quick onset of bivalirudin and ease of titration, it is likely that loading doses are unnecessary except in circumstances of supposed thrombosis or increased coagulation [6, 7].

3.1.2 Duration of Therapy

Another important aspect of the use of bivalirudin in ECMO is the duration of therapy. The longest length of use per manufacturer recommendation is up to 20 h in cases of acute coronary syndrome [16]; however, extracorporeal life support (ECLS) may be utilized for days, and even months. Duration of anticoagulation during this time remains undefined, and prolonged anticoagulation may increase the risk of serious adverse events [5]. In the largest adult study, bivalirudin was utilized for the duration of the ECMO run, with an average run time of 156.9 h, or approximately 6.5 days [11]. In fact, most studies demonstrated an average length of ECMO therapy of 5.9–9.9 days [4, 9, 12, 14, 15]; however, Jyoti et al. [14] reported an ECMO run time with the use of bivalirudin for 21 days. During this time, no major bleeding episodes took place, and no supplemental doses of bivalirudin were necessary to maintain anticoagulation targets [14]. Kaseer et al. [13] had a median ECMO duration of 13 days with a range of 3–70 days for their bivalirudin cohort. While there was no specific mention of these patients' outcomes, overall the bivalirudin group had similar safety outcomes as the heparin cohort [13].

In regard to duration of therapy and anticoagulation use, the case review provided by Jyoti et al. [4] demonstrated strong evidence for prolonged therapy with bivalirudin with minimal side effects. Although multiple units of packed red blood cells (pRBCs) were necessary because of hemolysis, total transfusion requirements have been shown to be decreased in patients receiving bivalirudin compared with heparin [14]. In fact, Ranucci et al. [9] demonstrated a significantly reduced need for fresh frozen plasma (FFP) and platelet concentrate transfusions in patients receiving bivalirudin when compared with heparin. As such, bivalirudin may prove to be a valuable option in patients with a preference for fewer transfusions, such as those awaiting heart transplantation.

3.2 Bivalirudin Use in Children Receiving ECMO

Studies evaluating the use of bivalirudin in ECMO in the pediatric population are even more limited. Indications for extracorporeal life support in children vary, with the majority of patients requiring ECMO due to congenital cardiac disease or acute respiratory distress syndrome. In most of the studies identified, heparin was utilized as first-line therapy. Reasons for initiation of bivalirudin infusion differed; however, a large number of patients required alternative therapy because of heparin resistance or a diagnosis of HIT [7, 17–19].

3.2.1 Dosing Strategies

In the largest pediatric study examined, Hamzah et al. [10] conducted a retrospective analysis comparing bivalirudin ($n = 16$) and heparin ($n = 16$). Their protocol initially dosed bivalirudin at 0.3 mg/kg/h for those with a creatinine clearance > 60 mL/min and at 0.15 mg/kg/h for those with renal dysfunction. No boluses were noted, and titrations were made in 0.05–0.1 mg/kg/h increments depending on distance from the target aPTT [10]. These authors reported that time to therapeutic anticoagulation was shorter with bivalirudin than with heparin (11 vs. 29 h; $p = 0.01$). Nagle et al. [7] performed a retrospective analysis that identified 12 pediatric patients utilizing bivalirudin for anticoagulation on ECMO. Four patients received a total of seven bolus doses due to suspected thrombus formation or subtherapeutic aPTT, and such doses ranged from 0.04 to 0.14 mg/kg with a median of 0.1 mg/kg. Initial bivalirudin infusion rates ranged from 0.05 to 0.3 mg/kg/h, with authors reporting increased initial infusion rates as experience with bivalirudin developed. Finally, the maintenance dose required to maintain the target aPTT goal ranged from 0.045 to 0.48 mg/kg/h with a median rate of 0.16 mg/kg/h, although the target aPTT was unspecified [7]. A study by Campbell et al. [20] that included 15 patients

on ECMO reported a median (interquartile range [IQR]) initial dose of 0.1 [0.05–0.18] mg/kg/h with a maximum dose of 0.44 [0.22–0.66] mg/kg/h. Similarly to Hamzah et al. [10], they noted a rapid time to therapeutic anticoagulation of 6.5 h [20].

In an additional report, Ezetendu et al. [17] described a 2-month-old infant requiring venous arterial (VA) ECMO due to respiratory syncytial virus (RSV) bronchiolitis and respiratory distress complicated by severe hemolysis and hyperbilirubinemia, which is believed to significantly interfere with heparin anti-Xa assay levels. Due to difficulties in achieving accurate and therapeutic anti-Xa levels, heparin was discontinued 2 days following cannulation. Bivalirudin infusion was subsequently initiated at a rate of 0.3 mg/kg/h. To maintain the target aPTT of 60–80 s, a maintenance dose range of 0.2–1 mg/kg/h was utilized. Following conversion to bivalirudin, target aPTT goals were maintained for the majority of the patient's ECMO run [17].

Preston et al. [18] and Pollak et al. [19] reported on two cases of HIT requiring replacement of heparin with bivalirudin in both an 8-year-old child utilizing veno-venous (VV) ECMO and a 5-day-old newborn placed on VA ECMO, respectively. Both case reports identified the use of loading doses, ranging from 0.4 to 1.6 mg/kg; however, maintenance doses differed significantly. Preston et al. [18] utilized a maintenance dose ranging from 1.2 to 1.8 mg/kg/h, and Pollak et al. [19] utilized a lower rate of 0.06–0.17 mg/kg/h. While this lower infusion rate initially resulted in maintenance of goal ACT range of 180–200 s, the infusion rate required significant escalation following diaphragmatic hernia repair. An infusion rate of as high as 1.6 mg/kg/h was required to maintain target level, much like that of Preston et al. [18]. Unfortunately, 7 days after the surgery, ECMO support was terminated and the patient died [18, 19].

As with dosing of bivalirudin in the adult population, significant interpatient variability is apparent in the pediatric population. Initial infusion rates seemed to be lower in studies that utilized loading doses, whereas the single study, which did not employ a loading dose, demonstrated the highest initial rate at 0.3 mg/kg/h [17]. In contrast to adult studies, the use of a loading dose in the pediatric population provided mixed effects on time to meet anticoagulation targets. Nagle et al. [7] reported a median time to initial goal aPTT of 4 h, with all patients meeting goal by 25 h post-infusion; however, only four of twelve patients received loading doses. In the case report by Ezetendu et al. [17], target aPTT goal was achieved within 11 h of bivalirudin initiation. Preston et al. [18] and Pollak et al. [19] omitted time until achievement of anticoagulation targets in their analyses. Unfortunately, such inconsistencies demonstrate the lack of an association between the use of loading doses and time to reach anticoagulation targets.

3.2.2 Duration of Therapy

Long-term data are limited, and current data vary substantially. Preston et al. [18] reported the longest duration of bivalirudin use in ECMO at 92 days of therapy in an 8-year-old male awaiting lung transplantation. However, the authors reported solely on the use of bivalirudin within the 48-h period of plasma exchange, so data on important adverse events that may have occurred beyond this timeframe are lacking [18]. Pollak et al. [19] described the second-longest course of ECMO at 21 days. While no significant bleeding or adverse events were described in the 14 days prior to surgery, the patient deteriorated rapidly following the operation, with renal failure, coagulopathy, and mortality noted. Time spent within range of anticoagulation targets was also not described [19].

Both Nagle et al. [7] and Ezetendu et al. [17] reported relatively shorter durations for ECMO therapy, at 9.4 and 5 days, respectively. According to Nagle et al. [7], the average percentage of time spent within goal aPTT range and within 90–110% of goal was 47.5% and 70.3%, respectively. Meanwhile, Ezetendu et al. [17] reported an average time spent within goal of 86.7% upon switching from heparin to bivalirudin. Several points should be considered in regard to these notable differences. First, Nagle et al. [7] reported significant confounding, which resulted from a delay of approximately 90 minutes between laboratory draw and reporting of aPTT. Additionally, changes in aPTT targets occurred throughout the study period based on assessment of clinical risk, without application of a standardized protocol [7]. As mentioned, in the retrospective study of 11 adult patients performed by Netley et al. [12], the use of a protocol for bivalirudin dose adjustment resulted in a time within therapeutic aPTT target range of 66.3%. Thus, application of such a protocol and uniform dose adjustments may have proven useful in improving time within anticoagulation targets in the study by Nagle et al. [7]. Second, the use of loading doses in Nagle et al. [7] would be expected to provide rapid escalation of the aPTT, resulting in an increased percentage of time spent within target range. However, given that bolus doses were only utilized in select patients, coupled with the lack of consistency between doses, it is not possible to analyze the impact of the loading dose on the time within therapeutic range for this population [7].

Additionally, adverse events that took place during bivalirudin therapy should be recognized. In Nagle et al. [7], four of twelve patients died while on ECMO, resulting in a survival rate until decannulation of 66.7%. The rate of survival to discharge was 41.7%, and causes of death were not identified. Head ultrasounds did not show intracranial hemorrhage in any patients while on bivalirudin therapy, and only two patients exhibited evidence of chest hemorrhage during this time [7]. In Ezetendu et al. [17], no incidence of bleeding,

thrombosis, or other critical complications occurred during the short 5-day course. In more recent literature, Hamzah et al. [10] actually concluded that the patients who received bivalirudin had a lower rate of observed significant bleeding events per 10 days of ECMO support. Similar to Ranucci et al. [9], Hamzah et al. [10] also found a significant lower amount of blood product replacement in the bivalirudin group.

Evidence surrounding safety and efficacy in long-term durations is scarce, and specific conclusions are difficult to make. Courses as long as 14 days have been reported without complications, with one study describing its use for as long as 92 days, although safety data are lacking [18, 19]. The cohort in Nagle et al. [7], which included patients requiring ECMO for pulmonary and cardiac indication, demonstrated a survival rate to discharge of only 41.7% after 9.4 days of mechanical life support. Current ELSO guidelines estimate survival rates of 50–60% in pediatric cardiac populations, whereas survival rates for ECMO due to pediatric respiratory failure have been described as being as high as 74% [2, 21]. Although Nagle et al. [7] demonstrated a lower rate of survival, the data provide evidence for efficacy of bivalirudin in short-term ECMO courses and supports the need for further, well-controlled studies.

3.3 Bivalirudin Use in Adults with Ventricular Assist Devices (VADs)

In addition to ECMO, another mode of MCS has gained recognition over recent years: VADs. As implied by the term, VADs differ from ECMO in that the devices provide cardiac support alone and do not offer oxygenation or assist respiratory function [22]. Whereas the pediatric population has seen an increase in VAD use as a bridge to transplantation, VAD use in adults has become increasingly accepted as destination therapy in the outpatient setting [23]. In fact, such devices are considered standard of care for most adults with end-stage heart failure who do not respond to medication management [22]. Although overall outcomes with VADs have proven successful, the use of bivalirudin for anticoagulation during adult VAD implantation remains largely undefined [1].

3.3.1 Dosing Strategies

In a recent retrospective study, Ljajikj et al. [24] examined the use of bivalirudin in 57 adult patients undergoing left VAD (LVAD) implantation while on ECLS. The bivalirudin group was composed of 21 patients who had received a diagnosis of HIT and were subsequently converted to argatroban, an alternative DTI. Argatroban was discontinued 6 h prior to planned surgery and bivalirudin initiated intraoperatively. A group of 36 non-HIT patients received heparin as an anticoagulant and served as the control group. In patients with pre-surgery ACT of less than 160 s, bivalirudin was initiated as a bolus of 0.5 mg/kg, followed by a continuous infusion rate of 0.5 mg/kg/h during LVAD implantation. In patients with a pre-surgery ACT of greater than 160 s, bivalirudin was initiated as a bolus of 0.25 mg/kg, followed by a continuous infusion rate of 0.25 mg/kg/h. Target ACT value, which was to be maintained from the beginning of LVAD attachment until initiation of the device, was 180–220 s [24].

In this study, the largest report examined, authors did not discover any statistically significant difference in the need for early (<7 days) surgical re-exploration due to persistent hemorrhage or cardiac tamponade following surgery. The incidence of delayed chest closures, stroke, and intracranial bleeding was lower in the bivalirudin study group, although this finding was not statistically significant. It should be noted that no adjustments to the initial infusion rates or additional bolus doses were required in any patients from the bivalirudin group [24].

In the next largest retrospective study of 14 patients (nine adults), performed by Bates et al. [25], a similar rate was utilized. Bivalirudin was initiated at a rate of 0.3 mg/kg/h and titrated to obtain a goal aPTT of 70–100 s. In contrast to Ljajikj et al. [24], patients included were those with long-term VAD use requiring bivalirudin due to various indications but was most often the result of suspected pump thrombosis (see Table 3). Treatment courses of bivalirudin, which occurred over the 7-year study period, were documented, with certain patients requiring more than one episode of bivalirudin use over this time. In the nine adult patients examined, ten bivalirudin treatment courses were recorded. The average infusion rates required to maintain anticoagulation targets were not reported [25].

Of the ten bivalirudin treatment courses, six patients experienced no complications (60%), two patients experienced gastrointestinal bleeding (20%), one patient experienced a major subdural hemorrhage attributed to a fall (10%), and one patient experienced hemorrhoidal bleeding (10%). A significant concern with bivalirudin use is the possibility of ineffective drug concentrations in areas of stagnant blood flow, which may result in thrombus occurrence [21]. However, no patients in the adult subgroup experienced complications due to thrombosis [22]. Overall, aPTT values ranged from 52 to 140 s during the course of bivalirudin infusions. As a result, the authors concluded that a bivalirudin infusion initiated at a dose of 0.3 mg/kg/h and titrated to maintain a designated anticoagulation target is a reasonable dosing strategy in the setting of several differing indications [25].

Finally, in a retrospective case series by Pieri et al. [4], use of a lower-dose bivalirudin infusion was examined in 12 adult patients requiring LVAD placement for dilated cardiomyopathy or cardiogenic shock. All patients received

an initial infusion rate of 0.025 mg/kg/h, without bolus, and rates were titrated to maintain a lower aPTT target of 45–60 s. The mean bivalirudin dose utilized over the course of therapy, ranging from 5 to 12 days, was 0.04 mg/kg/h. Additionally, overlap with warfarin was performed following LVAD implantation, with a target international normalized rate of 2–3, and aspirin was administered as soon as possible. Despite targeting a lower aPTT range, no patients experienced any thrombotic complications during bivalirudin therapy. No major bleeding complications occurred; however, two minor incidences of bleeding occurred from chest tubes. Both events resolved after temporary discontinuation or reduction of bivalirudin infusion. Furthermore, of a total of 648 aPTT measurements, a mere three levels were supratherapeutic (>90 s) [26].

As with its use in ECMO, examination of multiple published studies confirms the high degree of variability in bivalirudin dosing strategies. Initial infusion rates are heavily dependent upon center-specific anticoagulation targets. For example, Bates et al. [25] reported aPTT targets of up to 100 s in certain patients, whereas Pieri et al. [26] described aPTT rates greater than 90 s as supratherapeutic. Although bivalirudin infusion rates and use of loading doses varied, it should be noted that the largest study examined found no statistically significant differences in bivalirudin use when compared with the current standard of care, heparin. In fact, this study utilized a loading dose as well as the highest initial infusion rates yet still demonstrated a lower incidence of important adverse outcomes compared with heparin [26].

3.4 Duration of Therapy

The role of VADs as destination therapy has significantly increased in the adult population [1]. Consequently, the majority of studies evaluating bivalirudin use discuss its function as the primary anticoagulant during VAD implantation or during acute events in which heparin is unsuitable. As such, evidence evaluating long-term therapy in the adult population is limited.

Ljajikj et al. [24] described similar outcomes of interest and no difference in adverse events between the bivalirudin and heparin study groups; however, bivalirudin was only utilized for the duration of surgery, with patients converted postoperatively to argatroban for continued anticoagulation. Pieri et al. [26] discussed the use of bivalirudin for anticoagulation postoperatively, with the longest duration of therapy documented at 12 days before conversion to oral anticoagulation. Notably, all 12 patients included in the study survived to hospital discharge, and 11 patients survived to 1 year, with the exception of a single patient who died due to sepsis [26]. In the most comprehensive documentation of bivalirudin duration, Bates et al. [25] described courses of therapy in the adult population ranging from 3 to 69 days. Still, adverse events across patients did not appear to demonstrate an association with duration of infusion. For instance, one adult patient experienced a minor gastrointestinal bleed after 3 days of therapy, whereas a patient on bivalirudin for 48 days did not have any complications [25].

Bivalirudin has not been recommended by the manufacturers for use beyond 20 h in certain indications, but the nature of MCS lends itself to requiring prolonged courses of anticoagulation [16]. As multiple studies have confirmed, bivalirudin use beyond this time frame is a possible alternative to standard of care. Although use of bivalirudin has been reported for up to 48 days without complications, most data that have been examined limit its use to less than 2 weeks. Therefore, use of bivalirudin for short-term anticoagulation is a reasonable therapeutic option in patients for whom standard of care is unsuitable or otherwise inappropriate [26].

3.5 Bivalirudin Use in Children with VADs

Since VADs were first utilized in the pediatric population in the 1990s, the uses and indications have evolved considerably. Although the utility of VADs has grown, the most common use in pediatrics has remained consistent: bridge to transplantation [23]. In a study by Blume et al. [27] that included pediatric patients from as early as 1993, 77% of patients on VAD support were successfully bridged to transplant. VanderPluym et al. [28] tracked 43 patients in North America from 2013 to 2018 and found the indication for VAD was primarily bridge to transplant (72%), followed by bridge to recovery (19%), and bridge to decision (9%). As with bivalirudin use in pediatric ECMO, varying protocols, or the absence of a protocol in most cases, results in lack of standardization with regard to initial infusion rates and anticoagulation targets. A review of dosing strategies and relevant literature is provided.

3.5.1 Dosing Strategies

When examining dosing strategies in the pediatric VAD population, similarities may be drawn to initial infusion doses that are commonly used in the ECMO population. The initial infusion rate of 0.3 mg/kg/h utilized by both VanderPluym et al. [28] and Bates et al. [25], case series reports of 43 and 14 pediatric patients, respectively, was identical to that of Nagle et al. [7] and Ezetendu et al. [17]. Meanwhile, in a case report by Medar et al. [29], the authors stated an initial bivalirudin infusion rate of 0.15 mg/kg/h, 50% that of VanderPluym et al. [28] and Bates et al. [25]. Campbell et al. [20] reported that the median initial rate was similar between VAD and ECMO patients, at 0.1 mg/kg/h. Again, initial infusion rates were similar across studies, but anticoagulation targets and the average dosing required

to maintain the pre-specified goals varied drastically. For example, in the largest study examined, infusion rates began at a median of 0.3 mg/kg/h, yet maximum doses necessary to maintain aPTT goals ranged from 0.1 to 3.9 mg/kg/h [28]. In the case report by Medar et al. [29], this high variability was replicated; in one patient alone, maintenance infusion rates ranged from 0.15 to 2.3 mg/kg/h across a full VAD course of 122 days.

This high variability in dosing requirements for anticoagulation with bivalirudin has been demonstrated in several studies discussed so far. In fact, the most significant example examined thus far is reported by Nagle et al. [7], in which the authors demonstrated a maintenance dose range of tenfold in the pediatric ECMO population. Campbell et al. [20] had a less drastic but still statistically higher maximum dose in VADs versus ECMO: 0.7 and 0.44 mg/kg/h ($p = 0.048$), respectively. Explanations for this wide variability remain undetermined, but the pattern has been established in both adult and pediatric populations, regardless of the type of MCS. It is therefore likely that aforementioned differences in renal outcomes and patient-specific metabolism variances also play a large role in pediatric VAD patients [6].

3.5.2 Duration of Therapy

Given the nature of pediatric heart transplant, specifically the limited availability of neonatal and infant donors, and the fact that the majority of patients receive VADs as a bridge to transplant, the duration of therapy in this population is typically extended when compared with that of ECMO. Medar et al. [29] reported on a patient who received bivalirudin for 122 days. The authors reported that the patient did not experience any complications throughout this time. Indeed, the patient received a heart transplant, with no major bleeding events throughout surgery, and was successfully discharged at postoperative day 15 [29].

In the retrospective case series by Bates et al. [25], the median duration of therapy with bivalirudin in adults and children was reported as 21 days. However, within the seven episodes of bivalirudin use across the five pediatric patients, the authors described the longest duration of therapy at 113 days in a 15-day-old newborn with suspected HIT. Again, no complications of note were reported for this extended duration of anticoagulation therapy. Unfortunately, the patient did not receive a transplant and died, although this death was unrelated to bivalirudin use [25].

Finally, VanderPluym et al. [28] reported a median duration of VAD support of 57 days across the 43 pediatric patients examined. Duration of therapy ranged extensively, from 3 to 342 days. During this time, 23 patients received a total of 39 pump exchanges, with reasons for pump exchange including device malfunction secondary to pump thrombosis (19), replacement for device type or size (16), device failure (2), and undocumented (2) [28].

Within the seven episodes of bivalirudin use described by Bates et al. [25], the median duration of use was 40 days, which was similar to that of VanderPluym et al. [28]. Given the low availability of heart transplant donors, and a median transplant wait time of 45 days according to the UNOS database, pediatric patients may require VAD support for weeks or even months while hospitalized [23]. As such, data regarding the prolonged use of bivalirudin in VAD use is essential, particularly for patients with HIT or other such contraindications to first-line heparin therapy. Although a lack of standardization in regard to anticoagulation targets and dosing parameters is evident, reports of positive outcomes and lack of complications in patients receiving bivalirudin for more than 100 days provides promise for future studies.

4 Limitations

The key limitation to this review is reflected in the retrospective nature of every study examined. To date, prospective controlled trials of bivalirudin have yet to be conducted, resulting in a lack of standardization and an inability to accurately measure adverse events and complications. Additionally, a substantial amount of the data evaluated included case reports, which are usually more limited in terms of generalizability. Finally, a key shortcoming in this review is the lack of information regarding important details in the use of bivalirudin. Although initial infusion rates are stated in each study, maintenance infusion rates required to uphold anticoagulation targets are not consistently reported. Given the high amount of variability in titration, initial infusion rates are not necessarily reflective of actual dose requirements. Further studies are required to limit potential confounding and determine true average maintenance rates required to sustain anticoagulation targets.

5 Conclusion

Bivalirudin is a promising option for use in MCS in both pediatric and adult patients. The short half-life appears to be valuable in titration of anticoagulation, and its quick onset results in rapid time to reach therapeutic targets. Additionally, bivalirudin demonstrated successful outcomes both with and without the use of a loading dose, suggesting the possibility of center-specific protocols that utilize either. Although bivalirudin has primarily been examined as an alternative to heparin in cases of HIT or heparin resistance, evidence to date suggests possible utilization as the first-line anticoagulant in many other patients. Larger, prospective,

randomized controlled trials are necessary to determine the complete safety and efficacy of bivalirudin use in ECMO and VAD populations.

Declarations

Funding No external funds were used in the preparation of this manuscript.

Conflicts of interest Tori Taylor, Christopher T. Campbell, and Brian Kelly have no conflicts of interest that are directly relevant to the content of this article.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Material: Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Code availability Not applicable.

References

1. Raffini L. Anticoagulation with VADs and ECMO: walking the tightrope. Hematology. 2017;2017(1):674–80. https://doi.org/10.1182/asheducation-2017.1.674.
2. Mehta T, Sallehuddin A, John J. The journey of pediatric ECMO. Qatar Med J. 2017;2017(1):4. https://doi.org/10.5339/qmj.2017.swacelso.4.
3. Mazzeffi M, Greenwood J, Tanaka K, Menaker J, Rector R, Herr D, et al. Bleeding, transfusion, and mortality on extracorporeal life support: ECLS Working Group on Thrombosis and Hemostasis. Ann Thorac Surg. 2016;101(2):682–9. https://doi.org/10.1016/j.athoracsur.2015.07.046.
4. Pieri M, Agracheva N, Bonaveglio E, Greco T, De Bonis M, Covello R, et al. Bivalirudin versus heparin as an anticoagulant during extracorporeal membrane oxygenation: a case-control study. J Cardiothorac Vasc Anesth. 2013;27(1):30–4. https://doi.org/10.1053/j.jvca.2012.07.019.
5. Extracorporeal Life Support Organization. *ELSO Guidelines for Cardiopulmonary Extracorporeal Life Support* (Version 1.4). 2017. Retrieved from elso.org/Resources/Guidelines.aspx
6. Sanfilippo F, Asmussen S, Maybauer D, Santonocito C, Fraser J, Erdoes G, Maybauer M. Bivalirudin for alternative anticoagulation in extracorporeal membrane oxygenation: a systematic review. J Intensive Care Medi. 2016;32(5):312–9. https://doi.org/10.1177/0885066616656333.
7. Nagle E, Dager W, Duby J, Roberts A, Kenny L, Murthy M, Pretzlaff R. Bivalirudin in pediatric patients maintained on extracorporeal life support. Pediatr Crit Care Med. 2013;14(4):e182–8. https://doi.org/10.1097/pcc.0b013e31827200b6.
8. Gladwell T. Bivalirudin: a direct thrombin inhibitor. Clin Ther. 2002;24(1):38–58. https://doi.org/10.1016/s0149-2918(02)85004-4.
9. Ranucci M, Ballotta A, Kandil H, Isgrò G, Carlucci C, Baryshnikova E, Pistuddi V. Bivalirudin-based versus conventional heparin anticoagulation for postcardiotomy extracorporeal membrane oxygenation. Crit Care. 2011;15(6):R275. https://doi.org/10.1186/cc10556.
10. Hamzah M, Jarden AM, Ezetendu C, Stewart R. Evaluation of bivalirudin as an alternative to heparin for systemic anticoagulation in pediatric extracorporeal membrane oxygenation [published online ahead of print, 2020 May 13]. Pediatr Crit Care Med. 2020. https://doi.org/10.1097/PCC.0000000000002384.
11. Berei T, Lillyblad M, Wilson K, Garberich R, Hryniewicz K. Evaluation of systemic heparin versus bivalirudin in adult patients supported by extracorporeal membrane oxygenation. ASAIO J. 2018;64(5):623–9. https://doi.org/10.1097/mat.0000000000000691.
12. Netley J, Roy J, Greenlee J, Hart S, Todt M, Statz B. Bivalirudin anticoagulation dosing protocol for extracorporeal membrane oxygenation: a retrospective review. J Extracorpor Technol. 2018;50(3):161–6.
13. Kaseer H, Soto-Arenall M, Sanghavi D, et al. Heparin vs. bivalirudin anticoagulation for extracorporeal membrane oxygenation. J Card Surg. 2020;35(4):779–86. https://doi.org/10.1111/jocs.14458.
14. Jyoti A, Maheshwari A, Daniel E, Motihar A, Singh Bhathiwal R, Sharma D. Bivalirudin in venovenous extracorporeal membrane oxygenation. J Extracorpor Technol. 2014;46(1):94–7.
15. Koster A, Weng Y, Böttcher W, Gromann T, Kuppe H, Hetzer R. Successful use of bivalirudin as anticoagulant for ECMO in a patient with acute HIT. Ann Thorac Surg. 2007;83(5):1865–7. https://doi.org/10.1016/j.athoracsur.2006.11.051.
16. Mylan. Angiomax [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020873s036lbl.pdf. Revised 03/2016. Accessed 02/2020.
17. Ezetendu C, Jarden A, Hamzah M, Stewart R. Bivalirudin anticoagulation for an infant with hyperbilirubinemia and elevated plasma-free hemoglobin on ECMO. J Extracorpor Technol. 2019;51(1):26–8.
18. Preston T, Dalton H, Nicol K, Ferrall B, Miller J, Hayes D. Plasma exchange on venovenous extracorporeal membrane oxygenation with bivalirudin anticoagulation. World J Pediatr Congenit Heart Surg. 2014;6(1):119–22. https://doi.org/10.1177/2150135114553476.
19. Pollak U, Yacobobich J, Tamary H, Dagan O, Manor-Shulman O. Heparin-induced thrombocytopenia and extracorporeal membrane oxygenation: a case report and review of the literature. Journal of Extracorpor Technol. 2011;43(1):5–12.
20. Campbell CT, Diaz L, Kelly B. Description of bivalirudin use for anticoagulation in pediatric patients on mechanical circulatory support. Ann Pharmacother. 2020. https://doi.org/10.1177/1060028020937819.
21. Extracorporeal Life Support Organization. ELSO Guidelines for Pediatric Cardiac Failure. 2018. https://www.elso.org/resources/guidelines.aspx. Accessed 31 Aug 2020
22. Santamaria R, Jeewa A, Cedars A, Buchholz H, Conway J. Mechanical circulatory support in pediatric and adult congenital heart disease. Can J Cardiol. 2020;36(2):223–33. https://doi.org/10.1016/j.cjca.2019.10.006.
23. Dipchand A, Kirk R, Naftel D, Pruitt E, Blume E, Morrow R, et al. Ventricular assist device support as a bridge to transplantation in pediatric patients. J Am Coll Cardiol. 2018;72(4):402–15. https://doi.org/10.1016/j.jacc.2018.04.072.
24. Ljajikj E, Zittermann A, Morshuis M, Börgermann J, Ruiz-Cano M, Schoenbrodt M, et al. Bivalirudin anticoagulation for left ventricular assist device implantation on an extracorporeal life support system in patients with heparin-induced thrombocytopenia antibodies. Interact Cardiovasc Thorac Surg. 2017;25(6):898–904. https://doi.org/10.1093/icvts/ivx251.

25. Bates A, Buchholz H, Freed D, MacArthur R, Pidborochynski T, Conway J. Bivalirudin experience in a heterogeneous ventricular assist device population. ASAIO J. 2019. https://doi.org/10.1097/mat.0000000000001062.
26. Pieri M, Agracheva N, Di Prima A, Nisi T, De Bonis M, Isella F, et al. Primary anticoagulation with bivalirudin for patients with implantable ventricular assist devices. Artif Organs. 2013;38(4):342–6. https://doi.org/10.1111/aor.12168.
27. Blume E, Naftel D, Bastardi H, Duncan B, Kirklin J, Webber S. Outcomes of children bridged to heart transplantation with ventricular assist devices. Circulation. 2006;113(19):2313–9. https://doi.org/10.1161/circulationaha.105.577601.
28. VanderPluym C, Cantor R, Machado D, Boyle G, May L, Griffiths E, et al. Utilization and outcomes of children treated with direct thrombin inhibitors on paracorporeal ventricular assist device support. ASAIO J. 2019. https://doi.org/10.1097/mat.0000000000001093.
29. Medar S, Hsu D, Lamour J, Bansal N, Peek G. Use of bivalirudin as a primary anticoagulant in a child during Berlin Heart EXCOR ventricular assist device support. Perfusion. 2019;35(2):172–6. https://doi.org/10.1177/0267659119855853.
30. Brown MA, Najam F, Pocock ES, Munoz PF, Farrar KA, Yamane DP. A comparison of bivalirudin and heparin for patients on extracorporeal membrane oxygenation. Thromb Res. 2020;190:76–8. https://doi.org/10.1016/j.thromres.2020.04.009.
31. Heparin. Lexi-drugs online. Hudson (OH): Lexicomp Inc.: 2020 [updated 28 Aug. 2020; cited 31 Aug. 2020]. https://online.lexi.com. Accessed 31 Aug 2020. Subscription required to view.
32. Bivalirudin. Lexi-drugs online. Hudson (OH): Lexicomp Inc.: 2020 [updated 27 Aug. 2020; cited 31 Aug. 2020]. https://online.lexi.com. Accessed 31 Aug 2020. Subscription required to view.
33. Hasija S, et al. Randomized controlled trial f heparin versus bivalirudin anticoagulation in acyanotic children undergoing open heart surgery. J Cardiothorac Vasc Anesth. 2018;32(6):2633–40.
34. Young G, Yonekawa KE, Nakagawa PA, et al. Recombinant activated factor VII effectively reverses the anticoagulant effects of heparin, enoxaparin, fondaparinux, argatroban, and bivalirudin ex vivo as measured using thromboelastography. Blood Coagul Fibrinolysis. 2007;18(6):547–53. https://doi.org/10.1097/MBC.0b013e328201c9a9.