

# Perioperative care in an adolescent patient with heparin-induced thrombocytopenia for placement of a cardiac assist device and heart transplantation: case report and literature review

Mineto Kamata<sup>1</sup>Roby Sebastian<sup>1,2</sup>Patrick I McConnell<sup>3</sup>Daniel Gomez<sup>4</sup>Aymen Naguib<sup>1,2</sup>Joseph D Tobias<sup>1,2,5</sup>

<sup>1</sup>Department of Anesthesiology and Pain Medicine, Nationwide Children's Hospital, <sup>2</sup>Department of Anesthesiology and Pain Medicine, The Ohio State University College of Medicine, <sup>3</sup>Department of Cardiothoracic Surgery, Nationwide Children's Hospital, <sup>4</sup>Cardiovascular Perfusion Services and Heart Center, Nationwide Children's Hospital and The Ohio State University, <sup>5</sup>Department of Pediatrics, The Ohio State University College of Medicine, Columbus, OH, USA

**Abstract:** Heparin-induced thrombocytopenia (HIT) can cause life-threatening complications following the administration of heparin. Discontinuation of all sources of heparin exposure and the use of alternative agents for anticoagulation are necessary when HIT is suspected or diagnosed. We present the successful use of bivalirudin anticoagulation in an adolescent patient during cardiopulmonary bypass who underwent both placement of a left ventricular assist device and subsequent heart transplantation within a 36-hour period. The pathophysiology and diagnosis of HIT are reviewed, previous reports of the use of direct thrombin inhibitors for cardiac surgery are presented, and potential dosing regimens for bivalirudin are discussed.

**Keywords:** bivalirudin, anticoagulation, cardiopulmonary bypass, heart transplant

## Introduction

Heparin-induced thrombocytopenia (HIT) is a potentially life-threatening condition that may follow the administration of heparin. Based on the clinical picture and mechanism, HIT is classified as HIT type 1 (HIT-1) and HIT type 2 (HIT-2). HIT-1 is characterized by an early, transient, nonimmune-mediated decrease in platelet count following exposure to heparin.<sup>1</sup> While HIT-1 does not result in adverse clinical effects even without cessation of heparin therapy, significant morbidity and even mortality can occur with HIT-2. This immune-mediated complication occurs in ~1–5% of patients receiving unfractionated heparin (UFH) and <1% of patients receiving low-molecular-weight heparin (LMWH).<sup>2–4</sup> In children, the frequency of HIT-2 is reported to range from 2.3 to 3.7% with a 1–3% incidence in those receiving UFH during cardiac surgery.<sup>5</sup> There is a bimodal age distribution with a peak during the neonatal period and a second peak during adolescence, which may be reflective of the peak ages for the administration of heparin during surgical procedures.

HIT-2 results from the formation of a complex consisting of heparin, platelet factor 4 (PF-4), and immunoglobulin against them (usually IgG but also occasionally IgA or IgM).<sup>1</sup> The complex binds to and activates platelets via the Fc receptor (FcγRII) with the subsequent release of prothrombotic platelet-derived microparticles, resulting in platelet consumption and thrombocytopenia. These microparticles also promote excessive thrombin generation, frequently resulting in thrombosis. The immune complexes also interact with monocytes, leading to tissue factor production, which results in

Correspondence: Mineto Kamata  
Department of Anesthesiology and Pain Medicine, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205, USA  
Tel +1 614 722 4200  
Fax +1 614 722 4203  
Email Mineto.Kamata@Nationwidechildrens.org

antibody-mediated endothelial injury. Both of these latter processes contribute further to the activation of the coagulation cascade, thrombin generation, and thrombotic complications.

HIT-2 can cause limb- and life-threatening venous and arterial thrombosis (38–76% incidence) with a mortality rate of 20–30% if alternative anticoagulation therapy is not instituted.<sup>6,7</sup> The clinical presentation of patients with HIT may vary with clinical signs and symptoms related to either thrombocytopenia or thrombosis. Clinical symptomatology typically occurs 5–10 days after heparin exposure with a  $\geq 50\%$  decrease in platelet count and resistance to heparin anticoagulation or unexplained thrombotic events.<sup>8</sup> HIT is clinically judged using the following “4 T’s” scoring system: thrombocytopenia, timing of platelet count fall, thrombosis, and other causes for thrombocytopenia. The diagnosis of HIT is also based on laboratory findings, including an enzyme-linked immunosorbent assay (ELISA) and serotonin release assay.

We present the successful use of bivalirudin anticoagulation in an adolescent during cardiopulmonary bypass (CPB) who underwent both placement of a left ventricular assist device (LVAD) and subsequent heart transplantation within a 36-hour period. In both cases, anticoagulation was provided using bivalirudin. Options for anticoagulation during cardiac surgery in patients with HIT-2 are discussed. Previous reports of the use of direct thrombin inhibitors (DTIs) for cardiac surgery are reviewed with special attention to those involving assist device placement or cardiac transplantation.

## Case report

The requirement for patient consent to publish this case report was waived by the Institutional Review Board of the Nationwide Children’s Hospital (Columbus, OH, USA) in accordance with their policy. A 15-year-old 84 kg adolescent who was previously healthy other than attention-deficit hyperactivity disorder (ADHD) presented with a history of fever, fatigue, abdominal pain, malaise, and orthopnea for 2 weeks. Echocardiography showed severely depressed left ventricular systolic function with an ejection fraction (EF) of 7%. He was admitted to the cardiothoracic intensive care unit (CTICU) with a diagnosis of dilated cardiomyopathy and inotropic support instituted with a milrinone infusion. Magnetic resonance imaging (MRI) demonstrated a right ventricular thrombus, which necessitated anticoagulation with heparin. Heparin was started at 10 U/kg/hour and maintained at an infusion rate of 10–20 U/kg/hour to maintain a therapeutic antifactor Xa level of 0.5–1.0 IU/mL and an activated partial thromboplastin time (APTT) within the range of 60–85 seconds. The platelet count at admission was 140,000/mm<sup>3</sup> and reached a nadir of

82,000/mm<sup>3</sup> after 12 days of heparin therapy. The diagnosis of HIT was based on clinical and laboratory findings, including an ELISA and serotonin release assay. Anticoagulation was changed to argatroban and then transitioned to oral warfarin. After the prothrombin time international normalized ratio (PT-INR) stabilized with warfarin, an implantable cardioverter-defibrillator (ICD) was placed for nonsustained ventricular tachycardia on the 29th day of the hospitalization. Given the concerns of thrombosis, anticoagulation with warfarin was neither interrupted nor reversed with vitamin K. Although his myocardial function temporarily improved allowing for discharge home, he was subsequently readmitted to the CTICU with an acute deterioration of cardiac function and listed for heart transplantation. His cardiac function continued to deteriorate, and he underwent placement of an LVAD while waiting for a heart to be available.

## Perioperative management for LVAD

In the night before the surgery, anticoagulation with warfarin (PT-INR 2.12) was reversed with 10 mg of intravenous vitamin K. Other preoperative laboratory evaluations revealed a hemoglobin of 10.1 g/dL, a hematocrit of 30.6%, and a platelet count of 188,000/mm<sup>3</sup>. The patient was transported to the operating room for CPB and LVAD implantation with inotropic support, including milrinone (1.0 µg/kg/minute) and dobutamine (7.5 µg/kg/minute). After applying the American Society of Anesthesiologists’ (ASA) monitors, anesthesia was induced with fentanyl (6 µg/kg), etomidate (0.1 mg/kg), and midazolam (0.05 mg/kg). Endotracheal intubation was facilitated with rocuronium (1 mg/kg). Following anesthetic induction, a radial arterial cannula and a right internal jugular central venous cannula were placed. Anesthesia was maintained with isoflurane, a dexmedetomidine infusion (0.5 µg/kg/min), fentanyl (total intraoperative dose of 20 µg/kg), and rocuronium. Given the presence of HIT, a DTI (bivalirudin) was used for anticoagulation during CPB. A bolus dose of bivalirudin (1.5 mg/kg) was administered prior to CPB followed by a continuous infusion starting at 2.0 mg/kg/hour. Additionally, the CPB circuit was primed with bivalirudin (50 mg). The activated clotting time (ACT) was maintained at  $>400$  seconds, and the APTT was also monitored at various points throughout the case. Bivalirudin dosing and the ACT values are listed in Table 1. Due to his projected wait time for transplantation, a durable implantable LVAD was selected. Following implantation of a HeartMate II™ (St. Jude Medical, Pleasanton, CA, USA) continuous-flow LVAD and weaning from CPB, hemostasis was achieved by the administration of fresh frozen plasma (FFP) (25 mL/kg), platelet concentrates (7.3 mL/kg), cryoprecipitate (2.5 mL/kg),

**Table 1** Bivalirudin dosing and ACT values during CPB for LVAD implantation

Time	Bivalirudin bolus dose	Bivalirudin continuous dose	ACT	Comments
Start of case			126 (baseline)	
	50 mg for CPB priming 1.5 mg/kg	Infusion started at 2.0 mg/kg/hour		
CPB 0 minutes		Same	599	Hypothermia to 34°C
CPB 5 minutes		Same	456	
CPB 15 minutes		Increased to 2.25 mg/kg/hour		APTT 192 seconds
CPB 25 minutes	0.5 mg/kg	Increased to 2.5 mg/kg/hour	405	
CPB 40 minutes		Same	529	
CPB 60 minutes		Same	509	APTT >250 seconds
CPB 90 minutes	0.5 mg/kg	Same	514	Clot noted in CPB reservoir
CPB 100 minutes		Same		Warming to 37°C
CPB 115 minutes		Same	685	Nitric oxide started (for RV dysfunction)
CPB 124 minutes	0.5 mg/kg for CPB reservoir	Infusion discontinued		Weaned from CPB

**Abbreviations:** ACT, activated clotting time; APTT, activated partial thromboplastin time; CPB, cardiopulmonary bypass; LVAD, left ventricular assist device; RV, right ventricle.

and recombinant factor VIIa (90 µg/kg). Anesthesia, surgery, and CPB times were 593, 495, and 124 minutes, respectively. Inotropic support with milrinone and dobutamine was continued throughout the procedure. Following the procedure, the patient remained intubated, and he was transported to the CTICU. Postoperative laboratory evaluation at arrival to the CTICU revealed a prothrombin time (PT) of 18.1 seconds, a PT-INR of 1.46, an APTT of 54 seconds, and a fibrinogen of 251 mg/dL. During the initial 24 postoperative hours, there was a total drainage of 17 mL/kg from the chest tubes. The following blood products were transfused during this time: packed red blood cells (pRBCs) (12 mL/kg), FFP 3.6 (mL/kg), and platelets (3 mL/kg). He was extubated on postoperative

day (POD) 1. The plan was to initiate anticoagulation therapy with argatroban and then transition back to oral coumadin; however, on POD 2 while on no anticoagulation, a heart donor became available and the patient was proceeded to heart transplantation.

## Perioperative management for heart transplantation

Preoperative laboratory evaluation revealed a hemoglobin of 8.8 g/dL, a hematocrit of 26.7%, and a platelet count of 135,000/mm<sup>3</sup>. Inotropic support included milrinone (0.5 µg/kg/minute) and sodium nitroprusside (0.5 µg/kg/minute). Anesthesia was induced with fentanyl (4 µg/kg), midazolam (0.05 mg/kg), and propofol (1.5 mg/kg), followed by rocuronium for neuromuscular blockade. Anesthesia was maintained with isoflurane, a dexmedetomidine infusion (0.5 µg/kg/hour), fentanyl (total intraoperative dose of 12 µg/kg), and rocuronium. CPB management was similar to that used during LVAD placement. Bivalirudin was again used for anticoagulation with a continuous infusion that was started at 2.5 mg/kg/hour and proceeded by a bolus dose of 1.5 mg/kg. Additionally, the CPB circuit was primed with bivalirudin (50 mg). The bivalirudin dosing regimen and the ACT values are listed in Table 2. Post-CPB hemostasis and reversal of anticoagulation was performed with the administration of FFP (38 mL/kg), platelets (6.9 mL/kg), cryoprecipitate (1.1 mL/kg), and recombinant factor VIIa (90 µg/kg). Anesthesia, surgery, CPB, and aortic cross clamp times were 565, 455, 175, and 162 minutes, respectively. The patient was transported to the CTICU with his trachea intubated and mechanical ventilation provided. Milrinone and sodium nitroprusside were infusing at 0.5 µg/kg/minute. Postoperative laboratory evaluation at arrival to the CTICU revealed a PT of 23.3 seconds, a PT-INR of 2.04, an APTT of 64 seconds, and a fibrinogen of 243 mg/dL. Postoperative chest tube output for the first 24 postoperative hours was 19 mL/kg. During this time, the following blood products and colloids were administered: pRBCs (18 mL/kg), FFP (7.5 mL/kg), platelets (6.3 mL/kg), and albumin (2.4 mL/kg). The bleeding decreased and no transfusion was needed after POD 2. He was again extubated on POD 1. His hospital course was unremarkable. He was discharged home on POD 18 after heart transplantation.

## Discussion

Following the suspicion or diagnosis of HIT, all sources of heparin exposure should be discontinued immediately. As needed, alternative nonheparin anticoagulation agents should

**Table 2** Bivalirudin dosing and ACT values during CPB for heart transplant

Time	Bivalirudin bolus dose	Bivalirudin continuous dose	ACT	Comments
Start of case			130 (baseline)	
	50 mg for CPB priming			
	1.5 mg/kg	Infusion started at 2.5 mg/kg/hour		
CPB 0 minutes		Same	397	Hypothermia to 30°C
CPB 10 minutes	0.5 mg/kg	Infusion increased to 2.75 mg/kg/hour	480	APTT 197
CPB 30 minutes	0.7 mg/kg	Same	466	
CPB 45 minutes	0.25 mg/kg	Same	534	
CPB 65 minutes	0.25 mg/kg	Same	534	
CPB 85 minutes	0.1 mg/kg	Same	559	
CPB 100 minutes	0.8 mg/kg	Same	241	
CPB 105 minutes		Same	534	Warming to 37°C
CPB 120 minutes		Same	635	
CPB 130 minutes	0.25 mg/kg	Same		
CPB 140 minutes		Same	645	
CPB 155 minutes		Same	730	
CPB 165 minutes		Infusion discontinued	680	
CPB 170 minutes				Weaned from CPB
CPB 175 minutes				
CPB 180 minutes	0.5 mg/kg for CPB reservoir			
30 minutes after CPB			374	

**Abbreviations:** ACT, activated clotting time; APTT, activated partial thromboplastin time; CPB, cardiopulmonary bypass.

be initiated (Table 3). The choice of the alternative anticoagulant agent depends on several factors including patient-related factors (renal and hepatic function), local and regional availability of the specific agents, metabolic considerations, half-life, institutional experience, and available laboratory

monitoring. Although it has a lower chance of eliciting HIT, LMWH is contraindicated because of its high cross-reactivity with heparin–PF4 antibodies. The orally administered vitamin K antagonists (warfarin) are not effective as the initial, sole anticoagulation therapy in the acute phase of HIT because of a slow onset and the risk of causing limb or skin necrosis. However, warfarin can be administered in the event that long-term anticoagulation therapy is needed after the platelet count recovers. Although current guidelines recommend heparin bridging with discontinuation of warfarin in patients with significant thromboembolic risk undergoing surgery,<sup>9</sup> preliminary evidence demonstrates that pacemaker and ICD placement can be safely performed in selected patients without a perioperative pause in warfarin anticoagulation.<sup>10–12</sup> Given these data, we chose not to interrupt or reverse warfarin therapy prior to placement of the ICD in our patient.

When a patient with HIT requires elective cardiac surgery, surgery should be postponed until the heparin–PF4 antibody levels have become negative if this is clinically feasible. Heparin–PF4 antibodies are transient and are usually non-detectable after 100 days.<sup>13</sup> Heparin can be safely used for patients with previous HIT who require cardiac surgery if they no longer have circulating HIT antibodies.<sup>14,15</sup> However, it is generally recommended that both UFH and LMWH be avoided for pre- and postoperative anticoagulation. If a patient with a history of HIT requires cardiac surgery with CPB while the heparin–PF4 antibody is still present, alternative means of anticoagulation are required, generally the DTIs (Table 3).<sup>14–16</sup> DTIs act on the thrombin molecule, inhibiting the conversion of fibrinogen to fibrin.

Introduced in 1909, hirudin was the first parental anticoagulant available for clinical use.<sup>16,17</sup> It is a natural thrombin inhibitor, which is produced by the salivary gland of the leech.<sup>16</sup> Although hirudin was used for anticoagulation during the first clinical applications of hemodialysis, heparin subsequently became available in the early 1950s and, since then, has become the favored agent for parenteral anticoagulation. Hirudin is no longer available for routine clinical use. Lepirudin is a recombinant form of hirudin (r-hirudin), consisting of a single polypeptide chain of 65 amino acids. It forms an irreversible (1:1) complex with thrombin. The amino-terminal domain binds to the active site of the thrombin, and the carboxyl-terminal domain interacts with the fibrinogen-binding site, completely inhibiting the procoagulant actions of thrombin. Unlike heparin, lepirudin also inhibits clot-bound thrombin, including thrombin on fibrin that may line the CPB circuit. Lepirudin is primarily eliminated by the kidneys with a

**Table 3** Nonheparin anticoagulation

Anticoagulant	Administration	Anticoagulant monitoring	Metabolism	Elimination half-life	Antidote
Direct thrombin inhibitor					
Hirudin <sup>a</sup>	IV, subcutaneous	ECT	Renal	60–100 minutes	Meizothrombin, hemofiltration
Lepirudin <sup>b</sup>	IV, subcutaneous	APTT and ECT	Renal	80 minutes	N/A
Bivalirudin	IV, subcutaneous	APTT, ACT, and ECT	Enzymatic and renal	25 minutes	N/A
Argatroban	IV	APTT and ACT	Hepatobiliary	40–60 minutes	N/A
Heparinoid					
Danaparoid	IV, subcutaneous	Antifactor Xa	Renal	18–28 hours	N/A
Factor Xa inhibitor					
Fondaparinux	Subcutaneous	Antifactor Xa	Renal	15 hours	N/A
Antifibrinogen agent					
Ancrod <sup>a</sup>	IV	Fibrinogen level	Reticuloendothelial system	3–5 hours	FFP, cryoprecipitate
GP IIb–IIIa inhibitor					
Tirofiban	IV	N/A	Renal	2 hours	N/A

**Notes:** <sup>a</sup>No longer available for clinic use. <sup>b</sup>Not available in the USA.

**Abbreviations:** ACT, activated clotting time; APTT, activated thromboplastin time; ECT, ecarin clotting time; FFP, fresh frozen plasma; IV, intravenous; N/A, not applicable.

plasma half-life of 80 minutes. Given its renal excretion, its half-life is prolonged in renal insufficiency or failure and dose adjustments are needed based on the degree of renal dysfunction. In the absence of a known antidote or drug to reverse its effect, hemofiltration has been used to enhance the elimination of lepirudin at the end of CPB.<sup>18,19</sup> Although clinical trials have demonstrated its efficacy to provide anticoagulation, allergic reactions ranging from urticaria to hemodynamic instability have been reported.<sup>20,21</sup> These anaphylactoid reactions may occur regardless of previous exposure, although reexposure to lepirudin is associated with a greater risk when compared with first exposure.<sup>22</sup> Therefore, lepirudin administration should be limited to a single exposure whenever clinically feasible. Lepirudin is no longer available in the USA.

Argatroban is a DTI that was first described in Japan in 1981 for clinical use.<sup>23</sup> It is a small, synthetic, nonantigenic molecule derived from L-arginine. Argatroban binds directly and reversibly to the catalytic site of thrombin, thereby preventing the conversion of fibrinogen to fibrin. It undergoes hepatic metabolism with a half-life that is shorter than lepirudin (40–60 vs 80 minutes).<sup>24</sup> The half-life is significantly increased, and clearance decreased in patients with hepatic impairment, mandating dose reduction.<sup>25</sup> There is no antidote to reverse its anticoagulant effects. Anecdotal experience has demonstrated the successful use of argatroban for anticoagulation in pediatric patients during ECMO, CPB, and surgery for congenital heart disease.<sup>26,27</sup>

Bivalirudin, which was used for anticoagulation during CPB for both LVAD placement and heart transplantation in our patient, is also a parenteral DTI. It is a 20-amino acid synthetic peptide consisting of two hirudin peptide fragments connected by a tetraglycine spacer. Anticoagulation is achieved through specific and reversible interaction with the catalytic site of thrombin. The amino-terminal segment electively binds to the catalytic site of thrombin and the carboxyl-terminal portion binds to the fibrinogen site on thrombin. The half-life of bivalirudin is only 25 minutes, and it is predominantly (80%) eliminated through proteolytic cleavage within the plasma. A minority (20%) is excreted by the kidneys.<sup>28</sup> Despite limited dependence on renal excretion, its clearance is reduced by ~80% in patients with renal failure. As such, argatroban that undergoes hepatic metabolism is generally preferred in patients with renal insufficiency or failure.<sup>14</sup> As with the other DTIs, no antidote is available to reverse its anticoagulant effects. Although argatroban and bivalirudin are approved by the US Food and Drug Administration (FDA) for anticoagulation in adult patients with HIT, neither is approved for administration in the pediatric population.

Unlike heparin therapy where the ACT or heparin assays are readily available to monitor anticoagulation, there are no readily available laboratory monitor devices or tests to accurately and rapidly measure the therapeutic effect of the DTIs. Although the PT, INR, APTT, thrombin time, and ACT increase after the administration of bivalirudin, the best method for monitoring anticoagulation produced



**Table 4** Case reports of bivalirudin use in the pediatric population

Author and reference	Patient age	Initial bivalirudin bolus and (infusion) dose	Monitoring and target	Summary
<b>Cardiac surgery</b>				
Almond et al <sup>32</sup>	5 years	0.15 mg/kg (total 0.9 mg/kg) and 50 mg for CPB priming (0.25 mg/kg/hour)	ACT >400 seconds	The patient underwent orthotopic cardiac transplant with bivalirudin. Significant bleeding occurred after CPB that improved with blood products, factor VIIa, and ultrafiltration
Gates et al <sup>33</sup>	5 months	1 mg/kg (total 1.5 mg/kg) and 50 mg/400 mL for CPB priming (2.5 mg/kg/hour)		The patient underwent stage 2 Norwood. Hemostasis was achieved soon after MUF completion without blood products. Chest tube output in the first 4 hours after CPB was 4.5 mL/kg
Dragomer et al <sup>34</sup>	17 months	0.5 mg/kg (total 2.5 mg/kg) and CPB priming dose was not recorded (2.5 mg/kg/hour)		The ACT did not achieve the target range even after a total of 2.5 mg/kg of bivalirudin. Postoperative chest tube bleeding was minimal
Argueta-Morales et al <sup>35</sup>	2 cases: 3 years and 5 months	1 mg/kg and 50 mg for CPB priming (2.5 mg/kg/hour)		Bivalirudin was used for CPB for aortic valve repair and tricuspid valvuloplasty in two pediatric patients
Faella et al <sup>36</sup>	11 years	1 mg/kg (total 1.9 mg/kg) and 50 mg for CPB priming (2.5 mg/kg/hour)	APTT 2.5× baseline or ACT >400 seconds, whichever was lower	The patient was successfully placed on the ventricular assist device using bivalirudin during CPB
<b>Extracorporeal life support</b>				
Pollak et al <sup>37</sup>	5 days	0.4 mg/kg (0.15 mg/kg/h)	ACT 180–200 seconds	To maintain the target ACT, bivalirudin infusion had to be increased to 1.1–1.6 mg/kg/hour
Ranucci et al <sup>38</sup>	21 cases: 9 pediatric	Heparin 100 IU/kg bolus (0.03–0.05 mg/kg/hour)	ACT 160–180 seconds, APTT 50–80 seconds, and TGE r-time 12–30 minutes	A retrospective study comparing bivalirudin and heparin use for postoperative ECMO. Bivalirudin group had a better coagulation profile, less bleeding, and fewer allogeneic transfusions
Nagle et al <sup>39</sup>	12 cases: 1 day and 6 years	0.1 (range: 0.04–0.14) mg/kg (0.05–0.3 mg/kg/hour)	ACT 200–220 seconds	There was an observed increase in dose requirements with time, and inter- and interpatient variability in dose requirements
Preston et al <sup>40</sup>	8 years	0.75–1.6 mg/kg (1.2–1.8 mg/kg/hour)	APTT 60–80 seconds	Successful plasma exchange in a patient on VV ECMO support with continuous bivalirudin
<b>Ventricular assist device</b>				
Rutledge et al <sup>41</sup>	6 cases: 0.8–14 years	None (0.685 [range: 0.1–0.8] mg/kg/hour)	APTT 1.5–2.5× baseline and ACT 400–500 seconds for heart transplantation	The antithrombotic therapy was achieved by the combination of bivalirudin and epoprostenol. Five of the 6 patients underwent heart transplantation with bivalirudin ± epoprostenol or heparin
<b>Cardiac catheterization</b>				
Zamora <sup>42</sup>	2 months	0.5 mg/kg (0.25 mg/kg/hour)	ACT >200 seconds	A patient with anti-thrombin deficiency underwent stent placement
Breinholt et al <sup>43</sup>	2 years	0.75 mg/kg (1.75 mg/kg/hour)	ACT (not specified)	A patient with HIT-2 underwent recanalization of an occluded SVC and stent placement
Forbes et al <sup>44</sup>	110 cases: neonate to 16 years	0.75 mg/kg (1.75 mg/kg/hour)		PK/PD response of bivalirudin in the pediatric population was similar to that in adult
<b>Treatment of thrombosis</b>				
Young et al <sup>45</sup>	16 cases: 0.5–6 months	0.125, 0.25, or 0.5 mg/kg (0.125 or 0.25 mg/kg/hour)	APTT 1.5–2.5× baseline	A dose–response effect was seen for the continuous infusion, but not the bolus dose. Significant bleeding occurred in two cases
Rayapudi et al <sup>29</sup>	16 cases: neonate to 14 years	0–0.25 mg/kg (0.05–0.25 mg/kg/hour)		Positive correlation between the infusion rate and the APTT was observed. One patient developed hematuria after urethral catheter insertion
Malloy et al <sup>46</sup>	2 months	No bolus (0.1 mg/kg/hour)		The infusion was increased to a maximum of 0.58 mg/kg/hour
O'Brien et al <sup>47</sup>	18 cases: 9 months to 17 years	0.125 mg/kg (0.125 mg/kg/hour)		Following the bolus dose and the initial infusion rate, the majority of APTT values were within the target range

**Abbreviations:** ACT, activated clotting time; APTT, activated partial thromboplastin time; CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; HIT, heparin-induced thrombocytopenia; MUF, modified ultrafiltration; PK/PD, pharmacokinetic and pharmacodynamics; SVC, superior vena cava; TGE, thromboelastography; VV, venovenous.

by this agent remains to be established. Although there is a dose–response relationship between the concentration of bivalirudin and prolongation of the ACT or APTT at lower concentrations of bivalirudin (eg, for cardiac catheter procedures), neither correlate well at the higher concentrations required for CPB.<sup>29</sup> The ecarin clotting time (ECT) has been suggested to be superior to the ACT for bivalirudin anticoagulation monitoring during CPB. Anecdotal reports and case series suggest that the ACT can be used during CPB with the goal being an ACT of  $\geq 400$  seconds.<sup>30,31</sup> Given the lack of ready availability to ECT monitoring in most institutions, we chose to use a combination of ACT and APTT to monitor anticoagulation. As noted in our case, local clot formation can occur in areas of stagnant flow (eg, CPB reservoir and pericardial cavity) and may reflect local bivalirudin metabolism.

Given the shorter half-life and normal renal function in our patient, we chose to use bivalirudin during both LVAD placement and CPB in our patient. Anecdotal reports have demonstrated the efficacy of bivalirudin for providing anticoagulation in various clinical scenarios in the pediatric population during CPB as well as during heart transplantation (Table 4).<sup>29,32–47</sup> The first report of bivalirudin use in a pediatric patient involved its use for CPB during orthotopic heart transplantation in a 5-year-old child with HIT.<sup>32</sup> Prior to the initiation of CPB, the circuit was primed with a 50 mg bolus of bivalirudin. During CPB, a bivalirudin infusion was started at  $\sim 10\%$  of the recommended adult dose. This included an intravenous bolus dose of 0.15 mg/kg followed by an infusion at 0.25 mg/kg/hour. The ACT was used for monitoring anticoagulation, and repeated bolus doses of bivalirudin (total 0.9 mg/kg) were required during the first 30 minutes of CPB to achieve the target range of ACT  $>400$  seconds. Although significant bleeding occurred after separation from CPB, hemostasis was achieved with administration of blood products, including recombinant factor VII and ultrafiltration.

We report the successful use of bivalirudin to provide anticoagulation during LVAD placement and then CPB for heart transplantation in an adolescent with dilated cardiomyopathy and HIT. Bivalirudin is approved by the FDA for anticoagulation in adult patients undergoing percutaneous coronary intervention (PCI) with or at risk of HIT or HIT and thrombosis syndrome (HITS). However, bivalirudin is not approved for administration in the pediatric population. As with the other DTIs, no antidote is available to reverse its anticoagulant effects. The half-life of bivalirudin is shorter than the other DTIs and it is predominantly (80%)

eliminated through proteolytic cleavage within the plasma. As other anecdotal reports have demonstrated, bivalirudin was an effective method of anticoagulation during CPB for our patient with HIT during both procedures. Our dosing regimen included an initial bolus of 1.5 mg/kg to patient with 50 mg added to the priming volume of the CPB circuit. This was followed by a continuous infusion starting at 2.5 mg/kg/hour. This dosing regimen is similar to those reported for adults.<sup>48</sup> Given the decreased enzymatic metabolism with changes in body temperature, special precautions are needed when bivalirudin is administered for anticoagulation during CPB in the presence of hypothermia. In the absence of accurate monitoring for bivalirudin, the duration of hypothermia should be as short as feasible, and if possible, deep hypothermia should be avoided. The patient's temperature should be maintained normothermia at the end of CPB and into the postoperative period to ensure rapid metabolism. Following weaning from CPB, after the needed pump volume is reinfused to patient, a bolus dose of bivalirudin should be administered into the CPB circuit to prevent clot formation in reservoir in the event that a return to bypass support is needed. Additionally, continued circulation of the blood in the CPB machine is needed to prevent clot formation in stagnant areas. The remaining pump volume should be treated using a cell saver to clear any remaining bivalirudin. Although there is no specific monitoring device for the anticoagulation effect of bivalirudin, ACT prolongation to  $>400$  seconds or  $>2.5$  times baseline has been suggested.<sup>48</sup> In the absence of a known antidote to reverse its effect, modified ultrafiltration can be used to enhance the elimination of bivalirudin. The reader is referred to Warkentin and Koster<sup>48</sup> for additional useful information regarding bivalirudin use during CPB.

## Conclusion

We present the successful use of bivalirudin anticoagulation in an adolescent with HIT during CPB who underwent both placement of a LVAD and subsequent heart transplantation. Although bivalirudin is not currently approved for the administration in the pediatric population, anticoagulation for both cases was safely achieved using bivalirudin as has been reported in previous case reports. Advantages of bivalirudin when compared with other DTIs include a shorter half-life of bivalirudin and limited dependence on renal and hepatic clearance. Although reversal is not feasible, modified ultrafiltration can be used to enhance elimination.

## Disclosure

The authors report no conflicts of interest in this work.

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