



## Original Article

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**Corresponding author:**

Amy L. Kiskaddon;

Email: [amykiskaddon@gmail.com](mailto:amykiskaddon@gmail.com)

# Frequency, characteristics, antithrombotic therapies, and outcomes of thromboembolism in paediatric patients with CHD undergoing cardiac surgery: a single centre retrospective study

Amy L. Kiskaddon<sup>1,2,3,4</sup> , Arabela C. Stock<sup>4,5</sup>, Marisol Betensky<sup>1,2,6</sup>, Vera Ignjatovic<sup>1,2</sup>, Jamie L. Fierstein<sup>2</sup>, Shannon Frank<sup>4</sup>, James A. Quintessenza<sup>4</sup> and Neil A. Goldenberg<sup>1,2,6,7</sup>

<sup>1</sup>Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA; <sup>2</sup>Johns Hopkins All Children's Institute for Clinical and Translational Research, St. Petersburg, FL, USA; <sup>3</sup>Department of Pharmacy, Johns Hopkins All Children's Hospital, St. Petersburg, FL, USA; <sup>4</sup>Heart Institute, Johns Hopkins All Children's Hospital, St. Petersburg, FL, USA; <sup>5</sup>Division of Cardiac Critical Care, Johns Hopkins All Children's Hospital, St. Petersburg, FL, USA; <sup>6</sup>Cancer and Blood Disorders Institute, Johns Hopkins All Children's Hospital, St. Petersburg, FL, USA and <sup>7</sup>Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

**Abstract**

**Introduction:** Thromboembolism is a complication in paediatric patients with CHD requiring cardiac surgery. Previous research has focused on post-operative thromboembolism. This study aimed to describe thromboembolism frequency before or after cardiac surgery in children with CHD. **Methods:** We performed a single-centre retrospective study from October 2020 to June 2023 (inclusive). Patients were eligible for inclusion if they were <21 years of age and underwent cardiac surgery. Outcomes of interest included the occurrence and characteristics of thromboembolism in the 12 months before and after surgery, antithrombotic therapies, recurrent thromboembolism, and clinically significant bleeding. **Results:** Among 260 patients included, 35 (13.5%) developed an index thromboembolism. Twelve (34.3%) patients had an index thromboembolism <12 months before surgery and 23 (65.7%) had an index thromboembolism <12 months after surgery, including 8 (22.9%) patients who had thromboembolism during both exposure periods. The median interquartile range (IQR) time of thromboembolism relative to cardiac surgery was -26 (-4 to -140) days and 15 (4 to 41) days, respectively. Seven (20%) patients had arterial, 18 (51.4%) venous, and 3 (8.6%) had both arterial and venous thromboembolism. Median (IQR) antithrombotic therapy duration was 49 (24–84) days. Nine (25.7%) patients developed recurrent thromboembolism and five (14.3%) patients experienced clinically significant bleeding. **Conclusions:** The risk of thromboembolism and recurrence is high both before and after cardiac surgery among paediatric patients with CHD. Prospective multi-centre studies should seek to identify risk factors for preoperative and postoperative thromboembolism to inform the design of future risk-stratified thromboembolism prevention trials in children with CHD.

**Introduction**

Thromboembolism is a known complication in paediatric patients with CHD who undergo cardiac surgery, for which the frequency and timing of events have been poorly characterised and risk factors are as yet unclear. Paediatric patients with congenital heart surgery undergoing cardiac surgery appear to have an increased risk of thromboembolism when compared to other hospitalised children.

Several factors may contribute to the development of thromboembolism in this patient population, including altered blood flow, inflammatory processes, platelet activation, and the presence of foreign materials. Cardiopulmonary bypass is associated with endothelial disruption, platelet dysfunction, platelet activation, and inflammatory processes which collectively contribute to a pro-thrombotic state.<sup>1–3</sup> Hypoxaemia has also been theorised to contribute to the multifactorial aetiology of thromboembolism by mediating platelet activation and reduction in native anticoagulants.<sup>8–10</sup> Additionally, prosthetic shunts, as are often encountered in patients with a single ventricle physiology put patients at risk for thromboembolism, while Fontan circulation has been a reported risk factor for thromboembolism given associations with elevated levels of factor VIII and decreased protein C levels.<sup>2,8</sup> Lastly, cardiomyopathy, arrhythmias, and structural anomalies of the heart and great vessels, as

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frequently observed in patients with CHD, result in altered blood flow, increasing the risk of thromboembolism.<sup>11,12</sup>

Previous research has mainly focused on perioperative thromboembolism following cardiac surgery for CHD in children, with limited data on thromboembolism risks extending further post-operatively as well as pre-operatively in these patients. Furthermore, the risk of recurrent thromboembolism among paediatric patients with CHD and who develop pre- and post-operative thromboembolism has not been previously reported. Accordingly, the aims of this study were to evaluate occurrence rates, characteristics, and antithrombotic therapies for thromboembolism during a period of 12 months before and after cardiac surgery among paediatric patients with CHD patients, as well as to estimate the risks of recurrent thromboembolism and clinically significant bleeding.

## Materials and methods

### Study design

We performed a single-centre retrospective cohort study of patients <21 years of age who underwent cardiac surgery. The study was approved by the Johns Hopkins Medicine Institutional Review Board (IRB00389887), with a waiver of informed consent granted.

### Data collection

Data collection was conducted using the institution's surgical database and the electronic medical record by means of manual abstraction. Variables of interest included: age and age group (neonate: <28 days of age, infants 1 month to <12 months of age, children 1 year to <12 years of age, and adolescents 12–18 years of age), CHD diagnosis, surgical procedure, cardiac catheterisation  $\leq 30$  days prior to documented thromboembolism, presence of central venous or arterial catheters at time of thromboembolism, type of thromboembolism (venous, arterial) and anatomic site, antithrombotic therapies administered for thromboembolism, and chronic antithrombotic drug prophylaxis regimens, as applicable.

### Outcomes and outcome definitions

The primary outcome was the occurrence of a radiologic confirmed diagnosis of a thromboembolism less than 12 months before or less than 12 months following congenital cardiac surgery, as defined by the proportion of patients who developed at least one thromboembolism during the exposure period. Secondary outcomes included thromboembolism characteristics, antithrombotic regimens for thromboembolism treatment, and rates of recurrent thromboembolism and clinically significant bleeding.

Thromboembolism recurrence was defined as thromboembolism >7 days after an index thromboembolism in a separate anatomic site from the index thromboembolism, or at the same site if there had been interim radiologic evidence of resolution of the index thromboembolism.<sup>13</sup> Clinically significant bleeding was defined as the composite of major bleeding by the International Society on Thrombosis and Haemostasis paediatric criteria or severe/fatal bleeding by the criteria of Nellis *et al.*, and further characterised as related to antithrombotic therapy if bleeding occurred while receiving antithrombotic therapy, or within 24 hours of cessation of anticoagulation or 7 days of antiplatelet therapy.<sup>14,15</sup>

### Statistical analysis

Continuous variables were summarised with medians and interquartile ranges, while categorical variables were described using frequencies and percentages.

## Results

### Patient characteristics

Two hundred sixty neonates, infants, and children with CHD underwent cardiac surgery during the study period, defining the cohort. Of these, 35 (13.5%) patients undergoing 39 cardiac surgeries developed thromboembolism before or after cardiac surgery. Twenty-nine (82.9%) patients who developed a thromboembolism were neonates or infants and 16 (45.7%) had single ventricle physiology. Clinical characteristics are shown in Table 1.

Twelve (34.3%) patients had an index thromboembolism <12 months before surgery, of which 3 were incidental findings based on pre-surgical ultrasounds. Twenty-three (65.7%) patients had an index thromboembolism <12 months after surgery: 10 (28.6%) in the acute (<7 days) postoperative period, and 5 (14.3%) in the subacute (7 to <14 days) postoperative period. The median interquartile range (IQR) times to thromboembolism relative to cardiac surgery were –26 (–4 to –140) and 15 (4 to 41) days for the preoperative and postoperative thromboembolism groups, respectively (Table 2).

Nineteen (54.3%) patients had a venous index thromboembolism, with the most common site being lower venous (12, 34.3%). Additional sites for index thromboembolism events are listed in Table 2.

Sixteen (45.7%) patients had undergone a recent cardiac catheterisation (Table 1), and 23 (65.7%) patients had a central venous catheter-related or central arterial catheter-related index thromboembolism: 6 (50%) and 17 (73.9%) in the preoperative and postoperative periods, respectively (Table 2).

### Antithrombotic treatments for thromboembolism

The most common agent used in the acute thromboembolism (<7 days post-diagnosis of thromboembolism) and subacute (7+ days post-diagnosis of thromboembolism) periods was enoxaparin (20, 57.1%) and (16, 45.7%), respectively. Additional antithrombotic therapy details are provided separately in Table 2 for the pre- and post-operative periods.

### Outcomes of thromboembolism

Clinical outcomes of thromboembolism are summarised in Table 2. Of the 35 patients with thromboembolism, 9 (25.7%) developed at least 1 recurrent thromboembolism. Thromboembolism recurrences were the most common in the lower venous (3, 33.3%) and lower arterial (3, 33.3%) systems. Five patients (14.3%) developed clinically significant bleeding. Among these, 1 was anticoagulant-related.

## Discussion

This single-institutional retrospective study provides novel findings on the risk and timing of thromboembolism in relation to cardiac surgery among children with CHD, as well as the risk of thromboembolism recurrence. Of the 260 paediatric patients with CHD that required surgical repair, the thromboembolism occurrence rate was 13.5% in the 12 months before and after

**Table 1.** Patient characteristics

Variable	Patients with thromboembolism before surgery (n = 12)	Patients with thromboembolism after surgery (n = 23)	All patients (n = 35)
<b>Age at thromboembolism, n (%)</b>			
Neonate	6 (50)	3 (13.1)	9 (25.7)
Infant	5 (41.7)	15 (65.2)	20 (57.1)
Child	1 (8.3)	4 (17.4)	5 (14.3)
Adolescent	0 (0)	1 (4.3)	1 (2.9)
<b>Sex, n (%)</b>			
Male	10 (83.3)	9 (39.1)	18 (51.4)
<b>Race, n (%)</b>			
White	8 (66.7)	12 (52.2)	20 (57.1)
Black	3 (25)	7 (30.4)	10 (28.6)
Other	1 (8.3)	4 (17.4)	5 (14.3)
<b>Ethnicity, n (%)</b>			
Non-Hispanic	9 (75)	20 (87)	29 (82.9)
<b>Cardiac diagnosis, n (%)</b>			
Single Ventricle	5 (41.7)	11 (47.8)	16 (45.7)
Bi-ventricular	7 (58.3)	8 (34.8)	15 (42.9)
Heart Transplant	0 (0)	4 (17.4)	4 (11.3)
<b>Cardiac surgery case complexity (STAT category)<sup>1</sup> n, (%)</b>			
1	4 (33.3)	5 (21.7)	9 (25.7)
2	2 (16.7)	5 (21.7)	7 (20)
3	3 (25)	8 (34.8)	11 (31.4)
4	2 (16.7)	3 (13.1)	5 (14.3)
5	1 (8.3)	2 (8.7)	3 (8.6)
<b>CPB time, min<sup>2</sup> median (IQR)</b>	205 (130-253)	136 (110-196)	167 (120-226)
<b>Cross clamp time, min<sup>3</sup> median (IQR)</b>	70 (53-88)	63 (40-104)	75 (55-112)
<b>Procoagulant use intra-operative<sup>1</sup> n, %</b>	10 (83.3)	14 (60.8)	24 (68.6)
<b>Cardiac catheterisation ≤ 30 days prior to thromboembolism, n, %</b>	5 (41.7)	11 (47.8)	16 (45.7)

<sup>1</sup>35 patients with 39 cardiac surgery cases; 4 patients had 2 operations each during the study period.

<sup>2</sup>7 cases did not have CPB time.

<sup>3</sup>12 cases did not have cross-clamp time.

CPB = cardiopulmonary bypass; STAT = Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery.

cardiac surgery, with the majority of thromboembolism (80%) occurring post-cardiac surgery. This is concordant with prior work by Manlihot et al., reporting an overall thromboembolism rate of 11% in paediatric patients following cardiac surgery, despite our report being distinct from that of Manlihot by including pre-operative patients with CHD<sup>1</sup>.

Silvey et al. reported a similar rate of arterial and venous thrombosis in children post-cardiac surgery using a large database study.<sup>12</sup> We report in our study that most of the index thromboembolism were venous (62.9%), including 3 patients who had both arterial and venous thromboembolism. Compared to the work by Silvey et al., who reported similar rates, we report that venous thromboembolism was more common than arterial thromboembolism (53.4% vs. 22.9%).

In our study, we found that of the patients who developed a thromboembolism either before or after cardiac surgery, 45.7% had single ventricle physiology. Thrombosis in single ventricle patients is reported to occur in 8%–12% of paediatric patients with shunts, children who have undergone Fontan procedures for single ventricle physiology have a 17%–33% risk of thrombosis.<sup>16</sup>

Children with CHD undergoing cardiac surgery often have central venous and/or arterial catheters placed. Numerous factors, such as endothelial damage following central venous or arterial

access may precipitate such thromboembolism. Central venous and arterial catheters are known key contributors to thromboembolic events, with approximately 20% of paediatric (non-CHD) patients who have a central venous or arterial catheter developing a thromboembolism.<sup>17</sup> While CHD is a reported risk factor for developing thromboembolism and recurrent venous thromboembolism in the setting of central lines, research on thromboembolism risk factors among paediatric patients with CHD and central venous/arterial catheters is lacking. Future collaborative studies should address this important knowledge gap, to inform future risk-stratified thromboprophylaxis trials in children with CHD.

Published work is limited regarding antithrombotic therapy approaches employed for acute and subacute thromboembolism treatment in paediatric patients with CHD, duration of therapy, and clinical outcomes, including recurrent thromboembolism and clinically significant bleeding. In this study, we report that most patients were managed with enoxaparin in both the acute (57.1%) and subacute (45.7%) time periods. Major bleeding rates in non-CHD patients receiving low molecular weight heparin have been reported to range from 0 to 19%.<sup>18</sup> In our study of patients with CHD receiving anticoagulation for treatment of thromboembolism, we report 5 (14.3%) patients with clinically significant bleeding. The 25.7% rate of recurrent thromboembolism observed

**Table 2.** Thromboembolic events and outcomes

Variable	Patients with thromboembolism before surgery (n = 12)	Patients with thromboembolism after surgery (n = 23)	All patients (n = 35)
<b>TE prior to and after cardiac surgery, n (%)<sup>1</sup></b>	8 (66.7)	8 (34.8)	8 (22.9)
<b>Recurrent TE, n (%)</b>	4 (33.3)	5 (21.7)	9 (25.7)
<b>Time of thromboembolism prior to cardiac surgery, days, median (IQR)</b>	26 (4–140)	–	36 (4–140)
<b>Time of thromboembolism after cardiac surgery, days, median (IQR)</b>	–	15 (4–41)	15 (4–41)
<b>Types of index TE, n (%)</b>			
Arterial	3 (25)	5 (21.7)	8 (22.9)
Venous	9 (75)	10 (43.5)	19 (54.3)
Intracardiac	1 (8.3)	4 (17.4)	5 (14.3)
Venous and arterial	1 (8.3)	2 (8.7)	3 (8.6)
<b>Site of index TE, n (%)</b>			
Upper arterial	1 (8.3)	2 (8.7)	3 (8.6)
Upper venous	0 (0)	5 (21.7)	5 (14.3)
Lower arterial	0 (0)	6 (26.1)	6 (17.1)
Lower venous	7 (58.3)	5 (21.7)	12 (34.3)
Splanchnic	3 (25)	1 (4.3)	4 (11.4)
Intracardiac	1 (8.3)	4 (17.4)	5 (14.3)
<b>Lines at time of TE, n (%)</b>			
No lines	1 (8.3)	4 (17.4)	5 (14.3)
PICC	4 (33.3)	3 (13)	7 (20)
PICC and arterial	0 (0)	5 (21.7)	5 (14.3)
PICC and atrial	0 (0)	2 (8.7)	2 (5.7)
PICC, atrial, and arterial	1 (8.3)	0 (0)	1 (2.9)
Atrial	1 (8.3)	3 (13)	4 (11.4)
Atrial and arterial	0 (0)	2 (8.7)	2 (5.7)
Arterial, atrial, and CVC	0 (0)	1 (4.3)	1 (2.9)
Arterial and CVC	0 (0)	1 (4.3)	1 (2.9)
Umbilical	2 (16.7)	1 (4.3)	3 (8.6)
Umbilical and arterial	1 (8.3)	0 (0)	1 (2.9)
Peripheral (only)	1 (8.3)	2 (8.7)	3 (8.6)
Port	0 (0)	1 (4.3)	1 (2.9)
<b>Acute treatment for TE, n (%)</b>			
None	1 (8.3)	5 (21.7)	6 (17.1)
Enoxaparin	8 (8.3)	12 (52.5)	20 (57.1)
Unfractionated heparin	2 (16.7)	3 (13)	5 (14.3)
Bivalirudin	0 (0)	2 (8.7)	2 (5.7)
New/increased antiplatelet therapy	1 (8.3)	1 (4.3)	2 (5.7)
<b>Subacute treatment for TE, n, %</b>			
None	2 (16.7)	7 (30.4)	9 (25.7)
Enoxaparin	6 (50)	10 (43.5)	16 (45.7)
Bivalirudin	0 (0)	2 (8.7)	2 (5.7)
Unfractionated heparin	1 (8.3)	0 (0)	1 (2.9)
Rivaroxaban	0 (0)	1 (4.3)	1 (2.9)
New/increased antiplatelet therapy	3 (25)	3 (13)	6 (17.1)
<b>Treatment duration, days, median (IQR)</b>			
All TE	72 (53–84)	46 (17–82)	49 (24–84)
Arterial TE	84 (84–84)	17 (14–45)	42 (17–45)
Venous TE	70 (51–84)	76 (48–84)	50 (42–84)
<b>Mortality related to TE, n, %</b>	0 (0)	1 (4.3)	1 (2.8)

<sup>1</sup>8 patients total had a TE event both before and after cardiac surgery.

CVC = central venous catheter; PICC = peripherally inserted central catheter; TE = thromboembolism; UFH = unfractionated heparin.

in this study among paediatric patients with CHD requiring cardiac surgery warrants further—ideally multi-centre—validation and further investigation of prognostic factors for venous thromboembolism recurrence. Such studies will facilitate the design of risk-stratified clinical trials of antithrombotic approaches to preventing recurrent thromboembolism and its sequelae while minimising bleeding risk.

Limitations of this study include the relatively small sample size derived from a single institution, which requires caution regarding generalising its findings. This limitation emphasises the need for future larger, multi-centre studies. Additionally, given that a diagnosis of thromboembolism in this retrospective study relied on the presence of symptoms and documentation within the electronic medical record, these findings may underestimate the

true frequency of thromboembolism and its recurrence (especially regarding asymptomatic thromboembolic events); future prospective studies can mitigate this concern. Lastly, although we did not include vaso-inotropic scores, we did report the surgical case complexity (The Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery) mortality category and cardiac physiology as covariates for clinical severity. Notwithstanding these potential limitations, this study and its findings represent an important step in filling a critical knowledge gap on thromboembolism risk, characteristics, treatments, and outcomes of thromboembolism in children with CHD undergoing cardiac surgery.

In conclusion, we report in this single-centre retrospective study, a 13.5% incidence of index thromboembolism in children with CHD in the 12 months before and after cardiac surgery, with 34.2% of all index thromboembolism occurring prior to cardiac surgery, and a recurrence rate of 25.7%. Awareness of thromboembolism prior to cardiac surgery may be beneficial for optimising post-operative prevention strategies to minimise the recurrence of thromboembolism. Future multi-centre prospective studies are needed to validate these findings and evaluate risk factors for thromboembolism and thromboembolism recurrence in paediatric patients with CHD requiring cardiac surgery, to inform future risk-stratified trials of thromboembolism prevention and treatment in this vulnerable population.

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**Ethical standard.** The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the institutional committees at Johns Hopkins All Children's Hospital.

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