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Arterial thromboembolism, antithrombotic therapy, and risk of recurrent thromboembolism in children with CHD undergoing cardiac surgery

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Abstract

Introduction: Data on arterial thromboembolism in children undergoing cardiac surgery are limited. We sought to characterise, and estimate rates of, incident and recurrent arterial thromboembolism, and describe antithrombotic therapies for treatment in a large multinational population of children with CHD undergoing cardiac surgery. *Methods:* We queried the TriNetX global electronic health record (derived real-world data research platform) from 2017 to 2024 for patients less than 18 years of age and an index arterial thromboembolism within 1 year of congenital cardiac surgery. Data were descriptively analysed. *Results:* Of 20,102 children who underwent an index cardiac surgery for CHD, 206 (1.1%) developed an index arterial thromboembolism within 1 year of surgery: 111 (53.9%) had only arterial thromboembolism and 95 (46.1%) had concomitant venous thromboembolism. The most common anatomic site for arterial thromboembolism was the lower extremity ($n = 141$, 68.4%), and the most common surgery was the Glenn procedure ($n = 35$, 17%). Unfractionated heparin was utilised in 136 (67 %) and aspirin in 91 (44.2%) patients. Recurrent thromboembolism occurred in 36 (17.5%) patients within 1 year of the index thromboembolism. *Conclusions:* Among children undergoing congenital cardiac surgery, arterial thromboembolism was rare (1% of patients), but the 1-year risk of recurrent thromboembolism was high, at 17.5%. Multicentre prospective cohort studies are warranted to further evaluate risk factors for recurrent thromboembolism, to facilitate future risk-stratified interventional trials designed to reduce the high thromboembolism recurrence risk in these children.

Introduction

CHD represents a large group of congenital defects affecting approximately 1% of births in the United States.[1–3] Paediatric patients with CHD who undergo cardiac surgery are at an increased risk for thromboembolism due to multiple factors, including alterations in blood flow, inflammation, and platelet activation from surgically induced tissue injury and the physiological and pathological responses thereto.[4–11] Furthermore, many children with CHD undergoing surgery require the placement of central venous and/or arterial catheters to provide supportive care.[2,6,7] In children with CHD, the most concerning arterial thromboembolism is an ischaemic stroke but arterial thromboembolism at other sites can result in life-threatening shunt occlusion in patients with systemic to pulmonary shunt, limb ischaemia, and loss of access to an artery, which is essential for diagnostic or therapeutic cardiac catheterisation.[7–13]

Table 1. Patient characteristics and recurrent thromboembolism

	ATE $n = 111$	ATE and VTE $n = 95$	All Events $n = 206$
Age at index thromboembolism (years), mean ± standard deviation	**1.4 ± 3.82**	**0.68 ± 2.09**	**1.1 ± 3.1**
Sex,n (%)	58 (52.3)	47 (49.5)	105 (51.0)
Male	47 (42.3)	34 (35.8)	81 (39.3)
Female	6 (5.4)	14 (14.7)	20 (9.7)
Unknown			
Ethnicity, n (%)	52 (46.8)	61 (64.2)	113 (54.9)
Not Hispanic or Latino	29 (26.1)	10 (10.5)	39 (18.9)
Hispanic or Latino	30 (27.0)	24 (25.3)	54 (26.2)
Unknown			
Race, n (%)	43 (38.7)	48 (50.5)	91 (44.2)
White	8 (7.2)	14 (14.7)	22 (10.7)
Black or African American	8 (7.2)	10 (10.5)	18 (8.7)
Asian	3 (2.7)	0 (0)	3 (1.5)
American Indian or Alaska Native	3 (2.7)	0 (0)	3 (1.5)
Native Hawaiian/Other Pacific Islander	26 (23.4)	0 (0)	26 (12.6)
Other	20 (18.0)	23 (24.2)	43 (20.9)
Unknown			
Recurrent thromboembolism within 1 year of index thromboembolism, n (%)	14 (12.6)	22 (23)	36 (17.5)
One recurrent event	0 (0)	14 (15)	14 (6.8)
Two recurrent events	0 (0)	8 (8)	8 (3.4)
Three recurrent events			

ATE = arterial thromboembolism; VTE = venous thromboembolism.

Despite a growing appreciation for the increased risk of arterial thromboembolism and venous thromboembolism among paediatric patients with CHD, data on arterial thromboembolism in particular, its antithrombotic treatment regimens, and the risk of recurrent thromboembolism among children undergoing cardiac surgery for CHD are limited. Accordingly, the objectives of this study were to characterise incident arterial thromboembolism, antithrombotic therapies, and the risk of recurrent thromboembolism in a large multinational population of paediatric patients with CHD undergoing cardiac surgery.

Methods

This study utilised the TriNetX global electronic health record-derived real-world data research platform, with access to de-identified medical information from over 140 million patients across over 100 healthcare organisations, of which approximately 21 million are paediatric patients (less than 18 years of age). There were 140,576,102 patients from 104 healthcare organisations when the data were obtained on November 4, 2024. A study cohort was created using Current Procedural Terminology codes for congenital cardiac surgery (Supplemental Appendix A) and the International Statistical Classification of Diseases and Related Health Problems-10 codes for arterial thromboembolism events (Supplemental Appendix B). Patients were included if they had both a Current Procedural Terminology code for congenital heart surgery and an International Statistical Classification of Diseases and Related Health Problems-10 code for only arterial thromboembolism or a simultaneous arterial thromboembolism and venous thrombo boembolism that occurred within 1 year of cardiac surgery. Recurrent thromboembolism was defined as a new arterial or venous thromboembolism (using the aforementioned International Statistical Classification of Diseases and Related Health Problems-10 diagnoses) > 7 days after the original diagnosis date of index arterial thromboembolism, identified as a new instance of arterial thromboembolism or venous thromboembolism.[14]

Data collection included patient demographics, types of cardiac surgery, and antithrombotic medications employed in the acute (< 7 days) and subacute (>/= 7 days) periods post-diagnosis of arterial thromboembolism, as well as characteristics of the acute incident and recurrent thromboembolism. Medications included unfractionated heparin, enoxaparin, dalteparin, bivalirudin, argatroban, rivaroxaban, apixaban, edoxaban, aspirin, clopidogrel, cangrelor, tirofiban, eptifibatide, and warfarin. Congenital cardiac operations were classified as surgeries for congenital malformations: pulmonary artery, septal defects, shunts, single ventricle and other complex cardiac anomalies, cardiac valves, venous anomalies, aortic anomalies, great vessels, and other surgeries.

Descriptive statistics were utilised. Continuous variables were summarised with means and standard deviation, while categorical variables (including outcomes) were summarised using counts and frequencies. Frequencies were compared using the Chi-Squared test. Statistical analysis was performed via the statistical tools on TriNetX.

Results

From 2017 to 2024, 20,102 patients < 18 years of age were identified with a congenital cardiac surgery Current Procedural Terminology code. The mean (± standard deviation) age at index arterial thromboembolism was 1.1 (± 3.1) years. One hundred thirteen (51%) patients were male, 91 (44.2%) White race, and 91 (44.2%) non-Hispanic/non-Latino ethnicity (Table 1). Of the 20,102 patients, 206 (1%) developed an initial arterial thromboembolism within 1 year of surgery, with 111 (54%) and 95 (46%) having an arterial thromboembolism and arterial + venous thromboembolism as the index event, respectively.

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Table 2. Antithrombotic medication use

	ATE $n = 111$	ATE and VTE $n = 95$	All Events $n = 206$
Anticoagulants, n (%)			
Unfractionated heparin	83 (74.8)	78 (82.1)	161 (78.2)
Enoxaparin	14 (12.6)	39 (41.1)	53 (25.7)
Vitamin K antagonists	5 (4.5)	5 (5.3)	10 (4.9)
Bivalirudin	46 (43.8)	10 (10.5)	56 (27.2)
Direct oral anticoagulants*	0 (0)	10 (10.5)	10 (4.9)
Antiplatelet agents, n (%)			
Aspirin	43 (38.7)	48 (50.5)	91 (44.2)
Clopidogrel	10 (9.0)	10 (50)	20 (9.7)

*Includes rivaroxaban, edoxaban, apixaban, dabigatran. ATE = arterial venous thromboembolism; VTE = venous thromboembolism.

The most common anatomic location of index arterial thromboembolism was the lower extremity/abdominal aorta: 77 (69.4%) of patients with an index arterial thromboembolism (Table S1). For patients with an index arterial + venous thromboembolism, the lower extremity/abdominal aorta and femoral veins were the most common sites, in 64 (67.4%) and 30 (31.6%) of patients, respectively (Table S1).

The most common congenital cardiac surgery types within 1 year of index arterial thromboembolism included atrial septal defect in 25 (22.5%) and a Glenn procedure in 23 (20.7%) of patients; both scenarios provide routes through which thrombi may pass into the arterial circulation. The most common congenital cardiac surgery types within 1 year of index arterial + venous thromboembolism were pulmonary artery stenosis in 11 (11.6%) and the Glenn (classic and bi-directional) in 12 (12.6%) of patients (Table S2).

The most common antithrombotic therapies used to treat acute arterial thromboembolism was unfractionated heparin in 83 (74.8%) and 78 (82.1%) of patients with an index arterial thromboembolism or arterial + venous thromboembolism, respectively. One hundred twenty-one (58.7%) patients received an antiplatelet agent, with aspirin ($n = 91$, 75.2%) being the most common (Table 2). Thirty-six patients (17.5%) developed at least one recurrent thromboembolism (arterial or venous) within 1 year of the index arterial thromboembolism. Patients with index thromboembolism that was both arterial and venous were more likely to have recurrent thromboembolism than those with an arterial-only index thromboembolism (23% vs. 12.6%, $p = 0.046$). Fourteen (6.8%) and 8 (3.4%) patients developed two and three recurrent thromboembolism within 1 year, respectively.

Discussion

Few studies have characterised arterial thromboembolism in children with CHD undergoing cardiac surgery, and most have focused on single ventricle patients and/or the relationship to arterial cannulation.[9–15] Manlhiot et al., in a single centre retrospective study, reported that 41 of 1542 children (2.7%) undergoing cardiac surgery developed an extracardiac arterial thromboembolism, accounting for 41 (24%) of 171 patients who experienced embolism.[5] In a second single-centre retrospective study of 192 patients undergoing cardiac surgery, Manlhiot and colleagues reported that 70 of 513 thromboembolism (14%) were located in the central arteries.[16] In a single-centre retrospective study of 260 children undergoing cardiac surgery, we reported arterial thromboembolism in 10 (3.8%) of patients within 1 year of surgery, accounting for 29% of all 35 children with thromboembolism.[17] In this multinational retrospective study, we report an index arterial thromboembolism rate of 1%, mostly in very young children. It is possible that this rate is lower than those of the aforementioned studies, given that administrative datasets may underestimate event rates relative to institution-based retrospective analyses. We also evaluated recurrent thromboembolism risk in the present study; our finding of a 1-year thromboembolism recurrence risk of 17.5% (which, as noted above, may be an underestimate) raises substantive concern that current antithrombotic approaches for prevention of recurrent thromboembolism are suboptimal among children with CHD who have developed arterial thromboembolism following cardiac surgery and warrants prospective studies.

Guidance on the treatment of arterial thromboembolism in children with CHD is limited. Arterial thromboembolism treatments in the paediatric population are largely extrapolated from adult literature and include antiplatelet agents such as aspirin and anticoagulants such as intravenous unfractionated heparin, intravenous bivalirudin, subcutaneous low-molecular-weight heparin, oral vitamin K antagonists, and direct oral anticoagulants.[18] The direct oral anticoagulants have recently been studied for primary, rather than secondary, thromboembolism prevention.[19–20] The American Society of Haematology has issued treatment guidelines for venous but not arterial thromboembolism,[21] and the International Society on Thrombosis and Haemostasis recently identified devoted investigation of antithrombotic therapy approaches for arterial thromboembolism in children as an urgent unmet need.[22] There is a paucity of literature describing antithrombotic therapy types utilised in paediatric patients with CHD undergoing cardiac surgery who develop acute arterial thromboembolism, and their efficacy in preventing TE recurrence risk in the context of important risk factors such as age, CHD subtype, and surgical procedure type.

Limitations of this study include its retrospective design and the lack of detailed information on dosing and duration of antithrombotic treatments for the index arterial thromboembolism. Additionally, analyses of administrative datasets are limited by the potential for Current Procedural Terminology code and International Statistical Classification of Diseases and Related Health Problems-10 code misclassification of patients and outcomes misclassification. Furthermore, given the limitations of the dataset, we were not able to discern the temporal or anatomic relationships of arterial thromboembolism events to the insertion or presence of arterial catheters, cardiac catheterizations, placement of arterial monitoring, or attempted arterial septal defect closures by cardiac catheterization. Strengths include large sample size, geographical diversity, and the use of electronic health record-derived real-world data. In the context of these limitations and strengths, our findings are important in identifying a high risk of recurrent thromboembolism among paediatric patients with CHD undergoing cardiac surgery who previously developed arterial thromboembolism. Multicentre prospective studies are needed to substantiate and expand upon these findings, including the identification of recurrent thromboembolism risk factors, to inform the design of future risk-stratified interventional trials aimed at reducing the high risk of recurrent thromboembolism in these children.

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Conclusion

Although the overall risk of arterial thromboembolism in paediatric patients who underwent congenital cardiac surgery was low at 1%, the 1-year risk of thromboembolism recurrence was high, at 17.5%. Future studies evaluating the rate of, and risk factors for, recurrent thromboembolism are needed to inform the design of future risk-stratified interventional trials aimed at reducing the risk of recurrent thromboembolism in children undergoing congenital cardiac surgery.

Supplementary material. The supplementary material for this article can be found athttps://doi.org/10.1017/S1047951125001271.

Competing interests. Dr Goldenberg receives research support and salary support from the National Institutes of Health and, the National Heart Lung and Blood Institute for clinical and translational investigation in venous thromboembolism in patients < 21 years old. He receives or has recently received (past 12 months) consultancy fees from Anthos Therapeutics, Bayer, and the University of Colorado-affiliated Academic Research Organization CPC Clinical Research for roles in clinical trial planning or oversight committees (e.g., advisory committee; steering committee; data and safety monitoring committee) in pharmaceutical industry-sponsored pediatric multicentre clinical trials of antithrombotic agents. He also receives consultancy fees from Novartis for data and safety monitoring committee membership in multicentre clinical trials of an immunomodulatory agent. His employer, Johns Hopkins University, receives salary support on his behalf from Boehringer-Ingelheim for data coordinating centre leadership for a pediatric antithrombotic multicentre prospective observational study.

Dr Amankwah has recently received (in the past 12 months) consultancy fees from Boehringer-Ingelheim.

Dr Witt has received research and salary support from the Agency for Healthcare Research and Quality for clinical and translational investigation in warfarin therapy patient self-management in adult patients.

All other authors have nothing to disclose.

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