Cardiology in the Young

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A systematic review of the evidence supporting post-operative antithrombotic use following cardiopulmonary bypass in children with CHD

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Review

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Abstract

Objectives: To determine the optimal antithrombotic agent choice, timing of initiation, dosing and duration of therapy for paediatric patients undergoing cardiac surgery with cardiopulmonary bypass. *Methods:* We used PubMed and EMBASE to systematically review the existing literature of clinical trials involving antithrombotics following cardiac surgery from 2000 to 2020 in children 0–18 years. Studies were assessed by two reviewers to ensure they met eligibility criteria. *Results:* We identified 10 studies in 1929 children across three medications classes: vitamin K antagonists, cyclooxygenase inhibitors and indirect thrombin inhibitors. Four studies were retrospective, five were prospective observational cohorts (one of which used historical controls) and one was a prospective, randomised, placebo-controlled, double-blind trial. All included were single-centre studies. Eight studies used surrogate biomarkers and two used clinical endpoints as the primary endpoint. There was substantive variability in response to antithrombotics in the immediate post-operative period. Studies of warfarin and aspirin showed that laboratory monitoring levels were frequently out of therapeutic range (variably defined), and findings were mixed on the association of these derangements with bleeding or thrombotic events. Heparin was found to be safe at low doses, but breakthrough thromboembolic events were common. *Conclusion:* There are few paediatric prospective randomised clinical trials evaluating antithrombotic therapeutics post-cardiac surgery; most studies have been observational and seldom employed clinical endpoints. Standardised, validated endpoints and pragmatic trial designs may allow investigators to determine the optimal drug, timing of initiation, dosing and duration to improve outcomes by limiting post-operative morbidity and mortality related to bleeding or thrombotic events.

Over 40,000 children with congenital heart disease (CHD) undergo surgery in the United States each year, with the majority requiring cardiopulmonary bypass.[1] Cardiopulmonary bypass is known to significantly alter haemostasis through multiple mechanisms leading to a decrease in circulating factors and platelets, platelet dysfunction, inflammation and overall haemodilution.[2,3] The risks of cardiopulmonary bypass are more pronounced in children, with blood loss and blood product transfusion requirement inversely proportional to age and weight.[4,5] Blood product exposure has been associated with increased post-operative mechanical ventilation, longer ICU stays, increased systemic inflammatory response, increased post-operative infections and increased mortality.[6]

In addition to bleeding, alterations in the coagulation cascade from cardiopulmonary bypass can lead to thrombus formation.[7] Thrombosis is a potentially life-threatening complication, occurring in 4–15% of children with CHD undergoing surgery with cardiopulmonary bypass, and is associated with a five-fold increase in odds for post-operative mortality.[7–9] The highest risk children include those with shunted single ventricles or a Fontan circulation.[8] Additionally, children who have a post-operative chylothorax are at increased risk of thrombosis, due to the loss of the natural anticoagulants protein C and S, and other factors.[10]

To prevent coagulopathy-related post-operative morbidity and mortality, and improve outcomes, several antithrombotics are used in the post-operative setting, despite little dosing guidance and no disease-specific recommendations by the United States Food and Drug Administration.[11–13] Label guidance for appropriate indications and dosing may allow for improved efficacy with lower risk of adverse events. Studies of newer antithrombotics, such as direct oral anticoagulants or anti-platelet agents, may offer alternative options for post-operative coagulation management. However, studies to determine optimal drug and dosing strategies in children with CHD are difficult to perform, due to both limited patient numbers

and disease heterogeneity, as well as the challenge of obtaining informed consent in a vulnerable population where there may be parental reluctance to enroll in placebo-controlled trials.[14,15] This systematic review aims to summarise the existing literature of antithrombotic use following cardiac surgery with cardiopulmonary bypass in children with CHD to inform areas where further research is needed.

Materials and methods

Search strategy

We searched PubMed and EMBASE to identify studies investigating the use of antithrombotic medications in children after cardiac surgery with cardiopulmonary bypass, similarly to research previously described.[16] Studies from 2000 to 2020 were included to reflect medication use in the context of current clinical practice. We defined children as those from birth to age 18 years. The search terms "post-operative care," "heart surgery," "cardiopulmonary bypass," "pediatric" and "anticoagulation" or "antithrombotic" were used to generate an initial list of studies. We excluded animal studies, studies in languages other than English and studies focused on pre- or intra-operative medication use. Case reports, letters, editorials and comments were also excluded. The search strategies are shown in the Appendix.

Study selection

Identified studies were imported into EndNote (Version X9, Clarivate Analytics, Philadelphia, PA, USA). Two reviewers independently screened and reviewed study abstracts and titles. Studies were eligible for inclusion if the primary focus was antithrombotic administration in the post-operative period for children following cardiac surgery with cardiopulmonary bypass. The full article was then reviewed to ensure appropriateness prior to data extraction.

Data extraction and synthesis

A standardised data collection form was used to extract the relevant data from each eligible study. The following data were collected: study characteristics (including study design and years of study), study population characteristics (including age and cardiac defect), intervention (including medication administered and the presence and type of control used), study endpoints and results. For each medication, the dose, frequency, timing of initiation, primary outcome and secondary outcomes were compiled and analysed.

Results

A total of 422 studies were identified using our search strategy and 10 studies in 1929 children met our inclusion criteria (Fig 1).[17–25] Study characteristics are summarised in Table 1. All studies were performed at a single centre. Four studies were retrospective, five were prospective observational cohorts (one of which used historical controls) and one was a prospective, randomised, placebo-controlled, double-blind trial. Eight studies used surrogate biomarkers as the endpoint, such as activated partial thromboplastin time, international normalised ratio or thromboelastography with platelet mapping. The remaining two studies used clinical endpoints as the primary outcome, namely, incidence of bleeding or thromboembolism and catheter-associated thrombosis. No studies evaluated mortality as a primary outcome. One study evaluated pharmacokinetic/pharmacodynamic data.[17] Medications studied included vitamin K antagonists (warfarin [3/10]), cyclooxygenase inhibitors (aspirin [4/10]) and indirect thrombin inhibitors (unfractionated heparin [3/10]).[17–24] We did not identify any studies in our patient population that evaluated platelet inhibitors (e.g. clopidogrel), glycoprotein IIb/IIIa inhibitors (e.g. abciximab), direct thrombin inhibitors (e.g. bivalirudin) or direct factor Xa inhibitors (e.g. apixaban) in the immediate post-operative period.

Antithrombotics

Vitamin K antagonists

Vitamin K antagonists inhibit vitamin K epoxy reductase (*VKORC1*), an enzyme implicated in recycling oxidised vitamin K to the reduced form needed for the post-translational carboxylation of coagulation factors II, VII, IX and X, as well as proteins C and S.[28] Vitamin K antagonists have no activity against coagulation factors already released in circulation. Therefore, the onset of full anticoagulation effect can take up to 7 days, and there is a transient hypercoagulable state through the inhibition of proteins C and S post-translational carboxylation early in the treatment with vitamin K antagonists.[28]

The most commonly used vitamin K antagonist is warfarin, which is administered enterally. Warfarin is metabolised in the liver by cytochrome P450 isozymes, predominantly *CYP2C9*.[11] Numerous factors affect warfarin metabolism including age, diet, concomitant medications and genetic polymorphisms.[29,30] This variable metabolism combined with a narrow therapeutic index makes dosing challenging in the paediatric population and requires frequent blood draws for monitoring of international normalised ratio values.[28,31] The main adverse events associated with warfarin use are bleeding and thrombosis, and warfarin activity can be reversed with vitamin K or, in the acute setting, with prothrombin complex concentrate.[11,32] Because of age-related differences in concentrations of coagulation factors and *CYP2C9* and *VKORC1* enzyme activity, infants generally have the highest, and adolescents have the lowest, mg-per-kg dose requirements, but the optimal dosing, safety and efficacy of warfarin in paediatric populations are unknown due to a lack of adequate and well-controlled studies.[11,33–35] The usage of warfarin in paediatric populations remains off-label for all indications; in children with cardiac disease, it is often used after Fontan palliation or following mechanical valve insertion, and is typically initiated in the post-operative period.[8,17,18,31,36] Three studies of warfarin in 101 children met our inclusion criteria.[17,18,24]

In a single centre, prospective, observational cohort of five children after Fontan or mitral or aortic valve replacement, a personalised kinetic (K)/pharmacodynamic (PD) model to predict initial and maintenance dosing was compared with five historical controls who received conventional weight-based dosing.[17] This study's K/PD model included age, and *CYP2C9* and *VKORC1* genotypes as covariates, and was refined with bodyweight, baseline and target international normalised ratio and information about previous doses and international normalised ratio observations.[17,29,37] The K/PD model was first retrospectively validated in 60 patients with a median (range) age of 5.2 (1–15.9) years. The median (range) age of children in the prospective study was 6 (3.8–8.9) years for cases and 5.3 (3.4–9.3) years for controls. The starting warfarin dose for controls was 0.2 mg/kg with subsequent dosing based on response. The dose for cases was not reported. While the median time to achieve first therapeutic international normalised ratio level was longer in cases than controls (5 versus 2 days), cases

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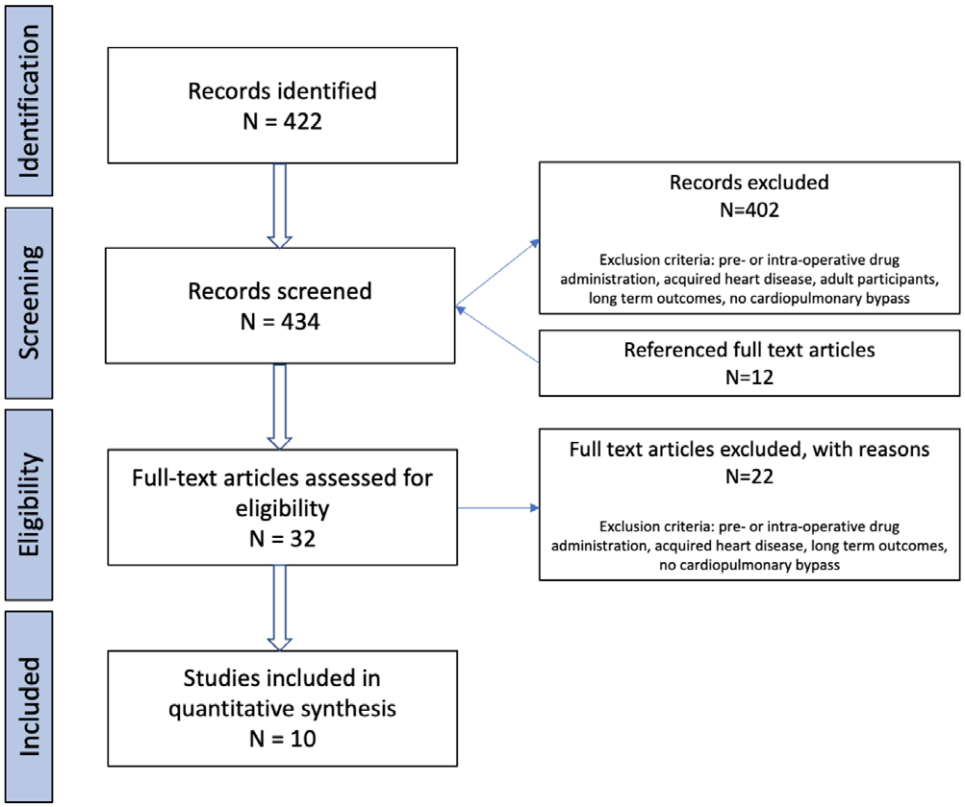

Figure 1. Summary of literature search strategy and results. This figure displays our literature search strategy, from record identification to screening, eligibility and finally study inclusion.

achieved a stable dose sooner than controls (29 versus 96.5 days). Additionally, cases had more time and measurements in the therapeutic range (70 versus 47.4% and 83.4 versus 62.3%, respectively). There was reduced likelihood of over anticoagulation based on supratherapeutic international normalised ratio in cases. Timing of warfarin initiation was not included in this study.

A single centre retrospective cohort of 59 patients (median [range] age 14.3 [0.2–44.8] years, 20% <5 years old) undergoing cardiac surgery demonstrated that initiation of warfarin within the first week was associated with shorter time to therapeutic international normalised ratio levels compared to initiation of warfarin more than 1 week post-operatively (2 versus 5 days, $p = 0.007$).[18] A heparin bridge was also associated with longer times to therapeutic international normalised ratio (2.5 versus 2 days, $p = 0.018$) and increased incidence of bleeding or need for blood transfusions ($p = 0.003$). In the overall cohort, the median time to initiation of warfarin post-operatively was 3 days. The median (interquartile range [IQR]) time required to reach a therapeutic international normalised ratio was 2 (2–4) days. A supratherapeutic international normalised ratio occurred in 15% (9/59) of patients and was associated with higher loading and maintenance dosing. Overall, 5% (3/59) of patients had a bleeding event, 7% (4/59) of patients received vitamin K as a rescue for elevated international normalised ratio and 5% (3/59) of patients were re-admitted for bleeding complications.

A single centre retrospective study of 32 children after Fontan palliation who were initiated on warfarin post-operatively showed that supratherapeutic international normalised ratio levels occurred in 12.5% (4/23) of children.[24] The median (IQR) age of children with non-supratherapeutic international normalised ratio values and supratherapeutic international normalised ratio values were 2.39 (2.19–2.61) years and 2.32 (2.18–2.8) years, respectively. Children at risk for supratherapeutic levels or rapid increases in international normalised ratio were started on warfarin earlier (2 versus 5 days post-operatively, $p = 0.037$). One child with an international normalised ratio of 1.44 (subtherapeutic) had haematochezia.

Overall, warfarin was well tolerated with low incidences of bleeding events and no thrombotic events in an overall small cohort across the age groups studied. Earlier initiation of warfarin was associated with higher international normalised ratio values, suggesting that when warfarin is started in the immediate post-operative period (within 3 days), lower doses may be beneficial to prevent supratherapeutic values.[18,24] A heparin bridge may delay time to therapeutic international normalised ratio and may increase incidence of bleeding adverse events.[18] Concomitant administration of other medications did not predict supratherapeutic international normalised ratio values.[18,24] Individualised dosing algorithms may be beneficial in children whose polymorphisms in *CYP2C9* and *VKORC1* are known. No included studies compared warfarin to other antithrombotics.

Indirect thrombin inhibitors

Heparin is a naturally occurring and heterogeneous group of sulphated glycosaminoglycans that enhance the serine protease activity of antithrombin III to inactivate thrombin, plasmin and coagulation factors IX, X, XI and XII.[12,31,38] Medical grade heparin sodium is derived from porcine intestinal mucosa and is mainly used intravenously.[28] Heparin is used as short-term prophylaxis in the post-operative setting or as a bridge until long-term

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Table 1. Characteristics of included antithrombotic studies and study populations

Reference	Medication studied	Study design (study years)	N	Study population age	Route, dose and time to drug initiation	Primary outcome	Findings
Vitamin K antagonists							
Al-Metwali et al[17]	Warfarin	Single centre, prospective, observational cohort with historical controls (2015–2016)	10	Warfarin naïve children following Fontan palliation or mitral or aortic valve replacement Median (range) age 6 (3.8–8.9) years for case children and 5.3 (3.4–9.3) years for controls	Oral Cases: Initiation and adjustment doses as predicted by personalised dosing algorithm Controls: 0.2 mg/kg loading dose with adjustments based on response Timing after surgery not defined	Time to first therapeutic INR, time to stable anticoagulation, % of INR measurements in range and % of time in therapeutic range	Median (range) time to first therapeutic INR was longer for cases compared with controls: 5 (2–6) versus 2 (1–3) days Median (range) time to stable INR dose was shorter for cases compared with controls: 29 (9–87) versus 96.5 (24–138) days Two case and one control did not reach stable INR dosing Cases had more time at therapeutic levels (median [range]: 83% [69–84%] versus 62% [38–71%]) and higher percent of INR checks in therapeutic range (median [range]: 70% [53–77%] versus 47% [44–55%]) *(low N precludes tests for significance)*
Lowry et al[18]	Warfarin	Single centre retrospective (2006–2011)	59	Patients following cardiac surgery Median (range) age 14.3 (0.2–44.8) years	Oral Loading dose of 0.2 mg/kg (max 5 mg), unless there is liver dysfunction or patient has undergone Fontan palliation, then loading dose 0.1 mg/kg (max 5 mg) Subsequent dosing based on INR Therapy started median (range) 3 (0–20) days post-operatively	Time to reach therapeutic anticoagulation (INR $\geq$ 2)	Median (IQR) time to therapeutic INR was 2 (2–4) days, with more variability seen in children <5 years (n = 12, IQR 1–8 days). Starting warfarin after 7 or more days post-operatively was associated with longer time to therapeutic dosing (median 5 versus 2 days, p = 0.007) 34/59 were bridged with UFH or LMWH. Children who were bridged had significantly more bleeding and blood transfusion requirements (p = 0.003) and longer time to therapeutic INR (median 2.5 versus 2 days, p = 0.018) than those who were not 9/59 patients had INR $\geq$ 4. These children received a higher starting dose (median 0.12 versus 0.09 mg/kg, p = 0.046) and maximal dose (0.19 versus 0.10 mg/kg, p = 0.008) No thrombotic events occurred

(*Continued*)

Table 1. (*Continued*)

Reference	Medication studied	Study design (study years)	N	Study population age	Route, dose and time to drug initiation	Primary outcome	Findings
Thomas et al[24]	Warfarin	Single centre, retrospective cohort (2009–2012)	32	Children with following Fontan palliation Median (IQR) age 2.39 (2.19–2.61) years for children who did not develop supratherapeutic INR and 2.32 (2.18–2.8) years for children who developed supratherapeutic INR	Oral Mean (±SD) starting dose 0.07 ± 0.02 mg/kg on median (IQR) POD 5 (3–6.5) for children who did not develop supratherapeutic INR and 0.08 ± 0.03 mg/kg on median (IQR) POD 2 (2–3) for children who did develop supratherapeutic INR	Development of supratherapeutic INR (INR > 2.5)	4/32 children developed supratherapeutic INR and 2 additional children had dose reduced due to rapidly rising INR Children with supratherapeutic INR had warfarin initiated significantly earlier (median 2 versus 5 days post-operatively, p = 0.037) but with no difference in starting dose or pre-treatment INR One patient had clinically significant bleeding with subtherapeutic INR No significant thromboembolic events occurred
Indirect thrombin inhibitors							
Schroeder et al[21]	UFH infusion	Single-centre, randomised, placebo-controlled, double-blinded trial (2005–2008)	90	Infants <12 months with intra-operative central venous catheter or intra-cardiac catheter placement Mean (±SD) age 4.2(±3) months	IV 10 U/kg/hour Infusion started mean 15.5 ± 13.2 hour post-operatively for treatment group and 14.1 ± 10.9 hour for placebo group	Development of catheter associated thrombus as imaged by echocardiogram or ultrasound	No difference between treatment or placebo arms in rate of thrombus development (8/53 versus 6/37, p = 0.89) or catheter malfunction (5/53 versus 4/37, p = 0.83). Catheters in place for ≥7 days were significantly more like to develop thrombus (OR 4.3, p = 0.02) and malfunction (OR 11.2, p = 0.008) PTT values were significantly higher in treatment group (mean [±SD] 52 ± 16 versus 42 ± 10 second, p < 0.001). Among treatment group, infants ≤ 30 days had a higher PTT than those > 30 days old (mean [±SD] 64 ± 16 versus 49 ± 15 second, p = 0.01). No thrombi were clinically significant
Vorisek et al[23]	UFH infusion	Single centre, retrospective cohort (2016–2017)	966	Children following cardiac surgery Median (IQR) age 1.37 (0.27–5.5) years	IV Low dose UFH (mean dose <15 U/kg/hour) High dose UFH (mean dose ≥15 U/kg/hour) Timing after surgery not specified	Incidence of bleeding and thrombosis	94/966 had bleeding events and 52/966 had thrombotic events Children who received high-dose UFH had significantly more bleeding (OR 2.35, 95% CI 1.45–3.95) and thrombotic events (OR 3.65, 95% CI 1.81–7.38) than those receiving low dose UFH. Odds for both bleeding and thrombosis were similar between low dose UFH children and those who did not receive UFH. Age was independently associated with both bleeding risk and thrombosis risk with neonates <1 month (bleeding: OR 8.5 95% CI 2.65–27.25; thrombosis: OR 8.19, 95% CI 1.76–38.09) and infants <1

Table 1. (*Continued*)

							year (bleeding: OR 4.36, 95% CI 1.41–13.49; thrombosis: OR 5.55 95% CI 1.23–25.06) having significantly higher odds than children over 10 years
Nair et al[25]	UFH infusion	Single centre prospective observational cohort (study years 2015–2016)	203	Children following cardiac surgery Median (IQR) age 0.33 years (0.03–2.37) pre-implementation and 0.39 years (0.10–2.11) post-implementation	IV Pre-implementation: UFH dosed at discretion of treatment team Post-implementation: UFH dosed based on coagulation management protocol and nomogram based on PTT and anti Xa levels	Percent time spent within as well as above or below the target range; number of lab draws and number of dosing changes; time to target range	Mean lab draws per day and dosing changes per day significantly increased post-implementation (mean [±SD] 2.14 ± 1.15 versus 2.38 ± 1.13, $p < 0.001$ for lab draws per day; 2.41 ± 0.96 versus 2.94 ± 0.97, $p = 0.0001$ for dosing changes per day). No difference seen in time to target range (9.2 ± 0.8 versus 9.3 ± 0.7 hours, $p = 0.95$) or percent time at target range, but less time was spent above target range post implementation (12.8 versus 4.4%, no significance given) The rate of clinically relevant bleeding significantly decreased post-implementation (4.14 to 1.62 events per 100 patient days, $p = 0.005$), although similar percentages of patients had a major bleeding event (2.3 versus 1.7%, $p = 0.78$). No difference in rate of clinically apparent thrombi was noted
Cyclooxygenase inhibitors							
Emani et al[26]	Aspirin	Single centre prospective observational (2013–2014)	95	Children following BT shunt, stage 1 palliation, Fontan procedure, intracardiac baffle, or coronary artery reconstruction Median (IQR) age 1.1 (0.23–3.1) years	Oral Median (IQR) dose 6.5 (4.2–9) mg/kg/day Therapy started a median (IQR) 4 (3–7) days post-operatively	Aspirin responsiveness testing (values of 550 or greater ARU indicate unresponsiveness) and rates of thrombosis	10/95 (10.5%) children were unresponsive to aspirin, with 4 of these patients being less than 1 month old 7/95 (7.4%) developed thrombosis post-operatively Thrombosis occurred more frequently in unresponsive children (1.2% of responders versus 60% of non-responders, $p < 0.001$)
Emani et al[27]	Aspirin	Single centre retrospective cohort (2013–2016)	430	Children following cardiac surgery at high risk for thrombosis (age <30 days at surgery, single-ventricle physiology, complex valve repair/replacement, intracardiac baffling, or ventricular assist device, or coronary artery reconstruction) Median (IQR) 1 (0.25–3) years	Oral Median (IQR) dose 6.3 (4.0–8.7) mg/kg/day Therapy started at a median (IQR) 7 (2–15) days and 3 (2–5) days post-operatively in children with thrombosis and those without, respectively	Aspirin responsiveness testing (values of 550 or greater ARU indicate unresponsiveness) and rates of thrombosis	Thrombosis occurred in 11/430 (2.6%) children: 0.6% of responders and 14% of non-responders 64/430 (15%) children with unresponsive to aspirin with initial dosing ARU > 553 had a sensitivity of 82% and specificity of 88% in predicting thrombosis

(*Continued*)

Table 1. (*Continued*)

Reference	Medication studied	Study design (study years)	N	Study population age	Route, dose and time to drug initiation	Primary outcome	Findings
							After adjusting for weight and initial aspirin dose, ARU was associated with increased odds of thrombosis (OR 30.1; 95% CI 6.3–144.3) 40/64 non-responders had dose escalation which significantly reduced ARU ($p < 0.001$). None of these had thrombosis
Mir et al[20]	Aspirin	Single centre prospective observational (study years not reported)	20	Infants with single ventricle following BT or Sano shunt placement Median (range) age 6 (4–75) days	Oral 20 mg daily started on POD 3–5 Dose increased to 40 mg daily if aspirin resistant after 5 days of therapy	Platelet inhibition after 5 days of aspirin therapy as measured by TEG-PM (values >50% AA inhibition considered adequate inhibition) and UTX (level less than 1500 pg/ml considered adequate inhibition)	16/20 infants were aspirin resistant after 5 days of therapy as assessed by TEG-PM and 0/16 resistant patients demonstrated improvement after five additional days with increased aspirin dose 0/20 infants achieved an adequate UTX level at 5 or 10 days of therapy although UTX levels did significantly decrease compared to prior to therapy initiation (mean 20,289 baseline versus 9346.50 pg/ml at 5 days, $p = 0.008$). There was no association between UTX levels and aspirin resistance as measured by TEG-PM
Truong et al[22]	Aspirin	Single centre prospective observational (2012–2014)	24	Infants <12 months following Norwood, aortopulmonary shunt alone. or cavopulmonary shunt Median (range) age 32 days (2–352 days)	Oral 3–5 mg/kg/day (minimum dose 20 mg) on POD 1	Platelet inhibition as assessed by TEG-PM (values >50% AA inhibition considered adequate inhibition)	8/21 had adequate platelet inhibition after the third dose of aspirin but AA inhibition was significant increased from pre-aspirin level (*difference not quantified*, $p < 0.001$) Aspirin dose (mg/kg) was not associated with level of AA inhibition Ten children had bleeding events, of which five were considered major, and two had thrombotic events. Children with bleeding had higher %AA inhibition pre-aspirin (45.5 versus 22.9%, $p = 0.02$) and after the third dose of aspirin (73.7 versus 48.5%, $p = 0.04$) compared to those without bleeds

AA = arachidonic acid; ARU = aspirin reaction units; BT = Blalock Taussig; FFP = fresh frozen plasma; INR = international normalised ratio; IQR = interquartile range; LMWH = low molecular weight heparin; OR = odds ratio; 95% CI = 95% confidence interval; POD = post-operative day; PTT = partial thromboplastin time; SD = standard deviation; TEG-PM = thromboelastography with platelet mapping; UFH = unfractionated heparin; UTX = urine thromboxane.

anticoagulation becomes therapeutic.[8,31,36] Heparin is mainly eliminated via enzymatic degradation and is less susceptible to individual genetic polymorphisms than warfarin.[28] Infants require higher doses per kilogram, due to increased clearance, increased volume of distribution and lower levels of antithrombin, which is required for efficacy.[28] Neonates must receive a preservative-free formulation, due to toxicity from the benzyl alcohol preservative.[12]

The main adverse events associated with heparin use are bleeding (particularly intraventricular haemorrhage in neonates) and, more rarely, heparin-induced thrombocytopenia.[28] Drug levels are monitored by measuring activated partial thromboplastin time or anti-Xa levels, and it is also important to monitor antithrombin III levels.[25,31] Protamine sulphate can be given to reverse the effect of heparin. Similar to vitamin K antagonists, there are no randomised controlled trials on dosing in this population for treatment or prevention of thrombosis and dosing recommendations are based on clinical experience and extrapolation from historical evidence in adults.[12] Three studies in 1259 children evaluated unfractionated heparin.[21,23,25] No studies of low-molecular weight heparin (e.g. enoxaparin, dalteparin) or fondaparinux met our inclusion criteria.

A retrospective single centre review of 966 children after cardiac surgery assessed the risk of bleeding or thrombosis based on exposure to lower dose (<15 U/kg/hour) or higher dose heparin (≥15 U/kg/hour).[23] In this study, 696 (72%) children, median (IQR) age 1.37 (0.27–5.5) years, were treated with heparin at least once during their ICU stay. Timing of usage after surgery was not assessed. In the entire cohort, 94 (9.7%) children had a bleeding event, and 52 (5.4%) children had a thrombotic event. Bleeding occurred most frequently within the first 36 hours after surgery without association of bleeding within 36 hours post-operatively with heparin use or intensity. However, on unadjusted analysis that included bleeding and thrombosis during the entire ICU stay, higher dose heparin was associated with increased bleeding and thrombosis compared with no heparin or lower dose heparin (bleeding: 17 versus 7 versus 8% respectively, $p < 0.001$; thrombosis: 12 versus 4 versus 3%, respectively, $p < 0.001$).[23]

On multi-variable analysis, higher dose heparin and younger age had higher odds of bleeding (higher dose versus lower dose heparin: odds ratio [OR] 1.97, 95% confidence interval [CI] 1.16–3.34; neonates <1 month: OR 8.5, 95% CI 2.65–27.25; infants <1 year: OR 4.36, 95% CI 1.41–13.49; 1–10 years: OR 2.34, 95% CI 0.79–6.96 versus children ≥10 years) and increased severity of bleeding (higher dose versus lower -dose heparin: OR 1.94, 95% CI 1.14–3.28; neonates <1 month: OR 8.61, 95% CI 2.70–27.39; infants <1 year: OR 4.26, 95% CI 1.38–13.13; 1–10 years: OR 2.32, 95% CI 0.78–6.85 versus children ≥10 years).[23] Similarly, on multi-variable analysis, higher dose heparin, younger age and previous history of thrombosis were associated with increased odds of thrombosis (higher dose versus lower dose heparin: OR 3.65, 95% CI 1.81–7.38; neonate <1 month: OR 8.19, 95% CI 1.76–38.09; infant <1 year: OR 5.55, 95% CI 1.23–25.06; 1–10 years: OR 1.84, 95% CI 0.40–8.48 versus children ≥10 years; history of thrombosis: OR 2.98, 95% CI 1.44–6.16).[23] Type of surgery was not associated with risk of bleeding or thrombosis.

A single centre prospective observational cohort of 203 patients pre- and post-implementation (pre-implementation: 87 patients, median [IQR] age 0.33 [0.03–2.37] years; post-implementation: 116 patients, median [IQR] age 0.39 [0.10–2.11] years) of an anticoagulation protocol post-cardiac surgery showed that titration using both activated partial thromboplastin time and anti-Xa levels decreased the incidence of clinically significant bleeding in heparinised children.[25] There were a higher number of blood samples sent (2.14 ± 1.15 versus 2.38 ± 1.13 draws per patient per day; $p < 0.01$) and an increased number of dosing changes after protocol initiation (2.41 ± 0.96 versus 2.94 ± 0.97 dosing changes per patient per day; $p = 0.001$). Time to target range and incidence of thrombus were similar before and after protocol initiation. While the incidence of clinically relevant bleeding during treatment decreased from 4.14 to 1.62 events per 100 patient-days post-implementation (risk ratio 0.39 [0.20–0.75], $p = 0.005$), the incidence of a major bleeding event, such as bleeding with haemodynamic instability or requiring surgical intervention, was similar before and after protocol initiation. The proportion of time spent above the target range was decreased after protocol implementation (12.8 versus 4.4% of patient hours) and the time within the target was similar. Antithrombin level was a significant predictor of anti-Xa levels ($p < 0.001$).

A single centre, randomised, placebo-controlled, double-blind trial evaluating the efficacy of continuous heparin infusion in preventing catheter-associated thrombosis in 90 infants (mean [±standard deviation] age 4.2 ± 3 months) showed that, while safe, heparin at low doses (10 U/kg/hour) did not reduce catheter-associated thrombus formation.[21] In this study, children were randomised to receive continuous heparin at 10 U/kg/hour or 5% dextrose as placebo, initiated 6–24 hours after arrival to the ICU, at the discretion of the treating physician. Overall, 15% (8/53) of children receiving heparin and 16% (6/37) of children receiving placebo developed a catheter-associated thrombus ($p = 0.89$). Children receiving low-dose heparin had higher mean partial thromboplastin time compared to those receiving placebo (52 versus 42 seconds, $p = 0.001$). In multi-variable analysis, catheters in place ≥7 days were associated with increased odds of catheter-associated thrombus (OR 4.3, $p = 0.02$) and catheter malfunction (OR 11.2, $p = 0.008$). Study group assignment, single ventricle anatomy, genetic syndrome and age <30 days were not significantly associated with increased catheter-associated thrombus or malfunction.[21] None of the identified thrombi were deemed clinically significant.

These studies show that heparin is safe at low doses, but it may not have a therapeutic advantage in the immediate post-operative period.[21,23] High-dose heparin may increase the risk of adverse events.[23] Protocol titration of heparin may decrease the occurrence of clinically relevant bleeding.[25] Younger children and those with a history of thrombosis may be particularly at risk for adverse events.[23] No studies compared heparin to other antithrombotics.

Cyclooxygenase inhibitors

Cyclooxygenase inhibitors act by acetylating cyclooxygenase-1 in platelets and irreversibly inhibiting thromboxane A_2, which inhibits platelet aggregation.[31,39] Since platelets cannot overcome this inhibition, the anti-platelet effects of cyclooxygenase inhibitors last for the duration of the platelet's lifespan (roughly 5–7 days).[39] In addition to anti-platelet effects, cyclooxygenase inhibitors also provide anti-inflammatory effects via cyclooxygenase-2.[39] The most commonly used cyclooxygenase inhibitor is aspirin, which affects both cyclooxygenase-1 and cyclooxygenase-2, with a slightly higher affinity for cyclooxygenase-1.[13,40] Aspirin is only available enterally, and is typically initiated in the early post-operative period for long-term prophylaxis in children with surgical shunts, those undergoing Fontan palliation, and in combination with warfarin or other anti-coagulants in those with certain prosthetic heart valves.[8,36,39]

Aspirin is metabolised by the liver, and clearance is slower in neonates than in older children and adults.[13] Aspirin displaces

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warfarin from binding sites on plasma proteins, increasing free drug concentration and the risk of warfarin toxicity. Additionally, ibuprofen can antagonise aspirin's platelet inhibition, making it less effective.[13] The main adverse effects associated with aspirin are bleeding, peptic ulcers and rarely, Reye's syndrome.[39] Aspirin levels are not routinely monitored. Aspirin resistance can be measured using tests such as thromboelastography with platelet mapping, urine thromboxane levels or aspirin responsiveness testing. However, standard laboratory values indicating aspirin resistance may not be associated with increased risk of thrombus.[20,22,26,27] As with most anti-thrombotics, its safety and efficacy in paediatric patients have not been well studied.[13] Four studies in 569 children met our inclusion criteria.[20,22,26,27]

In a single centre prospective observational cohort of 24 infants (median [range] age 32 [2–352] days) undergoing Norwood palliation or cavopulmonary shunt, conventional aspirin dosing (1–5 mg/kg/day) only achieved adequate platelet inhibition in the immediate post-operative period in 38% (8/21) of infants, as measured by thromboelastography with platelet mapping (goal ≥50% arachidonic acid inhibition).[22] Aspirin was initiated on the first post-operative day. A total of 8 (33%) infants had a bleeding event, and 2 (8%) had a thrombotic event, with 80% of these events being in the first week after surgery (median [range] days after surgery 7 [1–74]). In all cases, the infants had adequate platelet inhibition measured by thromboelastography with platelet mapping proximate to the events.[22]

In another single centre prospective observational cohort in 20 infants (median [range] age 6 [4–75] days) undergoing shunted single ventricle palliation, 80% of infants were aspirin resistant by thromboelastography with platelet mapping (goal ≥50% arachidonic acid inhibition), even with a dose increase, and no infants achieved adequate platelet inhibition measured by urine thromboxane levels (goal <1500 pg/ml).[20] All infants were started on a heparin infusion on the first post-operative day, which was continued until aspirin initiation on post-operative day 3–5. Aspirin was initially dosed at 20 mg/day and increased to 40 mg/day if the thromboelastography with platelet mapping obtained on day 5 showed <50% arachidonic acid inhibition. Urine thromboxane levels were high and decreased in response to aspirin administration, but did not reach the therapeutic goal of <1500 pg/ml. There were no bleeding or thrombotic events in this cohort.

Two studies evaluated rates of aspirin responsiveness and rates of thrombosis in children at high risk for thrombosis after cardiac surgery.[26,27] In a single centre prospective observational cohort of 95 children (median [IQR] age 1.1 [0.23–3.1] years), 10.5% of children were unresponsive to aspirin, as determined using a point of care aspirin responsiveness test (VerifyNow), with values of >550 aspirin reaction units indicating unresponsiveness.[26]

Across all age groups, children less than 1-month-old were more likely to be unresponsive to aspirin. Aspirin was initiated at a median (IQR) 4 (3–7) days post-operatively. In the entire cohort, 7.4% of children developed thrombus post-operatively, with thrombosis occurring more frequently in children unresponsive to aspirin (1.2% of responders developed thrombus versus 60% of non-responders, $p < 0.001$). Similarly, in a single centre retrospective cohort of 430 children (median [IQR] age 1 [0.25–3] years), 15% of children were unresponsive to aspirin.[27] In children who were unresponsive, the aspirin dose was doubled. This increase in dose significantly reduced aspirin reaction units ($p < 0.001$). Thrombus occurred in 2.6% of children, including 0.6% of responders and 14% of non-responders. Aspirin was initiated earlier post-operatively in children who did not develop thrombus compared to those who did (median [IQR] days 3 [2–5] versus 7 [2–15]). No children who had increased dose of aspirin subsequently developed thrombus. This study demonstrated that an aspirin reaction units >553 had a sensitivity of 82% and a specificity of 88% in predicting thrombosis.

Overall, early post-operative aspirin resistance is common, and may be more common in younger patients.[20,22,26,27] Earlier aspirin initiation may be associated with decreased risk of thrombosis.[27] The ideal laboratory tests associated with clinically meaningful aspirin resistance, optimal dose of aspirin and optimal timing of initiation remain unknown.

Discussion

We identified 10 drug trials in 1929 children after cardiac surgery across three anti-thrombotic medication classes from 2000 to 2020. Our review found that the overall evidence supporting the use of these drugs in children in the immediate post-operative setting for prevention or treatment of thromboembolism is limited. All studies were single-centre. Studies on warfarin and aspirin had small sample sizes, whereas studies on heparin included more patients. Only one study was randomised, placebo-controlled and double-blind. No studies directly compared medications.

To permit comparisons across studies and interventions in paediatric venous thrombosis, the International Society on Thrombosis and Haemostasis defined clinical and safety outcomes.[41] However, rather than solely choosing clinical endpoints, studies included in our review generally relied on laboratory endpoints, but were not consistent. For example, when studying warfarin, outcomes included development of supratherapeutic international normalised ratio, time to therapeutic international normalised ratio, time to stable international normalised ratio and time and number of measurements in the therapeutic range.[17,18,24] Clinical endpoints, such as bleeding or thrombotic events, may be more widely meaningful endpoints, but often come with confounding factors that are complex to evaluate and quantify. Measures of coagulation function that are downstream from the direct drug effect may also allow comparison across medication classes, but further studies should evaluate how these results relate to efficacy.

As in most paediatric disease processes, the relatively small number of outcomes require larger patient recruitment to ensure studies are adequately powered. This holds true for thrombosis, which affects at least 11% of children after cardiac surgery and places them at risk for severe complications.[7] While not exclusively in children with CHD, some recent studies with novel trial design have attempted to address this limitation. The Oral Rivaroxaban in Children with Venous Thrombosis (EINSTEIN Jr) study was a multi-phase trial evaluating rivaroxaban, a factor Xa inhibitor, versus standard anticoagulation in acute venous thromboembolism in all children <18 years old. Ultimately, rivaroxaban had a similarly low recurrence risk and reduced thrombotic burden without increased bleeding, but the study was not adequately powered to independently show non-inferiority for efficacy of rivaroxaban.[42] Factor Xa inhibitors may be an attractive alternative to standard therapies in children with CHD at risk for acute venothromboembolism in the post-operative period, but disease and bypass specific effects on drug efficacy and safety should be further evaluated. The Pharmacokinetic, Pharmacodynamic, Safety and Efficacy Study of Rivaroxaban for Thromboprophylaxis in Pediatric Participants 2–8 Years of Age After the Fontan Procedure (UNIVERSE) trial took advantage of the paediatric pharmacokinetic

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data available through the EINSTEIN Jr trial to streamline the study of the pharmacokinetic, pharmacodynamic, safety and efficacy of rivaroxaban compared to aspirin in children 2–8 years old within 4 months after Fontan.[43] UNIVERSE found that physiologically based pharmacokinetic model-based dosing resulted in exposures that matched adult reference exposures, and children who received rivaroxaban for thromboprophylaxis had a similar safety profile and fewer thrombotic events, although it was not statistically different than aspirin (NCT02846532).

In addition to the acute post-operative period, antithrombotic therapy is an important consideration in children with CHD receiving chronic outpatient treatment or for prevention of thromboembolism. Long-term prophylaxis with aspirin for children with shunts is associated with improved outcomes, and extrapolation of data from adult studies suggests the benefit of long-term prophylaxis with warfarin in children with mechanical valves, but timing of antithrombotic initiation in the immediate post-operative period to gain these benefits remains unclear.[44,45] There are multiple recent high quality studies of newer antithrombotics, such as direct factor Xa inhibitors or antiplatelet agents, in children with CHD from a long-term perspective that may help lay the foundation for additional therapeutic strategies in the acute post-operative setting and are discussed below.[43,46–48]

The Platelet Inhibition in Children on Clopidogrel (PICOLO) trial was a prospective, multi-centre, randomised, double-blind, placebo-controlled, dose-ranging study to determine the dose of clopidogrel, an antiplatelet agent, by pharmacodynamic assessment and to evaluate its safety in 73 children ≤2 years old with cardiovascular disease processes at risk for arterial thrombosis (e.g. stent placement, Kawasaki disease, systemic to pulmonary artery shunts, etc.).[46] Children were excluded if they had ongoing bleeding, risk of bleeding or had hepatic or renal failure. This study found that clopidogrel 0.2 mg/kg/day on a background of aspirin 4 mg/kg/day achieved platelet inhibition levels (50% arachidonic acid inhibition) similar to that of standard adult doses, which is a lower dose per kilogram body weight when compared with adults.

Another study evaluating clopidogrel was the Clopidogrel to Lower Arterial Thrombotic Risk on Neonates and Infants Trial (CLARINET). This was a multi-centre, double-blind, event-driven trial evaluating the safety and efficacy of clopidogrel versus placebo in 906 infants ≤92 days of age with cyanotic CHD palliated with a systemic to pulmonary artery shunt over a 6-month time period.[47] The dose of 0.2 mg/kg/day was derived from the PICOLO trial.[46] Similar to the PICOLO trial, children were excluded if they had active bleeding or were at increased risk of bleeding. Study protocol allowed concomitant aspirin use, which most children received. This study showed that clopidogrel did not reduce mortality or shunt-related morbidity. Clopidogrel did not demonstrate efficacy for preventing shunt thrombosis. This was likely due to the heterogeneity of disease processes in the study population and possibly due to the concomitant use of aspirin masking the potential benefit of clopidogrel.

Two additional studies of factor Xa inhibitors with results forthcoming will also provide more data and guidance on antithrombotics in children with CHD. The Safety of Apixaban on Pediatric Heart Disease on the Prevention of Embolism (SAXOPHONE) study is an open-label, randomised, phase II trial to evaluate the safety and efficacy of apixaban versus vitamin K antagonists or low molecular weight heparin in children with congenital or acquired heart disease who require anticoagulation.[48] ENNOBLE-ATE is a phase 3, multi-national, open-label, prospective, randomised, clincal trial to evaluate the efficacy and safety of edoxaban for venous thromboembolism in children 6 months to <18 years with cardiac disease.[49] Further study is required to identify optimal dosing strategies in the postbypass paediatric population and which children would benefit from these therapies.

Our objective was to evaluate the existing evidence for antithrombotic use in children with CHD following surgery with cardiopulmonary bypass. Significant study heterogeneity, limited enrolment and lack of validated, consistent endpoints make trial results difficult to translate into clinical practice. Studies tangentially applicable to the child with CHD in the early post-operative period have shown success in trial design and enrolment. Lessons learned from these studies, including collaboration across sites, and integrating pharmacokinetic/pharmacodynamic methods to determine dosing, can help inform future trial design focused on the immediate post-operative period. This may allow for improved evidence-based drug selection and delivery, resulting in improved outcomes in children with CHD undergoing surgery with cardiopulmonary bypass.

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