

The Dutch National guideline on the prevention of thromboembolic complications in pediatric patients with congenital and acquired heart disease

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Keywords: thromboprophylaxis, congenital heart disease, acquired heart disease, pediatric

Posted Date: September 25th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10948206/v1>

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Additional Declarations: No competing interests reported.

Abstract

Thromboembolic complications are a major cause of morbidity and mortality in children with congenital and acquired heart disease. Thromboprophylaxis with antiplatelet agents and/or anticoagulants is widely used, yet clinical practice varies due to limited pediatric evidence. This Dutch national guideline aims to harmonize thromboprophylactic strategies across the Netherlands,

introduce direct oral anticoagulants for eligible pediatric cardiac patients, identify knowledge gaps, and outline priorities for future research. A national multidisciplinary panel, including pediatric cardiologists, pediatric hematologists, a pediatrician, a pediatric intensivist, cardiothoracic surgeons, and a patient representative, developed the guideline with methodological support from the

Knowledge Institute of the Dutch Association of Medical Specialists. Seven key clinical questions were formulated, addressing thromboprophylaxis in children with shunts, Fontan circulation, percutaneous defect closures, stents, mechanical valves, and cardiomyopathy.

Systematic literature searches were performed, and study selection was conducted independently by two reviewers. Evidence was assessed using the GRADE methodology, which informed the development of evidence summaries, clinical considerations, and recommendations. The draft guideline underwent external review by professional societies and patient organizations, after which feedback was addressed and incorporated into the final document.

Introduction

In children with congenital and acquired heart disease, thromboembolic complications, including intracardiac thrombi, pulmonary embolism (PE), thrombosis on implanted devices, and systemic emboli to the central nervous system, are a major cause of mortality and morbidity.(1, 2)

To prevent thromboembolic complications, thromboprophylaxis is widely used in pediatric patients with congenital and acquired heart disease.(3) Commonly prescribed antithrombotic therapies include antiplatelet agents, such as acetylsalicylic acid (ASA) or clopidogrel, as well as anticoagulants. Until recently, standard-of-care anticoagulation relied on traditional agents, such as unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and/or vitamin K antagonists (VKA). These agents have been used with substantial variability across centers, largely because most treatment

strategies and dosing recommendations are extrapolated from adult data, small pediatric cohorts, or expert consensus. Over the past decade, direct oral anticoagulants (DOACs) have been introduced into pediatric practice, and three clinical trials have evaluated rivaroxaban, apixaban, and edoxaban against standard of care in selected pediatric cardiac populations.(4–6)

A new national guideline, initiated by the Dutch Society for Pediatrics, aims to harmonize thrombo-prophylactic strategies across the Netherlands, and introduce DOACs for eligible pediatric cardiac patients, while acknowledging that UFH, LMWH, and VKA remain essential options when clinically indicated. (Table 1) The guideline is publicly available through the Dutch Guideline Database

(<https://www.richtlijnendatabase.nl>). It is intended for pediatric cardiologists, pediatric intensivists, general pediatricians, pediatric hematologists, pediatric thoracic surgeons, anesthesiologists,

cardiologists involved in transitional care, and advanced care practitioners caring for children with congenital or acquired heart disease.

This article summarizes the methodology and recommendations of this new Dutch National guideline. It provides an overview of the available evidence and expert considerations regarding antithrombotic management in pediatric patients after common cardiac procedures, including aorto-pulmonary (AP) and right ventricle–pulmonary (RVP) shunts, Glenn and Fontan circulations,

percutaneous defect closures, post-stenting, and prosthetic valve replacement, as well as in children with cardiomyopathies. Finally, we identified knowledge gaps and made suggestions for further research.

Material and Methods

A national multidisciplinary expert panel was convened in 2023, comprising five pediatric cardiologists, two pediatric hematologists, one pediatrician, one pediatric intensivist, two

cardiothoracic surgeons from various academic centers, and one patient representative. An advisory group provided critical input during the development process and included a pediatric

anesthesiologist, a pediatric surgeon, a patient representative, and a clinical nurse specialist. All panel and advisory group members were officially appointed by their respective scientific or professional societies and adhered to the Code of Conduct to avoid conflicts of interest. Declarations of interest were collected, transparently managed throughout, and published with the guideline. The guideline was funded by the Quality Funds for Medical Specialists (SKMS). The funder had no influence on the content of the guideline.

The guideline development was supported by three methodologists from the Knowledge Institute of the Dutch Association of Medical Specialists. The process followed the methodological standards of the Federation of Medical Specialists, which is in adherence to the Appraisal of Guidelines for

Research and Evaluation II (AGREE II) instrument.⁽⁷⁾ Key clinical questions were developed using the PICO (Population, Intervention, Comparator, Outcome) format, based on topics from the previous Dutch guideline on antithrombotic therapy in pediatric cardiac patients of 2014, areas of clinical

uncertainty, and practice variation. Seven clinical questions were prioritized (Supplemental material 1), covering thromboprophylaxis in children with congenital or acquired heart conditions, including shunts, Fontan circulation, percutaneous defect closures, post-stenting management, mechanical valves, and cardiomyopathy.

Seven systematic literature searches were conducted in MEDLINE (via Ovid) and Embase (via

Embase.com) for studies published from 2014 (for post-stenting: 2004), the year of the previous guideline, through 2024. (Supplemental material 2) Studies were eligible if they met the following criteria: (1) Adherence to PICO, (2) Study design: systematic reviews, meta-analyses, randomized

controlled trials (RCTs), or comparative observational studies, (3) Full-text English or Dutch language publication, (4) Inclusion of > 20 participants (ten per group).

The panel members selected literature in pairs (independently of each other) based on title and

abstract, followed by full-text assessment by a methodologist. Evidence summaries were compiled by the methodologists. In addition, the titles and abstracts of studies cited in the previous Dutch guideline were reviewed for relevance (Supplemental material 3). Risk of bias was assessed using the Cochrane Risk of Bias tool for RCTs and ROBINS-I for observational studies. The certainty of the

evidence was determined according to the GRADE method.⁽⁸⁾ Panel members drafted the

considerations using the GRADE evidence-to-decision framework, incorporating scientific evidence,

clinical expertise, and patient values and preferences. Recommendations were formulated by consensus and categorized as strong or conditional. The draft guideline was circulated for external review to relevant professional societies and patient

organizations. All feedback was addressed and incorporated where appropriate. The final guideline was authorized by the Dutch Association of

Pediatrics (NVK), the Dutch Association of Anesthesiology (NVA), Dutch Association for Cardiothoracic Surgery (NVT), and the Patient Association for Congenital Heart Disease (PAH).

Results

Supplemental material 1 provides a detailed report of the literature summaries (including risk of bias assessments) and the conclusions for all seven clinical questions. Table 1 offers an overview of all

recommendations.

Question 1. What is the recommended antithrombotic strategy for primary thrombosis prevention in children receiving an AP and/or RVP shunt?

Recommendation

- Treat children as soon as possible after placement of an AP and/or RVP shunt with therapeutic heparin (UFH or LMWH) or intravenous ASA until enteral feeding can be initiated.
- Switch to oral antiplatelet therapy as soon as oral administration is feasible and continue for as long as the shunt remains in situ.

Summary of evidence

A systemic-to-pulmonary artery shunt is a surgically created connection that increases blood flow

from the systemic circulation to the pulmonary arteries in neonates with congenital heart disease and inadequate pulmonary perfusion. Common types include the AP shunt and the RVP or Sano shunt.

While these procedures serve as temporary measures to improve oxygenation or provide systemic circulation, they are associated with a significant risk of shunt thrombosis and mortality, particularly in the early postoperative period.(9–12) Thromboprophylactic strategies include the use of UFH, LMWH, antiplatelet therapy (e.g., oral or intravenous ASA, clopidogrel), or combinations thereof.

However, no randomized controlled trials have directly compared these approaches with placebo. The systematic literature search identified no new studies meeting the inclusion criteria for this clinical question. Two comparative studies conducted before 2014 were identified in the previous Dutch guideline, that compared thromboprophylaxis or placebo (11, 13). Li et al. conducted a large multicenter observational study involving 373 patients who underwent either a modified Blalock-

Taussig-Thomas (mBTT) shunt or Sano shunt procedure.(11) ASA use was associated with a substantial reduction in mortality in children with an mBTT shunt (Hazard Ratio [HR] 0.10; 95% CI

0.06–0.17). A similar trend was observed in the Sano subgroup (HR 0.68; 95% CI 0.09–5.33), although the wide confidence interval reflects imprecision and limited power. No data were available on shunt occlusion, thrombotic complications, stroke, or bleeding. Wessel et al. conducted a randomized

controlled trial, which included 906 neonates with cyanotic congenital heart disease and a systemic-to- pulmonary artery shunt. They assigned 467 infants to clopidogrel (0.2 mg/kg/day), and 439 infants to placebo, both in addition to conventional therapy (including ASA in 87.9% of infants).(13) The risk of shunt occlusion was slightly higher in the clopidogrel intervention group (27/467; 5.8%) than in the placebo group (21/439; 4.8%), with a RR of 1.21 (95% CI 0.69 to 2.11). The study reported a higher risk of (gastrointestinal) hemorrhage in the intervention group (10/464; 2.2%) than in the placebo group (5/436; 1.1%),

with RR of 1.88 (95% CI 0.65 to 5.45), but the certainty of evidence is very low due to very serious risk of bias. Infants treated with ASA monotherapy had a similar risk of shunt thrombosis (18/382; 4.7%) as those who received no thromboprophylaxis (3/57; 5.3%).

Clopidogrel monotherapy was associated with a lower rate of shunt thrombosis (1/53; 1.9%)

compared to no thromboprophylaxis (3/57; 5.3%), but this difference was not statistically significant (RR 0.36; 95% CI 0.04–3.34).

Other considerations

No studies were identified that addressed the optimal timing of initiating prophylaxis in the interval between surgery and the onset of enteral intake. In clinical practice, this gap is often managed with therapeutic doses of UFH or LMWH. Each agent has distinct advantages and limitations, and the choice between them should be guided by the clinical context as well as local experience and protocols. The key benefits and drawbacks of both options are summarized in Table 2. Although no studies have evaluated intravenous ASA in this setting, the expert panel considers it a plausible

alternative to heparin, particularly because it does not require laboratory monitoring or subcutaneous administration.

Conclusions and research needs

The panel issued a strong recommendation to initiate therapeutic anticoagulation (UFH, LMWH, or intravenous ASA) immediately after shunt placement and to continue this until enteral feeding is established, followed by oral antiplatelet therapy for the duration of shunt patency. Although the

certainty of evidence is low to very low, the potentially severe consequences of shunt thrombosis, together with the low treatment burden and high feasibility of prophylaxis, justify this approach. The panel also highlighted important research gaps, including the optimal timing of prophylaxis initiation,

comparative effectiveness of early postoperative anticoagulant strategies, the role of oral antiplatelet agents in different shunt types, identification of high-risk subgroups, and evaluation of

patient-centered outcomes such as quality of life, caregiver burden, injection-related pain, and hospital length of stay.

Question 2. What is the recommended antithrombotic strategy for primary thrombosis prevention in children undergoing a Glenn shunt or Partial Cavopulmonary Connection (PCPC) procedure?

Recommendation

- Treat children as soon as possible after the Glenn shunt or PCPC procedure with therapeutic heparin (UFH or LMWH).
- Switch to oral ASA as soon as oral administration is feasible.
- Consider anticoagulation (LMWH, VKA, DOAC) in conditions associated with an increased risk of thrombosis. (Table 3)

Table 3
Conditions with an increased risk of thrombosis which may lead to a higher intensity level of anticoagulation (3, 38)

Increased Thrombotic Risk
Bilateral superior vena cavae Ventricular dysfunction
Atrial arrhythmias
Small pulmonary arteries or superior vena cava Presence of thrombogenic foreign material
A non-occluded blind-ending pulmonary artery stump Stasis in a hypoplastic ventricle
Open fenestration History of thrombosis Thrombophilia
Protein-losing enteropathy

Summary of evidence

The Glenn shunt or PCPC procedure is part of the surgical palliation of children with a single (functional) ventricle. In this procedure, the superior vena cava (SVC) is connected to the pulmonary artery, enabling passive pulmonary blood flow and reducing the volume load on the single ventricle. Thrombotic complications, such as SVC thrombosis or PE, may compromise pulmonary perfusion or increase pulmonary vascular resistance, and may thereby negatively affect candidacy for future Fontan completion. Additionally, as the inferior vena cava (IVC) flow bypasses the pulmonary

circulation at this stage, paradoxical embolism into the arterial circulation remains a potential risk.

A systematic literature search from 2014 to February 2024 yielded no new studies that met the inclusion criteria. One study conducted before 2014 was identified from the previous Dutch guideline and included in the summary of literature. Manlhiot et al. conducted a retrospective cross-sectional study between 2003 and 2008, involving 139 patients with a Glenn shunt.(10) The study did not report specific inclusion or exclusion criteria. Patients receiving thromboprophylaxis, ASA, ASA plus enoxaparin, enoxaparin alone, or warfarin (with or without enoxaparin bridging), were compared to those who received no thromboprophylaxis. The use of thromboprophylaxis was associated with a

significantly lower risk of thrombotic complications within 3.5 years postoperatively. After adjusting for age at surgery, year of procedure, previous thrombotic events, postoperative extra

corporeal membrane oxygenation use, and deep hypothermic circulatory arrest, the adjusted HR was 0.2 (95% CI 0.1–0.9), indicating a substantial

protective effect. In patients without thromboprophylaxis, thrombus-free survival declined from 93% one week postoperatively to 59% at 3.5 years (a decrease of 34%). In contrast, in patients receiving

thromboprophylaxis, thrombus-free survival declined from 87% at one week to 68% at 3.5 years (a decrease of 18%).

Other considerations

There is no comparative evidence to guide when anticoagulation (LMWH, VKA, or DOAC) may be preferable to ASA. However, several clinical situations are considered to confer a higher thrombotic risk; these are summarized in Table 3.

Conclusions and research needs

Despite the very low certainty of evidence, the panel determined that the potentially severe consequences of thrombosis, combined with the low treatment burden and high feasibility of prophylactic ASA treatment, justify a strong recommendation.

The panel identified an urgent need for evidence on the incidence, timing, and predictors of thrombosis after the Glenn procedure, on long-term antiplatelet strategies including comparisons between ASA and agents such as DOACs, on the safety and feasibility of both prophylactic and therapeutic DOAC dosing, and on validated risk-stratification tools to identify children at highest thrombotic risk.

Question 3 What is the recommended antithrombotic strategy for primary thrombosis prevention in children after Fontan surgery?

Recommendation

- Treat children as soon as possible with therapeutic heparin (UFH or LMWH) after completion of the Fontan circulation.
- Switch to VKA (target international normalized ratio (INR) 2.0–3.0) or DOAC at therapeutic intensity (14) for six months, as soon as oral administration is possible.
- After six months, treat children with Fontan circulation without additional risk factors with DOAC at low intensity (6) or ASA.
- After six months, treat children with a Fontan circulation with additional risk factors (Table 3) with a DOAC at therapeutic intensity or VKA (target INR 2.0–3.0).

Summary of evidence

The final step to create the Fontan circulation is to connect the IVC to the pulmonary circulation,

either by a lateral tunnel, partly incorporating atrial tissue in the Fontan circulation, or by placing a Goretex tube between the IVC and the pulmonary arteries. In both approaches, a fenestration can be made between the Fontan-pathway and the atrium, creating a right-to-left shunt. Children with Fontan circulation have a markedly increased risk of thromboembolic complications due to multiple factors, including abnormal flow dynamics, endothelial dysfunction, and a prothrombotic state.

Reported incidences of thrombosis range from 4–19%, and stroke from 3–19%, even in patients receiving prophylaxis.⁽²⁾ The risk of thrombosis is greatest during the immediate postoperative period and remains elevated for up to six months after surgery, followed by a lower but gradually increasing risk in the years thereafter.⁽²⁾

The systematic review included ten studies comparing antithrombotic strategies, of which two had a follow-up of ≤ 1 year (6, 15) and eight had a follow-up of more than one year.^(16–23) Ankola et al. compared ASA, warfarin, and enoxaparin during the first 30 days postoperatively. The risk of

thrombotic complications was slightly higher with ASA (5/103; 4.9%) compared to warfarin (2/52;

1. 3.8%) with a RR of 1.26 (95% CI 0.25–6.29), while warfarin (2/52; 3.8%) appeared more effective than enoxaparin (1/13; 7.7%), with a RR of 0.50 (95% CI 0.05–5.10). ASA (5/103; 4.9%) showed a lower risk of thrombotic complications compared to enoxaparin (1/13; 7.7%) with a RR of 0.63 (95% CI 0.08–4.99).
2. Major bleeding events were rare across all groups. McCrindle conducted an RCT comparing

rivaroxaban at low intensity with ASA over 12 months.⁽⁶⁾ Thrombotic events were more frequent in the ASA group (2/34; 5.9%), with a RR of 3.76 (95% CI 0.35 to 40.04) favoring rivaroxaban (1/64;

1.6%). Major bleeding was very uncommon in both groups, but clinically relevant non-major bleeding (CRNMB) occurred slightly more often with ASA (RR 1.41; 95% CI 0.34–5.95).

Across seven studies with a follow-up duration of more than one year, ASA was consistently associated with a higher risk of thrombotic complications compared to warfarin, although not statistically significant (pooled RR 1.42; 95% CI 0.55–3.67).^{(16–}

19, 21–23) No clear difference was

observed in major bleeding risk between ASA and warfarin (RR 0.89; 95% CI 0.74–1.08), although ASA resulted in fewer minor bleeding events (RR 0.57; 95% CI 0.09–3.61). (19, 23) (Fig. 1).

Kawamatsu et al. provided retrospective comparative data for DOACs versus VKAs and antiplatelets in 102 patients aged > 15 years with Fontan circulations. (20) DOACs were given in therapeutic or low intensity dosages. DOACs demonstrated a markedly lower risk of thrombotic complications compared to VKAs (RR 0.10; 95% CI 0.01–1.80) and antiplatelets (RR 0.17; 95% CI 0.01–3.18). For major bleeding, DOACs were associated with a lower risk than VKAs (RR 0.19; 95% CI 0.02–1.50).

Other considerations

Two additional pediatric DOAC studies were not included in the systematic review because they did not focus exclusively on Fontan circulation. Portman et al. compared edoxaban with standard of care in 167 children with cardiac disease (44% Fontan) and observed very low rates of bleeding and no thrombotic events in the edoxaban arm. (4) Payne et al. evaluated apixaban in 188 children with congenital or acquired heart disease (74% single-ventricle) and similarly reported minimal bleeding and no thromboembolic events. (5)

Two recent network meta-analyses showed that any thromboprophylaxis (ASA, warfarin, or DOAC) reduces thromboembolism compared with no treatment. (24, 25) DOACs ranked highest for efficacy, while ASA showed the lowest major bleeding risk. Overall, DOACs appeared to offer the most favorable balance between efficacy and safety, though certainty remains low and heterogeneity substantial, underscoring the need for well-designed pediatric trials to refine agent selection, dosing, and duration in Fontan patients.

Conclusions and research needs

Although methodological limitations and wide confidence intervals preclude strong conclusions, the panel judged that the serious consequences of thrombosis, combined with the low burden and high feasibility of prophylactic therapy, justify strong recommendations. Full-dose anticoagulation is advised for the first six months after Fontan surgery, when thrombotic risk is highest, using either a VKA or DOAC based on patient preference and practical considerations. After this period, thrombotic risk decreases, and therapy may transition, after shared decision-making and bleeding-risk

assessment, to ASA or a low-intensity DOAC. In patients with additional risk factors (Table 3), therapeutic-intensity DOACs or VKAs (target INR 2.0–3.0) should be continued.

Future research should include well-designed pediatric comparative trials of DOACs, VKAs, and ASA, optimal treatment duration, high-risk subgroups and long-term outcome including safety, bleeding, and quality-of-life.

Question 4. What is the recommended antithrombotic strategy for primary thrombosis prevention in children with cardiomyopathy (particularly dilated cardiomyopathy (DCM), hypertrophic

cardiomyopathy (HCM), non-compaction cardiomyopathy (NCCM), and restrictive cardiomyopathy (RCM)) to prevent thrombosis?

Recommendation

- Use ASA for primary thrombosis prevention in children with cardiomyopathy and an ejection fraction below 30%.
- Discontinue primary thrombosis prevention if the ejection fraction has been stable > 30% for three months.

Summary of evidence

DCM is the most common form of cardiomyopathy in children. It is characterized by a dilated left ventricle and systolic left ventricular dysfunction, often leading to heart failure. Other forms of cardiomyopathy, such as HCM, NCCM, and RCM, less

frequently result in systolic dysfunction. A

(severely) reduced systolic dysfunction in cardiomyopathy may lead to thromboembolic events

because of stasis of the blood in the heart. The thrombi typically form in the left ventricle but can also develop in the atria and right ventricle. A thrombus formed in the left ventricle or atrium may

embolize, leading to a cerebrovascular accident (CVA) or peripheral arterial embolisms. A thrombus in the right ventricle can result in PE. Few studies reported on the incidence of thrombosis in children with dilated cardiomyopathy. The reported numbers varied between 6% and 15%.^(26–29) In adults with cardiomyopathy, the risk of thromboembolic complications is associated with the risk of atrial fibrillation. Adults with cardiomyopathy are recommended to be treated with anticoagulants in cases of atrial fibrillation combined with a high CHADSVASC score.⁽³⁰⁾ Reduced left ventricular function is one of the risk factors (along with other non-pediatric relevant risk factors like age, diabetes, and hypertension).⁽³¹⁾ In pediatric study populations with cardiomyopathy, both atrial fibrillation and the additional risk factors for thrombosis are very rare, and this recommendation is not directly

applicable. In general, systolic left ventricular dysfunction in children with (dilated) cardiomyopathy is assumed to be the most important risk factor leading to (intracardiac) thrombosis and

thromboembolic complications.

Our systematic search focused on the evidence of anticoagulant treatment of pediatric patients with cardiomyopathy (DCM, HCM, NCCM and RCM) to prevent thrombosis yielded only one article.⁽³²⁾

Irden et al. described the effect of treatment with ASA versus no ASA on intracardiac thrombi in

children with DCM.⁽³²⁾ Children with a left ventricular ejection fraction (LVEF) lower than 30% were treated with ASA, and children with LVEF higher than 30% were not treated with anticoagulants. The five children (out of 83 children) who developed an intracardiac thrombosis (ICT) were all in the

untreated group (LVEF > 30%). Children treated with ASA had a lower risk of thrombosis compared to those who did not receive thrombosis prophylaxis (RR = 0.17; 95% CI 0.01–2.19), a clinically relevant effect. Of the five patients with thrombotic complications, one patient had a PE, and one patient had both a CVA and a PE. Both patients died. Although ASA is thus associated with a lower risk of ICT in

this study, the evidence is considered very weak, as it was a small retrospective study where the decision to treat with ASA was based on LVEF at inclusion. No data on other relevant outcomes, such as mortality, bleeding, ischemic stroke, and quality of life, was available. There is no evidence

regarding the use of DOACs in children for this indication. In addition, no literature was found regarding the primary thrombosis prevention in children with NCCM, HCM, or RCM.

Other considerations

In the absence of robust pediatric evidence, decisions regarding thromboprophylaxis in

cardiomyopathy rely largely on pathophysiological rationale and the recognition that severely reduced systolic function increases the likelihood of intracardiac thrombosis. The panel considered

the balance between a potentially meaningful reduction in thromboembolic events and the relatively low bleeding risk associated with low-dose ASA, alongside its low cost and ease of use, especially in a population that may already face significant treatment burden.

Conclusions and research needs

Despite the very low quality of evidence, the panel chose to recommend ASA for primary prevention of thromboembolic complications in children with cardiomyopathy and a LVEF below 30%.

Future research should focus on prospective studies that determine the true incidence, predictors, and outcomes of thrombosis across cardiomyopathy subtypes. Comparative trials of ASA,

anticoagulants, and DOACs, along with evaluation of bleeding risk, stroke, mortality, and quality of life, are essential. Subgroup analyses to identify children who may benefit from intensified

prophylaxis, including those with severe chamber dilatation or arrhythmias, are needed to refine and individualize preventive strategies.

Question 5. What is the recommended antithrombotic strategy for primary thrombosis prevention in children after percutaneous atrial or ventricular septal defect (ASD or VSD) closure?

Recommendation

- Treat children as soon as possible after the percutaneous device-closure of ASD or VSD with LMWH in a therapeutic dose or intravenous ASA. As an alternative to intravenous ASA, an oral dose of ASA can be administered pre-procedure.
- Start oral ASA as soon as oral administration is possible, and continue for six months

Summary of evidence

After percutaneous device closure of an ASD or VSD, patients are at increased risk of thrombosis because the introduced device material may act as a nidus for thrombus formation, creating a

potential source of right- and left-sided emboli. The systematic search identified no pediatric studies evaluating thromboprophylaxis after ASD/VSD device closure.

Other considerations

In adults, the 2021 European Society of Cardiology guideline recommends six months of antiplatelet therapy following ASD device closure, likely based on the assumption that complete epithelialization occurs within that period.⁽³³⁾ This recommendation is not supported by randomized studies. ASA

treatment offers the lowest burden of side effects, is easy to administer, and is cost-effective.

Conclusion and research needs

Given the absence of evidence favoring a specific antithrombotic regimen, the low estimated

thrombogenic risk, primary related to platelet aggregation on the device, and in alignment with

recommendations in adults, the panel recommends treating patients with six months of antiplatelet therapy after ASD or VSD device closure. Because oral intake may be suboptimal immediately after

the procedure, bridging with therapeutic LMWH at the end of anesthesia may be considered, as oral therapy is usually feasible within 24 hours. Alternatively, peri-procedural antiplatelet therapy may be administered to ensure immediate platelet inhibition, for example as a single oral dose on the day

prior to the procedure or intravenously at the end of the intervention.

Priorities for research include: (1) incidence and timing of device-related thrombosis in children, (2) comparative studies of LMWH bridging vs. immediate antiplatelet strategies, (3) trials testing duration and type of antiplatelet therapy or alternative

anticoagulant treatment, and (4) patient-centered outcomes, such as bleeding, ease of administration, procedural burden, and length of stay.

Question 6. What is the recommended antithrombotic strategy for primary thrombosis prevention in children after the placement of a stent (systemic venous/systemic arterial/pulmonary venous/pulmonary arterial)?

Recommendation

- Treat children as soon as possible with ASA after stent placement in a high-flow area (pulmonary artery or aorta) for a period of three months.
- Treat children as soon as possible with dual antiplatelet therapy after stent placement with

achieved diameters of < 6 mm in the pulmonary arteries, particularly in a pulmonary vascular bed with multilevel stenoses (most often in patients with syndromic conditions): ASA for six months, combined with clopidogrel for the first three months. Consider administering the first dose of antiplatelet therapy orally pre-interventionally or intravenously immediately post-intervention.

- Treat children as soon as possible with ASA after stent placement in a right-sided low-flow area (systemic veins) without right-to-left shunt for a period of six months.
- Treat children as soon as possible with dual antiplatelet therapy after stent placement in a left-sided low-flow area (pulmonary veins) lifelong. Bridge with LMWH or UFH until oral medication

can be administered or administer the first dose of antiplatelet therapy orally pre-interventionally or intravenously immediately post-intervention.

- Treat children as soon as possible with dual antiplatelet therapy after stent placement in the ductus arteriosus or in an aorto-pulmonary shunt until the stent is removed. Bridge with LMWH or UFH until oral medication can be administered or administer the first dose of antiplatelet

therapy orally pre-interventionally or intravenously immediately post-intervention.

- Treat children as soon as possible with ASA after right ventricular outflow tract stenting until the stent is removed. Consider administering the first dose of antiplatelet therapy orally pre-interventionally or intravenously immediately post-intervention.
- Treat patients as soon as possible with lifelong ASA after percutaneous pulmonary valve implantation. Consider administering the first dose of antiplatelet therapy orally pre-interventionally or intravenously immediately post-intervention.

Summary of evidence

Stents are tubular metal meshwork that are placed in the bloodstream to guarantee patency of vessels or parts of the heart. After placement, blood comes into direct contact with the metal surface of the stent, creating a risk of thrombus formation that may occlude the stent or embolize distally, potentially resulting in distal vessel occlusion or infarction. The consequences of occlusion or

infarction depend on the location of the stent. Most importantly, stents in the pulmonary veins or pre-carotid systemic arteries can cause cerebral infarction; the same risk applies to stents in the systemic venous system when a right-to-left shunt is present. There are several risk factors for stent thrombosis, such as the diameter and tortuosity of the stent, and placement in a low flow region of

the bloodstream. Over time, neo-intimal proliferation occurs within the stent, eventually covering the metal mesh and eliminating direct contact between the stent and the bloodstream, thus decreasing

thrombosis risk.

Clinical practice regarding thromboprophylaxis after stent placement varies considerably, both in the postprocedural phase and during long-term management. The systematic search found no studies on thromboprophylaxis in children post stenting.

Other considerations

Extensive literature exists on thromboprophylaxis after coronary stenting in adults. However, these data cannot be directly extrapolated to children, where stents are placed in vessels of varying

diameters and risk profiles. Consequently, the panel based its recommendations on theoretical considerations and clinical practice.

Theoretically, stent location influences thrombosis risk: high-flow areas (e.g., systemic or pulmonary arteries) carry a lower risk, while low-flow areas (e.g., systemic veins or pulmonary veins) carry a

higher risk and greater potential consequences, such as cerebral infarction in the presence of a right-to-left shunt. Ooi et al. found no difference in rates of in-stent thrombosis between ASA and

anticoagulation in low-flow areas such as the Fontan circulation.⁽³⁴⁾ Given the absence of pediatric evidence and the estimated low thrombogenic risk, primarily related to platelet aggregation, most centers favor antiplatelet therapy for its safety, simplicity, and low cost. In cases where embolization from pulmonary veins could cause severe cerebral events, adding clopidogrel is defensible despite

the increased bleeding risk of dual therapy. Similarly, dual therapy after stenting of a ductus or central shunt is justified because these connections are critical for pulmonary blood flow. Pre-existing

thrombus may warrant anticoagulation, despite the associated increased bleeding risk.⁽³⁴⁾

Conclusion and research needs

The panel concluded that antiplatelet therapy, single or dual, depending on stent location and flow characteristics, offers the most appropriate balance of safety, feasibility, and biological plausibility, particularly because stent-related thrombus formation appears primarily platelet-driven. However, substantial knowledge gaps remain. Future research should focus on defining the true incidence,

timing, and predictors of stent thrombosis across various vascular territories, determining the optimal intensity and duration of antiplatelet therapy for different stent types and diameters, and clarifying

whether specific subgroups (e.g., small-diameter pulmonary artery stents, pulmonary venous stents, or patients with right-to-left shunts) require intensified therapy or prolonged prophylaxis.

Comparative studies of antiplatelet versus anticoagulant strategies, evaluation of bleeding risk with dual antiplatelet therapy, and assessment of patient-centered outcomes are also needed to inform more evidence-based, individualized treatment algorithms.

Question 7

What is the recommended antithrombotic strategy for primary thrombosis prevention in children after surgical heart valve replacement?

Recommendation

- Treat children as soon as possible with VKA after the placement of mechanical heart valves. For mechanical aortic valves, the recommended INR is between 2.0 and

3.0. For mechanical mitral valves, the recommended INR is between 2.5 and 3.5.

- Do not use antithrombotic prophylactic therapy after the placement of homografts or bovine pulmonary valved conduit.
- Treat children as soon as possible with ASA or VKA after placement of a biological heart valve prosthesis in the aortic position for three months.
- Treat children as soon as possible with VKA after placement of a biological tricuspid or mitral valve prosthesis for three months.

Summary of evidence

Children with prosthetic heart valves, especially mechanical heart valves, are at an increased risk of

thromboembolic complications. The choice of anticoagulant depends on valve type and position. The systematic literature review identified no RCTs evaluating different anticoagulant strategies in this population. Consequently, there is no direct evidence on the optimal approach to thrombosis prevention in children with prosthetic heart valves. Therefore, current recommendations are based on indirect evidence from adult studies and existing guidelines.(35–37)

Other considerations

Mechanical Heart Valve Prostheses: All children with mechanical heart valves require lifelong

anticoagulation with VKAs. In addition to the thrombotic properties of the intravascular prosthesis material, mechanical valves create abnormal flow conditions, with areas of low flow next to regions of increased shear stress, which can lead to platelet activation and, ultimately, valve thrombosis and embolic events.(35, 36) Oral VKA therapy should be initiated promptly, with therapeutic-dose bridging using UFH or LMWH until the target international normalized ratio (INR) is achieved and

remains stable for more than 24 hours. Target INR levels depend on prosthesis thrombogenicity and patient-specific risk factors, and minimizing INR variability is crucial, as large fluctuations independently increase the risk of adverse events.(37) In infants under six months, LMWH is

preferred because stable INR control is difficult to achieve. Adding low-dose ASA to VKA may further reduce thromboembolic risk but increases bleeding risk; therefore, dual therapy should be reserved for children with very high thrombotic risk, such as those with small mechanical mitral valves.(37)

Observational pediatric studies, mostly retrospective, reported low rates of thromboembolic events (0 to 1.3% per patient-year) and bleeding complications (0 to 2.3% per patient-year) with VKA

therapy, underscoring the need for frequent INR monitoring due to variable metabolism and

dietary influences.(3) Currently, there is no evidence to support the routine use of DOACs in children with mechanical valves prostheses.

Biological Heart Valve Prostheses: Homografts are frequently used in children due to favorable hemodynamic performance and a very low inherent thrombotic risk, generally negating the need for long-term anticoagulation.(36, 37) Similarly, no anticoagulation is required for the bovine

pulmonary valved conduit, unless there are other independent indications for anticoagulation or antiplatelet therapy. The biological nature of these valves results in rapid endothelialization and minimal thrombogenicity compared to mechanical or other bioprosthetic valves. In other

bioprostheses, ischemic stroke risk is elevated in the early postoperative phase, particularly within 90 to 180 days after implantation. The risk is highest for mitral and tricuspid valves and lower for aortic valves.(36) Anticoagulation in this phase aims to reduce the risk of thromboembolic events until the prosthetic valve is fully covered with endothelial tissue. The optimal antithrombotic strategy in the

early postoperative phase remains uncertain. Several observational studies in adults, support the use of VKA for the first three months in patients with mitral or tricuspid valve bioprostheses. For aortic bioprostheses, either a platelet inhibitor or VKA should be considered for three months after surgical implantation.(37)

Conclusions and research needs

Current recommendations for anticoagulation in children with prosthetic heart valves are based almost entirely on extrapolated adult data and low-quality pediatric evidence. VKAs remain the cornerstone of therapy for all mechanical valves, while biological valves generally require no

long-term anticoagulation except during the early postoperative period for certain bioprosthetic positions. Evidence for DOAC use in this population is lacking. Future pediatric research should include prospective, multicenter studies to define optimal anticoagulation strategies for

children with mechanical heart valves, as well as risk-stratification approaches to enable truly individualized antithrombotic therapy.

Discussion

This paper provides an overview of available evidence and expert considerations regarding antithrombotic management in pediatric patients after common cardiac procedures, including AP and RVP shunts, Glenn and Fontan circulations, percutaneous defect closures, post-stenting, prosthetic

valve replacement, and cardiomyopathies. We used the GRADE evidence-to-decision framework to explicitly combine evidence and structured expert considerations to identify balanced

recommendations that include perspectives on harms and benefits of potential interventions, patient preferences, sustainability, health equity, and cost. For all recommendations, parents and caregivers generally value strong protection against thrombosis, and the burden of anticoagulation is viewed as acceptable considering the potential severity of thrombotic events. All antithrombotic agents are

reimbursed and widely available in the Netherlands, ensuring equitable access. The relatively low cost and high feasibility of anticoagulant strategies further support their use, and these treatments are already standard practice in all Dutch centers. Finally, prophylaxis is considered ethically

acceptable and may reduce overall resource use by preventing complications requiring intensive interventions.

Strengths of this guideline are the structured methodological framework, and the systematic literature reviews performed by a national, multidisciplinary panel supported by independent

guideline methodologists. However, the certainty of evidence is predominantly low to very low, with few pediatric RCTs, heterogeneous populations and interventions, and reliance on indirect evidence and expert consensus for several recommendations. Moreover, across all clinical questions, substantial research gaps were identified, and the guideline outlines priorities for future studies to strengthen the evidence base and support more precise, individualized thromboprophylactic

strategies.

In conclusion, this guideline provides a structured and harmonized national approach to

thromboprophylaxis in pediatric cardiac patients, while acknowledging the limited evidence base and emphasizing the need for future research to strengthen and refine clinical practice.

Abbreviations

ASA	acetylsalicylic acid
ASD	atrial septum defect
AP	aorto-pulmonary
CI	Confidence interval
CVA	cerebrovascular accident
DOAC	direct oral anticoagulants
DCM	dilated cardiomyopathy
HCM	hypertrophic cardiomyopathy
HR	Hazard ratio
INR	international normalized ratio
ICT	intracardiac thrombosis
IVC	inferior vena cava
LMWH	low-molecular-weight heparin
LVEF	left ventricular ejection fraction
mBTT	modified Blalock-Taussig-Thomas shunt
NCCM	non compaction cardiomyopathy
PCPC	Partial Cavopulmonary Connection
PE	pulmonary embolism
PICO	Population, Intervention, Comparator, Outcome
RCM	restrictive cardiomyopathy
RR	Relative risk
RVP	right ventricle-pulmonary
SVC	superior vena cava
UFH	unfractionated heparin
VKA	vitamin K antagonists
VSD	ventricular septum defect

Declarations

This article is adapted from the Dutch clinical guideline published on Richtlijnen.nl (Richtlijn Preventie van trombose bij kinderen met een hartaandoening) and has been translated into English.

The development of the Dutch guideline was funded through the Dutch Quality Funding for Medical Specialists (SKMS)

Author Contribution

CO, AH: translating, manuscript writing RB, TC, ML, LN, AO: literature search, data analysis, table and figure preparing GB, MM, HN, EP, LP, PR, AR, MS, HT: manuscript writing All authors reviewed the manuscript

Data Availability

All data supporting the findings of this study are available within the paper and its Supplementary Information.

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Tables

Table 1: Overview of recommendations

AP/RVP-shunt	- Treat children as soon as possible after placement of an AP and/or RVP shunt with therapeutic heparin (UFH or LMWH) or intravenous ASA until enteral feeding can be initiated. - Switch to oral antiplatelet therapy as soon as oral administration is feasible and continue for as long as the shunt remains in situ.
Glenn shunt	- Treat children as soon as possible after the Glenn shunt or PCPC procedure with therapeutic heparin (UFH or LMWH). - Switch to oral ASA as soon as oral administration is feasible. - Consider anticoagulation (LMWH, VKA, DOAC) in conditions associated with an increased risk of thrombosis. (Table 3)
Fontan	- Treat children as soon as possible with therapeutic heparin (UFH or LMWH) after completion of the Fontan circulation. - Switch to VKA (target INR 2.0-3.0) or DOAC at therapeutic intensity (14) for six months, as soon as oral administration is possible. - After six months, treat children with Fontan circulation without additional risk factors with DOAC at low intensity (6) or ASA. - After six months, treat children with a Fontan circulation with additional risk factors (table 3) with a DOAC at therapeutic intensity or VKA (target INR 2.0–3.0).
Cardiomyopathy	- Use ASA for primary thrombosis prevention in children with cardiomyopathy and an ejection fraction below 30%. - Discontinue primary thrombosis prevention if the ejection fraction has been stable >30% for three months.
Percutaneous ASD/VSD closure	- Treat children as soon as possible after the percutaneous device-closure of ASD or VSD with LMWH in a therapeutic dose or intravenous ASA. As an alternative to intravenous ASA, an oral dose of ASA can be administered pre-procedure.

	- Start oral ASA as soon as oral administration is possible, and continue for six months
Stents	- Treat children as soon as possible with ASA after stent placement in a high-flow area (pulmonary artery or aorta) for a period of three months. - Treat children as soon as possible with dual antiplatelet therapy after stent placement with achieved diameters of <6 mm in the pulmonary arteries, particularly in a pulmonary vascular bed with multilevel stenoses (most often in patients with syndromic conditions): ASA for six months, combined with clopidogrel for the first three months. Consider administering the first dose of antiplatelet therapy orally pre-interventionally or intravenously immediately post-intervention. - Treat children as soon as possible with ASA after stent placement in a right-sided low-flow area (systemic veins) without right-to-left shunt for a period of six months. - Treat children as soon as possible with dual antiplatelet therapy after stent placement in a left-sided low-flow area (pulmonary veins) lifelong. Bridge with LMWH or UFH until oral medication can be administered or administer the first dose of antiplatelet therapy orally pre-interventionally or intravenously immediately post-intervention. - Treat children as soon as possible with dual antiplatelet therapy after stent placement in the ductus arteriosus or in an aorto-pulmonary shunt until the stent is removed. Bridge with LMWH or UFH until oral medication can be administered or administer the first dose of antiplatelet therapy orally pre-interventionally or intravenously immediately post-intervention. - Treat children as soon as possible with ASA after right ventricular outflow tract stenting until the stent is removed. Consider administering the first dose of antiplatelet therapy orally pre-interventionally or intravenously immediately post-intervention. - Treat patients as soon as possible with lifelong ASA after percutaneous pulmonary valve implantation. Consider administering the first dose of antiplatelet therapy orally pre-interventionally or intravenously immediately post-intervention.
Valve replacement	- Treat children as soon as possible with vitamin K antagonists (VKAs) after the placement of mechanical heart valves. For mechanical aortic valves, the recommended INR is between 2.0 and 3.0. For mechanical mitral valves, the recommended INR is between 2.5 and 3.5. - Do not use antithrombotic prophylactic therapy after the placement of homografts or bovine pulmonary valved conduit. - Treat children as soon as possible with ASA or VKA after placement of a biological heart valve prosthesis in the aortic position for three months. - Treat children as soon as possible with VKA after placement of a biological tricuspid or mitral valve prosthesis for three months.

Table 2 Overview antithrombotic drugs

	ACTION	FORMULATION	MONITORING	TREATMENT OF BLEEDING	OTHER
ANTIPLATELET THERAPY					
<i>ACETYLSALICYLIC ACID</i>	Blocks COX-1	Oral and intravenous	No routine monitoring	Local	Consider the
	to reduce platelet aggregation (irreversibly)			hemostasis is usually sufficient; platelet transfusion is required in life-threatening bleeding	half-life; platelet function recovers only after 5–7 days
<i>CLOPIDOGREL</i>	Blocks P2Y ₁₂ receptor to reduce platelet aggregation (irreversibly)	Oral	No routine monitoring; consider CYP2C19 genotyping to assess response	Local	Consider the
				hemostasis is usually sufficient; platelet transfusion is required in life-threatening bleeding	half-life; platelet function recovers only after 5–7 days
UNFRACTIONATED HEPARIN (UFH)	Enhances antithrombin to inhibit thrombin (IIa) and factor Xa	Intravenous	Frequent monitoring of aPTT (or anti-Xa level)	Protamine sulfate neutralizes UFH. (full reversal)	Short half-life (30–60 min); useful when rapid reversibility is needed (ICU or planned procedures). Risk of HIT
LOWMOLECULAR WEIGHTHEPARIN (LMWH)	Enhances antithrombin to inhibit	Subcutaneous	Monitoring of anti-Xa levels in select	Protamine partially reverses LMWH	Longer half-life, more predictable

	factor Xa > IIa.		cases.	(~60%).	kinetics, and lower HIT risk than UFH.
VITAMIN K ANTAGONISTS (VKA)	Inhibits vitamin K–dependent clotting factors (II, VII, IX, X).	Oral	Frequent monitoring of INR	Vitamin K orally or intravenously; PCC for rapid reversal.	Home monitoring with CoaguChek is possible. Many food and drug interactions.
DIRECT ORAL ANTI COAGULANTS (DOAC)	Reversibly, directly inhibits factor Xa (apixaban, edoxaban, rivaroxaban) or factor IIa (dabigatran).	Oral	No routine monitoring; anti-Xa or diluted thrombin time in select cases	PCC	Do NOT use in patients with mechanical valves or antiphospholipid syndrome (APS). Avoid if creatinine clearance <30 mL/min (dabigatran) or <15 mL/min (apixaban, rivaroxaban, edoxaban). Some drug–drug

ACTION	FORMULATION	MONITORING	TREATMENT OF BLEEDING	OTHER
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interactions exist, though fewer than with VKAs.

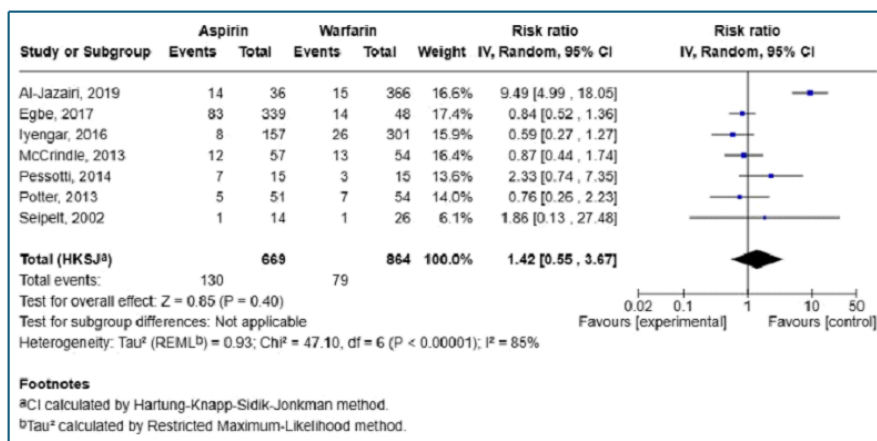
Abbreviations: PCC prothrombin complex concentrate, HIT heparin induced thrombocytopenia, aPTT activated partial thromboplastin time, ICU intensive care unit

Table 3 Conditions with an increased risk of thrombosis which may lead to a higher intensity level of anticoagulation (3, 38)

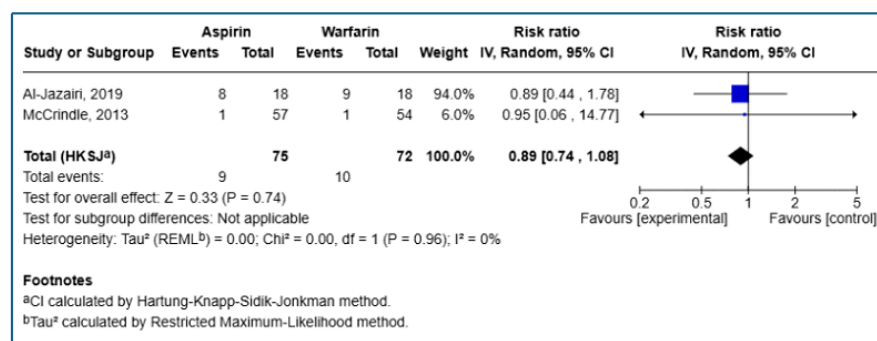
Increased Thrombotic Risk
Bilateral superior vena cavae Ventricular dysfunction
Atrial arrhythmias
Small pulmonary arteries or superior vena cava Presence of thrombogenic foreign material
A non-occluded blind-ending pulmonary artery stump Stasis in a hypoplastic ventricle
Open fenestration History of thrombosis Thrombophilia
Protein-losing enteropathy

Figures

(a)



(b)



(c)

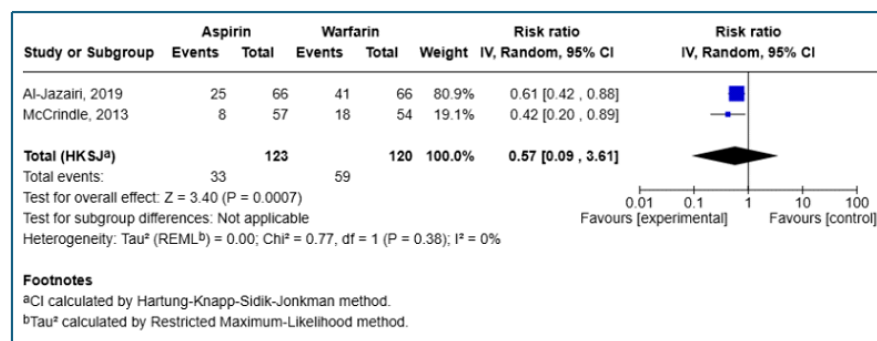


Figure 1

Forest plots of acetylsalicylic acid versus warfarin in patients after Fontan procedure for the outcome (a) thrombotic complication, (b) major bleeding, and (c) minor bleeding.

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