AHA Scientific Statement

Prevention and Treatment of Thrombosis in Pediatric and Congenital Heart Disease

A Scientific Statement From the American Heart Association

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1. Introduction

Thrombosis has long been recognized as a potentially life-threatening complication in children with congenital heart disease (CHD), children with acquired heart disease, and in adults with CHD. High-risk groups include patients with shunt-dependent single ventricles (shunt thrombosis, 8%–12%; 4% risk of death resulting from shunt failure), postoperative central lines (13% thrombosis in central venous lines [CVLs]), Fontan circulation (17%–33% incidence of thrombosis after Fontan), arrhythmias, Kawasaki disease with coronary aneurysms, and cardiomyopathy/myocarditis.

Table 1. Description of Recommendations and Levels of Evidence

Class of Recommendation	
I	Evidence or general agreement that a given procedure or treatment is useful and effective
II	Conflicting evidence or a divergence of opinion about usefulness/efficacy
IIa	Weight of evidence/opinion is in favor of usefulness/efficacy
IIb	Usefulness/efficacy is less well established by evidence/opinion
III	Evidence and/or agreement that the procedure/treatment is not useful/effective and in some cases may be harmful
Levels of Evidence	
A	Multiple randomized trials with large numbers of patients (strongest weight of evidence)
B	Limited number of randomized trials with small number of patients Careful analyses of nonrandomized studies Observational registries (Intermediate weight of evidence)
C	Expert consensus is the primary basis for the recommendation (Lowest rank of evidence)

Although the prevalence, risk factors, and management of some of these situations have been well described (ie, Kawasaki disease), for the management of others (ie, anticoagulation after the Fontan operation), there is a paucity of data, and controversy exists even among experts. Although as with many pediatric diseases, a lack of randomized, controlled trials limits the ability to make recommendations beyond "expert consensus," to date there is no published work that focuses solely on the important complication of thrombosis in pediatric and CHD.

The charge for this writing group was to critically review and summarize the available data on thrombosis in this patient population and to make recommendations when appropriate. The anticipated readership is the multidisciplinary specialists who care for children with congenital and acquired heart disease and adults with CHD, including pediatric and adult subspecialists in cardiology, critical care, cardiothoracic surgery, anesthesiology, hematology, general surgery, infectious diseases, and nursing. The writing group is composed of pediatric cardiologists, adult cardiologists with expertise in adult CHD, cardiothoracic surgeons, hematologists, neurologists, nurses, and basic scientists. We followed the methodology proposed by Gibbons et al[1,2] and outlined in the 2006 Methodologies and Policies American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines. After careful review of the applicable published data, recommendations were generated as standalone statements graded by class of recommendation and level of evidence as shown in Table 1.

Table 2 summarizes this approach, along with the assigned wording that goes with each class. By definition, the levels and

Table 2. Applying Classification of Recommendation and Level of Evidence

SIZE OF TREATMENT EFFECT

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/ Test / Treatment COR III: No benefit / Not Helpful / No Proven Benefit COR III: Harm / Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

classes are weighted. A *Class I* recommendation ("is recommended") is very different from a *Class IIb* recommendation ("effectiveness is not well established"). Likewise, a *Level of Evidence A* recommendation (multiple randomized trials) is very different from a *Level of Evidence C* recommendation (expert consensus only).

The reader is asked to pay particular attention to the level, class, and assigned wording of each recommendation. This is of utmost importance in translating these recommendations to patient care.

It is the anticipation of the writing group that this work will serve as a springboard to the medical and scientific communities for much-needed research on the causes of, risk factors for, prevention of, and treatment of thrombosis in children with heart disease and in adults with CHD.

2. Hemostasis in Children

Normal physiological hemostasis is dependent on maintaining a fine balance between thrombosis (clotting) and hemorrhage (bleeding), the fundamentals shown in Figure 1. Hemostasis can be described as the interaction of platelets with damaged vascular endothelium followed by activation of specific proteins to produce a fibrin platelet plug that will prevent bleeding but will not result in pathological thrombosis. The initial model describing

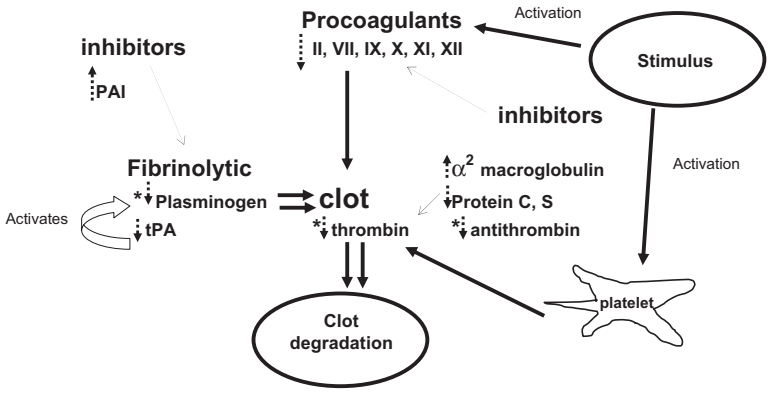

Figure 1. Hemostasis is kept in check by 2 systems: coagulation (thrombus formation) and fibrinolysis (thrombus degradation). Each system is composed of proteins that, when activated by a stimulus, interact with cellular components, including platelets and tissue factor–bearing cells. PAI indicates plasminogen activator inhibitor; and tPA, tissue plasminogen activator. Single arrows (⟶)demonstrate steps in thrombus formation. Double arrows (⟹) demonstrate steps in thrombus degradation. Light dotted arrows (⟶)indicate inhibitors of coagulation and fibrinolysis. Dashed arrows (⇢) indicate differences in children versus adults. Dashed arrows with asterisks (*⇢)indicate the most important differences influencing anticoagulant therapy in children.

hemostasis (coagulation and fibrinolysis), the cascade model, excluded important cellular involvement in coagulation[3,4] and thus has been revised to the cell-based model (Figure 2), which is a more accurate reflection of in vivo processes.[4]

Cell-based coagulation has been described to have 3 phases (Figure 2): initiation of coagulation on tissue factor (TF)–bearing cells, amplification of the procoagulant signal by thrombin generated on the TF-bearing cell, and propagation of thrombin generation on the platelet surface. Importantly, the model also accounts for the regulation of thrombin and fibrin production (fibrinolysis; Figure 3).

2.1. Initiation of Coagulation

Initiation of coagulation occurs on intact cells or cellular fragments (monocytes, macrophages, neutrophils, activated endothelial cells, smooth muscle cells, apoptotic cells, platelet microparticles, and circulation vesicles) that have the transmembrane glycoprotein TF.[4] TF becomes accessible by a number of different mechanisms, including exposure on activated endothelial cells in damaged vessel wall (surgery, trauma), through aberrant expression by activated monocytes or endothelial cells when stimulated by sepsis (various different organisms) or through cytokine production during inflammation.[6] Partially exposed TF binds and activates factor VII (FVII); the complex factor VIIa (FVIIa)–TF then activates factor IX (FIX) and factor X (FX). Factor Xa (FXa) then activates factor V (FV), resulting in a small amount of thrombin (factor IIa [FIIa]) generation.

In blood, platelets circulate and are prevented from interacting with normal endothelium, which produces the

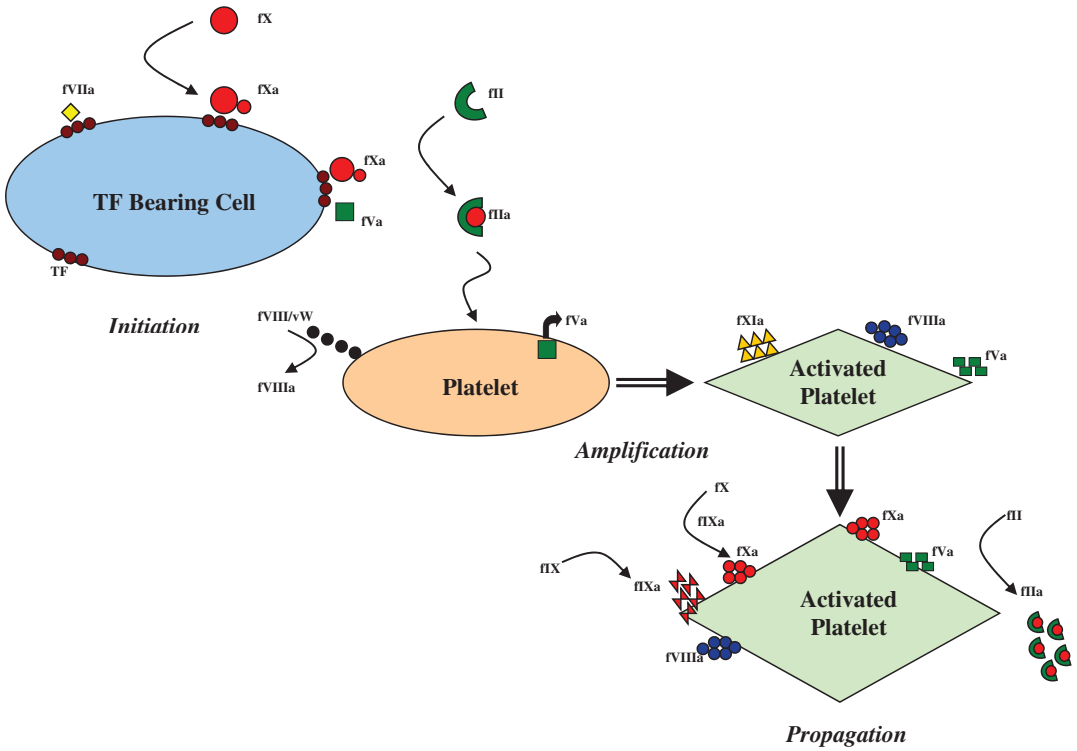

Figure 2. Cell-based model of coagulation. In this evolving structural-functional scheme, coagulation occurs in 3 phases: initiation, amplification, and propagation. f Indicates factor; TF, tissue factor; and vWF, von Willebrand factor. See text for further explanation. Adapted from Becker[5] and reproduced with kind permission from Springer Science and Business Media. Copyright © 2005, Springer. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaption.

platelet-inhibiting substances nitric oxide and prostacyclin. Disruption of vascular endothelium results in subendothelial collagen exposure, to which circulating von Willebrand factor (vWF) multimers (bound to factor VIII [FVIII]) bind. Circulating platelets then bind to vWF through receptor glycoprotein Ib-IX-V (Figure 4).

Increased shear stress, such as occurs normally in arterioles or pathologically in stenotic vessels, can result in platelet activation independently of endothelial damage resulting from vWF multimer extension exposing active sites to bind platelet glycoprotein Ib-IX-V. Platelets bind and become temporarily tethered to vWF. The bond is then released; platelets roll on the endothelium; and a new glycoprotein Ib-IX-V/vWF bond forms.[7] In the absence of endothelial damage or an artificial "vascular" surface (foreign surfaces of extracorporeal life support, including cardiopulmonary bypass [CPB], extracorporeal membranous oxygenation [ECMO], ventricular assist devices, mechanical heart valves, and vascular stents and shunts), pathological thrombosis may not occur because studies demonstrate that activated platelets are removed from the circulation.[8]

2.2. Amplification

Platelet activation results in secretion of intracellular granule collections followed by a number of reactions, one of the most important being activation of glycoprotein IIb/IIIa and binding of circulating fibrinogen, which result in platelet bridging and aggregation.[9] Amplification occurs as the small amount of thrombin generated on the TF-bearing cell activates platelets, FVIII, FV, and FXI. FXIa activates more FIX (accelerated by FVIIIa); FVa accelerates the action of FXa.

2.3. Propagation

Adherent and aggregating platelets are responsible for localizing coagulation reactions that lead to thrombin generation at the site of endothelial damage. Propagation occurs through FIXa binding to activated platelets and causing more FX activation. FXa and FVa complex to activated platelet membranes, resulting in a burst of thrombin generation. Roles of thrombin include conversion of soluble fibrinogen to a fibrin network (coagulation), activation of platelets through G-coupled protease–activated receptors,[4] and constriction of endothelium-denuded vessels.

2.4. Regulation of Thrombin and Fibrin

The regulation of thrombin and fibrin generation occurs through termination of coagulation, elimination of fibrin, and stabilization of thrombus (Figure 3).

Initial termination occurs as endothelial cells and platelets release TF pathway inhibitor, which inhibits TF, FVIIa, and FIXa. Antithrombin inhibits thrombin, FIXa, FXa, FXIa, and FVIIa-TF complex. Protein C is activated by protein S and thrombin/thrombomodulin complex and inhibits FVa and FVIIIa. Activated platelets release protease nexin II, an inhibitor of soluble-phase FIXa.

Elimination of fibrin and fibrinolysis is initiated through the attraction of plasminogen and tissue-type plasminogen activator (tPA) to the lysine residues of fibrin. Single-chain urokinase plasminogen activator binds to plasminogen. tPA converts plasminogen to plasmin; plasmin converts single-chain urokinase plasminogen activator to urokinase plasminogen activator, which produces additional plasmin from plasminogen. Plasmin then digests fibrin into soluble fragments, including d-dimer.

Stabilization of coagulation counteracts fibrinolysis through the following 4 reactions. First, FXIIIa, activated by thrombin, converts loosely interlaced fibrin into a tightly knit aggregrate. Second, thrombin-activatable fibrinolytic inhibitor, activated to thrombin-activatable fibrinolytic inhibitor-a when exposed to thrombin-thrombomodulin complex,

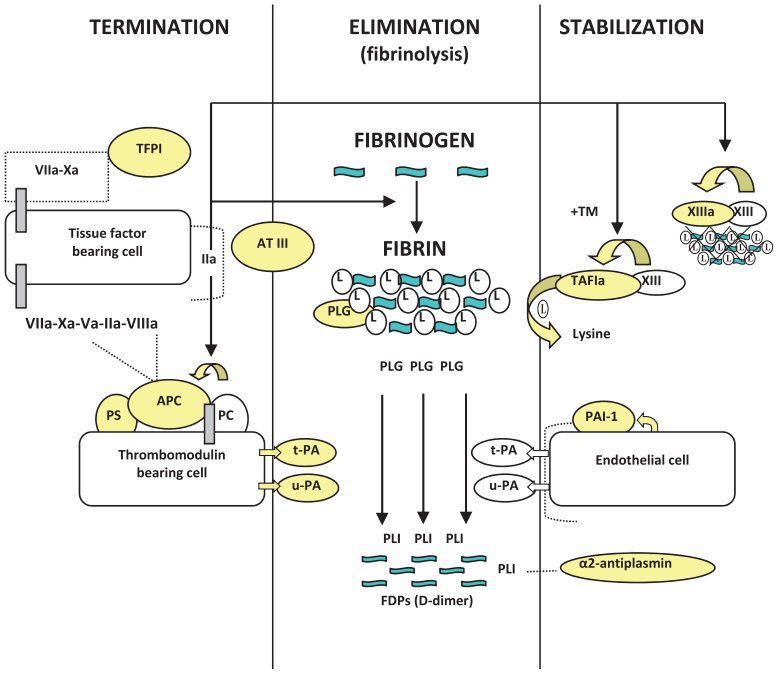

Figure 3. Regulation of fibrin and thrombin production **Left**, Plasmin (PL1), generated from plasminogen (PLG) by tissue plasminogen activator (t-PA) and urokinase plasminogen activator (u-PA), breaks fibrin into degradation products (FDPs). **Right**, Factor XIIIa, thrombin-activatable fibrinolysis inhibitor (TAFIa), plasminogen activator inhibitor type 1 (PAI-1), and α2-antiplasmin promote fibrin stability. The dotted lines indicate inhibition of thrombin (IIa) formation or thrombin activity by tissue factor pathway inhibitor (TFPI), antithrombin III (ATIII), and activated protein C (APC) in the presence of protein S (PS). TM indicates thrombomodulin. Adapted from Becker[5] and reproduced with kind permission from Springer Science and Business Media. Copyright © 2005, Springer. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaption.

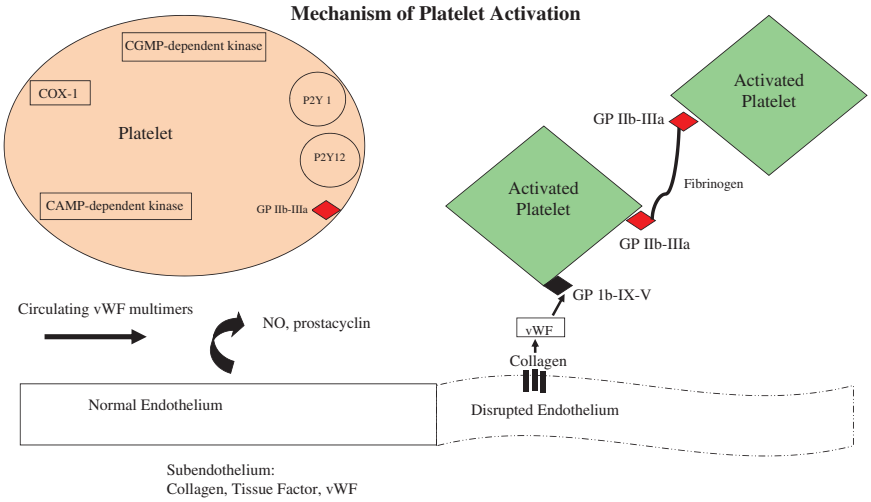

Figure 4. The mechanism of platelet activation. Platelets are prevented from adhesion to the endothelium through nitric oxide (NO) and prostacyclin production. When the endothelium becomes disrupted, collagen is exposed and binds to von Willebrand factor (vWF). Platelet receptor glycoprotein (GP) Ib-IX-V binds to vWF and ultimately activates platelet receptor glycoprotein IIb-IIIa. Circulating fibrinogen binds glycoprotein IIb-IIIa between activated platelets, resulting in a platelet-fibrinogen plug at the site of injury. Thrombin production then results in clot formation through alteration of fibrinogen into fibrin. Mechanisms of antiplatelet agents: Aspirin inhibits cyclooxygenase-1 (COX-1). Prostacyclin increases cAMP-dependent protein kinase A (PKA). Dipyridamole increases cGMP-dependent protein kinase G (PKG). Direct thrombin inhibitors inhibit thrombin, which activates protease-activated receptor 1 (PAR 1). Abciximab inhibits the glycoprotein IIb-IIIa platelet receptor.

removes lysine residues from fibrin, impairing the capacity of fibrin to bind plasminogen and tPA. Third, plasminogen activator inhibitor type 1 rapidly and reversibly inhibits tPA and urokinase plasminogen activator. Fourth, α^2 antiplasmin inhibits plasmin.

2.5. Developmental Hemostasis

The balance of hemostasis is maintained in infants and children despite very different levels of constituent proteins and inhibitors of coagulation (decreased FII, FVII, FIX, FX, FXI, FXII, protein C, protein S, and antithrombin; increased α^2 macroglobulin) and fibrinolysis (decreased tPA, plasminogen, and increased plasminogen activator inhibitor type 1), which approach adult levels later in childhood or at puberty.[10–12] These normal physiological differences in hemostasis are called developmental hemostasis.

In vitro studies demonstrate altered platelet function in neonates, although children are similar to adults. Neonatal platelets have been demonstrated to be hyporeactive to the platelet-activating agents thrombin, adenosine, phosphate/epinephrine, and thromboxane A_2.[13] However, the bleeding time in neonates, a reflection of platelet function, is normal because of increased red blood cell size, hematocrit, and vWF multimers.

2.6. Laboratory Measures of Hemostasis

2.6.1. Common Measures of Hemostasis

Measures of hemostasis ought to be drawn peripherally, particularly if low-dose heparin is administered through the central line to maintain patency. Test results on samples drawn from central lines may be artificially prolonged as a result of heparin contamination.

The partial thromboplastin time (PTT) and prothrombin time (PT)–international normalized ratio (PT-INR) are the most common tests measured, are based on the cascade model of anticoagulation, and do not reflect the complexity of hemostasis.

The PTT measures contact factors (FXI, FXII), FII, FVIII, FX, and the conversion of fibrinogen to fibrin. The PT-INR measures factors synthesized in the liver, including vitamin K–dependent factors (FII, FVII, FIX, FX). The conversion to INR is an attempt to account for different analyzers and thromboplastin reagents used in PT testing. In children and neonates, the normal PTT and PT-INR values are age dependent secondary to hemostatic protein differences present during normal developmental hemostasis.[10–12]

The laboratory tests included in the initial hemostatic workup of a child should include the PT-INR, PTT, fibrinogen levels, and platelet count. A prolonged PTT or INR can be a result of a number of different phenomena and does not necessarily predict the clinical risk of bleeding in a patient. For example, in a patient with normal age-appropriate test results, clinical bleeding may still occur. Prolongation of the INR or PTT requires formal evaluation to determine the cause. These patients are sometimes thought to be "autoanticoagulated"; however, this may be a misnomer, with the patient continuing to be at risk for developing thrombosis, depending on the cause of the abnormal test. In a patient who is not anticoagulated, a number of clinical scenarios (section 2.6.3, Hemostasis Monitoring: Practical Considerations) may result in prolongation of the INR or PTT and either affect the risk for bleeding or thrombosis or have no effect (heparin contamination of a central line blood sample used for testing).

In adults, elevated d-dimer levels are indicative of active coagulation and fibrin production. D-dimers have not been formally evaluated in children; therefore, the pretest likelihood of confirmed thrombosis is unknown.[14,15] If baseline

hemostatic test results are abnormal, experts in hemostasis (eg, hematology) should be consulted for further evaluation.

2.6.2. Global Measures of Hemostasis

Global measures of hemostasis, including the activated clotting time (ACT) and thromboelastogram, may be more representative of hemostasis because these tests use whole blood, which includes cellular components in the test systems.

2.6.2.1. Activated Clotting Time

The ACT uses activated whole blood and measures clotting time in seconds. This point-of-care (POC) test is used during CPB and ECMO to monitor anticoagulation, specifically heparin effect. There are no well-designed studies evaluating the safety and efficacy of the use of ACTs to monitor anticoagulation in children. Importantly, the ACT does not solely or accurately reflect the effect of heparin.[16–18]

2.6.2.2. Thromboelastogram

The thromboelastogram uses activated whole blood to measure hemostasis (formation of a clot) and fibrinolysis (clot degradation). The most common devices used to measure thromboelastography are the ROTEM (Pentafarm, Munich, Germany) and the TEG (Haemonetics, Braintree, MA). Although some normative thromboelastography data are available in children, formal well-designed studies are required to evaluate the precision, accuracy, and application of the measure in children.[19,20]

2.6.3. Hemostasis Monitoring: Practical Considerations

The following clinical scenarios may result in abnormal hemostatic laboratory results and may predispose the patient to an increased risk of bleeding and/or thrombosis.

2.6.3.1. Risk of Bleeding

- Congenital or acquired decrease in hemostatic protein(s) (increased INR, increased PTT, decreased fibrinogen)
- Excessive fibrinolysis (increased INR), hypothermia, for example, after post surgery, during CPB, or because of medical illness or gestational age (increased INR, increased PTT)
- Acidosis, for example, in medical illness or cardiac illness (increased INR, increased PTT, decreased fibrinogen, decreased platelet count)
- Acquired inhibitor to one of the proteins in the hemostatic pathway (increased INR, increased PTT)

2.6.3.2. Risk of Thrombosis

- Antiphospholipid antibody (increased INR, increased PTT)

2.6.3.3. Risk of Both Bleeding and Thrombosis

- Liver congestion resulting in decreased vitamin K–dependent proteins, including proteins C and S (increased INR)
- Consumption of coagulation factors, including disseminated intravascular coagulation (DIC; increased INR, increased PTT, decreased fibrinogen, decreased platelet count)

3. Agents for the Treatment and Prevention of Thrombosis

A number of antithrombotic agents, including anticoagulant, antiplatelet (molecular targets for agents; Figure 4), and fibrinolytic agents, are available for the treatment and prevention of thrombosis in children and young adults with heart disease (Table 3). Most of these agents are being used off label in children. The agents most studied in children are heparin, low-molecular-weight heparin (LMWH), and warfarin. Dosing nomograms available for each were published in *Chest* in 2008.[21] All agents have side effects (Table 3), with the development of heparin-induced thrombocytopenia (HIT) resulting from the use of heparin being the most clinically significant.

Direct thrombin inhibitors are new agents that are available for parenteral administration in HIT and orally for thromboprophylaxis in adults. Few studies have been carried out in children; therefore, these agents should be reserved for the indication of HIT and used by experts with extreme caution.

3.1. Heparin-Induced Thrombocytopenia

HIT occurs in ≈2% of adult patients and <1% of pediatric patients who are exposed to heparin. Antibodies (immunoglobulin G) are produced to the complex of platelet factor 4, a protein on the surface of activated platelets, and heparin and result in thrombocytopenia with extreme platelet activation[61,62] and resultant hypercoagulability. The diagnosis of HIT is made from a combination of clinical signs and laboratory confirmation of heparin-dependent platelet-activating antibodies or their inference from a positive test for platelet factor 4/heparin-reactive antibodies.

The clinical signs of HIT include thrombocytopenia (platelet drop of 50% within 24 hours) 5 to 8 days after the first heparin exposure (or sooner if heparin exposure has occurred in the past few weeks or months because HIT antibodies are transient) when other causes of thrombocytopenia are judged less plausible.[61]

Two laboratory assays are available to detect HIT antibodies: platelet serotonin-release assay (SRA) and platelet factor 4–dependent enzyme immunoassays (EIAs).[61] The SRA has high sensitivity and specificity for detecting HIT antibodies and thus is the gold standard laboratory assay, but it is technically demanding, performed by few centers, but available by referral. The anti–platelet factor 4/heparin EIA is the laboratory test most commonly carried out using a validated commercial assay. This test has the same high sensitivity as the SRA; however, a lower specificity results in a high false-positive rate (≈50% of patients clinically suspected to have HIT and a positive EIA actually have HIT).[63–66] Warkentin et al[67] recently compared EIA test results (in optical density [OD] units) to the gold standard SRA.

- More than 2.0 OD units had ≈90% predictivity presence of platelet-activating antibodies and a positive SRA.
- EIA ≥1.4 OD units equaled a 50% probability of the presence of platelet-activating antibodies (This threshold was considerably higher than the manufacturer's recommended cutoff of 0.4 OD units).

Table 3. Antithrombotic and Fibrinolytic Therapy

Anticoagulant and Mechanism of Action	Properties	Indications	Contraindications	Dose	Target Range	Monitoring	Side Effects
UFH Potentiates the inhibition of factors XIIa, XIa, Xa, IXa, IIa by antithrombin	t½ dose dependent. Hepatic and renal clearance. Completely reversible with protamine sulphate. Poorly bioavailable, requires frequent blood monitoring. Antithrombin required to achieve heparin effect. If no heparin affect is achieved with high doses of heparin, determine antithrombin level because antithrombin supplement may be required.	Treatment of thrombosis or increased risk of thrombosis when the risk of bleeding is considerable (ie, postoperative period) or when the child undergoes frequent invasive procedures requiring reversal of anticoagulation.	HIT Poor venous access because of parenteral administration. Frequent monitoring is required.	Age-dependent therapeutic dosing: <12 mo of age=28 U·kg^{-1}·h^{-1}. ≥12 mo of age=20 U·kg^{-1}·h^{-1}.[21,22] Low dose is commonly 10–15 U·kg^{-1}·h^{-1}.	Gold standard measure is anti–factor Xa 0.35–0.7 U/mL. If anti–factor Xa is not possible, then PTT 1.5–3 times baseline PTT. (Note: therapeutic PTT range should be established by each laboratory, is laboratory test reagent dependent, but is usually between 60 and 100 s. Lower PTTs may minimize bleeding postoperatively.)	Every 24 h at minimum. UFH level is gold standard (0.35–0.70 U/mL). If it is necessary to use a PTT to monitor therapy, the PTT range must be determined by each hospital to correspond to UFH 0.35–0.7 U/mL.	Hemorrhage reported as 6.6%–24%.[23,24] HIT, 0%–2.3%.[25] May be associated with osteoporosis.
LMWH Same as UFH but greater inhibition of factor Xa	t½=5 h. Highly bioavailable, "stable drug." Renally cleared. Not fully reversible. Low dependence on antithrombin. Requires 24 h to clear anticoagulant effect.	For treatment of thrombosis or as thromboprophylaxis when bleeding risk is considered stable or as a bridge between heparin and warfarin postoperatively or when a child has poor venous access.	High risk for bleeding. Reversal required frequently for interventions. Hold LMWH for 24 h before the procedure. Renal insufficiency.	Age-dependent dosing	Doses are titrated to target LMWH level (anti–factor Xa) of 0.5–1.0 U/mL.	LMWH level (anti–factor Xa) target 0.5–1.0 U/mL. Dose titrated to achieve level. Minimum monthly levels INR or PTT will not be affected.	Hemorrhage reported as 4.8%–8.1%.[23,26] No evaluation of risk of HIT or osteoporosis.
Enoxaparin every 12 h	t½=3–6 h	Stable anticoagulant effect required		Age-dependent dosing: < 2 mo=1.5 mg/kg per dose. ≥2 mo=1.0 mg/kg per dose.[27] Recent work indicating higher doses are necessary in neonates to rapidly achieve target levels. Given every 12 h.		LMWH level 4–6 h after dose	
Tinzaparin every 24 h	t ½ = 3–6 h	Needle-phobic children on long-term therapy		0–2 mo=275 U/kg per dose. 2–12 mo=250 U/kg per dose. 1–5y=240 U/kg per dose. 5–10 y=200 U/kg per dose. >10 y=175 U/kg per dose.[21,28] Given every 24 h.		Age-dependent LMWH levels: <5 y=2 h after dose. ≥5 y=4 h after dose.[28]	

(Continued)

Table 3. Continued

Anticoagulant and Mechanism of Action	Properties	Indications	Contraindications	Dose	Target Range	Monitoring	Side Effects
VKA							
Warfarin Specifically inhibits the γ-carboxylation of the vitamin K–dependent factors II, VII, IX, and X and protein C, S, and Z	t½=36–42 h. Oral administration. Hepatic metabolism.	Long-term anticoagulant therapy	Relative: <1 y of age unless mechanical valve in situ	Load: 0.2 $mg \cdot kg^{-1} \cdot d^{-1}$ except for patients with Fontan, then 0.1 $mg \cdot kg^{-1} \cdot d^{-1}$. Maintenance: individualized dosing titrated to INR.	Target INR range, 2–3. Mechanical mitral valves, 2.5–3.5.	INR daily until therapeutic, then decreased frequency when stable with minimum monthly testing. Test INR with illness, medication, or diet change.	Hemorrhage, 0.5% per patient-y. Increases with INR >8. Prosthetic valves 0.4% per patient-y.[29,30] Tracheal calcification, hair loss, decreased bone mineral density.[31,32]
Antiplatelet therapy (Figure 3)							
Aspirin[21,33] Inhibition of COX-1 and COX-2 activity	Oral t½ is dose dependent. 15–20 min for parent drug. Irreversible platelet inhibition. Is commonly recommended to discontinue ASA 7 d before surgery to allow full platelet regeneration.	Thromboprophylaxis of stents. Shunts: Blalock-Taussig, Norwood, Glenn, bicaval-pulmonary Fontan. Valves: Bioprosthetic, mechanical, in addition to OAT for patients at high risk of thrombosis.	Ibuprofen within 4 h of ASA dose. Bleeding. Varicella, fever resulting from risk for Reyes syndrome. Lack of pharmacokinetic/pharmacodynamic data.	Low dose is commonly 1-5 $mg \cdot kg^{-1} \cdot d^{-1}$. Maximum 81–325 $mg \cdot d^{-1}$.[21,33]	None studied	There are no studies that link outcome to measuring aspirin effect.	Bruising, confusion, vertigo, nausea, vomiting, tinnitus, abdominal pain, cramping, burning, fatigue, bleeding
		Kawasaki disease		80–100 $mg \cdot kg^{-1} \cdot d^{-1}$ during acute phase of illness, then 3-5 $mg \cdot kg^{-1} \cdot d^{-1}$ for additional 6–8 wk[34–36]			
Clopidogrel[37,38] Inhibition of ADP-induced platelet aggregation. No effects on arachidonic acid metabolism.	t½=7 h. Renal clearance. Hepatic metabolism.	Failure of antiplatelet therapy in select circumstances. Antiplatelet therapy in varicella or 1 wk before and 6 wk after varicella vaccine in place of ASA.	Paucity of pharmacokinetic/pharmacodynamic data	0.2-1 $mg \cdot kg^{-1} \cdot d^{-1}$.[37,38] Completed study in CHD and shunts (www.clinicaltrials.gov, NCT00396877).	None studied	There are no studies that link outcome to measuring clopidogrel effect.	Fatigue, vertigo, stomach upset or pain, bruising, bleeding, diarrhea
Dipyridamole[39,40] Adenosine reuptake inhibitor 2 Mechanisms have been proposed for increase in cAMP, a platelet inhibitor.	t½=10 h		Lack of pharmacokinetic/pharmacodynamic data	1-5 $mg \cdot kg^{-1} \cdot d^{-1}$ [39,40]	None studied	There are no studies that link outcome to measuring dipyridamole effect.	Chest pain, angina pectoris, headache, vertigo, ECG abnormalities
		Ventricular assist devices		4 $mg \cdot kg^{-1} \cdot d^{-1}$ divided 4 times a day. Maximum 15 $mg \cdot kg^{-1} \cdot d^{-1}$.			

(Continued)

Table 3. Continued

Anticoagulant and Mechanism of Action	Properties	Indications	Contraindications	Dose	Target Range	Monitoring	Side Effects
Abciximab[41] Glycoprotein IIb-IIIa inhibitor	Monoclonal antibody; prevents binding of fibrinogen and vWF, inhibiting platelet aggregation. t½=10–30 min. Renal excretion.	Kawasaki disease in addition to standard therapy	Lack of pharmacokinetic/pharmacodynamic data	0.25-mg/kg bolus, then 0.125 $\mu g \cdot kg^{-1} \cdot min^{-1}$ every 12 h[41]	None studied	There are no studies that link outcome to measuring abciximab effect.	Bleeding, hypotension, nausea, vomiting, vertigo, irritation at injection site
Direct thrombin (IIa) inhibitors							
Argatroban[43] Completed trial in children (www.clinicaltrials.gov, NCT00039858)	Hepatic clearance. t½=40–50 min. Not reversible.	HIT[43]	Paucity of pharmacokinetic/pharmacodynamic data	Age-dependent dosing: 6 mo–6 y=0.5–1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. ≥6–16 y=1–2 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Continuous infusion (maximum 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$).[42,43]	1.5–3 times baseline PTT (not to exceed 100 s). ACT 180–220 or 250–300 s.[44]	PTT 2 h after start of infusion and each dose change	Hemorrhage 6%–15% with therapeutic PTT[46]
		ECMO[42,44]		ECMO 50 μg/kg per 750 mL circuit prime, then 100 μg/kg per bolus if not already anticoagulated, then 1-2 $\mu g \cdot kg^{-1} \cdot min^{-1}$[44]			
		Cardiac catheterization/coil[45]		150 μg/kg.[45]			
Bivalirudin[43,47]	Enzymatic 80% and renal 20% clearance. t½=25 min. Reversible.	Treatment[43,47]	Lack of pharmacokinetic/pharmacodynamic data.	<6 mo=0.125-mg/kg IV bolus, then 1.25 $mg \cdot kg^{-1} \cdot h^{-1}$.[43,47] No data available for children >6 mo.	ACT 2.5 times baseline. PTT 1.5–2.5 times baseline. ACT 400–500 s.	Data on monitoring in children are lacking. Suggested from adult data: ACT 5 min after IV bolus. PTT 2 h after start of therapy and each dose change. Elevates INR.	2.4% hemorrhage[43]
		CPB[47]		50 mg to circuit, then 1-mg/kg IV bolus, then 2.5 $mg \cdot kg^{-1} \cdot h^{-1}$.[47]			
Lepirudin[48] (R-hirudin)	Renal clearance. t½=80 min. Not reversible.	HIT	Lack of pharmacokinetic/pharmacodynamic data.	0.2 mg/kg (maximum 44 mg/h) IV bolus, then 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$ (maximum 16.5 mg/h).	PTT 1.5–2 times baseline. Optimal PTT <65 s.	Data on monitoring in children are lacking. Suggested from adult data: PTT 4 h after start of therapy and each dose change.	Not reported in children. In adults, 17% hemorrhage; 30% develop anti-lepirudin antibodies.
Heparinoid Danaparoid[21,48,49] Inhibition of factor Xa (not available in the US)	Renal clearance. t½=24 h	HIT treatment	Lack of pharmacokinetic/pharmacodynamic data.	30-U/kg IV bolus, then 1.2–2 $U \cdot kg^{-1} \cdot h^{-1}$[21,48]	Anti–factor Xa 0.4–0.8 U/mL[48,50]	Data on monitoring in children are lacking. Suggested from adult data: 4–6 after bolus or each dose change.	Hemorrhage

(Continued)

Table 3. Continued

Anticoagulant and Mechanism of Action	Properties	Indications	Contraindications	Dose	Target Range	Monitoring	Side Effects
Thrombolytic therapy							
Alteplase/ activase.[21,49] Converts plasminogen into plasmin. Plasmin degrades fibrin (cross-linked) and fibrinogen.	t½=4 min. Reversible with Amicar. FFP 10–20 mL/kg before alteplase infusion as a plasminogen source. Keep fibrinogen >100 and platelets >50 000. Note: continue heparin during alteplase administration, ie, 10 μg·kg^{-1}·h^{-1}. If continuing heparin after alteplase, increase to age-appropriate dose, ie, ≥12 mo=20 μg·kg^{-1}·h^{-1}. <12 mo=28 μg·kg^{-1}·h^{-1}.	Arterial thrombosis. Pulmonary embolism (massive or unresponsive to anticoagulation therapy). DVT when there is a risk for loss of life, organ, or limb. MI (ie, coronary thrombosis in Kawasaki disease).	Active bleeding, significant potential for local bleeding surgery <10 d postoperatively for general surgery and <3 wk for neurosurgery, hypertension, arteriovenous malformations, and recent severe trauma.	For selected arterial thrombosis, pulmonary embolism, and DVT, the following have been used: Systemic: (1) 0.5 mg·kg^{-1}·h^{-1} IV for 6 h.[51] (2) Continuous infusion of lower dose 0.1–0.3 mg·kg^{-1}·h^{-1} for 12–24 h (reported in prosthetic valve thrombolysis).[51a] (3) Low dose 0.03–0.06 mg·kg^{-1}·h^{-1} (maximum 2 mg/h) for 12–48 h in selected situations.[52,53] Catheter directed: 2 dosing regimens reported: 0.025 mg·kg^{-1}·h^{-1} [53a] or 0.5–2 mg/h every 12–24 h.[54,55] Pharmacomechanical thrombolysis has also been reported in children.[56] For coronary thrombosis, data in children are lacking. Strategies that have been used include (1) 0.1–0.6 (commonly 0.5) mg·kg^{-1}·h^{-1} IV for 6 h.[51] (2) as per adult guidelines, 0.2 mg/kg IV (maximum 15 mg), then 0.75 mg/kg over 30 min (maximum 50 mg) followed by 0.5 mg/kg over 60 min (maximum 35 mg), maximum total dose 100 mg.[57] (3) low-dose tPA combined with abciximab (Kawasaki disease section in the text). In stroke, see text.		Reassess thrombus with imaging at the completion of the infusion. Retreatment may be indicated once hematologic parameters are acceptable.	Hemorrhage requiring transfusion 20-30% Minor bleeding 54-68%.[58–60]

ACT indicates activated clotting time; ADP, Adenosine diphosphate; ASA, acetylsalicylic acid; cAMP , cyclic adenosine monophosphate; CHD, congestive heart disease; COX, cyclooxygenase; CPB, cardiopulmonary bypass; DVT, deep venous thrombosis; ECMO, extracorporeal membranous oxygenation; FFP, fresh-frozen plasma; HIT, heparin-induced thrombocytopenia; INR, international normalized ratio; IV, intravenous; LMWH, low-molecular-weight heparin; MI, myocardial infarction; OAT, oral anticoagulant therapy; PCI, percutaneous continuous infusion; PTT, partial thromboplastin time; t½, half-life; tPA, tissue-type plasminogen activator; UFH, unfractionated heparin; VKA, vitamin K antagonist; and vWF, von Willebrand factor.

- With 0.4–1.0 OD units, the probability of platelet-activating antibodies being present (and hence a diagnosis of HIT being tenable), was very low (≈5%).

This quantitative interpretation of OD values in the EIA as a way to predict the likelihood of a positive SRA may assist physicians in judging the appropriate pre-SRA test probability of a patient having HIT, once the result of the EIA is known. Use of this conceptual framework could help reduce the potential for HIT overdiagnosis and avoid excess use of pharmacological therapies specifically reserved for HIT for which scant data exist in children. In the presence of unexplained thrombocytopenia in a child with repeated heparin exposures, HIT should be considered and the local expert on HIT consulted for management (section 3.1, Heparin-Induced Thrombocytopenia, and section 10.1.4, HIT and Alternatives to Heparin for Anticoagulation for CPB in Children With CHD).

If HIT is the probable diagnosis in children or adults, all heparin must be avoided, including heparin line flushes and low-dose heparin infusions in lines (venous and arterial) or in total parenteral nutrition therapy. If anticoagulation is required, argatroban and lepirudin have been approved in adults in the United States. Bivalirudin has also been used in adults and children but is not approved for use in HIT (Table 3).

3.2. Measures of Anticoagulant Effect

3.2.1. Activated PTT

The PTT is used to measure the effect of different anticoagulants on the coagulation system, including direct thrombin inhibitors and unfractionated heparin (UFH; Table 3).

3.2.2. Anti-FXa Levels

Anti-FXa levels (heparin levels) are used to measure the effect of UFH and LMWH on coagulation. Recommended heparin levels in children requiring therapy have been extrapolated from adult studies. There are no pediatric studies establishing the safety and efficacy of any laboratory test to measure the effects of heparin. Studies have demonstrated poor correlation between PTTs and heparin levels in children.[68] In infants, the PTT does not correspond to anti-FXa levels because of developmental hemostasis. In children or adults with high FVIII or fibrinogen levels (nonspecific acute-phase reactants) or in the presence of an antiphospholipid antibody or nonspecific inhibitor, the PTT is not a good reflection of heparin effect.

LMWH is a short-chain heparin that does not influence the PTT; therefore, the anti-FXa level is the only measure of the effect of LMWH therapy.

3.2.3. International Normalized Ratio

A PT converted to an INR is used to monitor the anticoagulant effect of the vitamin K antagonist (VKA) warfarin. Target therapeutic INRs for specific indications have been extrapolated from adult guidelines.[21,69,70]

3.2.4. Activated Clotting Time

The ACT is a POC test that measures the time (in seconds) required for whole blood to clot when an activating agent is added. This test is used to measure hemostasis during CPB and ECMO. Studies demonstrate the poor correlation of ACT with the PTT or anti-FXa level in patients receiving UFH during CPB or ECMO. Although many healthcare professionals use the ACT to measure anticoagulation, the ACT does not solely reflect the effect of heparin but also reflects recent infusion of blood products (section 2.6.2.1).

3.2.5. Thromboelastography

Measurement of hemostasis in the presence of UFH can be performed with thromboelastography. A variation of TEG, TEG with platelet mapping (TEG-PM, Haemanetics, Braintree, MA), measures platelet inhibition in the presence of antiplatelet agents such as aspirin, dipyridamole, and clopidogrel. There is a paucity of data, however, on the validity, accuracy, and application of TEG-PM in children (section 2.6.2.2).

3.3. Long-term Management of Children on Anticoagulation Medications

3.3.1. General Principles

Many children with CHD require long-term thromboprophylaxis to decrease the morbidity and mortality secondary to thromboembolic phenomenon. The sequelae of venous thromboembolism are life-threatening and can include organ failure, pulmonary embolism (PE), embolic stroke, and sepsis. An aspect of surgical palliation for many children with CHD is the placement of systemic to pulmonary artery shunts, which vary in their diameter, flow characteristics, and composition. Shunt thrombosis in infants has been reported to be 8% to 12% in different series and is usually life-threatening unless quickly resolved.[71,72] In addition, the placement of mechanical heart valves in children requires long-term oral anticoagulation equaling considerable patient-years.[73–75] Likewise, many patients with single-ventricle palliation or a history of vascular thrombosis require long-term oral anticoagulation. The advances in medical and cardiosurgical techniques have led to improved survival in children with CHD; thus, the overall use of anticoagulation has increased.

The level of anticoagulation achieved in children requiring oral anticoagulant therapy (warfarin) must be closely monitored to avoid both thrombogenic and hemorrhagic complications. Warfarin functions as an anticoagulant by reducing the functional plasma concentration of vitamin K–dependent factors (FII, FVII, FIX, FX) and has a narrow therapeutic index that necessitates frequent monitoring of the PT, expressed as an INR. The effectiveness and safety of warfarin are maximized by the maintenance of a target INR range, below which effectiveness is lost and above which the bleeding risk is unacceptably high.[69]

3.3.1.1. Special Considerations With Warfarin Therapy in Children

Monitoring warfarin in children is difficult[21,76] because they often have the following:

- Complex underlying health problems, which result in frequent reversal for invasive interventions, multiple medication changes, and adjustments during routine pediatric and lesion-specific illnesses[76]

- Multiple simultaneous medications that interfere with warfarin metabolism
- Inconsistent nutritional intake and normal age-appropriate fluctuations in daily intake
- Increased susceptibility to the common cold and flu as part of normal growth and development
- Requirement for more frequent INR monitoring than their adult counterparts because of the complexity of their underlying medical conditions and fluctuations in warfarin requirements as outlined above[21,77–79]
- Poor venous access that interferes with the ease of blood draws for a medication that has a narrow therapeutic index
- Anxiety and needle phobias

Children with CHD present increased challenges because lifelong anticoagulation represents many more years on drug than an adult who started therapy much later in life. In addition, there are data to strongly suggest that long-term warfarin therapy in children may be associated with osteoporosis.[31] Streif et al[76] evaluated warfarin use among 319 infants and children, 52% with CHD, and found that children were within their therapeutic range only 50% of the time. However, with standardized education programs on warfarin therapy, the time in therapeutic range can be improved.[80,81]

3.3.1.2. Special Consideration With Warfarin Therapy in Neonates and Infants

Warfarin therapy in neonates and infants is associated with even greater challenges because of physiologically decreased plasma levels of vitamin K–dependent factors in newborns, increased variability in nutritional intake, higher weight-based warfarin dose requirements, and less time in the therapeutic range.[76] In general, warfarin therapy is not recommended in infants <1 year of age unless the infant requires anticoagulation of a mechanical valve.[21]

For infants requiring warfarin therapy, daily monitoring of their nutritional intake is critical. Nutritional concerns are addressed in section 3.3.3, Food and Drug Interactions.

3.3.1.3. Special Consideration With Warfarin Therapy in Children With Fontan Circulation

Thromboembolic events within Fontan circuits are a major cause of early morbidity and mortality, with reported incidences of thrombosis and stroke from 3% to 16% and from 3% to 19%, respectively.[82,83] Although no-well designed studies have evaluated the safety and efficacy of warfarin use in children after the Fontan procedure, it may be prescribed for thromboprophylaxis with a target INR of 2 to 3[21] (section 7.2, Incidence, Treatment, and Prevention of Stroke in Adults With CHD, and section 9.2, Long-term Anticoagulation in the Patient With a Palliated Single Ventricle). Importantly, children with Fontan procedures require less warfarin than both children with other CHDs and children without CHD. The lower warfarin dose requirement for children after the Fontan procedure is independent of age. Warfarin is commonly loaded at 0.1 mg/kg daily with the final dose titrated to INR levels. (The common loading dose for children without Fontan circulation is 0.2 mg/kg daily; Table 3.)

3.3.2. POC INR Monitoring

Use of the POC INR device provides a way to simplify and improve oral anticoagulation management in children.[84–86] Several devices are currently approved for use in children. The CoaguChek (Roche Diagnostics, Basil, Switzerland) has been the device most evaluated in children for INR testing either in a healthcare facility (hospital or clinic) or in the home with INR results phoned to an anticoagulation clinic or physician.[77,87–92] The available POC INR devices vary in their ease of use, blood sample volume required, technique of application of blood sample to meter, need for external quality control testing, refrigeration of test strips, and device portability.

In general, the POC INR device requires a minimal blood volume, produces an INR result within 1 minute, enables timely drug dose adjustment, and allows prompt attention to INR values outside the therapeutic range. An INR measurement can be performed at the patient's convenience and eliminates the need for the patient to visit a laboratory. This convenience facilitates more frequent INR testing. Furthermore, in randomized trials comparing POC with laboratory-based INR monitoring, POC-based monitoring has been shown to improve the quality of anticoagulation control (time in the therapeutic range) and to reduce thromboembolic and hemorrhagic events.[85]

POC INR devices measure a thromboplastin-mediated clotting time from a finger-stick capillary whole-blood sample. Although having unique characteristics, POC INR devices have a similar mode of action. Each device uses coded test strips (cartridges). The test strip is inserted into the device and warmed to 37°C. A drop of capillary whole blood is placed onto the test strip and is drawn into the machine by capillary action. The capillary blood sample combines with an activator of the coagulation system (thromboplastin) and continues to flow through the device until clot formation is detected. The time elapsed from the whole blood and thromboplastin mixing to detection of clot formation equals the PT, which is converted to an INR. Most POC devices report the result as either the PT or INR.[93]

Numerous studies have assessed the accuracy and precision of POC INR devices in children. In general, when comparisons are made between laboratory-based and POC-based INR measurements, the differences between values are <15%. Such a difference is similar to the difference found when the same sample is tested in different laboratories using different instruments or different thromboplastin reagents.[94]

Although there may be numeric differences in INR results between POC- and laboratory-based INR measurements (eg, INR of 2.2 and 2.9), such a numeric difference may not be clinically important. One way to assess whether the difference in INR results is clinically important is based on whether the difference in INR results in different dosing of warfarin. For example, INR measurements of 2.2 and 2.9 with POC- and laboratory-based methods, respectively, would not typically lead to a change in warfarin dose. On the other hand, INR measurements of 2.9 and 3.6 (same numeric difference) may result in a dose reduction in the latter case. Given these considerations, there are several ways to determine whether the INR results are clinically

comparable (ie, not leading to different warfarin dosing) or clinically different (ie, leading to different warfarin dosing). Thus, INRs from a POC device and laboratory may be considered comparable if they satisfy the following criteria for agreement[95,96]:

- Both INRs are within the targeted INR range (eg, INR of 2.2 and 2.9) for patients receiving warfarin with a targeted INR range of 2.0 to 3.0.
- Both INRs are within 0.5 units, regardless if 1 or both are within the targeted INR range (eg, INR of 2.9 and 3.4) for patients receiving warfarin with a targeted INR range of 2.0 to 3.0.

Before routine measurement of INRs with a POC INR meter can be recommended for clinical use, we suggest the following considerations be addressed to ensure proper use of the INR device and optimal patient safety:

- Patients selected for POC INR use must demonstrate good adherence to treatment.
- At least 2 comparisons between POC-based and laboratory-based INR measurements should be done to evaluate the accuracy of the POC INR device in a given patient. The above-mentioned criteria for agreement can be used to assess accuracy in INR measurements of the POC device.
- Patients and personnel in whom INR measurements with a POC INR device are planned should participate in a standardized educational program to ensure proficiency in the testing technique. A standardized validated educational tool, available online at www.ThrombosisCanada.ca. See KIDCLOT XS © POC. This tool describes the CoaguChek XS meter.
- The patient or family should have a relationship with an anticoagulation clinic or doctor familiar with POC INR meter testing.

Ongoing quality assurance (laboratory-meter comparisons) should be performed every 6 to 12 months or after test strips (cartridges) are changed to reassess device accuracy and the integrity of the test strips.

Recommendations for the POC Monitoring in Children on Warfarin

1. **INR testing should occur in infants and children at a minimum of every 4 weeks once a stable dose of warfarin has been achieved. More frequent INR testing is recommended in infants and children receiving warfarin with any change in diet or medication or when an illness occurs (*Class I; Level of Evidence B*).**
2. **POC INR monitoring for children should be accompanied by a patient education program that includes guidelines on warfarin management (*Class I; Level of Evidence C*).**
3. **In children, at least 2 comparisons between POC-based and laboratory-based INR measurements should be done to evaluate the accuracy of the POC INR device in a given patient. The above-mentioned criteria for agreement can be used to assess accuracy in INR measurements of the POC device (*Class I; Level of Evidence B*).**
4. **POC INR monitoring of warfarin therapy is reasonable in children (*Class IIa; Level of Evidence B*).**

3.3.3. Food and Drug Interactions

It is a challenge to consistently achieve therapeutic INR levels in children who are on warfarin therapy because the ability to do so is affected by their dietary intake of vitamin K and by the possibility of numerous drug interactions. A child's oral intake of vitamin K varies as a result of the type and amount of fluids and solid foods ingested as the child goes through the various developmental stages.

Fluctuations in the level of vitamin K are known to affect the body's response to warfarin therapy. An increase in one's dietary intake of vitamin K may result in a subtherapeutic INR, thus increasing the risk for a thromboembolic event. There is virtually no vitamin K in breast milk (0.3 μg/100 kcal), but commercial infant formulas contain vitamin K (8–16 μg/100 kcal), so attention must be given to trends such as an increase in the volume of formula consumed per day or if there is a switch from breastfeeding to a commercial formula. For the breastfed infant, the use of oral vitamin supplements can be considered by the healthcare provider.

The most common dietary sources of vitamin K are dark green vegetables and oils. Although children in general do not normally consume a large amount of dark green vegetables, it is not uncommon to see them consume vitamin K food sources such as broccoli, soybeans, pickles, lettuce, and salad dressing. It is best to educate the caregiver about the foods that are high in vitamin K and to look into the family's dietary habits. A mutual plan can then be developed that will involve minimal changes on the family's part, including consistency in vitamin K intake[97] from week to week, and limiting high sources of vitamin K foods if necessary.[98]

In regard to cooking oils, there are 141 μg vitamin K/100 g of canola oil, whereas corn oil contains only 2.91 μg. Processed foods and fast foods can be significant sources of vitamin K because of the oils used to produce them.[99] Soybean oil used in fast food restaurants may contain as much as 193 μg vitamin K/100 g of oil. According to the US Department of Agriculture, a cup of raw spinach contains 144.9 μg vitamin K, whereas a cup of frozen spinach that has been cooked has 1027.3 μg vitamin K. The fat substitute Olestra is found in many snack foods. Olestra potato chips were cited in 1 source to contain 347 μg vitamin K/100 g chips.[99] From this information, families can be taught to change their cooking oil, to use fresh instead of frozen green vegetables, to read snack food labels, and to cut down on the amount of fast food eaten each week.

Children with CHD are a population in which enteral nutrition may be needed to supplement caloric intake because of their increased energy expenditure. Pediatric oral supplements may vary in vitamin K content from having no vitamin K per 8 oz as in Boost Breeze to 12 μg/8 oz in Nutren Jr and 30 μg/8 oz in Boost. One study postulated that the protein of some enteral feeding products appears to bind with warfarin, decreasing its bioavailability and resulting in subtherapeutic anticoagulation levels.[100] The use of enteral nutrition should be evaluated

carefully before a decision is made to incorporate it into a child's medical regimen.

The number of drugs that have been reported in the literature to interact with warfarin continues to increase. Holbrook et al[101] conducted a review of the literature from October 1993 to March 2004 that looked at publications involving warfarin and drug interactions. Drugs that were associated with the occurrence of thrombosis were put under the category of highly probable for causing warfarin inhibition. These drugs are also used in the pediatric population. They include carbamazepine, cholestyramine, griseofulvin, mercaptopurine, nafcillin, phenobarbital, ribavirin, rifampin, sucralfate, and Trazodone. The reference also included lists of drugs that were under the categories of probable and possible for causing warfarin inhibition. Rifampin was noted in another article to stimulate the enzyme CYP 2C9, resulting in an inhibitory effect on warfarin.[102]

The majority of the studies that have been done on drug interactions with warfarin are unfortunately single case reports and are not easily transferable to clinical practice. The child with CHD is often on multiple medications and varying dosages, which makes warfarin management difficult.[103] These medications may be related to the heart condition itself or to contracted illnesses that may sporadically occur. Families need to be taught the importance of reporting new illnesses and any newly prescribed or over-the-counter medications to the person who is managing the warfarin dosing.

To prevent thromboembolic complications in children who are on warfarin therapy, recommendations should include providing a standardized anticoagulation educational program for the child/family and the logistics for reaching a designated member of the anticoagulation team.[104] It should also include checking the PT-INR within a few days if there is a significant dietary change, if any new drug is added, or if an existing drug is discontinued[105] because the child's INR level can quickly fall out of the therapeutic range, placing the child at risk for a thromboembolic event.

Recommendations for Chronic Warfarin Management in Children

1. **Anticoagulation education should be provided for the infant or child who has been started on warfarin, including the indication for the child being placed on warfarin, the risks associated with the anticoagulation therapy, and the importance of PT-INR monitoring (*Class I; Level of Evidence B*).**
2. **Anticoagulation education should be provided for the infant or child who has been started on warfarin, including information on nutritional sources that are high in vitamin K, common drugs that inhibit the effect of warfarin, and the importance of notifying the healthcare provider(s) in charge of warfarin dosing when there is an intercurrent illness, a significant dietary change, initiation of a new drug, or discontinuation of or change in the dose of an existing drug (*Class I; Level of Evidence B*).**
3. **In infants and children, the PT-INR should be checked at the time of or within a few days of an intercurrent illness, a significant dietary change by history, or a change in the patient's routine medication regimen that may have a significant impact on the effect of warfarin (*Class I; Level of Evidence B*).**

3.3.4. Relationship of Genetic Polymorphisms and Warfarin Metabolism

On August 16, 2007, the US Food and Drug Administration (FDA) approved updated labeling for warfarin to state that "people's genetic makeup may influence how they respond to the drug." The news release stated that the labeling changes highlight the "opportunity for healthcare providers to use genetic tests to improve their initial estimates of what is a reasonable warfarin dose for individual patients. Testing may help optimize the use of warfarin and lower the risk of bleeding complications from the drug." In addition, the FDA funded research with the goal of developing genetically based instructions for warfarin dosing.[106,107] Although drug-related risks can include life-threatening bleeding from excess anticoagulation or can allow clot formation from inadequate anticoagulation, potentially resulting in a stroke, an intracardiac clot, or a malfunctioning prosthetic valve,[108,109] the risk in children has not been studied extensively.[110]

On September 17, 2007, the FDA approved the Nanosphere Verigene Warfarin Metabolism Nucleic Acid Test capable of detecting variations in the metabolism of 2 genes, *CYP2C9* and *VKORC1*. The frequency of these abnormalities varies among individuals and among people of different races and nationalities (Figure 5).[111–114]

Warfarin is a VKA. It is completely absorbed orally, and 98% to 99% is bound to plasma proteins.[69,116,117] It exists as 2 optically active mirror-image isomers, the R and S enantiomers. The S enantiomer is 2 to 5 times more active than the R enantiomer. The S isomer is metabolized in the liver cytochrome P450 complex (CYP2C9), converted to 6- and 7-hydroxywarfarin, and excreted in the bile. R warfarin is metabolized in the liver by CYP1A1, CYP1A2, and CYP3A4 and is excreted in the urine.

Warfarin limits the availability of the reduced form of vitamin K that is formed by the cyclical interconversion of vitamin K (reduced hydroquinone form, vitamin KH_2) and vitamin K epoxide, K>O.[118,119] It alters the function of the vitamin K epoxide reductase enzyme VKORC1. This enzyme controls the regeneration of vitamin K from vitamin K epoxide (vitamin K>O). When the vitamin K cycle is so altered, the reduced vitamin K cofactor needed for γ-glutamyl carboxylase, an enzyme active in the posttranslational γ-carboxylation of factor proteins, is affected. As a consequence, clotting factors II (prothrombin), Vll, lX, and X do not function normally. Proteins C, S, and Z are affected to a lesser extent[116] (Figure 6).

The gene for the enzyme VKORC1 is on the short arm of chromosome 16.[115,120,121] Both the warfarin S and R enantiomers block VKORC1 activity. Two VKORC1 polymorphisms affect warfarin dosing: a G→A transition in the VKORC1 promoter polymorphism at −1639 G→A and a C→T transition found in intron 1 at 1173 C→T.[122]

The *CPY* gene maps to chromosome 10q24.2.[115] Polymorphisms (variant alleles) are described that commonly

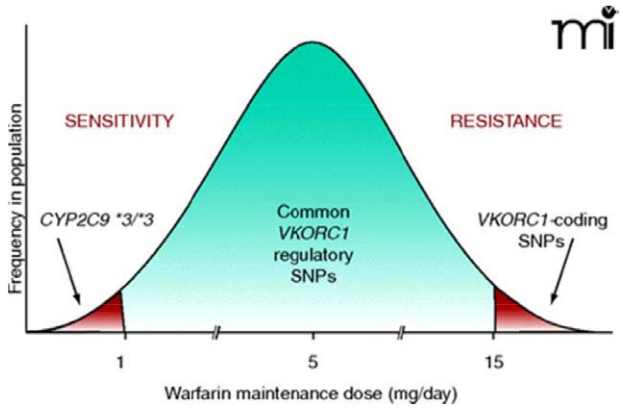

Figure 5. Genetic mutations affecting warfarin sensitivity and resistance. Genetic liabilities for warfarin sensitivity and resistance. Coding-region mutations in the *VKORC1* gene can cause warfarin resistance that necessitates daily doses in excess of 15 mg/d. Conversely, mutations in the *CYP2C9* gene, especially homozygosity for the *CYP2C9*3* allele, can result in sensitivity to the drug such that doses less than 1 mg/d are sufficient to achieve therapeutic anticoagulation. Non-coding region polymorphisms in *VKORC1* also influence warfarin dose across the "normal" dosing range. Adapted from Rettie and Tai.[115]

alter the metabolism of warfarin. CYP2C9*1 is the wild type, or normal type. CYP2C9*2 and CYP2C9*3 are alleles that commonly affect warfarin metabolism. Patients with the *2 and*3 variant alleles of *CYP2C9* require a lower dose of warfarin than the patients with the wild type. There is a tendency for these patients to have bleeding, particularly during the period when the medication is started.[123] The frequency of these variant alleles is ≈40% in white populations.[115] The frequency is less, 1% to 3%, in patients of African descent. East Asian patients do not exhibit the CYP2C9*2 allele. The CYP2C9*3 allele is present in only 1% to 3% of Chinese, Korean, and Japanese patients.[124] Clinical studies of testing for these genes in patients who are taking warfarin have been reported.[125–129] The AEI-Brookings Joint Center for regulatory studies produced a working paper[130] estimating that the healthcare benefits and cost savings to adult Americans resulting from personalized genetic warfarin dosing decisions could avoid 85 000 serious bleeding events and 17 000 strokes annually. A recent Letter to the Editor commented that these estimates were too optimistic and that the results of clinical trials are required to enable an accurate economic forecast to be made.[131] A cost-effectiveness study in pharmacogenetic warfarin dose selection for patients with nonvalvular atrial fibrillation (AF) found that the benefit was seen only in those patients who were at high risk for hemorrhage.[132]

A randomized study of patients initiating warfarin anticoagulation[133] showed the benefit of a combined clinical and pharmacogenetic algorithm but failed to meet the study outcome of altering out-of-range INR values. There is no agreement that clinic-based testing for warfarin genetic polymorphisms should be implemented before randomized, controlled studies demonstrate its utility.[69,131,134]

The advent of genetic testing on individuals taking warfarin and other medications may have an effect on public policy, particularly concerning access to laboratory testing, quality of laboratory results, patient privacy, and physician comfort in understanding and effectively using the results of pharmaceutical testing.[135] Controlled studies are needed to clarify these issues. In the interim, it is left to the discretion of the prescribing physician to choose to test all patients initiating warfarin therapy or to reserve testing for patients who are difficult to manage.

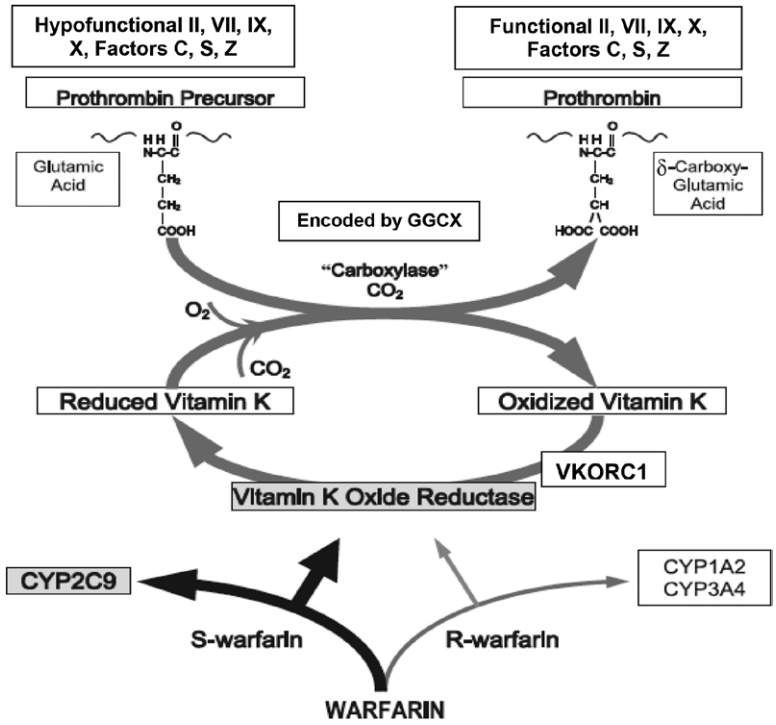

Figure 6. Warfarin, a vitamin K antagonist, exists as 2 optically active mirror-image isomers, the R and S, with the S enantiomer 2 to 5 times more active than the R. Warfarin limits the availability of the reduced form of vitamin K by altering the function of the vitamin K epoxide reductase enzyme VKORC1. This results in altered δ-carboxylation by δ-glutamylcarboxylase, GGCX, and decreased procoagulant activity of the vitamin K–dependent coagulation factors II (prothrombin), VII, IX, and X. Proteins C, S, and Z are affected to a lesser extent. Adapted from Ansell et al[69] with permission from Elsevier. Copyright © 2008, American College of Chest Physicians. Adapted from Yin and Miyata[119] with permission from Elsevier. Copyright © 2007, Elsevier. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

4. Propensity to Coagulopathy in CHD

4.1. Propensity to Coagulopathy in Children With Heart Disease

Children with cardiac disease often have disruptions in the balance of hemostasis, which paradoxically could result in bleeding, thrombosis, or both. Cyanotic CHD is more commonly reported to have known hemostatic abnormalities[136–142] compared with acyanotic CHD[143] and acquired heart disease (Kawasaki disease, cardiomyopathy).

Studies in children with CHD have reported abnormalities in the proteins listed below and abnormalities in hemostatic function, which can result in bleeding and/or thrombosis. In many children, <1 abnormality is present. The following abnormalities have been demonstrated:

- Coagulation proteins: II, V, VII, VIII, IX, and X, and fibrinogen: decreased; VIII: increased[136–143]
- Inhibitors of coagulation: proteins C and S and antithrombin: decreased[136–143]
- Fibrinolytic proteins: plasminogen: decreased[143]
- Prothrombotic genetic polymorphisms identified: factor V Leiden, prothrombin gene 20120, plasminogen G4/G4, methylene tetrahydrofolate reductase 677[144,145]

Abnormalities in hemostatic function include the following:

- Increased coagulation[146–151]
- Increased or decreased fibrinolysis[146,147,152]
- Increased or decreased platelet numbers and function[146,148,153,154]
- Other factors: endothelial vascular damage resulting from placement of a central line, CPB, ECMO

4.1.1. Abnormalities in Hemostatic Proteins in Children With CHD

Levels of coagulation proteins, fibrinolytic proteins, and inhibitors have been demonstrated to be abnormal in children with CHD (cyanotic and acyanotic) compared with age-matched control subjects.[136–143] Depending on the abnormality or abnormalities present, these children can be at risk for bleeding or thrombosis. The reason for the decreased production and delayed normalization of coagulation protein levels (anticoagulant and procoagulant factors) is unknown in cyanotic and acyanotic heart disease. In cyanotic heart disease, this abnormality is hypothesized to be a result of cyanosis, low cardiac output, or a genetic predisposition.[136] Hepatic synthetic ability does not appear to be abnormal.[136]

In children with acyanotic CHD, certain coagulation factors have been shown to be decreased in an age-dependent manner, making them similar to those measured in cyanotic CHD[143]:

- At0 to 3 months of age: decreased levels of protein C, antithrombin, FII, FV, FVII, FVIII, FIX, FX, and plasminogen[143]
- At 3 to 12 months of age: decreased levels of protein C, antithrombin, FII, FV, FVII, and FX[143]
- At 12 to 48 months of age: decreased levels of protein C, FII, FV, FVII, and FX[143]

However, in children with acyanotic CHD, normal age-appropriate levels are achieved by 5 years of age, which differs from children with cyanotic CHD.[136,143]

In children with cyanotic CHD, studies before 1998 reported decreased protein C, protein S, and FVII levels; however, these studies did not use age-appropriate normal values, which renders the study results invalid.[138,139] Recent prospective studies using homogeneous patient cohorts demonstrate decreased protein C, antithrombin III (AT III), FII, FV, FVII, FX, and plasminogen before Fontan surgery and increased FVIII and decreased protein C after Fontan surgery.[136,140–142,146] Increased FVIII levels have been demonstrated to be associated with an increased risk for thrombosis.[15]

Nowak-Gottl et al[144] reported 44 neonates and infants with increased levels of plasminogen activator inhibitor-1, indicating that fibrinolysis may be decreased in some children with CHD.

Abnormalities in the protein structure of factor V Leiden, the prothrombin gene 20210, and methylene tetrahydrofolate reductase 677 (hyperhomocystinemia) have been described in children with heart disease, which may predispose them to an increased risk for thrombosis.[144,145]

4.1.2. Abnormalities in Hemostatic Function in Children With CHD

4.1.2.1. Risk of Thrombosis

Historically, alterations in blood flow, blood composition, and vessel wall integrity were first recognized as the most important elements involved in thrombus formation by Rudolph Virchow. This triad is known as the Virchow triad.[155] Abnormalities in each dimension of the Virchow triad (blood flow, blood composition, and vessel wall integrity) have been reported in children with heart disease.

4.1.2.2. Abnormalities in Blood Flow

Blood consists of plasma and a suspension of red blood cells and platelets. Blood flow is indirectly proportional to resistance; that is, as resistance increases, blood flow decreases. Resistance is typically affected by the diameter of vessel, with a lesser amount of influence from blood viscosity and vessel length. In healthy vessels, the flow is laminar (fluid flows in parallel layers with no disruption between the layers); however, in diseased, stenotic vessels, the flow is turbulent (chaotic resulting in eddies of flow). In children with CHD, the pulmonary vascular bed is the foremost source of resistance.

Vessel diameter is the most important determinant of flow. Changes in vessel diameter occur with physiological contraction and relaxation of the vascular smooth muscle. Alterations in vessel diameter may be congenital or acquired. Acquired alterations may be secondary to central line placement (either arterial or venous), the presence of atheromatous plaque, or constructed cardiac shunts (eg, the Blalock Taussig shunt), all of which result in decreased flow. Within small vessels or shunts, red blood cells interact as a result of low shear rates, resulting in increased blood viscosity. In addition, alterations in blood flow may occur secondary to nonpulsatile flow (such as after bidirectional cavopulmonary anastomosis or Fontan) or vessel or chamber dilatation (such as with

dilated cardiomyopathy). As a result, children with CHD with extreme alterations in blood flow (stenotic or static) may be at increased risk of thrombosis.

Children with cyanotic CHD may develop hyperviscosity and blood stasis over time. DIC has been described to occur as a result of hyperviscosity and blood stasis (section 4.1.3.1, Polycythemia and Hyperviscosity), resulting in widespread deposition of fibrin and platelets and activation of coagulation. Increased levels of a protein indicating the activation of coagulation, F1.2, have been demonstrated in children with cyanotic CHD.[146,147]

Thrombosis may occur with either altered blood flow or hyperviscosity if the balance of hemostasis is shifted in the direction of coagulation.

4.1.2.3. Abnormalities in Blood Composition

Levels of hemostatic proteins may alter the balance of hemostasis and result in thrombosis (section 4.1.1, Abnormalities in Hemostatic Proteins in Children With CHD).

Microparticles, a sensitive marker of platelet activation, play an important role in hypercoagulable scenarios such as HIT. Both decreased platelet count and increased levels of platelet microparticles have been demonstrated in cyanotic CHD, with levels proportional to the hematocrit.[148]

4.1.2.4. Abnormalities in Vessel Wall Integrity

In cyanotic CHD, hypoxemia is thought to activate neutrophils, which release vasoactive and chemotactic substances, causing endothelial injury and subsequent activation of platelets and coagulation.[156]

Kawasaki disease, a vasculitic process of unknown origin, affects small to medium arteries, in particular the coronary arteries, resulting in aneurysm development. Some data suggest that activation of coagulation occurs as a result of vessel wall damage, as indicated by decreased antithrombin levels and depletion of the proteins of the fibrinolytic system.[157] However, the authors did not compare values with age-related normal values.

The majority of children with heart disease necessitating surgery require the placement of a central venous or arterial line for supportive care. Thrombosis has been demonstrated to be associated with the placement of a central line.[158] At least 20% of children with heart disease and central venous or arterial lines have been demonstrated to develop line-related thrombosis,[159,160] hypothesized to occur as a result of damage to the endothelium caused by line placement and infusate administration.[158]

Although not studied in children, adults with cardiomyopathy have been demonstrated to have increased markers of coagulation activation, including fibrinopeptide A (a protein produced during ongoing coagulation when fibrinogen is changed to fibrin) and thrombin-antithrombin complexes (complexes produced during ongoing coagulation when antithrombin neutralizes thrombin).[161]

4.1.3. Risk of Hemorrhage

Bleeding can occur as a result of decreased levels of coagulation proteins (section 4.1.1, Abnormalities in Hemostatic Proteins in Children With CHD), increased fibrinolysis, or decreased platelet number or function.

Children with cyanotic CHD are known to be at risk for bleeding, with different abnormalities and origins hypothesized, including polycythemia, hyperviscosity, thrombocytopenia, platelet function abnormalities, DIC, and abnormal fibrinolysis.

4.1.3.1. Polycythemia and Hyperviscosity

In cyanotic CHD, hyperviscosity can occur as a result of increased red cell production and can be further exacerbated by iron deficiency anemia. The right-to-left shunting of blood in the cyanotic child results in low systemic arterial oxygen saturation and tissue oxygenation. In an attempt to increase tissue oxygenation, the kidneys release erythropoietin to stimulate the bone marrow to produce increased numbers of red cells (erythrocytosis). Red cells contain hemoglobin, which is the most critical factor in tissue oxygenation, in conjunction with cardiac output, the availability of oxygen to red cells on passage through the lungs, and the affinity of oxygen for the hemoglobin molecule (affected by hemoglobin structure, pH, and 2,3-diphosphoglycerate levels). Arterial oxygen tension plays a minor role in tissue oxygenation. In the presence of a large right-to-left shunt and arterial hypoxemia, erythropoietin does not return to normal levels but continues to try to achieve normal tissue oxygenation by increasing red cell mass and hemoglobin concentration, known as decompensated erythrocytosis. Increased red cell mass causes increased blood viscosity, which is the limiting factor in oxygen delivery to tissues because it further decreases flow in small capillaries.[162] Aortic oxygen saturations <75% may be the critical saturation level below which decompensated erythrocytosis occurs.

Increasing red cell mass is accompanied by increased iron requirements. In the absence of adequate iron, iron deficiency occurs, resulting in decreased hemoglobin (hypochromic) in the red cell and a shape change from a biconcave disk to a myocytic microsphere 8 μm in diameter. This microcytic red cell is relatively rigid and less deformable, especially in the microcirculation, where vessels are 4 to 6 μm in diameter. Microcytic hypochromic iron-deficient red cells have decreased oxygen-carrying capacity as a result of reduced mean hemoglobin levels and reduced deformability in capillaries. As children with cyanotic CHD age, blood viscosity increases, causing further decreases in tissue oxygenation.

4.1.3.2. Platelet Abnormalities

Decreased platelet number[148,153,154] and function have been described in cyanotic CHD. Thrombocytopenia has been hypothesized to occur as a result of polycythemia and hyperviscosity triggering DIC. Platelet counts and hematocrit levels may be inversely related to mildly decreased platelets (100 000–150 000 per 1 mm^3), reported more often than more severe thrombocytopenia (<50 000 per 1 mm^3).[148] In addition, thrombocytopenia caused by hyperviscosity has been hypothesized to develop as a result of vascular stasis, widespread fibrin and platelet deposition, and consumption of coagulation proteins (FV, FVIII, and fibrinogen).[149–151] The decrease in platelet count and coagulation factors can result in bleeding or thrombosis. However, the development of DIC is controversial because many of the published studies used inappropriate amounts of anticoagulant to collect

blood samples for testing. Polycythemia reduces the amount of plasma in a given volume of whole blood; therefore, less anticoagulant should be used to avoid measuring falsely low levels of coagulation factors. Platelet aggregation studies have demonstrated decreased platelet function, which appears to be related to the severity of polycythemia (hemoglobin >19 g/L and hematocrit >59%) and the patient's age (>45 years).[153] Platelet survival has also been demonstrated to be <80 hours, with normal survival time being 80 to 130 hours.[163,164] Decreased platelet count has been demonstrated in cyanotic CHD with levels directly related to the hematocrit.[148]

4.1.3.3. Increased Fibrinolysis

Fibrinolysis has been demonstrated to be increased as indicated by increased levels of d-dimers.[147,152] This finding also supports the hypothesis of DIC in cyanotic CHD.

4.2. Propensity to Coagulopathy in Adults With CHD

There are limited data on the presence of a specific coagulopathy in adults with CHD. A study performed in a broad population of patients with cyanotic CHD demonstrated evidence of increased platelet aggregation with higher levels of platelet P-selectin and thrombin-antithrombin complex and lower levels of protein C activity and thrombomodulin.[165] These findings are also suggestive of endothelial dysfunction known to be present in cyanotic patients. Another study showed that P-selectin levels and β-thromboglobulin levels correlated positively with hematocrit in the presence of secondary erythrocytosis, whereas protein C, protein S, and platelet levels showed a negative correlation.[166]

Limited data also suggest that the erythrocytosis present in patients with cyanotic heart disease is associated with a bleeding diathesis.[167]

More study is warranted to further elucidate a potential coagulopathic state. Even in the absence of coagulopathy, a number of clinical risk factors for thromboembolic events exist in adults with CHD. These include an atrial-level shunt, atrial arrhythmias (especially AF), ventricular dysfunction, Fontan circulation (especially with protein-losing enteropathy), pregnancy, and oral contraception.

5. Consequences of Thrombosis in Patients With CHD

In patients with division of the circulations, that is, no potential for left-to-right or right-to-left shunting, the most significant consequences of thrombi are stroke if the thrombus is on the arterial (systemic) side and PE if the thrombus is on the venous (pulmonary) side. Patients with CHD who have either the potential for shunting (in either direction) or obligatory intracardiac mixing of systemic and pulmonary venous return before going to both the lungs and the head (as is the case in single-ventricle physiology) have the potential for additional mechanisms of life-threatening thrombi. Arterial thrombi in patients with CHD may result in limb ischemia or stroke, as in patients without CHD. Arterial thrombi in patients with CHD, however, may also result in the inability to access an artery for an essential diagnostic or therapeutic cardiac catheterization. In addition, one of the most devastating arterial thrombi in children with CHD is the complete occlusion of a systemic to pulmonary artery shunt, which is fatal unless immediately relieved.

Concerning venous thrombi, although epidemiologic studies have demonstrated that infants and children have decreased venous thrombosis compared with adults,[168–170] which is a result of unique protective mechanisms (increased α_2-macroglobulin,[171] decreased thrombin generation, and altered vessel wall properties[10–12,168,172,173]), children with CHD have increased risk for developing thrombosis (section 4.1). In addition to the development of pulmonary emboli, patients with CHD are at risk for other life-threatening venous thrombi. Essential cardiac catheterizations necessary for diagnosis, therapy, or surgical staging may be impossible in the presence of thrombi in veins of the upper or lower body. Thrombosis of the veins of the upper body may make it impossible for a single-ventricle patient to go on to a bilateral cavopulmonary anastomosis (bidirectional Glenn) or a Fontan palliation. Thrombi in the Fontan circulation may result in Fontan failure or death either by sending emboli to the pulmonary bed, resulting in increased pulmonary vascular resistance and poor Fontan hemodynamics (cyanosis if fenestrated or low cardiac output if not fenestrated), or by decreasing pulmonary blood flow and consequently pulmonary venous return and cardiac output. This scenario is also possible in the patient with a cavopulmonary anastomosis (bidirectional Glenn).

The ability to relieve both arterial and venous obstructions via the placement of endovascular stents has been lifesaving in many patients with CHD. Thrombosis of these stents, on either the arterial or venous side, may also be life-threatening.

The next 2 sections of this article discuss stroke in patients with CHD and the consequences of venous thrombosis in patients with CHD, including the incidence, diagnosis, and treatment of PE. The reader is also directed to section 8.1, Early Postoperative Anticoagulation for Palliated CHD, and section 8.2, Long-term Anticoagulation in the Patient With a Palliated Single Ventricle.

6. Thrombotic Complications Associated With Pediatric Cardiovascular Surgery

Although thrombotic complications in patients undergoing cardiac surgery for pediatric and congenital cardiac disease have been a longtime concern for the physician caring for them, there is a paucity of data on the overall incidence, risk factors, and outcome.

Early work by Giglia et al[174] reviewing a 9-year experience at the Children's National Medical Center revealed an overall incidence of clinically evident thrombotic events to be 3.6% of 1930 total cardiac operations. The median age at presentation was 2.6 months (range, 3 days–21.2 years), and the median time after operation was 21 days (range, 0 days–9.4 years). Single-ventricle disease was present in 35.8%; 41.1% of the thrombi were deep venous and associated with

central lines. Multiple thrombotic events (2–5) occurred in 22.6%. Treatment was given for 74.0% of the events (heparin, 68.5%; urokinase, 35.2%; warfarin, 25.9%; tPA, 18.5%; operation, 18.5%; LMWH, 13.0%; and balloon dilation, 3.7%). Minor complications of therapy occurred in 6 patients; 1 patient died during the infusion of tPA. Thrombus resolution was complete in 40.7% and partial in 11.1%. Twenty-five patients were alive at a median follow-up of 2.0 years, 24 were asymptomatic, and 28 died (52.8%), 11 of whom (20.8%) were felt to have died as a direct result of the thrombus. The diagnosis was thought to be delayed in 43.4% and was not made until autopsy in 17.0%. Age <1 year was found to be associated with the development of thrombi ($P<0.001$).

A recent publication by Manlhiot et al[175] from the Hospital for Sick Children in Toronto and McMaster Children's Medical Centre revealed that 171 of 1542 cardiac operations (11%) over a 39-month period were complicated by thrombotic events (60% of the 444 thrombi resulted in symptoms). Factors associated with significantly increased odds of thrombosis were age <31 days, baseline oxygen saturation <85%, previous thrombosis, heart transplantation, use of deep hypothermic circulatory arrest, longer cumulative time with central lines, and postoperative use of extracorporeal support. Serious complications of thrombosis occurred with 64 of 444 thrombi (14%) in 47 of 171 patients (28%) and were associated with thrombus location, symptomatic thrombi, and partially/fully occluding thrombi. Thrombosis was associated with longer intensive care unit stay (additional 10.0 days; $P<0.001$) and hospital stay (additional 15.2 days; $P<0.001$); higher odds of cardiac arrest (odds ratio [OR], 4.9; $P<0.001$), catheter reintervention (OR, 3.3; $P=0.002$), and reoperation (OR, 2.5; $P=0.003$); and increased mortality (OR, 5.1; $P<0.001$). Long-term outcome assessment was possible for 316 thrombi in 129 patients. Of those, 197 (62%) had resolved at the last follow-up. Factors associated with increased odds of thrombus resolution were location (intrathoracic, 75%; extrathoracic arterial, 89%; extrathoracic venous, 60%; $P<0.001$), nonocclusive thrombi (OR, 2.2; $P=0.01$), older age at surgery (OR, 1.2 per year; $P=0.04$), higher white blood cell count (OR, 1.1 per 10^9 cells/mL; $P=0.002$), and lower fibrinogen (OR, 1.4 per 1 g/L; $P=0.02$) after operation.

7. Incidence, Treatment, and Prevention of Stroke

7.1. Incidence, Treatment, and Prevention of Stroke in Children With CHD and Acquired Heart Disease

7.1.1. Incidence and Risk Factors

Neurological morbidity among children with CHD has been the subject of increasing interest as their survival has improved and imaging technology has advanced. Detection and characterization of neurological injury among infants with CHD are challenging because of the almost uniform absence of localizing clinical deficits in children <6 months of age and the confounding effects of sedation and analgesia during the perioperative period. Magnetic resonance imaging (MRI) in prospective cohort studies of infants with CHD is the most sensitive and accurate means of identifying cerebral injuries.[176–180] These studies have revealed a wide spectrum of cerebral disorders and provided important insights into their timing and pathogenesis. Stroke syndromes related to thromboembolic disease represent only 1 aspect of this spectrum of cerebral abnormalities, which includes cerebral dysmaturity, periventricular leukomalacia, ischemic stroke, hemorrhage, and disturbed cerebrovascular physiology. Ischemic stroke, moreover, may result from critical hypoperfusion in selectively vulnerable regions or from thromboembolic occlusion on either the arterial or venous side of the circulation. Antithrombotic treatment would have a role only in the prevention of ischemic injuries related to embolic or thrombotic arterial or venous occlusive events.

7.1.1.1. Stroke After the Fontan Operation

Evidence on the incidence and risk factors for thromboembolic stroke in children with heart disease is available from several single-center cohort studies of children with CHD, whereas very little is published on acquired heart disease. du Plessis et al[181] described a retrospective cohort with a 2.6% incidence of stroke among 645 children with CHD after undergoing a Fontan procedure between 1978 and 1993. Diagnosis was based on the appearance of clinically evident focal neurological signs or symptoms, which varied in time of onset from early postoperatively (<3 days) in a minority of subjects (4 of 17 cases) to >6 months postoperatively (7 of 17 cases). Intracardiac thrombus was detected by echocardiogram in 6 of 17 cases, but no other risk factor was identified. Two of 15 (13%) long-term survivors had recurrent stroke. Two of the 17 patients were treated with warfarin. No conclusions could be drawn about the relative benefit of antiplatelet or anticoagulation treatment. In a study from the same era, Day et al[182] reported a 12% incidence (8 of 68 cases) of cerebrovascular events among children who underwent Fontan procedures. All patients had residual right-to-left shunts, but the risk of stroke was not related to cardiac anatomy, Fontan type, or pulmonary vascular resistance. Strokes occurred despite concurrent treatment with aspirin or warfarin in 2 of these cases. Jahangiri et al[183] found a 1.7% incidence (1 in 57 cases) of stroke among patients surviving Fontan procedures, and the stroke occurred in a patient who was being treated with warfarin at a therapeutic level at the time of the stroke. Rosenthal et al[184] reported cerebral thromboembolic events in 4.2% (3 of 70 patients) in another retrospective single-center cohort study of patients surviving Fontan procedures and followed up for a median of 5 years postoperatively. In a more recently published study, Barker et al[185] retrospectively reviewed 402 children who underwent Fontan procedures between 1975 and 1998 for single-ventricle defects and were followed up for a median of 3.5 years postoperatively. They found a 9% incidence (38 of 402) of cerebrovascular events, which were considered to be primary (without antecedent or provoking illness) in only 18% (7 of 38). Strokes were considered secondary (attributed to other illness or procedures) in 82% of cases. Inciting illness or events included surgical procedures (40%), catheterization (5%), shortness of breath on exertion (8%), ECMO (5%), and cardiac arrest (8%). Stroke risk

was not related to Fontan type. Interestingly, in this study, an analysis of antithrombotic treatment practices showed a lower risk of stroke in patients on antithrombotic treatment with aspirin or warfarin (2.4/1000 patient-years) compared with those not treated with antithrombotic drugs (13.4/1000 patient-years).

More recent single-center cohort studies suggest that the incidence of overt clinical stroke after early childhood repair of CHD may have declined in the past decade, during which time routine prophylaxis with aspirin has become more widely practiced. These studies report rates ranging from 0% to 1.4 %.[186–189] Kaulitz et al[189] described an older cohort that underwent Fontan or Glenn procedures at a median of 66 months of age and were followed up for a median of 91 months. In this older cohort, which had all types of thrombotic and thromboembolic events, including stroke, risk factors had begun to emerge such as protein-losing enteropathy, ventricular dysfunction, prolonged immobilization, and cardiac arrhythmias, problems more common in children with CHD who survive into adolescence and young adulthood. A number of other smaller single-center cohort studies, most of them retrospective, have described the incidence of stroke among older patients surviving reoperation in adolescence and young adulthood to range from 1% to 7%.[190,191]

7.1.1.2. Stroke in Neonates and Children With CHD

A number of prospective cohort studies have used MRI to more fully characterize the incidence of clinically covert strokes in very young infants with CHD, both preoperatively and postoperatively. Mahle et al[176] reported ischemic stroke incidences of 8% preoperatively and 16% postoperatively. McQuillen et al[192] found MRI evidence of stroke, all clinically silent, in 21% preoperatively and an additional 9% postoperatively among infants undergoing operative repair of CHD. In this study, the performance of a balloon atrial septostomy was the only factor identified as an independent risk factor. Seizures are often the only clinical manifestation of stroke in newborns and young infants. Clancy et al[193] applied this observation in a prospective cohort study of 183 infants subjected to continuous electroencephalographic monitoring for 48 hours after surgical correction of CHD. Subclinical seizures were identified in 11% of patients, who then underwent brain MRI. MRI disclosed stroke as the cause of the seizures in 25% (5 of 20 cases) of infants who had postoperative seizures.

7.1.1.3. Hemorrhage in Infants With CHD

The incidence of hemorrhage is less well characterized than ischemic injury in children with CHD. Tavani et al[148] described the results of imaging in a prospective cohort of children with CHD who underwent brain MRI preoperatively and postoperatively. They found intracranial hemorrhage in 55% (13 of 24 infants). All of these bleeds were classified as small or incidental and included small subdural (52%), choroid plexus (33%), and parenchymal (5%) bleeds. Postoperative MRI was obtained in 23 of 24 infants and showed minor radiologic progression of hemorrhage in 43%. All children were assessed prospectively by clinical neurologic examination, and none were judged to be clinically symptomatic of hemorrhage preoperatively or postoperatively.

7.1.2. Treatment of Stroke in Children

A recently published AHA scientific statement reviewed the diagnostic evaluation and treatment of stroke in infants and children.[194] Readers are referred to the original article for a detailed literature review and evidence-based guidelines for the management of ischemic stroke, intracranial hemorrhage, and cerebral sinovenous thrombosis. Several of the most salient points from that document are summarized here.

In the acute phase of ischemic stroke (first week), it is reasonable to provide general supportive interventions as recommended for stroke from any cause. These include optimization of oxygenation and systemic perfusion pressures, correction of anemia, normalization of serum glucose levels, prevention of hyperthermia, and treatment of clinically evident seizures with anticonvulsants. These recommendations are in line with published AHA guidelines for the treatment of acute stroke in adults.[195] The safety and efficacy of thrombolysis for acute stroke in children have not been established. The writing committee for the AHA pediatric stroke guidelines concluded that there are currently insufficient data to make a treatment recommendation for thrombolysis.

7.1.3. Prevention of Stroke in Children With CHD and Acquired Heart Disease

Effective stroke prevention in children with heart disease rests on a clear delineation of the pathophysiological mechanisms contributing to stroke in a given child. Cardiac disease itself and its treatment are the most obvious stroke risk factors in these children. However, primary or acquired cervical and cerebrovascular disease and prothrombotic conditions may contribute independently to stroke risk in these children.

Cardiac risk factors include specific structural heart disease with right-to-left shunts or complete mixing, as well as cardiac dysfunction, and are compounded by the added risk of surgery and endovascular procedures. Primary prevention strategies surrounding these periods of increased risk are addressed in other sections of this document. Interventions targeting the underlying cardiac cause of stroke are described in the AHA pediatric stroke management guidelines[194] and include therapy for congestive heart failure, palliation or repair of structural heart defects via surgical or endovascular approaches, and resection of atrial myxoma.

The potential role of prothrombotic disorders in children with heart disease who suffer a stroke is illustrated in the study by Strater et al.[196] In this prospective consecutive cohort study of 162 children with ischemic stroke, 38 children (23%) had cardiac disorders. Compared with a control group matched for age and geographic residence, the children with stroke and heart disease had an increased prevalence of ≥1 prothrombotic abnormalities, including the presence of lipoprotein(a), anticardiolipin antibodies, and protein C deficiency. In a related longitudinal cohort study evaluating stroke recurrence risk factors, Strater et al[197] found stroke recurrence in the cardiac population to be 2.7% at a median of 44-month follow-up after the first stroke. Risk of recurrent stroke was greater in children who had ≥1 prothrombotic risk factors. To date, there have been no clinical trials specifically evaluating the effectiveness of antithrombotic treatments in secondary stroke prevention among children with heart disease. In the report by Barker et

al[185] on outcome of patients with single-ventricle defects after Fontan palliation, an analysis of antithrombotic treatment practices showed a lower risk of stroke on antithrombotic treatment with aspirin or warfarin (2.4/1000 patient-years) compared with those not treated with antithrombotic drugs (13.4/1000 patient-years).

Cervical or cerebral vascular abnormalities may contribute further to stroke risk in children with heart disease. Several genetic syndromes feature both heart disease and vascular disease, notably Williams syndrome,[198] Alagille syndrome,[199] and PHACES (Posterior fossa malformations–hemangiomas–arterial anomalies–cardiac defects–eye abnormalities–sternal cleft and supraumbilical raphe) syndrome.[200] The spectrum of vascular lesions includes cervical arterial stenoses and obstructions, moyamoya disease, and aneurysms. Early identification of these syndromic diagnoses in the course of providing cardiac care could provide opportunities for evaluating and managing cerebrovascular disease in a proactive manner. The role of cerebrovascular abnormalities in children with heart disease who have stroke was further illustrated by Ganesan et al[201] in an article describing risk factors in a 20-year cohort of children with ischemic stroke. A previous diagnosis of heart disease was known before stroke onset in 31 of the 212 patients (15%) in this cohort. Previously undiagnosed cardiac abnormalities were found in an additional 7% of patients in this cohort who underwent cardiac evaluation for their stroke. Vascular imaging revealed arterial occlusive or stenotic lesions or dissection in 8 of the 10 cardiac patients in this cohort who underwent vascular evaluation.

Treatment recommendations for the secondary prevention of stroke in children with heart disease have been described in detail in the AHA scientific statement on childhood stroke.[194] To briefly summarize, the childhood stroke writing committee stated that it is reasonable to initiate systemic anticoagulation in children with stroke from confirmed or suspected cardiac embolism (not related to patent foramen ovale [PFO]). For subsequent decisions on the duration of anticoagulation, it is reasonable to take into account the nature and expected management of the heart defect, the presence of additional stroke risk factors such as thrombophilia, and the presence of cervical or cerebral vascular disease. Transition to aspirin is reasonable in children judged to have a low risk of cardiac embolism. There are insufficient data to support a recommendation concerning the risk versus benefit of antithrombotic treatment for stroke that is judged to be related to transcardiac embolism through a PFO. Individual factors are taken into account, including the results of thrombophilia evaluation, presence of venous thrombosis, and underlying chronic disease state.

In addition, there are insufficient data to make a recommendation for PFO closure in the prevention of recurrent childhood stroke.

Although summarized above, see the recommendations in the AHA scientific statement on management of stroke in infants and children.[194]

Recommendations for the Evaluation of the Child With Stroke and Heart Disease

1. **For purposes of fully characterizing stroke risk factors in children with heart disease who have had a stroke, a transthoracic echocardiogram is recommended, with particular focus on identifying intracardiac thrombi and risk factors for thrombi, that is, ventricular dysfunction, blood stasis, chamber dilatation, or right-to-left shunt. A transesophageal echocardiogram is recommended if transthoracic imaging is deemed suboptimal by the attending physician team and there are no contraindications (*Class I; Level of Evidence C*).**
2. **For purposes of fully characterizing stroke risk factors in children with heart disease who have had a first stroke, it is reasonable to consider carrying out an expanded evaluation for inherited or acquired prothrombotic risk factors and to perform cervical and cerebrovascular imaging to fully characterize intrinsic vascular risk factors (*Class IIa; Level of Evidence B*). The prothrombotic risk factors that should be assessed are ideally determined in consultation with pediatric thrombosis experts because this field is evolving rapidly. It would be reasonable to include the following factors in an initial evaluation: protein C, protein S, AT III, lipoprotein(a), homocysteine level, anti-cardiolipin antibodies, lupus anticoagulant, mutations of factor V Leiden, and prothrombin genes.**

Recommendations for the Management of Stroke in Infants and Children With Heart Disease

See the AHA scientific statement on the management of stroke in infants and children.[194]

7.2. Incidence, Treatment, and Prevention of Stroke in Adults With CHD

There are numerous mechanisms for stroke in the adult with CHD. Most do not appear to be related specifically to a hypercoagulable state and occur as a result of paradoxical embolization across an atrial-level shunt or stasis in the setting of atrial arrhythmias. At-risk patients include those with d-transposition of the great arteries palliated with atrial switch surgery who have a residual baffle leak, fenestrated Fontan patients, those with mitral obstruction, and patients with Ebstein anomaly with an atrial-level shunt. Atrial arrhythmias place these patients at additional risk. A study from the Mayo Clinic suggested that iron deficiency in cyanotic patients, caused in many patients by repeat phlebotomy, can lead to stroke, possibly as a result of the reduced oxygen-carrying capacity of the red cells and reduced deformability of the cells.[202]

Concerning the adult patient with an open Fontan fenestration, no study to date has shown that a patent fenestration in isolation is a risk factor for thrombosis or stroke. It is recognized by the writing group that there have been *Class I* recommendations for the use of warfarin in the adult with an open Fontan fenestration.[203] After much discussion, the writing group has agreed to grade this recommendation *Class IIa*, *Level of Evidence C* until further data are available.

Patients with isolated PFO or atrial septal defects are also at risk for cardioembolic stroke. In a subset of the Warfarin-Aspirin Recurrent Stroke Study (WARSS) trial, which randomized patients to warfarin (INR, 1.4–2.8) or aspirin (325 mg daily), those patients with prior cardioembolic stroke and PFO

documented by transesophageal echocardiography showed no benefit for warfarin compared with aspirin, although this study was underpowered to demonstrate superiority.[204] Because there may be an increased incidence of hypercoagulable states among patients with PFO who have a stroke, evidence of a hypercoagulable disorder should be sought, and warfarin can be considered if found.[205] Many excellent reviews have examined the benefit of PFO closure with a percutaneous device compared with antithrombotic therapy for the secondary prevention of cardioembolic stroke.[206,207]

A recent randomized trial was published in which 909 patients were randomized to device closure or antithrombotic therapy with warfarin, aspirin, or both. The cumulative incidence of the primary end point (stroke, transient ischemic attack, death resulting from any cause, and neurological death) was 5.5% in the PFO closure group compared with 6.8% in the medical therapy group (hazard ratio=0.78; P=0.37). No deaths from neurological causes occurred during the 2-year follow-up period. In patients with recurrent neurological events, a cause other than paradoxical embolus was usually found.[208] In light of these findings and in the absence of FDA approval of device closure for PFO, this procedure should be considered only for patients with recurrent stroke or transient ischemic attack who have been on antithrombotic therapy and in whom no other cause can be identified. At the present time, PFO closure cannot be recommended for those with a first event. Randomized, controlled trials should continue with newer devices and optimal medical therapy.

Recommendations for antithrombotic therapy in patients with ischemic stroke have been covered in detail in recent publications,[209] and only those specifically related to CHD including PFO will be addressed here. Ischemic strokes in the setting of CHD may be classified as cardioembolic (with a defined source) or cryptogenic (with no definite source). Strokes associated with PFO and no other source have been classified as cryptogenic and may account for up to 20% of strokes in the adult population.[209] The recommendations for patients with AF who are usually assumed to have cardioembolic strokes caused by left atrial thrombus are covered separately.

Recommendations for Management of Cryptogenic Stroke and Patent Foramen Ovale in Adults

1. **In adult patients with cryptogenic stroke, a PFO, and no other risk factors,* we recommend antiplatelet therapy over no therapy (*Class I; Level of Evidence B*).**
2. **In adult patients with cryptogenic stroke, a PFO, and no other risk factors,* the use of antiplatelet agents over anticoagulation with warfarin is reasonable (*Class IIa; Level of Evidence B*).**
3. **Warfarin is reasonable for high-risk adult patients with cryptogenic stroke and PFO who have other indications for oral anticoagulation such as those with an underlying hypercoagulable state or evidence of venous thrombosis (*Class IIa; Level of Evidence C*).**
4. **The addition of warfarin (INR, 2–3) to aspirin may be considered for adult patients with cardioembolic stroke who have a recurrent cerebral ischemic event on aspirin (*Class IIb; Level of Evidence C*).**
5. **PFO closure may be considered for adult patients with recurrent cryptogenic stroke on medical therapy (*Class IIb; Level of Evidence B*).**
6. **PFO closure by surgery or device is not indicated for primary stroke prevention in adult patients with PFO (*Class III; Level of Evidence C*).**

*Risk factors include hypercoagulable state, venous thrombosis, and AF.

Recommendations for Stroke Prevention in Adults With CHD

1. **Warfarin is recommended in adult patients with CHD who have paroxysmal, persistent, or permanent AF/atrial flutter, refractory interatrial tachycardias, or a history of embolic stroke (*Class I; Level of Evidence C*).**
2. **Warfarin is recommended in adult patients with Fontan circulation who have a documented atrial thrombus, atrial arrhythmia, or a thromboembolic episode (*Class I; Level of Evidence C*).**
3. **Long-term warfarin therapy is reasonable for primary stroke prevention in adult patients with Fontan circulation who have a documented atrial-level shunt (*Class IIa; Level of Evidence C*).**
4. **Phlebotomy is reasonable in adult patients with hemoglobin >20 mg/dL and hematocrit >65% with hyperviscosity symptoms (ie, headache and lethargy) in the absence of dehydration and iron deficiency (*Class IIa; Level of Evidence C*).**
5. **Phlebotomy is reasonable in adult patients with CHD before noncardiac surgery when the hematocrit is >65% (*Class IIa; Level of Evidence C*).**
6. **Aspirin may be reasonable in adult patients with atrial septal defect, no prior history of stroke, and no arrhythmias (*Class IIb; Level of Evidence C*).**
7. **Phlebotomy is not indicated for adult patients with CHD, hemoglobin <20 mg/dL, and/or hematocrit <65% who have no symptoms attributable to hyperviscosity (*Class III; Level of Evidence C*).**

8. Venous Thrombosis in CHD Including Thrombus Associated With CVLs and PE

As discussed, patients with CHD may have life-threating venous thrombosis in addition to pulmonary emboli, including thrombi in conduits, bilateral cavopulmonary anastomoses, and Fontan circuits. The instigating thrombi for many of these obstructions are related to indwelling CVLs.

8.1. Incidence, Prevention, and Treatment of Thrombosis in Children With CVLs

Thrombosis related to CVLs may occur as a result of the thrombogenic surface of the CVL, blockage of the vessel with alteration in blood flow, or damage to the vascular endothelium by the CVL or infusate. Obstruction of the large veins of the upper body may present with superior vena cava syndrome, sometimes manifesting as pleural or chylous effusions. Thrombolytic therapy, balloon dilation, transcatheter thrombectomy, and stent placement have been reported with some success.[53a,58,211] PE may occur when the CVL is removed[212] or

when lytic therapy is used to clear the thrombotic obstruction as the clot lyses and the thrombus migrates.[213]

The incidence of CVL-associated venous thromboembolic events was 13% as documented by venogram in infants and children (158 evaluable patients, all >3 months of age) in the multicenter Prophylaxis of Thromboembolism in Kids Trial (PROTEKT) trial.[214] In published series, ≈90% of neonates and 50% of children with venous thrombosis had a CVL.[169,215] More specifically, in symptomatic and asymptomatic neonates and children with CHD, a prospective cohort study demonstrated an incidence of thrombosis of 25% resulting from CVL placement,[216] which is similar to other non-CHD pediatric populations.[217,218]

The safety and efficacy of prophylaxis in children to prevent CVL-associated thromboembolic events have not been established. The PROTEKT trial,[214] although underpowered, did not find a benefit for the use of prophylactic LMWH. The effectiveness of the routine use of low-dose UFH as thromboprophylaxis in infants with heart disease and a CVL in the early postoperative period also is not well established, although recent limited data do not support its use. Schroeder et al[219] in a recent randomized, placebo-controlled, single-center study determined that although low-dose heparin infusion was safe, there was no difference in the incidence of CVL-associated thromboembolic events between heparin and placebo groups (5% versus 16%, respectively).

A meta-analysis of previously reported randomized trials found that prophylactic heparin significantly lowered the incidence CVL-associated thromboembolic events in adults, which may have been related to decreased bacteremia.[220] In addition, there is a reported association between thrombosis and peripherally inserted catheter–associated bloodstream infection in neonates (n=882 neonates, 1540 peripherally inserted catheters; $P<0.05$).[221] Although not reported, likely because of low numbers, there may also be an increased risk of shunt thrombosis in neonates with infection.

Compared with adults, radiographically confirmed asymptomatic CVL-related thromboses in infants and children are clinically important for a number of reasons:

- Increasing evidence supports the association of CVL-associated thrombosis and CVL-related sepsis. Prophylactic heparin was shown to decrease CVL-associated thrombosis in adults, bacterial colonization, and probably CVL-related bacteremia.[221]
- In children, CVL-associated thrombosis is the most common source of PE[222,223] resulting in mortality.[157] In addition, CVL-associated thrombosis may result in loss of vascular access important for life-saving therapy in certain illnesses, including heart transplantation.[28,169,213]
- Many children with CHD have persistent right-to-left intracardiac shunts with the potential for venous emboli to travel through the heart to the brain with resultant stroke.[158,213]

Recommendations for Prophylaxis of CVLs in Children With CHD

1. **Because children with CHD may be prone to coagulopathy and CVLs are prone to associated thrombi, removal of CVLs in children with CHD is recommended as soon as they are no longer clinically essential. Daily assessment by the medical team for the need of each CVL, considering alternative access (ie, peripheral intravenous line), is recommended (*Class I; Level of Evidence C*).**
2. **It is reasonable to consider the removal of a CVL if associated thrombus has been identified by diagnostic imaging studies (*Class IIa; Level of Evidence C*). The risk of embolization should be taken into account in this decision. The thrombus should be followed by serial diagnostic imaging studies.**
3. **Anticoagulation is reasonable for the treatment of a documented acute venous thrombus associated with a CVL if there are no contraindications. Clinical symptoms and the extent of the thrombus should be taken into account in this decision (*Class IIa; Level of Evidence B*).**
4. **In infants or children with a CVL who will ultimately require a palliative Fontan procedure, low-dose intravenous heparin may be reasonable until the CVL is removed (*Class IIb; Level of Evidence C*).**
5. **In infants or children with heart disease and the presence of a CVL in combination with concomitant bacteremia or a hypercoagulable risk factor (increased hematocrit, history of thrombosis, confirmed thrombophilic abnormality), low-dose intravenous heparin may be reasonable until the CVL is removed (*Class IIb; Level of Evidence C*).**

8.2. PE in CHD

Thrombosis in the pulmonary artery known as PE may result from embolism of an anatomically distant clot or occur within the pulmonary artery itself. Most commonly, PE is part of the spectrum of deep venous thrombosis. The consequences of PE are severe and include mortality and morbidity such as cardiopulmonary compromise and pulmonary hypertension (PH). The incidence of symptomatic venous thrombosis and PE in infants and children appears to be rare, although to date there have been no large prospective studies with sensitive diagnostic techniques. In neonates, 3 prospective registries (from Germany, the United Kingdom, and Canada) reported the incidence of venous thrombosis but not PE.[169,215,224] The incidence of PE in children was reported in 3 registries (from Canada, the United Kingdom, and the Netherlands) to occur in 17% of children with confirmed venous thrombosis with an overall incidence of 0.86 events per 10 000 hospital admissions.[168,169,224] In those children with PE, there was a 10% mortality rate as a direct result of PE. Retrospective autopsy studies in children have indicated an incidence of PE at autopsy of 0.73% to 3.7%, depending on the population studied.[225,226] The incidence of PE in children is less than in adults and may be related to unique protective mechanisms, including decreased thrombin

generation, increased levels of the inhibitor of coagulation α^2-macroglobulin, and enhanced antithrombotic potential of the vessel wall[12,13,168–172] (section 2.5, Developmental Hemostasis).

8.2.1. Groups at High Risk for PE

Cohorts of infants and children with acquired or CHD are at risk for the development of PE as a result of risk factors unique to heart disease, including altered hemostasis (section 4.1, Propensity to Coagulopathy in Children With Heart Disease), and other general risk factors, including most commonly the presence of a CVL.[222,227] The clinical challenge is that many patients with PE are asymptomatic, including children with CHD and young adults after the Fontan procedure (17% prevalence).[228]

8.2.2. Diagnosis of PE in Children

8.2.2.1. Clinical Presentation of PE in Children

Patients with PE may be asymptomatic[228] or have signs of cardiac or respiratory compromise, including chest pain, increased cyanosis, increased respiratory rate, increased heart rate, hypotension, and decreased oxygen saturation from the patient's baseline. Abnormal laboratory testing may include arterial blood gas with decreased P_{O_2} and increased P_{CO_2}, and blood lactic acidosis.

8.2.2.2. Diagnostic Studies

There have been no studies determining the sensitivity and specificity of radiographic testing for PE in infants and children. The diagnosis of PE in pediatrics is limited by the small size of the pulmonary vasculature and the invasive nature of the available tests, including the requirement for vasculature access, general anesthesia in an unstable population, and large amounts of radiation exposure. See Table 4 for available tests, advantages, limitations, and recommendations.

8.2.3. Treatment of PE in Children

In the absence of properly designed clinical trials to evaluate the safety and efficacy of therapy, adult treatment guidelines for PE are used in infants and children.[230]

8.2.3.1. Thrombectomy

Thrombectomy has been described in case reports and small case series in children for massive thrombosis or PE.[231–233]

8.2.3.2. Thrombolytic Therapy

(Section 3 and Table 4.)

Thrombolytic therapy has been described in case series of small numbers of children with venous thrombosis but not specifically PE.[21,58,227] There are reports describing the use of alteplase (tPA) in varying doses, low[52] (0.01 $mg \cdot kg^{-1} \cdot h^{-1}$) to high[60] (0.1–0.6 $mg \cdot kg^{-1} \cdot h^{-1}$) dose. Bleeding risk ranges from 3% to 27%, and efficacy ranges from 0% to 97%,[60] with most case series reporting 40% to 97%. After surgery, thrombolytic therapy poses a high risk of bleeding. In single-ventricle patients with PE or shunt thrombosis, postoperative catheterization with transcatheter thrombolysis[53a,58] or thrombectomy has been used.[211] Catheter-directed balloon dilation with or without stent placement have been used, although published data is sparse.

8.2.3.3. Anticoagulant Therapy

The mainstay of therapy of PE in adults is anticoagulant therapy. UFH and LMWH have been used in infants and children to treat PE.[23] Oral VKAs have been used in children >12 months of age to complete therapy.[21]

Recommendations for the Management of PE in Children With Heart Disease

1. **Infants and children with PE and heart disease who are clinically stable should be treated with anticoagulation according to the guidelines for deep venous thrombosis as outlined in *Chest* (2008)[21] (*Class I; Level of Evidence B*). See Table 4 for diagnostic testing and section 3 and Table 3 for specific medications and monitoring guidelines.**
2. **In infants and children with PE and heart disease who have life-threatening cardiorespiratory compromise, indicated by cardiovascular collapse, respiratory distress, hypotension, hypoxia, lactic acidosis, and a positive radiographic test for PE, an urgent surgical or interventional consultation should be initiated. Rapid removal of pulmonary thrombus by thrombolytic therapy, pulmonary embolectomy, or stent placement can be beneficial (*Class IIa; Level of Evidence C*).**

8.2.3.4. Vena Caval Filters

Vena caval filters (VCF) can be placed in special circumstances to prevent PE. These devices are restricted to children >10 kg in weight to have an inferior vena cava large enough to allow the VCF. The complications of VCF placement include extension of thrombosis to the level of the filter, thrombus formation in the filter basket, and migration or perforation of the inferior vena cava. The filter is placed via the femoral or jugular approach; temporary or removable filters may remain in place 10 days to 3 months, whereas permanent filters are intended to remain in situ for life. The availability of a skilled pediatric procedural radiologist with experience in this field is a major determinant in the risks and benefits of placement in patients.

Recommendations for the Use of VCF in Children With CHD and PE

1. **Children with heart disease, a PE, and a contraindication to anticoagulation (active or high risk for hemorrhage) or failed anticoagulation[21,234–236] should be considered for a VCF placement (*Class I; Level of Evidence C*).**

8.3. Special Considerations in Adults With CHD

8.3.1. PE and In Situ Thrombosis

Patients with Fontan circulation are at risk for pulmonary thromboembolic events, and those with PH are at risk for in situ thrombosis of the pulmonary arteries. In patients

Table 4. Diagnostic Methods for Pulmonary Embolism: Advantages and Disadvantages

Test	Advantages	Disadvantages	Sensitivity/ Specificity	Positive test	Recommendations
Pulmonary angiogram with/without cardiac catheterization		Invasive, sedation or general anesthesia, radiation exposure, femoral artery access used	High sensitivity, gold standard test	Intraluminal filling defect	1. Diagnostic test in patients with congenital heart disease and postoperative PE (*Class IIa; Level of Evidence: C*) 2. May be necessary to diagnose PE in small children or if distal vessel PE 3. Diagnostic test for aortopulmonary shunt thrombosis (*Class IIa; Level of Evidence: C*)
Spiral CT (CT angiography)	Fast, test most commonly used	Radiation exposure, sedation or general anesthesia	Sensitivity 85% in adults for more central defects	Intraluminal filling defect in a lobar or main pulmonary artery	1. First line test (*Class IIa; Level of Evidence: C*) 2. Technical issues in single-ventricle palliated patients (contrast streaming); may result in false positives.
MRI	No radiation	Not feasible if child has cardiorespiratory compromise re length of time to complete Sedation or general anesthesia	Sensitivity and specificity good in adults	Filling defect in vascular tree	Cautioned in compromised patient secondary to the need for lengthy anesthesia and/or deep conscious sedation
TEE or TTE	Noninvasive, fast	Identification of thrombus in the pulmonary arteries or cavopulmonary connections may be difficult.	Probably low sensitivity and specificity, especially for peripheral PE and in the single-ventricle patient	In a 2-ventricle patient, may demonstrate a massive central PE	May not be diagnostic, especially in the single-ventricle patient; elevated RV pressure, decreased RV function, or intracardiac thrombus may be corroborating data in the 2-ventricle patient, as may be SVC, baffle, or conduit thrombus in the cavopulmonary anastomosis patient
Ventilation/perfusion scan	Noninvasive	Limited in infants and young children secondary to the need to cooperate for ventilation scan (if not intubated) and difficulty of the study with an increased respiratory rate	Probably low in altered circulation of single-ventricle patients	High-probability scan as per PIOPED criteria[229]	Not a first-line diagnostic test
Chest x-ray	Noninvasive, must accompany ventilation/ perfusion scan to rule out other pulmonary pathology	May be normal in the presence of PE	Poor		Must accompany a ventilation/perfusion scan

CT indicates computed tomography; MRI, magnetic resonance imaging; PE, pulmonary embolism; PIOPED, Prospective Investigation of Pulmonary Embolism Diagnosis study; RV, right ventricular; SVC, superior vena cava; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography.

with an atrial-level shunt, a venous thrombus can result in paradoxical embolization to the systemic circulation. The target INR in patients with PE arising in either the right atrium or the venous circulation is 2 to 3.0. In most patients with CHD, indefinite anticoagulation with warfarin should be considered.

The diagnosis and management of in situ thrombosis are less well established, but warfarin anticoagulation should be considered unless the patient has active uncontrolled hemoptysis. This risk of long-term anticoagulation in patients with PH is probably higher, and no controlled trials are available. Therefore, the target INR is usually in the lower range of 2 to

2.5, and the published guidelines make a specific recommendation in this regard.[143,171,182–185,203,230,237–240]

9. Thrombosis Particular to CHD: Primary Prevention and Treatment

9.1. Early Postoperative Anticoagulation for Palliated CHD

9.1.1. The Systemic to Pulmonary Artery Shunt

Infants with CHD often require palliation with a systemic to pulmonary artery shunt either as a bridge to a 2-ventricle repair (eg, tetralogy of Fallot) or as part of a more complex palliation (eg, patients with single-ventricle anatomy). The shunt may originate from a systemic artery (eg, right innominate artery) or from a ventricle as in the case of hypoplastic left heart syndrome (Norwood procedure, right ventricle–pulmonary artery) and insert into the left, right, or main pulmonary artery. First used in the late 1970s, polytetrafluoroethylene shunts have become the preferred graft material for the systemic to pulmonary artery shunt.[241,242]

Thrombosis is a significant cause of or contributor to polytetrafluoroethylene systemic to pulmonary shunt failure both in the immediate postoperative period and between phased palliation or corrective operations.[71,242–244] Risk of shunt occlusion is associated with but not limited to conditions that cause intravascular volume depletion, persistently draining pleural effusions, or infection. Partial shunt occlusion commonly manifests as the inability to correct hypoxemia with increasing inspired oxygen delivery. Complete shunt occlusion in patients who depend on the shunt as the sole source of pulmonary blood flow is life-threatening and requires emergent efforts to reestablish shunt patency.

Acute shunt thrombosis has long been a recognized complication.[241,242] Al Jubair et al[71] reported their nonblinded retrospective findings of a large cohort of shunt-palliated cyanotic heart disease patients. The study group included patients with either classic (native arterial) or polytetrafluoroethylene systemic to pulmonary shunts. The authors reported an overall rate of 9.3% shunt failure, with 20% occurring shortly after surgery. In a separate study of 206 neonates undergoing shunt placement as part of their initial palliation, 20 (9.7%) required surgical or transcatheter shunt intervention before hospital discharge.[245] Nine patients (4.4%) required urgent intervention, with ECMO necessary in 6 patients. The mechanism of shunt dysfunction was thrombosis (33%), distortion (38%), a combination of thrombosis and distortion (19%), and indeterminate (10%). Significant univariate risk factors for shunt intervention were heterotaxy, congenital abnormality, and smaller shunt size for the subgroup with a modified Blalock-Taussig shunt. Patients requiring shunt intervention had a significantly higher incidence of infection and need for ECMO and a longer hospital stay. Survival at 5 years was 41.2% for those requiring early shunt intervention compared with 76.8% for those who did not (P=0.002). Fenton et al[246] reported an overall 4% risk of death (7 of 169) resulting from shunt thrombosis, with one third of patient deaths occurring between hospital discharge and the next planned cardiac surgery as a result of this complication.

Complete shunt occlusion must be immediately recognized and managed emergently with anticoagulation (heparin 50–100 U/kg), increased systemic systolic blood pressure (phenylephrine to effect) to maximize shunt perfusion pressure, and controlled ventilation (to maximize oxygen delivery and minimize oxygen consumption). Alternative interventions include the use of epinephrine (10 μg/kg) if more readily available than phenylephrine, emergent catheterization to remove thrombus, or emergent sternotomy for thrombectomy (to milk shunt of thrombosis). If these maneuvers are not immediately successful, the patient will likely require ECMO, if available, for stabilization.

Chronic polytetrafluoroethylene shunt narrowing secondary to an organized thrombus and myofibroblastic proliferation is common. Wells et al[243] reported that most of the 155 polytetrafluoroethylene shunts examined at the time of elective takedown (mean age, 8 months) had developed some compromise of the graft with an organized thrombus often evident (luminal compromise, 34±22%). Perhaps limited by inadequate power, no risk factor other than smaller shunt size could be identified in this cohort. Using a broader definition for shunt thrombosis and longer follow-up, Li et al[72] reported a 12% incidence (99 of 1004 patients) of shunt thrombosis. Such past and current experiences raise the question of timing for prophylactic antithrombotic therapy in these patients.

The clinical diagnosis of partial shunt thrombosis is best determined by angiogram largely because corrective transcatheter intervention can then ensue. Thrombosis appears as a filling defect but can be difficult to differentiate from kinking or distortion of the shunt, particularly at the takeoff or insertion. Alternatively, cardiac computed tomography or MRI may reveal evidence of shunt or pulmonary architectural abnormalities. Isolated thrombosis can usually be relieved by balloon dilation alone, whereas shunt distortion with or without thrombus often requires stent placement or surgical revision.[247,248]

Early shunt intervention is associated with increased mortality (median, 59% at 5 years).[245] Early outcomes for the patients stabilized with ECMO for shunt occlusion is favorable, but late mortality is significant. In this series, 4 patients (80%) died at a median age of 5.7 months (range, 5.1–10.9 months). In a larger series of patients with hypoplastic left heart syndrome (1998–2005; n=382), there was 100% early survival for patients requiring ECMO (n=5) for shunt occlusion[249] Children's Hospital Boston reported 83% early survival in 12 patients requiring ECMO support for acute shunt occlusion.[250]

9.1.2. Cavopulmonary Anastomosis and Early Postoperative Venous Thrombosis

After superior cavopulmonary anastomosis or Fontan palliation, patients are at increased risk of developing pleural effusions.[251] These effusions can drain significantly. Chylothoraxes are associated with an increased risk of thrombosis,[252] likely because of the loss of important proteins, including proteins C and S. In addition, loss of AT III can limit the effectiveness of heparin, which is often the first-line anticoagulant. Serious complications can include pulmonary artery thrombosis and cerebral sinovenous thrombosis. Venous flow patterns through

the pulmonary arteries put these infants at much higher risk of pulmonary artery thromboses. Transcatheter mechanical clot removal or tPA may be necessary for pulmonary artery or superior vena caval thrombosis.

Not only can draining pleural effusions result in a hypercoagulable state, but fluid losses can result in dehydration and relative systemic hypotension. Systemic hypotension with the elevated superior vena caval pressures can compromise cerebral perfusion pressure. This clinical scenario can result in cerebral sinovenous thrombosis and associated stroke.[253]

9.1.3. Postoperative Risk Factors for Early Thrombosis

CPB in children results in platelet activation and an initial drop in platelet count.[254–256] In neonates, the platelet count then rises over the subsequent few weeks after surgery, thus supporting the management strategy of using antiplatelet therapies.

The increased risk of thrombosis in infants and children after palliative cardiac surgery is well described. Causes include abnormal blood flow patterns, cyanosis resulting in an increased hematocrit, abnormal endothelial function, and documented abnormal maturation in coagulation factors.[139,172,182] The reported incidence of thrombosis (5%–33%) varies by definition and diagnostic approach.[82,83,91,257,258] The embolic potential and intracardiac shunting in these patients leaves them at risk for acute shunt occlusion.

Chylothoraxes after cardiac surgery are associated with an increased incidence of venous thrombosis.[252] Multivariate analysis found only a higher central venous pressure to be related to the risk of chylothorax. Patients with significant drainage will have low measured levels of AT III, protein C, and protein S, creating a hypercoagulable state.

9.1.4. Anticoagulation Therapies

The use of anticoagulation immediately after systemic to pulmonary shunt placement remains controversial because there are no prospective studies testing the efficacy or safety of such treatment in preventing shunt thrombosis. In the Al Jubair et al[71] retrospective review, patients who received heparin intraoperatively and for 48 hours after surgery had a rate of early shunt failure of 1.4% compared with 3.4% in patients who did not receive heparin (P=0.29). It is worth noting that the use of early postoperative heparin in neonates who often have transthoracic intracardiac lines is not without risk. An unrecognized hemopericardium in a neonate can easily result in cardiac arrest. Concurrent arguments against postoperative heparin infusion have been raised in the literature.[259–261] Confounding the determination of a relative risk-to-benefit ratio for antithrombotic treatment in the immediate postoperative patient are the numerous postoperative risk factors described above. If heparin is used, whether to use a low-dose versus full systemic heparinization to achieve a therapeutic PTT also remains a question. Alternative monitoring to achieve therapeutic anti-FXa and AT III levels is practiced in some institutions.

Antiplatelet therapies have been the mainstay of long-term anticoagulation in pediatric-aged patients with systemic to pulmonary shunts. Low-dose aspirin has been used for the prevention of long-term thrombotic complications for some time given the perceived low risk-to-benefit balance. In the same retrospective series noted above, patients receiving low-dose aspirin experienced a 6.7% rate of shunt failure compared with 11% in those who did not receive aspirin (P=0.18).[71] Recently, the results of a large multicenter observational trial in which infants palliated with aortopulmonary shunts who were prospectively monitored for clinical outcome demonstrated that those receiving low-dose aspirin were found to have a reduced risk of shunt thrombosis (P=0.008) and death compared with those infants not receiving aspirin.[72] The antiplatelet effect of other pharmacological agents has contributed favorably to outcome in various adult cardiovascular diseases. In 2 smaller single-institution series, aspirin use was not found to be a significant predictor of interstage death (n=146; P=0.49) or shunt failure (n=313; P=0.18), but this may be attributable to inadequate power or skewing by aspirin dosing adjusted for shunt size.[71,246]

Clopidogrel (Plavix, Bristol-Myers Squibb; Iscover, Sanofi-Aventis; Clopilet, Sun Pharmaceuticals) is a potent oral antiplatelet agent that functions by an irreversible blockade of the adenosine diphosphate receptor ($P2Y_{12}$) on platelet cell membranes, which inhibits platelet aggregation by blocking activation of the glycoprotein IIb/IIIa pathway. Using a primary composite outcome of death, shunt thrombosis, or thrombosis-related cardiac intervention at up to 120 days of age was prospectively analyzed in infants (n=906) with systemic-to-pulmonary-artery shunts, randomized to clopidogrel versus placebo, in addition to their conventional anticoagulation. No difference was observed in primary composite outcome rates between the 2 groups (19.1% for clopidogrel, 20.5% for placebo). Concomitant aspirin therapy was received by 88% of patients. No difference was found in mortality (11.8% for clopidogrel, 13.9% for placebo) or shunt thrombosis (5.8% for clopidogrel, 4.8% for placebo) between the 2 groups. The percentage of patients with bleeding events (18.8% for clopidogrel, 20.2% placebo) and severe bleeding events (4.1% clopidogrel, 3.4% placebo) did not differ between groups.[262]

The use of tPA for shunt occlusion outside site-specific delivery in the catheterization suite has not been described. In a cohort of children (n=80) who were not postoperative but had intravascular thrombosis, the incidence of bleeding with tPA (average dose, 0.5 $mg \cdot kg^{-1} \cdot h^{-1}$) was 39%.[58] This high incidence of bleeding complications cautions against its use for shunt thrombosis especially, if preparing for interventional catheterization, surgery, or ECMO.

Warfarin Therapy

In the future, maintaining therapeutic warfarin in neonates should be easier with the growing experience with home self-monitoring coagulometers, currently used primarily for adults with mechanical valves and atrial arrhythmia. In the absence of data to demonstrate superiority of warfarin over LMWH or antiplatelet therapies, many institutions favor the latter in neonates.

Low-Molecular-Weight Heparin

LMWH has advantages over UFH in that it can be used on an outpatient basis with infrequent testing of anti-FXa levels. The disadvantage of LMWH compared with aspirin is that it

requires twice-daily subcutaneous injections. However, the successful experience of using an indwelling subcutaneous catheter (Insuflon, Unomedical, Birkerod, Denmark), changed weekly, in neonates has been reported, with induration and bruising being frequent side effects.[263]

Recommendation for Thrombus Prevention in Systemic to Pulmonary Artery Shunts, Thrombus Prevention in Cavopulmonary Anastomoses in the Early Postoperative Period, and Prevention of Postoperative Venous Thrombus in Other CHDs in Infants and Children

1. **In the absence of increased risk of bleeding, long-term use of low-dose aspirin is recommended therapy for the prevention of long-term polytetrafluoroethylene systemic to pulmonary shunt thrombosis in infants and children (*Class I; Level of Evidence B*). The incidence of complications from low-dose aspirin in neonates, however, has not been reported.**
2. **After surgical placement of a polytetrafluoroethylene systemic to pulmonary shunt, it is reasonable to initiate a continuous low-dose heparin infusion in infants and children in the early postoperative period when concerns over surgical bleeding have been resolved (*Class IIa; Level of Evidence C*).**
3. **In infants and children with a recently placed polytetrafluoroethylene systemic to pulmonary artery shunt who have an increased risk factor for thrombosis (eg, suspected or confirmed infection, known CVL-associated thrombus, stented shunt, or hypercoagulable state), systemic heparinization is probably recommended in the early postoperative period (*Class IIa; Level of Evidence C*).**
4. **In the event of clinical evidence of acute polytetrafluoroethylene systemic to pulmonary shunt thrombosis, immediate intervention should be initiated. It is reasonable that initial management includes (1) systemic anticoagulation with a bolus of intravenous heparin (50–100 U/kg) and consideration of ongoing heparin infusion, (2) increasing systemic blood pressure (eg, intravenous phenylephrine or epinephrine to effect) in an effort to improve flow through the shunt, and (3) intubation, mechanical ventilation, and neuromuscular blockade to maximize oxygen delivery and to minimize oxygen consumption (*Class IIa; Level of Evidence C*). Interventional catheterization, manual shunt manipulation, surgical shunt revision, or ECMO should be anticipated.**
5. **For infants, children, and adolescents with a sustained high risk for thrombosis (eg, stented shunt or hypercoagulable state), combined anticoagulation plus antiplatelet therapy (eg, LMWH plus oral low-dose aspirin or clopidogrel) may be considered (*Class IIb; Level of Evidence C*).**
6. **In infants, children, and adolescents with chronically draining pleural effusions of significant volume, it may be reasonable to closely monitor anticoagulation status (clotting studies, AT III, and anti-FXa levels (*Class IIb; Level of Evidence C*). Anticoagulation may require modification with neurology input if a cerebral venous infarct develops (section 7, Incidence, Treatment, and Prevention of Stroke).**
7. **The systemic administration of thrombolytic agents (eg, tPA) may be harmful for the treatment of polytetrafluoroethylene systemic to pulmonary artery shunt thrombosis because of the high incidence of bleeding complications and the possibility of subsequent interventional catheterization, surgical shunt manipulation/revision, or ECMO (*Class III; Level of Evidence C*). There is a paucity of data on catheter-directed thrombolytic therapy in this situation.**

9.1.5. Thrombosis Secondary to Indwelling CVLs in the Early Postoperative Period

See section 8.1, Incidence, Prevention, and Treatment of Thrombosis in Children With CVLs.

9.2. Long-term Anticoagulation in the Patient With a Palliated Single Ventricle

Thrombosis is an important cause of morbidity and mortality for patients who have undergone palliative procedures for a functional single ventricle. Although data are limited, currently available information suggests that the risk of thrombosis after bidirectional cavopulmonary anastomosis is low. However, areas of blood flow stasis such as the interconnecting pulmonary artery segment in the setting of bilateral bidirectional cavopulmonary anastomosis[264] or a blind-ended pulmonary artery stump[265] are recognized sites at high risk for thrombus. Hypoplastic cardiac chambers with poor inflow and outflow such as the left ventricle in hypoplastic left heart syndrome are also important sites for thrombus at any time in the patient's course even after the bidirectional cavopulmonary anastomosis.

More is known about thrombosis after the Fontan procedure.[189] The prevalence of thrombosis as noted in cross-sectional studies using transesophageal echocardiography ranges from 17% to 33%.[258] Retrospective reviews report varying risks of thrombosis and thrombosis-related events (both systemic venous thrombosis and primary stroke). The variance is dependent on many factors, particularly the duration of the observation period and whether the review was focused on thrombosis (3%–15% for thrombosis, 3%–9% for events) or on outcomes after Fontan in general (1%–7% for thrombosis, 1%–12% for events).[83]

The detection of thrombosis or the occurrence of a related event is probably not associated with a uniform risk over time. When reported, there appears to be a higher risk within the perioperative period up to 3 to 12 months after Fontan, followed by a lower and constant level of risk, which then increases at 5 to 10 years after Fontan.[184,266,267] There may be some utility to matching the need for and degree of anticoagulation therapy to the magnitude of risk with the recognition that the risk may change over time. Patients who have had previous thrombosis or related events are at high risk for recurrence. Other risk factors have been reported inconsistently and with less rigorous evidence and include atriopulmonary Fontan connection type, Kawashima connection type, presence of thrombogenic foreign material, dilated atrium,

arrhythmias, ventricular dysfunction, prolonged immobilization, and protein-losing enteropathy.[83]

Several studies have described intrinsic and acquired alterations in thrombophilia factors such that single-ventricle patients may be predisposed to both bleeding and thrombosis.[140,141,146,268–270] These alterations may be related to inflammation, ventricular dysfunction, lower cardiac output, higher venous pressures, nonpulsatile systemic venous flow, chamber dilatation, subclinical hepatic dysfunction, and lower systemic oxygenation. The role of these alterations in clinical decision making is unknown in terms of their contribution to risk and requirement for screening and management.

Transthoracic echocardiography performed as part of routine follow-up of Fontan patients remains the mainstay for surveillance for thrombosis. However, for patients with suboptimal imaging related to the presence of indwelling foreign material, poor transthoracic windows, or posterior location of areas at higher risk of thrombosis, periodic transesophageal echocardiography may be indicated for surveillance.[271,272] The utility of MRI for surveillance and diagnosis of thrombosis is unknown. For patients with thrombosis suspected on clinical grounds or from transthoracic echocardiography, diagnostic confirmation with transesophageal echocardiography, MRI, computed tomography, computed tomographic angiography, nuclear medicine lung perfusion scan, or venography/angiography may be indicated.

Given that thrombosis has an important impact on morbidity and mortality for patients with a functional single ventricle, there may be some role for preventive antithrombotic therapy. The timing of initiation and selection of agent and target level of antithrombotic therapy may be individualized according to the presence and magnitude of risk factors and the patient's clinical state. Antiplatelet therapy is reasonable after initial palliation involving a systemic to pulmonary arterial shunt (section 9.1.1, The Systemic to Pulmonary Artery Shunt) and may be reasonable after bidirectional cavopulmonary anastomosis. Antiplatelet therapy for long-term antithrombotic therapy is probably indicated after Fontan procedure, although long-term therapy with warfarin may be indicated after the Fontan procedure for higher-risk patients. Given that there is some evidence that the first 3 to 12 months after Fontan procedure may be a higher-risk period, warfarin or LMWH may be indicated, particularly for patients at increased risk. Likewise, given that older patients may be at higher risk, escalation or initiation of antithrombotic therapy therapy may be indicated in adolescence or adulthood. Decisions about prophylactic antithrombotic therapy must balance the potential benefit against the risks, expense, and inconvenience.

Until very recently, there were no published clinical trials of antithrombotic therapy in single-ventricle patients. Seipelt et al[267] noted in an observational study that Fontan patients taking either aspirin or warfarin had lower event rates than those not on any antithrombotic therapy. Other similar studies with few events concluded that there was no benefit to antithrombotic therapy.[189,273,274] A protocol aimed at reducing risk factors for thrombosis that included postoperative aspirin as the sole antithrombotic agent showed no thrombotic events at midrange follow-up (mean follow-up, 40 months).[186]

Monagle et al[275] recently reported the first multicenter, randomized trial in this area comparing aspirin (5 $mg \cdot kg^{-1} \cdot d^{-1}$) with warfarin (started within 24 hours after heparin lead-in with a target INR of 2–3) for 2 years in patients after the Fontan operation. Children were screened at 3 months and 2 years with transthoracic and transesophageal echocardiography. Of the 111 patients enrolled, there were 13 thromboses in the heparin/warfarin group (3 clinical, 10 by routine echocardiography) and 12 thromboses in the aspirin group (4 clinical and 8 by routine echocardiography). Cumulative risk for thrombosis was similar for both groups (P=0.45). Major bleeding occurred in 1 patient in each group, although minor bleeding was significantly increased in the heparin/warfarin group. There were 2 deaths, 1 in each group. Both patients had thrombi, but their deaths were judged by the authors not to be related to the thromboses. Although there was no significant difference between heparin/warfarin and aspirin as primary prophylaxis in the first 2 years after the Fontan operation, the authors concluded that because the thrombosis rate was suboptimal for each group, alternative therapies needed to be investigated.

Clearly, the evidence base to guide decisions on antithrombotic therapy and clinical protocols is limited, and further well-designed clinical trials are needed, including those that evaluate the child beyond the early post-Fontan period through adolescence and into adulthood. As suggested by Kaulitz et al[189] in 2005 and Canter[276] in 2011, the risk of thromboses in the Fontan patient may change over time as additional potential risk factors come into play (ie, ventricular dysfunction, arrhythmia prolonged immobilization, protein-losing enteropathy, prolonged pleural effusions, prior thrombi). In addition, work by Odegard and colleag ues[136,137,140,141] has shown that patients with single-ventricle physiology were more likely to have coagulation abnormalities compared with age-matched control subjects at all stages of the single-ventricle palliation and that FVIII levels increased after the Fontan procedure in patients followed up longitudinally from stage I. It is not known, however, if this change in coagulation profile persists (or changes) over years and whether it correlates with the risk of future thrombotic events. That is, do post-Fontan coagulation profiles change over time, and are they predictive of a "coagulopathic potential" in a given patient? Before recommendations can be made for long-term antithrombotic therapy strategies in the Fontan patient, a better understanding of the risk factors, the potential additive effect of multiple risk factors, and the potential change in risk factors over time is essential. With this, better risk stratification and the development of more effective risk reduction strategies, including safer and more effective antithrombotic therapy, can be investigated.

Recommendations for Long-term Prevention of Thrombosis in the Patient With a Palliated Single Ventricle

1. **Patients with a palliated single ventricle should undergo clinical assessment for the anatomic and**

hemodynamic risk factors for thrombus.† Risk factors for thrombus should be ameliorated (ie, arrhythmias, ventricular dysfunction, prolonged immobilization) and minimized (blind-ended pulmonary artery stump, prolonged immobilization) when possible (*Class I; Level of Evidence B*).

2. **For patients with a palliated single ventricle, serial clinical assessment and monitoring for changes in anatomic and hemodynamic thrombotic risk factors† are indicated because risk factors may change over time (*Class I; Level of Evidence C*). New risk factors for thrombus should be ameliorated (ie, arrhythmias, ventricular dysfunction, prolonged immobilization) and minimized (prolonged immobilization) when possible (*Class I; Level of Evidence C*).**
3. **Patients with a palliated single ventricle should be monitored for thrombosis with periodic transthoracic echocardiography (with focused attention to the identification of thrombi) as part of routine follow-up assessments (*Class I; Level of Evidence C*).**
4. **For patients with a palliated single ventricle, if thrombosis is suspected on clinical grounds or from transthoracic echocardiography, diagnostic confirmation with transesophageal echocardiography, MRI, computed tomography, computed tomographic angiography, nuclear medicine lung perfusion scan, or venography/angiography can be useful (*Class IIa; Level of Evidence C*).**
5. **Long-term antiplatelet therapy for prevention of thrombosis is reasonable after the Fontan procedure (*Class IIa; Level of Evidence C*).**
6. **Initiation of antithrombotic therapy or an increase in the magnitude of antithrombotic therapy for prophylaxis (change in agent, ie, from antiplatelet to anticoagulant or higher target levels) is probably reasonable if anatomic or hemodynamic risk factors† are present (become present) at any stage in the single-ventricle pathway (*Class IIa; Level of Evidence C*).**
7. **For patients with a palliated single ventricle, other imaging modalities (in addition to echocardiography) used to detect thrombosis such as transesophageal echocardiography or MRI may be considered for surveillance for patients with anatomic or hemodynamic risk factors† (*Class IIb; Level of Evidence C*).**
8. **Long-term prophylactic antiplatelet therapy may be reasonable in infants and children after a superior cavopulmonary anastomosis (*Class IIb; Level of Evidence C*).**
9. **Prophylaxis with warfarin or LMWH may be reasonable in infants and children for 3 to 12 months after the Fontan procedure (*Class IIb; Level of Evidence C*).**
10. **Long-term therapy with warfarin may be reasonable after the Fontan procedure for patients with anatomic or hemodynamic risk factors† (*Class IIb; Level of Evidence C*).**
11. **Initiation of antithrombotic therapy or an increase in the magnitude of antithrombotic therapy (change in agent, ie, from antiplatelet to anticoagulant or higher target levels) for prophylaxis after the Fontan procedure may be reasonable in adolescence or adulthood (*Class IIb; Level of Evidence C*).**

†Risk factors supported by focused retrospective observational studies include atriopulmonary type of Fontan connection, bilateral bidirectional cavopulmonary anastomoses, hypoplastic cardiac chambers with flow stasis, presence of a blind-ended pulmonary artery stump, and a history of previous thrombosis. Additional potential factors supported by general retrospective observational studies or expert opinion include protein-losing enteropathy, prolonged pleural effusions, prolonged immobilization, ventricular dysfunction, arrhythmia, presence of thrombogenic foreign material, atrial-level fenestration, Kawashima connection, and an abnormal thrombophilia profile.

9.3. Anticoagulation for Prosthetic Valves

9.3.1. Anticoagulation for Prosthetic Valves in Children

In children, valve replacement is performed for the treatment of both acquired heart disease and CHD. In contrast to adults with acquired heart disease in whom nearly all valve replacement involves valves on the left side, in children, both right- and left-side valves may require replacement. Replacement valves may be tissue (allografts or xenografts) or mechanical. Long-term anticoagulation is generally not necessary for tissue valves. Tissue valves, particularly xenografts, deteriorate rapidly in children when used in the aortic or systemic atrioventricular (mitral) valve position. As a consequence of the unacceptable performance of these bioprosthetic valves, mechanical valves are commonly used for systemic valve replacement in children. In children, as in adults, anticoagulation is necessary for mechanical valves to prevent thromboembolic complications. Despite anticoagulation, patients remain at risk for thromboembolic complications, and anticoagulation therapy carries with it the additional risk of bleeding. The risk of thromboembolic and bleeding complications is present even in patients with optimally managed anticoagulation and is influenced by patient factors and valve position. Tissue valves are generally considered to be more durable when placed on the right side for replacement of the pulmonary and tricuspid valves. Furthermore, because of lower pressure and reduced blood flow velocity in the right side of the heart, even greater degrees of anticoagulation are necessary for a mechanical valve in these positions. Although recommendations for the type of prosthetic valve replacement are beyond the scope of this statement, it is common for bioprosthetic valves to be used on the right side and mechanical valves to be used on the left side in children.

Currently manufactured mechanical valves have a single tilting disk such as the Medtronic Hall valve (Medtronic, Minneapolis, MN) or a bileaflet design such as the St. Jude (St. Jude Medical, St. Paul, MN), Carbomedics (Austin, TX), ATS (ATS Medical, Minneapolis, MN), or On-X (Medical Carbon Research, Austin, TX) valves. Prosthetic valve failure is rarely reported in the current era. In adult populations, the incidence of thromboembolic complications among patients with a mechanical valve in the aortic position varies between 1.4 to 2.7 per patient year and bleeding complications vary between 0.7 and 3.0 per patient year.[277] The risk of thromboembolic and bleeding complications of mechanical valves in the aortic position in children is less well known.[278–281] Among 37 studies addressing anticoagulation and thromboembolic complications in children receiving mechanical aortic valve replacement, 34 were exclusively retrospective analyses.[29,30,39,40,73–75,282–309] The largest experience included 91 patients, and only 8 studies included >50 patients.[29,30,40,288,289,292,293,303] Anticoagulation was commonly performed with warfarin or other VKAs, and when specified, the INR range was between 1.5 to 2.5 and 2.5 to 3.5. Follow-up was limited, with only 12 studies having an average

follow-up of >5 years.[29,282–285,288–290,293,294,300,307] These 12 studies include experience with 496 patients undergoing mechanical aortic valve replacement. Thromboembolic complications among patients anticoagulated with warfarin ranged from 0% to 5.3% per patient year. The rates of thromboembolic complications were higher among series including ball-cage mechanical valves, in which the range of thromboembolic complications was between 1.3% and 5.3% per patient year.[292,293,300,307] Among 8 studies with an average follow-up >5 years including 288 patients undergoing mechanical aortic valve replacement with either tilting disk valves or a bileaflet valve and anticoagulated with warfarin with a target INR between 2.5 to 3.0 and 3.0 to 3.5, the risk of thromboembolic complications was between 0% (3 studies summarizing a total experience with 78 patients reported no incidence of thromboembolic complications)[284,285,288] to 1.3% per patient year.[39,282–285,288–290] Among 12 retrospective studies of pediatric patients receiving mechanical aortic valves anticoagulated with warfarin or other VKAs with >5-year follow-up, the bleeding risk was between 0% (5 studies summarizing experience with 186 patients reported no incidence of bleeding complications)[282–285,289] and 2.3% per patient year. Among patients receiving either tilting disk or bileaflet mechanical aortic valves anticoagulated with warfarin or other VKAs, the risk of bleeding was <1% per patient year.

The risk of anticoagulation-related complications is greater for mechanical valves in the systemic atrioventricular (mitral) valve position. In 2 prospective studies of adult patients with a combined enrollment of >1000 patients, the performance of bileaflet mechanical valves in the mitral position was evaluated. The incidence of both thromboembolic events and bleeding complications was between 1% and 3% per patient year.[280,310] Ten-year freedom from thromboembolic complications was 85.5% with a 10-year freedom from bleeding of 81.7%.[280] Using a minimum of 5 years of follow-up as the inclusion criterion, there are 8 retrospective studies summarizing experience with 296 pediatric patients that assessed the risk of anticoagulation with warfarin or other VKAs for a mechanical valve in the systemic atrioventricular (mitral) valve position.[283–285,311–315] Aspirin and dipyridamole were used along with warfarin in 1 study that included 30 patients.[315] The target INR varied between 2.0 to 3.0 and 3.0 to 4.0. The risk of thromboembolic complications reported was between 0% (3 studies summarizing experience with 95 patients reported a 0% incidence of thromboembolic complications)[285,312,313] and 1.2% per patient year, and the risk of bleeding was between 0% (1 study summarizing the experience with 31 patients)[312] and 1.4% per patient year. A single multicenter, prospective study[316] summarized the experience with 139 patients <5 years of age at the time of mitral valve replacement. Ninety-eight percent of the patients received a mechanical valve, and anticoagulation was performed with warfarin, although the target INR was not specified. Thrombosis of the prosthetic valve occurred in 3% and stroke occurred in 2%; no time-to-event analysis was performed, although the risk of thromboembolic complications was in the range of 1% per patient year, and bleeding events were not mentioned.

Anticoagulation with warfarin and other VKAs requires frequent testing and adjustment to maintain adequate anticoagulation. Despite these efforts, thromboembolic and bleeding complications occur as summarized above. It has been suggested that pediatric patients are at lower risk for thromboembolic and bleeding complications, and several studies have looked at minimizing anticoagulation or the exclusive use of antiplatelet agents, usually aspirin, with or without dipyridamole. A retrospective summary of 48 patients receiving a bileaflet mechanical valve on the systemic side (aortic, mitral, or both) and receiving no anticoagulation identified a thromboembolic risk of 5.7±2.1% per patient year.[297] It is noteworthy that the thromboembolic complications occurred in the last 14 months of follow-up, suggesting that the time-related risk may not be constant. The authors concluded that anticoagulation was necessary for patients with a mechanical valve. In a retrospective study, 28 patients receiving a left-side mechanical valve received either warfarin (n=18) or aspirin with dipyridamole (n=10). Five patients receiving warfarin had a bleeding complication, and transfusion was performed in 2 of these patients. The risk of bleeding among patients receiving warfarin was 22% per patient year. Patients receiving only aspirin and dipyridamole had a 12% per patient year risk of thromboembolic complications, and all of these events were life-threatening, necessitating emergency surgery.[306] These authors suggested that aspirin and dipyridamole alone were inadequate anticoagulation for children receiving mechanical valves. In a retrospective study of 51 patients receiving a tilting disk mechanical valve in the aortic position, the authors compared aspirin with dipyridamole (n=45) and with warfarin (n=6). There were no thromboembolic events and 4 minor bleeding complications. The authors concluded that aspirin alone or in combination with dipyridamole was sufficient anticoagulation for mechanical valves in the aortic position, but the average follow-up was only 36.5 months and, as suggested by the authors, may not be adequate time to identify the real risk of thromboembolic complications.[304] Three studies from the same institution evaluated aspirin with dipyridamole for anticoagulation of pediatric patients receiving a bileaflet mechanical valve. In the first study, 34 patients were placed on aspirin and dipyridamole only, and no thromboembolic complications were reported with an average follow-up of just under 2 years.[74] In 2 subsequent studies, a total of 136 patients were followed up prospectively and were treated with warfarin or aspirin with dipyridamole. Assignment to treatment group was not randomized, and patients with a mitral prosthesis were more often assigned to warfarin. There was no difference in freedom from thromboembolic complications or bleeding between the 2 strategies, and the average follow-up was >5 years in both studies.[286,291] The authors concluded that anticoagulation with aspirin and dipyridamole was a safe and reasonable strategy for the management of patients with mechanical valves on the left side.

The studies of anticoagulation for mechanical valves in systemic circulation in the pediatric age group are nearly all retrospective, and the risk of thromboembolic and bleeding complications is therefore likely to be underestimated. Among the 3 prospective studies, there is 1 multi-institutional observational study that provides little information on anticoagulation and anticoagulation-related complications. In 2 prospective studies comparing antiplatelet agents with VKAs, assignment to treatment group was not randomized. Overall, the numbers are too small, the follow-up is too short, and the quality of studies is inadequate to make evidence-based recommendations other than some form of anticoagulation is necessary

for pediatric patients receiving mechanical valves for left-side valve replacement. As a consequence, the most prudent action concerning anticoagulation of both pediatric patients and adult patients with CHD receiving mechanical valves is to follow the recommendations of the ACC/AHA guidelines for management of patients with valvular heart disease but without strong data in the pediatric age range and with only a *Level of Evidence C* (Table 5).[317]

In contrast to acquired heart disease in adults, replacement of the pulmonary and tricuspid valves is common in children. Right ventricular outflow tract reconstruction (pulmonary valve replacement) is accomplished with a variety of bioprosthetic valves and valved conduits, including allografts and both porcine and bovine xenografts.[318–324] The risk of systemic embolization is essentially nonexistent. Some authors have reported using aspirin after implantation of bioprosthetic valves in the pulmonary position, but this practice is uncommon. Anticoagulation has been reported rarely for thrombotic complications that impair valve function or place the patient at risk for significant PE.[318,320] The risk of thromboembolic complications after bioprosthetic replacement of the pulmonary valve appears to be very low, and for the patient without additional risk factors, there is no indication for anticoagulation.[318–321,323,324] The use of mechanical valves for pulmonary valve replacement has been reported. In 2 series totaling 13 patients in whom aspirin and/or dipyramidole were used without VKAs, early valve failure was common, occurring in 7 of 13 patients within 1 year of valve implantation.[325,326] In 2 series totaling 42 patients, VKAs were used with a target INR of 2.5 to 4.0 and 3.0 to 4.5, and with a mean follow-up of 35 months to 5.5 years, the authors reported a zero incidence of valve failure.[327,328] These data support the notion that higher levels of anticoagulation are necessary for mechanical valves on the right side. The data are inadequate to make specific recommendations concerning anticoagulation of mechanical valves in the pulmonary position.

Replacement of the tricuspid valve (right-side atrioventricular valve in the pulmonary ventricle) is rare; the most common indication is Ebstein anomaly, followed by pulmonary atresia and tetralogy of Fallot.[329] Bioprosthetic valves are used most commonly. The largest North American experience comes from a single institution, the Mayo Clinic, and because of the risk of acute thrombotic complications, particularly in the presence of decreased right ventricular function, Mayo Clinic reports using anticoagulation with VKAs for 3 to 6 months after tricuspid valve replacement with a bioprosthetic valve (target INR, 2–3; in addition, all patients receive aspirin).[330–332] It is probably reasonable to assume that patients with other diagnoses undergoing tricuspid valve replacement with a bioprosthetic valve would also benefit from short-term anticoagulation. Mechanical valves have occasionally been used for replacement of the tricuspid valve, but reports in the pediatric age group or even isolated to CHD are rare. One report includes 23 patients who underwent replacement of the tricuspid valve with a St. Jude mechanical valve.[333] There were 4 patients with CHD, and the youngest patient was 5 years old. The target INR for VKAs was 2.0 to 3.0, and the use of aspirin was not mentioned. These authors reported a 2.9% per patient year risk of valve thrombosis. In another report, 52 adult patients underwent tricuspid valve replacement with a mechanical valve, and 9.6% were reported to have CHD.[334] With a mean follow-up of 7.9 years, 8 patients had valve thrombosis despite the use of VKAs with a target INR of 2.5 to 3.5. Although it is clear that patients who undergo tricuspid valve replacement with a mechanical valve are at risk for thrombotic complications and should receive anticoagulation with VKAs and aspirin, the data are inadequate to make specific recommendations about the degree of anticoagulation.

When interruption of warfarin therapy is required for dental work or surgery, the need for bridging therapy depends on the relative risk of thrombosis during the time required for the procedure. In addition to the baseline clinical risk factors (eg, type of valve or position of valve), the surgery itself may induce a relative hypercoagulable state. Guidelines for the management of bridging therapy are well outlined in the guidelines on valvular disease and are not repeated here.[317]

Thrombotic occlusion of a prosthetic valve has an incidence of 0.5% to 6% per patient-year.[335–339] The risk of valve thrombosis is not linear and is more frequent early after replacement. Presentation of patients ranges from asymptomatic to cardiogenic shock.[339] Pediatric patients, particularly infants, may be at increased risk for thrombotic occlusion of a prosthetic valve because of the smaller size of the prosthesis and the increased difficulty in achieving stable anticoagulation. The diagnosis is confirmed by echocardiography, and if the transthoracic echocardiogram is inconclusive, fluoroscopy or transesophageal echocardiography is indicated. Treatment may include emergency surgery with thrombectomy or another valve replacement, fibrinolytic therapy, or intravenous heparin, depending on the condition of the patient and the clot burden.[51a] Fibrinolysis would appear to be an attractive option because repeat surgery is avoided, but complications are common. In adults, success is ≈75% with a 25% rate of complications such as bleeding, systemic thromboembolism, failure resulting in reoperation, and death.[335,336,341–346] There is experience with thrombolytic therapy in children for thrombotic occlusion of prosthetic valves, and the results seem similar to the adult experience.[51a,345,347–351] The management of pediatric patients with valve thrombosis should mirror that outlined for adults in the ACC/AHA guidelines for management of patients with valvular heart disease and the eighth edition of the American College of Chest Physicians evidence-based clinical practice guidelines.[317,352]

Recommendations for Anticoagulation for Prosthetic Valves in Children

1. **After aortic valve replacement with bileaflet mechanical or Medtronic Hall prostheses, in patients with no risk factors,‡ warfarin is indicated to achieve an INR of 2.0 to 3.0. If the patient has risk factors, warfarin is indicated to achieve an INR of 2.5 to 3.5 (*Class I; Level of Evidence C*).**
2. **After aortic valve replacement with Starr-Edwards valves or mechanical disk valves (other than Medtronic Hall prostheses), in patients with no risk factors,‡ warfarin is indicated to achieve an INR of 2.5 to 3.5 (*Class I; Level of Evidence C*).**
3. **After mitral valve replacement with any mechanical valve, warfarin is indicated to achieve an INR of 2.5 to 3.5 (*Class I; Level of Evidence C*).**

4. **After aortic or mitral valve replacement with a bioprosthetic valve and no risk factors,‡ low-dose aspirin is indicated (*Class I; Level of Evidence C*).**
5. **After aortic valve replacement with a bioprosthetic valve and risk factors,‡ warfarin is indicated to achieve an INR of 2.0 to 3.0 (*Class I; Level of Evidence C*).**
6. **After mitral valve replacement with a bioprosthetic valve and risk factors,‡ warfarin is indicated to achieve an INR of 2.0 to 3.0 (*Class I; Level of Evidence C*).**
7. **For those patients who are unable to take warfarin after mitral or aortic valve replacement, low-dose aspirin is indicated (*Class I; Level of Evidence C*).**
8. **On the basis of adult guidelines, the addition of low-dose aspirin to therapeutic warfarin is recommended for adult patients with mechanical heart valves and adult patients with bioprosthetic valves who have risk factors‡ (*Class I; Level of Evidence C*). Data in children are limited.**
9. **During the first 3 months after aortic valve replacement with a mechanical prosthesis, it is reasonable to give warfarin to achieve an INR of 2.5 to 3.5 (*Class IIa; Level of Evidence C*).**
10. **During the first 3 months after aortic or mitral valve replacement with a bioprosthetic valve, in patients with no risk factors,‡ it is reasonable to give warfarin to achieve an INR of 2.0 to 3.0 (*Class IIa; Level of Evidence C*).**
11. **After pulmonary valve replacement with a bioprosthetic valve, it is reasonable to forgo anticoagulation (*Class IIa; Level of Evidence C*).**
12. **After tricuspid valve replacement with a bioprosthetic valve with or without decreased function, it is reasonable to give warfarin to achieve an INR of 2.0 to 3.0 for 3 to 6 months after implantation (*Class IIa; Level of Evidence C*).**
13. **After tricuspid valve replacement with a bioprosthetic valve, it is reasonable to give life-long low-dose aspirin (*Class IIa; Level of Evidence C*).**
14. **After tricuspid valve replacement with a bioprosthetic valve in a patient with decreased right ventricular function or risk factors,‡ long-term anticoagulation with warfarin to achieve an INR of 2.0 to 3.0 may be reasonable (*Class IIb; Level of Evidence C*).**

‡Risk factors include previous thromboembolism, systemic ventricular dysfunction, and hypercoagulable condition.

Table 5. Recommendations for Antithrombotic Therapy in Adult Patients With Left-Sided Prosthetic Heart Valves

	Low-Dose Aspirin	Warfarin (INR, 2.0-3.0)	Warfarin (INR, 2.5-3.5)	No Warfarin
Mechanical prosthetic valves				
AVR, low risk				
<3 mo after valve replacement	Class I	Class I	Class IIa	
>3 mo after valve replacement	Class I	Class I		
AVR, high risk	Class I		Class I	
MVR	Class I		Class I	
Biological prosthetic valves				
AVR-low risk				
<3 mo after valve replacement	Class I	Class IIa		Class IIb
>3 mo after valve replacement	Class I			Class IIa
AVR, high risk	Class I	Class I		
MVR, low risk				
<3 mo after valve replacement	Class I	Class IIa		
>3 mo after valve replacement	Class I			Class IIa
MVR, high risk	Class I	Class I		

Depending on patients' clinical status, antithrombotic therapy must be individualized. In adult patients receiving warfarin, aspirin is recommended in virtually all situations. Data in children are limited. Risk factors: atrial fibrillation, left ventricular dysfunction, previous thromboembolism, and hypercoagulable condition. INR should be maintained between 2.5 and 3.5 for aortic disk valves and Starr-Edwards valves. AVR indicates aortic valve replacement; INR, international normalized ratio; and MVR, mitral valve replacement.

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9.3.2. Special Considerations for Anticoagulation in Adults With CHD and Prosthetic Valves

Guidelines for anticoagulation in the adult with a prosthetic valve are well established despite the lack of evidence from randomized, clinical trials on optimal therapeutic strategies. There is no reason to believe that adults with congenital valve disease should be managed differently from those with acquired valve disease. The relative risk of thromboembolic events is lowest for mechanical valves in the aortic position and somewhat higher in the other valve positions. It is also higher for older-style valves such as the Starr-Edwards and Bjork-Shiley than for new valves such as the St. Jude bileaflet valve and the Medtronic-Hall single disk valve. Other clinical risk factors that increase the risk of a thromboembolic event include atrial arrhythmias, previous thromboembolism, ventricular dysfunction, and a hypercoagulable state. Warfarin therapy with a target INR of 2.5 to 3.5 is indicated for those at highest risk for thromboembolism, and an INR of 2 to 3 can be used for those at lower risk (Table 5). For patients with >1 mechanical valve, the higher range should be targeted. Although few data exist for management of right-side mechanical valves, a higher target INR is advised.

In adult patients with a bioprosthetic valve, warfarin is indicated in all patients only for the first 3 months after valve replacement and in patients with additional risk factors such as AF. The recommendations for aspirin are included in Table 5.

When interruption of warfarin therapy is required for dental work or surgery, the need for bridging therapy depends on the relative risk of thrombosis during the time required for the procedure. In addition to the baseline clinical risk factors (type of valve, position of valve, etc), the surgery itself may induce a relative hypercoagulable state. Guidelines for the management of bridging therapy are well outlined in the guidelines on valvular disease and are not repeated here.[317,353]

10. CPB and ECMO for Infants and Children With CHD

10.1. Anticoagulation for CPB in Children With CHD

10.1.1. General Comments on Anticoagulation for CPB in Children With CHD

Optimal anticoagulation during CPB will prevent clot formation within the CPB circuit and minimize consumption of coagulation factors. Heparin achieves anticoagulation by amplifying the activity of AT III. Heparin binds to a lysine residue on AT III and increases the thrombin inhibition of circulation AT III by a thousand-fold or more.[354,355] AT III also inhibits FIXa, FXa, FXIa, FXIIa, kallikrein, and plasmin.[356,357] During the first 2 decades of open heart surgery, heparin dosing for CPB was determined by trial and error, with supplementation based on presumed heparin half-life in the circulation. Widely differing dosing strategies were used that did not take into account interindividual differences in response to heparin. The development of a rapid test for the detection of the heparin effect, the ACT, identified the shortcomings of the empirical approach.[358,359] Studies in adults using ACT alone or combined with heparin concentration assays compared with empirical dosing demonstrate that these tests generally either result in a decrease in postoperative bleeding or transfusion requirements or at worst have neutral results, suggesting that the use of these tests to guide heparin therapy is probably beneficial.[360–377] The anticoagulation strategies for children are borrowed from the adult experience, and few studies address the pediatric age range specifically, despite the fact that factors known to prolong ACT, such as hypothermia, hemodilution, and decreased platelet function, are prevalent in pediatric cardiac operations. The optimal target ACT that will prevent clot formation within the CPB circuit is not precisely known, but clot formation is unlikely with an ACT >300 seconds. Common ACT targets are therefore placed above this 300-second baseline with the goal of achieving a margin of safety.[358,377] Commonly, a target ACT >480 seconds is used in neonates, infants, and children.[378] In adults, some authors recommend an ACT >400 seconds.[17,358] The commonly accepted, higher pediatric target of 480 seconds may offset the potential for factors such as hypothermia and hemodilution to prolong the ACT and may provide a further margin of safety. However, some congenital heart surgery programs also routinely target an ACT >400 seconds in all of their pediatric patients without obvious differences in outcomes. There are inadequate data to recommend either 400 or 480 seconds or some value in between as the optimal target ACT for anticoagulation for CPB. Manufacturers of CPB equipment have used surface modification, including heparin bonding, with a goal of minimizing activation of the coagulation system during CPB. There are inadequate data to recommend specific anticoagulation protocols for surface-modified CPB circuits.

Common techniques for heparin dosing in children include empirical weight-based ACT-guided dosing, heparin dose-response curve (HDRC), or HDRC combined with heparin concentration testing using heparin protamine titration (HPT). Regardless of the anticoagulation strategy, additional heparin is commonly included in the pump prime to adequately anticoagulate this additional circulating volume and as a safety factor if systemic heparinization is inadequate.[379] The amount of heparin added to the pump prime varies between 1 and 5 U/mL, but 2 to 3 U/mL is most commonly used. Empirical dosing of heparin for anticoagulation for CPB in neonates, infants, and children commonly includes a loading dose of heparin of between 300 and 400 U/kg. The ACT is measured before the initiation of CPB to ensure that anticoagulation is adequate. The HDRC is another method to determine heparin dosing and, as originally described, is derived from 2 measurements of ACT, 1 before heparin administration and 1 after administration of a partial dose of heparin, most commonly 200 U/kg.[359] The dose of heparin required is then determined by drawing a line from the ACT at baseline to the value after partial heparinization to identify the additional heparin needed to achieve the target ACT. The ACT at subsequent intervals, at least every 30 minutes, can be plotted against the HDRC to estimate the additional dose of heparin required to maintain the target ACT. The HPT method of heparin concentration measurement uses a series of tubes with several dilutions of protamine to which fixed volumes of the patient's blood are added. The lowest concentration of protamine that results

in clotting is identified; from this information, the heparin concentration can be determined and subsequent dosing to maintain the target heparin concentration calculated. An automated system in common clinical use (Hepcon HMS, Medtronic Hemotec, Inc, Englewood, CO) combines the ACT, HDRC, and HPT. Three single-center, randomized, controlled studies have compared the Hepcon HMS device with empirical weight-based ACT-guided dosing of heparin in children. Codispoti and colleagues[380] in a study including both infants and children showed a benefit of the Hepcon HMS system in terms of decreased blood loss and transfusion. Guzzetta and colleagues[381] studied infants <6 months of age and failed to identify a decrease in blood loss or transfusion in these younger patients. More recently, Gruenwald and colleagues[382] reported on the outcomes of 90 patients <1 year of age randomized to either weight-based ACT-guided dosing or the Hepcon HMS device. The authors found that Hepcon HMS underestimated the anti-FXa level and therefore resulted in a higher heparin dose in the Hepcon HMS group. In an initial subgroup of 33 patients, the Hepcon HMS

Table 6. Heparin Monitoring During CPB: Comparison of Studies

Investigator	Year	n	Design	Blood Loss	Transfusion	Hematologic Benefit in Experimental Group
ACT vs empiric heparin dosing						
Babka et al[360]	1977	20	RCT?	↓	NA	NA
Verska[361]	1977	114	His. Con.	↓	↓	NA
Roth et al[362]	1979	56	His. Con.	→	→	→aPTT
Akl et al[363]*†	1980	120	His. Con.	→	↓	NA
Papaconstantinou and Radegran[364]	1981	126	His. Con.	↓	↓	NA
Jumean and Sudah[365]†‡	1983	77	His. Con.	↓	→	NA
Dearing et al[366]	1983	648	RP seq.	↓	↓	↓TT, ↓Re-Op
Niinikoski et al[367]	1984	100	RP seq.	↓	→	↑Hct, ↓aPTT
Lefemine and Lewis[368]	1985	61	Unknown	→	NA	↑Plts
Preiss et al[369]	1985	350	RP	→	↓	↓Surgical time
Heparin concentration vs empiric heparin dosing						
Jobes et al[370]	1981	46	RCT	→	NA	NA
Bowie[371]	1985	150	RCT	↓	↓	NA
ACT vs heparin concentration						
Gravlee et al[372]	1990	21	RCT	ACT<HC	NA	↓FPA during CPB
Urban et al[373]	1991	38	RCT	→	→	NA
Gravlee et al[374]	1992	63	RCT	→	→	
Despotis et al[375]	1995	254	RCT	→	HC<ACT	
Codispoti et al[380]†§	2001	26	RCT	HC<ACT	HC<ACT	↓Thrombin, ↓Fibrinolysis
Koster et al[376]	2002	200	RCT	→	→	
Guzzetta et al[381]†‖	2008	25	RCT	→	→	↓Thrombin ↓VIII cons.
Gruenwald et al[382]†¶	2010	57	RCT	→	↓	↓Thrombin ↑Plts

ACT indicates activated clotting time; aPTT, partial thromboplastin time; CPB, cardiopulmonary bypass; FPA, fibrinopeptide A; HC, heparin concentration; Hct, hematocrit; His. Con, historical control group; Plts, platelets; RCT, randomized, controlled trial; Re-Op, reoperation; RP, retrospective; seq., sequential; TT, thrombin time; ↓VIII cons., decreased factor VIII consumption; ↓, decrease in blood loss or transfusion in the experimental group; and →, no difference in blood loss or transfusion between the experimental and control groups.

*Includes 20 pediatric patients.

†Including pediatric patients.

‡Age range, 5 months to 22 years.

§Infants and children.

‖All patients <6 months of age.

¶All patients <1 year of age.

group had increased chest tube output and a greater number of transfusions. In addition, they had worse clinical outcomes, including longer intensive care unit length of stay and longer duration of mechanical ventilation. The authors then changed the protocol, increasing the amount of protamine administered to 1.5 times the amount indicated by the Hepcon HMS device. Fifty-seven patients were then randomized to this modified protocol, and those in the Hepcon HMS group had decreased blood transfusions, a shorter length of stay in the intensive care unit, and shorter duration of mechanical ventilation. It is noteworthy, however, that the authors could not demonstrate a difference in chest tube output.[382] The available POC tests to guide anticoagulation on CPB; the ACT and heparin concentration testing with HPT and the strategies of applying these tests; empirical weight-based ACT-guided dosing, HDRC, and combined HDRC-HPT have been shown to have variable correlation with heparin activity as determined by anti-FXa levels. An understanding the limitations of these tests and strategies especially when applied to the smallest and youngest patients is essential to the safe conduct of CPB. The results of comparative studies of dosing of UFH for CPB are summarized in Table 6.

10.1.2. Reversal of Heparin With Protamine

Heparin remains the anticoagulant of choice for CPB in part because of the ease with which it can be neutralized by protamine. Protamine is a polycationic protein originally derived from salmon sperm. Heparin, a polyanion, binds ionically to protamine, which neutralizes the anticoagulant action of heparin.[383] Protamine contains 2 active sites, 1 that neutralizes heparin and 1 that exerts an anticoagulant effect that is independent of heparin. The anticoagulant effect of protamine is mild and only clinically apparent at doses that are severalfold higher than those required for heparin neutralization.[384,385] The result is a generous therapeutic range. One milligram of protamine neutralizes ≈85 U heparin.[358] Several dosing strategies have been used. The primary hazard of inappropriate protamine dosing is inadequate reversal.

Practically, there are 3 strategies used for protamine dosing, which mirror the strategies for heparin dosing. The first is a fixed-dose ratio of protamine to heparin. For each 100 U heparin administered, 1.0 to 1.3 mg protamine is administered. This method may be suitable for operations with a short duration of CPB, <90 minutes, but with a longer duration of heparinization, the clearance of heparin from the circulation must be taken into account. Both the HDRC and HPT can be used to estimate the dose of protamine necessary to reverse circulating heparin. The HDRC can be used to estimate the concentration of heparin from the most recent ACT; the dose of protamine necessary for reversal can then be calculated. The advantages of this method in adults include a lower total protamine dose and less blood product transfusion.[386] The problem with this method is the reliance on the ACT, which can be affected by a number of variables, including hypothermia and anemia, both common situations in pediatric heart surgery.[387] HPT can be used to determine the heparin concentration and the protamine dose necessary for reversal. In adults, this strategy has been associated with a lower total protamine dose combined with less postoperative bleeding.[388] As stated, there are 3 randomized, controlled trials looking at the Hepcon HMS system for determination of protamine dosing for heparin neutralization. In 1 study, 26 infants and children were randomized to the Hepcon HMS or a fixed-dose regimen (1 mg protamine for each 100 U heparin administered). The Hepcon HMS resulted in a lower protamine dose, less blood loss, less blood product administration, and less evidence of hemostatic activation.[380] In a second study, 25 infants <6 months of age were randomized to heparin-protamine titration or a standard dose of 4 mg/kg protamine. The investigators found that patients randomized to the Hepcon HMS received less protamine and had less evidence of hemostatic activation, but a reduction in blood product transfusion was not demonstrated.[381] More recently, using a modified protocol in which the protamine dose given was 1.5 times that indicated by the Hepcon HMS, Gruenwald and colleagues[382] found that infants managed with the Hepcon HMS had decreased blood transfusions, shorter intensive care unit length of stay, and shorter duration of mechanical ventilation, but the authors could not demonstrate a difference in chest tube output. Regardless of the specific strategy to determine the quantity of protamine necessary for reversal of heparin, an ACT or heparin level as determined by HPT is measured 5 to 10 minutes after protamine administration to confirm satisfactory reversal. If there is evidence of residual heparin, additional protamine can be administered and the reversal rechecked.

Recommendations for Anticoagulation for CPB in Children With CHD

1. **CPB should be conducted with the assistance of a qualified perfusionist (*Class I; Level of Evidence C*).**
2. **Anticoagulation for CPB is commonly accomplished with UFH. Unless contraindicated as a result of HIT, anticoagulation for CPB should be accomplished with heparin. A loading dose of 300 to 400 U/kg is given intravenously or by direct injection into the atrium. Heparin is also added to the pump prime. An ACT is determined 2 to 5 minutes after the administration of heparin. The target ACT should be achieved before the initiation of CPB, and additional heparin should be given if the ACT is below the target value. An ACT should be checked at least every 30 minutes during CPB, and heparin should be supplemented to maintain the target ACT (*Class I; Level of Evidence C*).**
3. **Alternatively, heparin dosing can be determined with the HDRC method. The target ACT should be achieved before the initiation of CPB, and additional heparin should be given if the ACT is below the target value. The ACT should be checked at least every 30 minutes during CPB, and heparin should be supplemented to maintain the target ACT (*Class I; Level of Evidence C*).**
4. **Alternatively, heparin dosing can be determined using the HDRC combined with determination of heparin concentration using the HPT. Confirmation of a heparin concentration that corresponds to the target ACT should be obtained before the initiation of CPB. Repeat heparin concentration testing with HPT**

and ACT should be obtained at least every 30 minutes on CPB (*Class I; Level of Evidence C*).

5. **For a hemodynamically unstable patient, it is reasonable to initiate CPB before obtaining confirmation of heparin dosing if heparin has been administered by CVL or direct atrial injection. The heparin dose should be 400 U/kg, and 5 U/mL should be included in the pump prime to ensure adequate anticoagulation (*Class IIa; Level of Evidence C*).**

Recommendations for Reversal of Heparin With Protamine

1. **The anticoagulation effect of heparin should be reversed with protamine. This can be accomplished with a fixed-dose ratio of protamine to heparin. For each 100 U heparin administered, 1.0 to 1.3 mg protamine should be administered. This method is suitable for operations with a short duration of CPB (<90 minutes) (*Class I; Level of Evidence C*).**
2. **For operations with longer durations of CPB, it is recommended that the dose of protamine for heparin reversal be estimated with the ACT-HDRC method or the heparin-protamine titration method (*Class I; Level of Evidence C*).**

10.1.3. Heparin Resistance

There is no universal definition of heparin resistance, but it can be loosely defined as the need for a substantially higher-than-normal heparin dose to achieve a satisfactory safe level of anticoagulation or an inability to achieve satisfactory safe levels of anticoagulation. Practically, this is defined as the inability to achieve an ACT >300 seconds after administration of >600 U/kg heparin. A number of clinical situations are associated with important heparin resistance: AT III deficiency (familial or acquired), preoperative heparin treatment, extreme thrombocytosis, septicemia, and hypereosinophilic syndrome.[389–397] AT III deficiency can be inherited or acquired. Congenital AT III deficiency follows an autosomal-dominant transmission pattern with a prevalence of 1 in 2000 to 1 in 20 000. These individuals usually have AT III levels <50% of normal and present as teenagers or young adults with lower-extremity venous thrombosis and PE.[398,399] Normal newborns and infants typically have low levels of AT III in the range of 20% to 80% of adult levels. AT III levels approach adult values at 6 months of age. The decreased levels of AT III in neonates and infants do not result in thrombosis and may be offset by a similar decrease in other clotting factors (section 2.1, Hemostasis in Children).

AT III deficiency is suspected when the ACT fails to prolong beyond 300 seconds despite the administration of >600 U/kg heparin. Treatment includes transfusion of fresh-frozen plasma or AT III concentrate. There are no studies comparing fresh-frozen plasma with AT III concentrate. Data supporting treatment of heparin resistance with fresh-frozen plasma are isolated to retrospective studies and case reports.[400–404] Studies supporting AT III supplementation for the treatment of heparin resistance include 4 randomized, controlled trials showing prolongation of ACT or a reduction in hemostatic activation.[405–415] AT III concentrate is a stable, lyophilized product derived from pooled normal human plasma, purified, and heat treated at 60°C for 10 hours to eliminate the possibility of viral transmission.[416,417] No cases of viral transmission have been attributed to AT III supplementation.[418–421] Additional advantages of AT III over fresh-frozen plasma include diminished volume load, absence of transfusion-related complications, and rapid availability. The advantages of treatment with fresh-frozen plasma include lower cost, but this must be balanced against the paucity of data supporting the effectiveness of fresh-frozen plasma. No studies have addressed the treatment of heparin resistance in neonates, infants, and children.

Recommendations for the Treatment of Heparin Resistance in Children With CHD

1. **Patients who exhibit heparin resistance (ACT <300 seconds after >600 U/kg heparin) should receive AT III concentrate (*Class I; Level of Evidence C*).**
2. **For patients who exhibit heparin resistance (ACT <300 seconds after >600 U/kg heparin), treatment with fresh-frozen plasma is reasonable (*Class IIa; Level of Evidence C*).**

10.1.4. HIT and Alternatives to Heparin for Anticoagulation for CPB in Children With CHD

Although a mild decrease in platelet count is common after the initiation of heparin therapy (formally called type I HIT), a more serious form of HIT (formally called type II HIT) is associated with a hypercoagulable state with arterial and venous thrombosis occurring ≥5 days after heparin therapy and is the result of a complex immune response that includes immunoglobulin G directed at the heparin platelet factor 4 complex.[422] HIT is increasingly recognized as a complication of heparin therapy in adults. It has been described in pediatric patients but may be less prevalent or less severe.[423–426] In patients with a recent history of HIT requiring cardiac surgery, alternatives to heparin may be necessary. Alternatives to heparin in pediatric patients undergoing operations with CPB include danaparoid and the direct thrombin inhibitors argatroban and bivalirudin. Danaparoid is a synthetic heparinoid compound prepared from porcine intestine that consists of heparan sulfate (84%), dermatan sulfate (12%), and chondroitin sulfate (4%) and is devoid of heparin or heparin fragments. Similar to heparin, it exerts its antithrombotic effect principally through AT III–mediated inhibition of FXa.[427,428] A recent review of children treated with danaparoid for anticoagulation for CPB included all previously published reports plus data on unpublished patients obtained through a compassionate-use program of the manufacturer. Three patients, ranging in age from 2 months to 14 years, were identified.[429–431] Two of these 3 patients survived. Danaparoid is not available for use in the United States.

Argatroban, a synthetic direct thrombin inhibitor derived from L-arginine, inhibits thrombin by binding to its catalytic site. Pediatric experience with argatroban is limited to case reports and a single nonrandomized, open-label study. The case report experience includes 8 infants ranging in age from 2 weeks to 9 months.[44,423,425,432–434] Outcomes were not provided

for all patients, but at least 1 patient was reported to die of hemorrhage; bleeding was noted in 3 others, and recombinant FVIIa was used in 1 patient. An open-label, uncontrolled study of argatroban was performed in 18 seriously ill patients <16 years of age who required an alternative to heparin. The number of patients who underwent cardiac procedures or extracorporeal support is not provided. Most patients had HIT or suspected HIT, including 8 patients <6 months of age, 6 patients between 6 months and 8 years of age, and 4 patients between 8 and 16 years of age. During the 30-day study period, thrombotic events occurred in 5 patients, 2 patients during and 3 patients after argatroban therapy. Major bleeding occurred in 2 patients. One patient experienced an intracranial hemorrhage after 4 days of argatroban therapy in the setting of sepsis and thrombocytopenia. Another patient completed 14 days of argatroban treatment in the study but experienced an intracranial hemorrhage while receiving argatroban after completion of the study.[435,436] The safety and effectiveness of argatroban, including the appropriate anticoagulation goals and duration of therapy, have not been established among pediatric patients.

Bivalirudin is a synthetic analog of hirudin, the anticoagulant found in medicinal leeches. There is minimal experience with the use of bivalirudin in children for the treatment and prevention of thrombosis.[437–439] There are 2 case reports of successful use of bivalirudin for anticoagulation for CPB in children.[47,440]

Recommendations for Anticoagulation of Children With HIT and CHD

1. **For patients in whom anticoagulation with heparin is contraindicated because of HIT and in whom surgery cannot be avoided or delayed until HIT antibodies are no longer detectable, it is reasonable to use the direct thrombin inhibitors argatroban or bivalirudin or the heparinoid danaparoid for anticoagulation, although these medications are off-label for HIT in children in the United States (*Class IIa; Level of Evidence C*).**

Table 7. Studies Comparing Lysine Analogs With Placebo in Children

Study	Year	Design	n	Redo, %	Cyanotic, %	Age	Bleeding	Tx	Fx	Re-ex	Load	Infusion	Prime
ε-Aminocaproic acid													
McClure and Izsak[446]	1974	RCT	56	NA	54	> 2 y	↓	NA	→	NA	75	15	510 mg/ UPRBCs
Williams et al[455]	1999	Case-control	140	94	NA	<12 mo–21 y	↓	→	↓	↓	150	30	0
Rao et al[454]	2000	RCT	170	NA	100	2 mo–14 y	↓	↓	↓	↓	100*	0	100
Chauhan et al[453]	2000	RCT	140	NA	100	2 mo–13 y	↓	↓	↓	↓	100*	0	100
Chauhan et al[451]	2004	RCT	100	NA	100	2 mo–14 y	↓	↓	↓	↓	100*	0	100
Tranexamic acid													
Zonis et al[451]	1996	RCT	82	29	22	1 d–14 y	↓→†	↓→†	NA	NA	50	0	0
Reid et al[450]	1997	RCT	41	100	54	6 mo–12 y	↓	→	→	NA	100	10	100
Levin et al[147]	2000	RCT	56	NA	50	1 d–16 y	→	→	→	NA	50	0	0
Chauhan et al[449]	2003	RCT	120	NA	100	2 mo–14 y	↓	↓	↓	↓	10‡	0	0
Chauhan et al[448]	2004	RCT	150	NA	100	2 mo–15 y	→	→	→	→	50	0	0
							↓	↓	→	↓	10	1	0
							↓	↓	↓	↓	10‡	0	0
							↓	↓	↓	↓	20*	0	0
Chauhan et al[451]	2004	RCT	100	NA	100	2 mo–14 y	↓	↓	↓	↓	10*	0	10
Bulutcu et al[447]	2005	RCT	50	NA	100	2 mo–10 y	↓	↓	↓	NA	100	8	100

Fx indicates laboratory evidence of fibrinolysis; NA, not applicable; RCT, randomized, clinical trial; Redo, reoperation; Re-ex, re-exploration; Load, loading dose of lysine analog; Tx, transfusion; UPRBCs, units of packed blood cells; ↓, decreased in treatment group; and →, no change from control group.

*Loading dose repeated after protamine administration.

†Effect identified in cyanotic patients; no effect identified in acyanotic patients.

‡Loading dose given after anesthetic induction, on cardiopulmonary bypass, and after protamine administration.

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10.1.5. Prevention and Treatment of Postoperative Coagulopathy

Post-CPB bleeding remains an important cause of mortality and morbidity after cardiac surgery. Strategies to limit bleeding include prophylactic treatment with antifibrinolytic agents and postoperative treatment with agents to promote clotting. The aim is to limit bleeding and therefore limit transfusion. Antifibrinolytic agents include aprotinin and the lysine analogs, ε-aminocaproic acid (EACA), and tranexamic acid (TXA).

Antifibrinolytics

tPA is produced during CPB and directly cleaves plasminogen to plasmin. The lysine binding sites on plasmin attach to fibrinogen and fibrin, and proteolysis results in the disruption of fibrin, which is needed to cross-link platelets and produce clot. The lysine analogs bear structural similarity to lysine, competitively bind to plasmin and plasminogen, and prevent breakdown of fibrin or fibrinogen. There are considerable data among adults undergoing cardiac surgery indicating that the lysine analogs result in reduced blood loss and need for transfusions.[441–444] These same studies indicate that the risk of complications such as stroke, thrombosis, and renal failure is not associated with the use of lysine analogs. There have been 11 comparative studies of lysine analogs in pediatric patients totaling >1000 patients.[147,445–455] These are well described in a recent review and meta-analysis, and Table 7 summarizes the results of these studies.[445,456] These studies are of varying quality, and more than half of the patients have come from a single institution, the All-India Institute of Medical Sciences. Furthermore, factors known to affect postoperative bleeding such as younger age, cyanosis, and reoperation are not always included. As an example, no patients undergoing stage I palliation of hypoplastic left heart syndrome are included in these studies. Only 1 study used measured arterial saturation to assign patients to the category of cyanotic CHD.[451] In other studies, it appears that the anatomic diagnosis (ie, tetralogy of Fallot) was the criterion because no arterial saturation data are provided. Only 2 studies focused on patients undergoing reoperation, 1 study looking at EACA and another evaluating TXA.[450,455] Both of these studies showed a decrease in bleeding in the group receiving a lysine analog, but both studies failed to show a reduction in transfusion.

A recent publication linked the Society of Thoracic Surgeons' Congenital Heart Surgery database with the Pediatric Health Information database that is maintained by the Children's Health Corporation of America. In this observational study, data were available on >22 000 patients and comparative data for a subgroup of 4685 patients. This study suggested relatively equivalent results between aprotinin and EACA in pediatric patients but improved outcome with TXA in terms of lower mortality and bleeding overall, and this benefit extended into the neonatal age range.[457]

A recent retrospective study of antifibrinolytics use in pediatric patients compared 70 patients treated with TXA with 70 patients treated with aprotinin and found that the outcomes were similar in terms of bleeding, re-exploration, intensive care unit length of stay, and transfusion, except that patients receiving TXA received more platelet transfusion.[458]

An additional recent retrospective review compared 34 neonates who received aprotinin (before May 2008) and 42 neonates who received TXA (after May 2008).[459] Aprotinin was associated with reduced perioperative blood product use, improved early indexes of postoperative recovery, and attenuated indexes of cytokine activation.

In a third recent report, 160 pediatric patients undergoing cardiac surgery were randomized to receive TXA compared with no antifibrinolytic. In this study, roughly half the patients were cyanotic. Allocation to treatment was further stratified according to the presence of cyanosis. Patients receiving TXA had decreased chest drainage at 6 and 24 hours, but the authors did not find a difference in transfusions.[460]

Thrombotic or other extravascular complications are rarely reported in the available studies. There is a single case report of fatal aortic thrombosis during EACA therapy in a child on ECMO.[461] Within the published dose ranges, thrombosis appears to be a rare complication in both the adult and pediatric literature, suggesting that the lysine analogs are reasonably safe. The published data further suggest that the lysine analogs reduce bleeding and transfusions with the caveat that not all patient populations have been thoroughly studied. Furthermore, an analysis of the available studies suggests a modest benefit of TXA over EACA.

Aprotinin is a serine protease inhibitor that is also classified as an antifibrinolytic. In addition to inhibiting plasmin, aprotinin prevents platelet activation on bypass and has measurable anti-inflammatory properties. Multiple randomized, controlled trials in adults have shown that aprotinin is effective in reducing blood loss and transfusion.[443,462] In a series of studies using prospectively collected data on >4000 patients analyzed with propensity-adjusted multivariable logistic regression, the Ischemia Research and Education Foundation identified an increased risk of renal failure, myocardial infarction, heart failure, stroke, encephalopathy, and late mortality among patients receiving aprotinin.[463,464] A multicenter, blinded, randomized, controlled trial comparing the lysine analogs with aprotinin identified an increased risk of mortality among patients receiving aprotinin.[465] In the recent publication linking the Society of Thoracic Surgeons' Congenital Heart Surgery database with the Pediatric Health Information database, information on antifibrinolytics use and outcome was available on >22 000 pediatric patients operated on between 2004 and 2008.[457] Aprotinin was used in >7000 patients, and compared with no antifibrinolytic therapy, aprotinin was associated with decreased bleeding and mortality without an increase in dialysis. In addition, in the recent report by Graham et al,[459] aprotinin was associated with reduced perioperative blood product use, improved early indexes of postoperative recovery, and attenuated indexes of cytokine activation. In 2007, the FDA limited the use of aprotinin to high-risk adult cardiac surgical patients. Although off-label use of aprotinin was common among congenital heart surgeons, high-quality studies were lacking.[466–468] The FDA has never approved a specific pediatric indication for aprotinin, and with the 2007 restrictions, it is no longer available for pediatric cardiac surgery in the United States.

Desmopressin (DDAVP) is a synthetic analog of the natural pituitary hormone 8-arginine vasopressin and is approved for replacement therapy in patients with pituitary insufficiency. Desmopressin is also indicated for the treatment of mild type I von Willebrand disease and mild hemophilia A with FVIII levels at least 5% of normal because it promotes the release

of vWF and FVIII from the endothelium. Among patients with von Willebrand disease, hemophilia A, and other platelet hemostatic disorders, preoperative administration of DDAVP may be useful for those patients undergoing cardiac surgery. In patients without a platelet hemostatic defect, the prophylactic administration of DDAVP to improve hemostasis after cardiac surgery has been studied, and the results are summarized in 3 meta-analyses, indicating no benefit.[469–471]

Furthermore the clinical practice guidelines produced by the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists do not recommend the prophylactic use of DDAVP.[472] A randomized, prospective trial in children undergoing cardiac surgery also failed to identify a benefit for the prophylactic use of DDAVP.[473]

Human-derived medium-purity FVIII concentrates complexed to Willebrand factor (Humate-P) are approved for pediatric patients with Von Willebrand disease for the prevention of excessive bleeding during and after surgery. This applies to patients with severe von Willebrand disease and patients with mild to moderate von Willebrand disease in whom the use of desmopressin is known or suspected to be inadequate.[474] Reports of the use of vWF in pediatric patients undergoing cardiac surgery are limited to case reports.

Recombinant FVIIa

Recombinant FVIIa is approved in the United States for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to FVIII or FIX and in patients with congenital FVII deficiency. More recently, recombinant FVIIa has been used off-label for salvage situations associated with persistent bleeding in cardiac operations.[475] There are small, single-center experiences in pediatric patients with intractable hemorrhage after cardiac surgery, among patients with known factor deficiency or coagulopathy after cardiac surgery, and among patients placed on ECMO after cardiac surgery with intractable hemorrhage.[476–485] These studies suggest that recombinant FVIIa is effective in decreasing postoperative bleeding, but thrombotic complications have been reported, including an arterial thrombus in an infant requiring amputation of a leg.[484] The dose used among pediatric patients with intractable hemorrhage after cardiac surgery ranges from 30 to 180 μg/kg (recommended dose for patients with hemophilia, 90 μg/kg).[476,478,479] A single randomized, blinded, controlled study has evaluated the prophylactic use of recombinant FVIIa to reduce time to chest closure and to decrease transfusion among infants undergoing cardiac surgery. This study included 76 patients: 40 received 40 μg/kg recombinant FVIIa, and 36 received placebo. Time to chest closure was significantly prolonged in the recombinant FVIIa group, and there was no difference in transfusions between the 2 groups.[486]

Recommendations for the Prevention and Treatment of Postoperative Coagulopathy in Children With CHD

1. **For patients >12 months of age with CHD who require operations using CPB and who are at increased risk for bleeding, it is reasonable to use the lysine analog TXA (*Class IIa; Level of Evidence B*).**
2. **For patients ≤12 months of age with CHD who require operations using CPB and who are at increased risk for bleeding, it is reasonable to use the lysine analog TXA (*Class IIa; Level of Evidence B*).**
3. **For patients >12 months of age with CHD who require operations using CPB and who are at increased risk for bleeding, it may be reasonable to use the lysine analog EACA (*Class IIb; Level of Evidence B*).**
4. **For patients ≤12 months of age with CHD who require operations using CPB and who are at increased risk for bleeding, it may be reasonable to use the lysine analog EACA (*Class IIb; Level of Evidence B*).**
5. **Among postcardiotomy patients with life-threatening hemorrhage despite every effort at surgical hemostasis and unabated by blood product transfusion, the use of recombinant FVIIa may be considered (*Class IIb; Level of Evidence C*).**
6. **Use of DDAVP might be considered for patients with specific platelet dysfunction such as type 1 von Willebrand disease and excessive bleeding after cardiac surgery (*Class IIb; Level of Evidence C*).**
7. **DDAVP is not indicated for routine prophylactic use to reduce bleeding or blood transfusion after cardiac operations in children (*Class III; Level of Evidence B*).**

10.2. Anticoagulation for Cardiac ECMO in Children With CHD

ECMO is a closed CPB circuit designed to provide support for intermittent periods, generally <14 days. Two methods of support are commonly used. Venovenous ECMO is a strategy in which blood is withdrawn from the venous system and returned to the venous system to exchange oxygen and carbon dioxide. Venovenous ECMO is used for patients with isolated respiratory failure with preserved cardiac function. Venoarterial ECMO provides cardiopulmonary support by removing deoxygenated venous blood, exchanging oxygen and carbon dioxide, and pumping it back into the patient's arterial circulation.[487] All circuits contain an oxygenator, pump, and heat exchanger. Originally, a silicone membrane oxygenator was used routinely, although today the oxygenator is commonly a hollow fiber design. The pump may be either a roller pump or a centrifugal pump.

Although ECMO was originally developed for support of the patient with respiratory failure, it was quickly applied to patients undergoing cardiac surgery as a form of mechanical support.[488,489] Among patients with CHD, ECMO is used most commonly for cardiac support and may be used preoperatively, postoperatively, for cardiac arrest, and as a bridge to transplantation.[490–492] Postcardiotomy ECMO refers to the use of ECMO to support the circulation of patients after cardiac surgery and is the most common indication for ECMO support among patients with CHD. Among large centers, postcardiotomy ECMO is used in 2% to 5% of all postoperative patients.[493] According to the Extracorporeal Life Support Organization registry, cardiac ECMO was used in >600 patients in 2006 and 2007; more than half the patients were <30 days of age.[494] In this youngest age group, survival was 35% to 40%. In older patients, survival was better, 47% to 49% in patients 31 days to 1 year of age and 58% to 59%

in patients 1 to 16 years of age, and is consistent with large single-center experiences.[494,495]

Like CPB, ECMO exposes the blood to a large surface area of foreign material and would result in thrombus formation if not for the use of anticoagulation. Bleeding complications are common, and despite anticoagulation, thrombotic and thromboembolic complications are also common on ECMO.[496] In an autopsy series of 78 adult patients placed on venoarterial ECMO for postcardiotomy failure, about one third of the patients were found to have venous thrombus formation and systemic thromboembolic events, and most of these were not identified before death.[497] In the most recent report from the Extracorporeal Life Support Organization registry, thrombotic, thromboembolic, and bleeding complications were identified frequently, and the youngest patients were at the greatest risk.[494] It has been generally accepted that for patients on ECMO, a lower level of anticoagulation is necessary compared with patients undergoing surgery using CPB, but a recent study suggested improved survival for patients on ECMO with higher heparin doses.[498]

The typical anticoagulation protocol includes a loading dose of 100 U/kg heparin before ECMO cannulation and a continuous infusion of heparin to maintain the ACT between 180 and 220 seconds. The ACT is checked every hour during extracorporeal support, and the heparin infusion is adjusted to maintain the target ACT. Although the ACT is a convenient POC test, it must not be relied on exclusively for the management of anticoagulation on ECMO. Additional laboratory tests are essential for adequate anticoagulation and should include at least daily anti-FXa levels, PT, PTT, fibrinogen, platelet count, and AT III levels. In particular, the PTT and anti-FXa levels are important confirmatory tests and should be repeated as necessary to confirm adequate anticoagulation. Prolongation of the PTT to 1.5 to 2.5 times the control value and an anti-FXa level of 0.3 to 0.7 U/mL have been suggested as suitable targets for anticoagulation of patients on ECMO.[499,500] In addition, the ECMO circuit must be visually inspected for clots on a regular basis. For patients who cannot be weaned from CPB, it is reasonable to forego the loading dose of heparin because the patient should already be suitably anticoagulated and additional heparin may increase the risk of bleeding. AT III deficiency can occur during ECMO support, especially in patients <1 year of age, and should be suspected if increasing heparin is necessary to maintain the target ACT. Transfusion with fresh-frozen plasma or supplementation with AT III can be given to correct AT III deficiency. Follow-up laboratory testing should be performed as needed to confirm that the coagulation defect has been corrected.

Postcardiotomy ECMO may be indicated for failure to wean from CPB or for intractable low output or cardiac arrest in the postoperative period. These patients have an increased risk of bleeding. In particular, patients who cannot be weaned from CPB and in whom heparin is not reversed have a greatly increased risk of bleeding on ECMO. Ongoing bleeding on ECMO is associated with poor survival; therefore, there must be diligent and ongoing efforts to achieve hemostasis. Above all, every effort must be made to identify and control surgical bleeding sites. Additional efforts are targeted at correcting hematologic deficiencies, including maintaining the hemoglobin >10 mg/dL, platelet count >100 000 per 1 mm^3, fibrinogen >200 mg/dL, and AT III >1 U/mL.[501]

In an effort to limit contact activation during ECMO support, internal surface modifications have been made to ECMO materials. Among the most commonly used is covalently bonded heparin (Carmeda, Medtronic Cardiopulmonary, Anaheim, CA). This has been applied to all components of the circuit, including the internal tubing surfaces, cannulas, heat exchanger, and oxygenator. Alsoufi and colleagues[501] reported the outcome of 3 adult patients supported with a heparin-bonded ECMO circuit for postcardiotomy failure. All 3 patients were weaned from support, and 2 were long-term survivors. Two of these patients were maintained for periods of time without systemic heparinization. One was maintained without heparin for the entire 57 hours of extracorporeal support, and 1 patient was maintained for 2 periods of 9 and 37 hours without heparin. Muehrcke et al[502] reported their experience with 30 patients supported for 62.8±41.1 hours using a heparin-bonded circuit for venoarterial cardiac support. In all but 5 patients, heparin was not routinely used. This experience included 2 patients <19 years of age. Thromboembolic complications were common. Limb ischemia related to cannulation site occurred in 70%, oxygenator failure occurred in 43%, cerebrovascular accidents occurred in 10%, and intracardiac thrombus was identified in 20%. Some authors have reported using little or no additional heparin in pediatric patients placed on heparin-bonded ECMO circuits for postcardiotomy support, although little or no data are provided on thromboembolic complications.[503,504] A recent retrospective review included 25 pediatric patients supported with ECMO after cardiac surgery. Fourteen patients were supported with standard heparinization, and 11 patients were supported with heparin-bonded circuits. The patients were of similar disease severity, age, and size. The patients supported with a heparin-bonded circuit had a lower ACT and chest tube output; in addition, they received less blood product transfusion.[504]

There are limited data on the use of the antifibrinolytic agents aprotinin, EACA, and TXA to control bleeding and to decrease transfusions in congenital heart surgery patients supported on ECMO. In a multicenter, randomized, blinded, placebo-controlled trial comparing placebo with EACA, 29 noncardiac neonates were enrolled (EACA, n=13; placebo, n=16). There was no statistical difference in the incidence of significant intracranial hemorrhage or thrombotic complications between groups. The authors concluded that EACA in neonates receiving ECMO is safe but may not decrease the overall incidence of hemorrhagic complications.[505] In a single-institution series, 82 of 129 patients supported on ECMO for cardiac indications received EACA. Indications for EACA use included a preexisting or anticipated surgical procedure and profound coagulopathy. Among patients receiving EACA, surgical site bleeding occurred in 10% compared with 30% reported to the Extracorporeal Life Support Organization registry. There was no difference in the occurrence of intracranial hemorrhage or thrombotic complications. Rates of bleeding and transfusion were not different between the EACA and control groups, but EACA was used in those patients deemed to be at higher risk of bleeding.[506] A single study has evaluated the use of TXA among patients undergoing repair of

diaphragmatic hernia while supported on ECMO. This was a retrospective study using historic controls. The authors identified important thrombotic complications in 2 of 10 patients receiving TXA. Patients receiving TXA had less bleeding and received fewer transfusions than control patients. They concluded that TXA decreased bleeding and transfusion but may be associated with a risk of thrombotic complications.[507] Small single-center series suggest that aprotinin may be useful in the management of life-threatening hemorrhage in patients on extracorporeal support; however, aprotinin is currently unavailable in the United States and Canada.[508] Very little is known about dosing strategies for any of the antifibrinolytics in patients supported on ECMO. In the largest single-center experience reported, the dose of EACA included a loading dose of 100 mg/kg followed by a continuous infusion of 30 $mg \cdot kg^{-1} \cdot h^{-1}$ for 72 hours. If bleeding persisted, the infusion was continued. Target ACTs were between 180 and 200 seconds.[506] There is a report of fatal thrombosis in a neonate with respiratory insufficiency supported on ECMO using this dosing and anticoagulation strategy for EACA.[461]

Recently recombinant FVIIa has been used off-label for salvage of patients with persistent bleeding on ECMO. The data on the use of recombinant FVIIa among patients with severe bleeding on ECMO are limited to case reports and small single-institution series.[483–485,509,510] In case reports and small uncontrolled series, bleeding was reported to decrease after the administration of recombinant FVIIa.[482,483,509] Two studies compared outcome among patients receiving recombinant FVIIa on ECMO with historic controls. Veldman and colleagues[485] reported on 7 patients receiving recombinant FVIIa for intractable hemorrhage while on ECMO. Two patients developed occlusive thrombosis of the oxygenator, although rates of ECMO circuit occlusions and mortality were deemed not to differ from historic controls. Neither the reduction of chest tube output nor the decrease in blood product transfusion requirements reached statistical significance. Agarwal and colleagues[484] reported 11 patients who received recombinant FVIIa on ECMO for severe bleeding and compared their outcome with those of 15 historic controls. Both bleeding and transfusion were decreased. Thrombotic complications occurred in 2 patients, including oxygenator occlusion requiring emergent circuit change, limb ischemia necessitating lower-extremity amputation, and intracardiac thrombus requiring surgical thrombectomy. The overarching findings with respect to the use of recombinant FVIIa for patients with severe bleeding on ECMO include a reduction in bleeding and transfusion requirements but at the cost of significant risk of thrombotic complications in both the patient and the ECMO circuit.[510] The usual dose of recombinant FVIIa is 90 μg/kg, although half-dose and multidose dosing strategies are commonly used.

Postcardiotomy ECMO support is used in critically ill patients who otherwise have little chance of survival. Ongoing bleeding and continuous transfusion frequently complicate the course of these patients and affect survival. Every effort should be made to achieve surgical control of bleeding. Simultaneously, every effort should be made to correct coagulation deficiencies. The use of heparin-bonded circuits with minimal heparinization may be considered a strategy to decrease the risk of bleeding in high-risk patients. Use of minimal heparinization and decreased ECMO flow may predispose to thrombus formation within the ECMO circuit; therefore, with prolonged periods of decreased flow, the level of anticoagulation should be increased. For patients with ongoing bleeding despite efforts at surgical hemostasis and correction of coagulation deficiencies, the addition of the EACA may be considered. Although recombinant FVIIa has been used in patients with severe hemorrhage on ECMO, there are substantial risks of thrombotic complications, and the data on the risks and benefits are inadequate to develop specific recommendations. Caution should be exercised in combining strategies to control bleeding on ECMO. Specifically, the combination of strategies such as the use of antifibrinolytic agents with minimal heparin or recombinant FVIIa has not been adequately studied, and the risk-to-benefit ratio cannot be ascertained.

Recommendations for Anticoagulation of Children With CHD on ECMO

1. **ECMO should be conducted with the assistance of a qualified extracorporeal technologist (*Class I; Level of Evidence C*).**
2. **Anticoagulation for ECMO should include the administration of 100 U/kg heparin before ECMO cannulation and a continuous infusion of heparin to maintain the ACT between 180 and 220 seconds. Additional hematologic laboratory data are essential to management and should be checked at least daily, including anti-FXa levels, hemoglobin, hematocrit, PT, PTT, and AT III. These studies should be repeated as necessary to confirm adequate anticoagulation and correction of coagulation defects (*Class I; Level of Evidence C*).**
3. **For patients with ongoing bleeding on ECMO, every effort should be made to achieve surgical control of bleeding (*Class I; Level of Evidence C*). Simultaneously, every effort should be made to correct coagulation deficiencies, including maintaining the hemoglobin >10 mg/dL, platelet count >100 000 per 1 mm^3, and fibrinogen >200 mg/dL (*Class I; Level of Evidence C*).**
4. **Transfusion of fresh-frozen plasma or AT III supplementation should be given to correct AT III deficiency (*Class I; Level of Evidence C*).**
5. **For patients who cannot be weaned from CPB, it is reasonable to forego the loading dose of heparin before the initiation of ECMO because the patient should already be suitably anticoagulated and additional heparin may increase the risk of bleeding (*Class IIa; Level of Evidence C*).**
6. **The use of heparin-bonded circuits with minimal heparinization may be considered as a strategy to decrease the risk of bleeding in high-risk patients (*Class IIb; Level of Evidence C*).**
7. **For patients with ongoing bleeding despite efforts at surgical hemostasis and correction of coagulation deficiencies, the addition of the lycine analog EACA may be considered (*Class IIb; Level of Evidence C*).**

11. Primary Prevention and Treatment of Thrombi in Children With Arrhythmias

A variety of rhythm disorders or conditions either require anticoagulation or can make the anticoagulation management of other conditions more complex. Most notable is the presence of atrial arrhythmias. In 2006, the ACC, AHA, and European Society of Cardiology published updated practice guidelines for AF.[511] These guidelines are an excellent and very comprehensive review of all aspects of AF. Age-specific references were made as to how age was a factor in the development of AF and the risk of stroke.[511]

11.1. Atrial Arrhythmias

Intra-atrial Reentrant Tachycardia/Atrial Flutter

Pediatric and adult CHD patients who have had surgery involving their atria are at increased risk for intra-atrial reentrant tachycardia (IART)/atrial flutter (AFL) and AF. This includes patients who have had a Senning, Mustard, or Fontan palliation. It is not an uncommon practice to anticoagulate pediatric and adult CHD patients who are in IART/AFL. A study by Feltes and Friedman[512] demonstrated by transesophageal echocardiography that 8 of 19 patients (42%) with AFL (n=18) and atrial tachycardia (n=1) had atrial thrombi. Of these 8 patients, 7 also had transthoracic echocardiography, but thrombus was identified in only 1 patient. Left atrial appendage flow has also been demonstrated to be reduced during AFL, although better than that seen in AF.[511,513] Atrial stunning with limited mechanical contraction after direct current conversion has also been described.[514]

Atrial Fibrillation

AF in young people is seen most often in association with CHD.[515] Although IART and AFL are more common in CHD patients, Kirsh and associates[516] demonstrated that 20% of a CHD cohort requiring cardioversion had AF. This is more often true for CHD patients in their adult years. However, although rare, AF is seen in younger patients with no other associated heart disease, also known as lone AF. AF in adults without CHD is the most common arrhythmia seen in adult cardiology clinical practice.[511] It is usually related to age and is associated with hypertension, coronary disease, and heart failure. Recommendations for anticoagulation in adults with atrial fibrillation and atrial flutter are listed in Table 8.

Risk Associated With AF

The risk of stroke in adult AF patients is well established. One published method of assessing risk can be characterized by using the $CHADS_2$ scoring system derived from other studies establishing AF risk (Table 8).[518] A more recent scoring system, CHA2DS2-VASc, gives 2 points for age ≥75 years and for a history of stroke, transient ischemic attack, or thromboembolism. The other factors of CHF/LV dysfunction, hypertension, diabetes mellitus, vascular disease, age 65-74 years, and female gender all get 1 point. A score of ≥2 is considered high risk, and anticoagulation therapy is recommended.[518a] There are no studies specifically addressing the risk of AF in pediatric patients, but with the use of the scoring systems, the risk for most young people for stroke with AF is very low.

The presence of thrombi in the left atrial appendage is a well-established risk factor for stroke or embolization. Spontaneous echo contrast can be seen in AF and is a result of low-flow states in the atrium. Spontaneous echo contrast and AF are independent risk factors for thrombus formation.[511,519,520] Although anticoagulation with a VKA such as warfarin will diminish the size of an intracardiac thrombus, it does not have a significant effect on spontaneous echo contrast.[521] When either spontaneous echo contrast or thrombi are seen by transesophageal echocardiography, anticoagulation is recommended for at least 3 weeks before cardioversion.[511]

Electromechanical Dissociation (Atrial Stunning)

Prolonged AF and IART/AFL can result in electromechanical dissociation. Electromechanical dissociation refers to the lack of atrial wall movement despite ECG evidence of sinus or organized atrial activity. This is common in AF and in IART/AFL after cardioversion.[514] One study demonstrated a higher incidence of left atrial thrombi correlating with lower intra-appendage velocities during AFL.[514] Although there is concern that the conversion of AF or IART/AFL via direct current, overdrive atrial pacing, or medication will result in the first postconversion sinus beat causing dislodgement of thrombus at the moment of conversion, a greater risk may be when the atria regain mechanical contraction with sinus rhythm several days to weeks later.[511,522–524]

Timing of Direct Current Cardioversion

Patients who have AF but are already anticoagulated with an INR 2.0 to 3.0 or those certain of the onset of AF by abrupt onset of symptoms can be cardioverted electively within 48 hours of the onset of symptoms.[511] On the other hand, those patients uncertain of the onset of symptoms or those presenting >48 hours after symptom onset should undergo transesophageal echocardiography if cardioversion is indicated and the recommended 4 weeks of therapeutic anticoagulation before cardioversion is unachievable.[511] Transesophageal echocardiography has become the standard premanagement procedure recommended in adults with AF because of its excellent views of the left atrial appendage.[511,525] When no thrombus is found, anticoagulation with LMWH or intravenous heparin (PTT, 1.5–2.0 times control) is recommended before cardioversion, and therapeutic anticoagulation with a VKA (INR, 2.0–3.0) should be continued for at least 4 weeks. When a thrombus has been found, the recommendation for adult patients is anticoagulation with a VKA for 4 weeks before cardioversion and repeat transesophageal echocardiography to confirm the resolution of thrombus. In adults, anticoagulation is recommended for a minimum of 4 weeks after cardioversion,[511] Although there are currently no data in the pediatric age group on the timing or need for anticoagulation after cardioversion, it is common pediatric practice to continue postcardioversion anticoagulation, barring individual patient contraindications.

One study in young patients (age, 3 months–49 years; median, 20.5 years) found that transthoracic echocardiogram had a high sensitivity for atrial thrombi, with 10 postoperative CHD patients found to have a suspected thrombus.[526]

Transesophageal echocardiography confirmed a right atrial thrombus in only 3 patients. None of those patients had a left atrial thrombus. The authors suggested that transthoracic echocardiogram should be used as a screening tool, with

transesophageal echocardiography used only to confirm findings of a thrombus. Although this study reports reliable transthoracic echocardiogram detection of right atrial thrombi, the absence of identifying left atrial thrombi in patients who had only transthoracic echocardiogram without transesophageal echocardiography confirmation does not indicate that transthoracic echocardiogram is sufficient to rule out a left atrial thrombus

Anticoagulation Approach to IART and AF

To date, there are no published studies of anticoagulation with atrial arrhythmias in pediatric patients alone. Therefore, experience from the adult literature must be used as a surrogate for data specific for the pediatric age group. However, some inferences can be gained from the existing adult literature. For patients with lone AF (AF with no associated heart disease), Kopecky et al[527] demonstrated that the risk of stroke is very low in those patients <60 years of age. The authors suggest that routine anticoagulation may not be needed for primary prevention. However, for those patients with ≥1 risk factors for stroke, the ACC/AHA/European Society of Cardiology 2006 guidelines recommend anticoagulation with an INR of 2.0 to 3.0.[511] For those in whom VKAs are contraindicated, aspirin is recommended as an alternative. Anticoagulation in patients with IART/AFL who are refractory to treatment should be managed the same as for AF.[511]

For those patients who undergo surgical procedures and do not have mechanical valves, the ACC/AHA/European Society of Cardiology guidelines state that VKA anticoagulation can be interrupted for a week without the use of heparin for procedures that carry a risk of bleeding.[511] For those patients with mechanical valves, substitution with UFH is recommended while VKA anticoagulation is held.

New Anticoagulation Agents

In October 2010, it was announced that the FDA approved use of dabigatran etexilate in adults with AF. Dabigatran is a direct thrombin inhibitor that has the advantage of not requiring regular monitoring like warfarin with periodic INRs. In 2009, a large study of 18 113 AF patients was published by Connolly et al.[528] Patients were randomly assigned to receive either 110 or 150 mg dabigatran or standard warfarin treatment, including monitoring of INRs. The study showed similar rates of stroke and system embolization between groups treated with dabigatran 110 mg and with warfarin. Patients treated with dabigatran 150 mg had lower rates of stroke and systemic embolization but similar rates of major hemorrhage.

The FDA also has approved a new FXa inhibitor called rivaroxaban in adults for postoperative thromboprophylaxis in patients who have undergone hip or knee replacement surgery and for the prevention of stroke and systemic embolism in adults with nonvalvular AF.[529] A large trial, ROCKET-AF (Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), has recently been published in which 14 000 AF patients were randomized to rivaroxaban or warfarin.[530] There are no studies demonstrating the use of dabigatran or rivaroxaban in pediatric patients or in adults with CHD. Several other FXa inhibitors are undergoing large trials in AF patients, but those medications have not yet been FDA approved.

Recommendations for Anticoagulation in Children With Atrial Arrhythmias

1. **Pediatric patients with IART (including AFL) or AF who are not anticoagulated and have clear evidence of onset <48 hours should be cardioverted. Transesophageal echocardiography does not need to be done (*Class I; Level of Evidence B*).**
2. **Pediatric patients with IART (including AFL) or AF believed to be present or potentially present >48 hours should undergo echocardiographic screening for intracardiac thrombi or spontaneous echo contrast. Transesophageal echocardiographic screening is more sensitive but more invasive than transthoracic echocardiogram and is indicated when the accuracy of transthoracic screening is subject to uncertainty, typically beyond the toddler age group. In patients with a thrombus who are hemodynamically stable in whom the heart rate is acceptable or can be controlled, anticoagulation with a VKA should be initiated to achieve an INR of 2.0 to 3.0 for 4 weeks**

Table 8. Anticoagulation Recommendations for Atrial Fibrillation and Atrial Flutter

Warfarin (INR, 2.0–3.0)	Warfarin (INR, 2.5–3.5)	ASA (81–325 mg)*
Systemic atrial enlargement	Prior thromboembolic event on lower therapeutic dose of warfarin†	All other congenital heart disease patients
Systemic ventricular dysfunction	Mitral valve bioprosthesis	
Fontan circulation	Mechanical valve prosthesis†	
Ebstein anomaly with atrial-level shunt		
Prior thromboembolic event on no anticoagulation		
Aortic valve bioprosthesis		
All other conditions with other risk factors‡		

ASA indicates acetylsalicylic acid; and INR, international normalized ratio.
*Clopidogrel can be considered in those with aspirin allergy.
†Low-dose ASA is recommended in addition to warfarin.
‡Congestive heart failure, hypertension, and diabetes mellitus.
Adapted from Bonow et al[317] and Warnes et al.[203]

before cardioversion is performed (*Class I; Level of Evidence B*).

3. **Pediatric patients without contraindication who have a history of recurrent AF and stroke or heart failure should be on long-term anticoagulation, with a VKA goal INR of 2.0 to 3.0 (*Class I; Level of Evidence B*).**
4. **Pediatric patients who have a history of recurrent AF and stroke or heart failure with contraindications to VKA should receive long-term aspirin (*Class I; Level of Evidence C*).**
5. **In pediatric patients with refractory IART (ie, cannot be kept out of IART despite treatment), long-term anticoagulation with a VKA with an INR of 2.0 to 3.0 may be reasonable (*Class IIb; Level of Evidence C*).**
6. **For pediatric patients with paroxysmal AF and no other risk factors,§ including lone AF, long-term anticoagulation is not indicated (*Class III; Level of Evidence C*).**
7. **For pediatric patients with recurrent but convertible IART with no other risk factors,§ long-term anticoagulation is not indicated (*Class III, Level of Evidence C*).**

11.2. Pacemakers and Internal Cardiac Defibrillators

Implantation of pacemaker or internal cardiac defibrillator leads in children requires more advance planning than in adults because of anatomic and size concerns. This includes decisions about transvenous or epicardial approaches, placement of systems in patients with single ventricles, maintenance of venous patency after lead placement, and consideration of anticipated somatic growth of the patient. Placement of leads in patients with either left-to-right or right-to-left intracardiac shunts raises concerns about the possibility of a paradoxical embolus. Silka and Rice[531] reported a patient with a small ventricular septal defect and left-to-right shunt who suffered a cerebral embolic event 30 days after transvenous pacemaker placement. Hemodynamic evaluation demonstrated a brief shunt reversal, creating a paradoxical right-to-left shunt through the defect. Khairy et al[532] demonstrated that transvenous leads were a multifactorial independent risk for emboli regardless of shunt direction. In addition, some patients had embolic complications despite aspirin or warfarin with a therapeutic INR.

Venous thrombosis is reported to occur in 3% to 25% after implantation of transvenous pacemaker and internal cardiac defibrillator leads in adult patients.[533–535] The risk of venous thrombosis in children has serious implications in that it may represent a loss of future access for replacement leads as old leads fracture. Considering the potential for many decades of life with a pacing system, maintenance of venous patency is desirable. Data are inconclusive for showing that anticoagulation prevents thrombosis in these patients. Figa et al[536] reviewed risk factors for venous obstruction in pediatric patients with transvenous leads. A cross-sectional pacemaker lead area of >6.6 mm^2/m^2 body surface area increases the risk for thrombosis. Depending on the leads selected (pacemaker versus internal cardiac defibrillator, stylet driven versus guide catheter driven) and number of leads to be placed, consideration should be given to the placement of epicardial systems in smaller patients.

When performing implantation of cardiac implantable electronic devices (pacemakers and internal cardiac defibrillators), there is evidence that warfarin should be continued without heparin substitution during those procedures.[537,538] Heparin administration is associated with a higher incidence of postoperative pocket hematoma.[537] Moreover, an increased risk for device infection is produced by reentering the wound when evacuating a hematoma. The same is true for LMWH.[539]

Recommendations for Anticoagulation in Children With Pacemakers and Internal Cardiac Defibrillators

1. **In pediatric patients who need pacing systems, depending on the types of leads and number of leads to be placed, it may be reasonable to consider a nontransvenous system in smaller children to avoid venous thrombosis (*Class IIb; Level of Evidence C*).**
2. **For pediatric patients already anticoagulated with a VKA and a therapeutic INR, it may be reasonable to consider proceeding with a cardiac rhythm device implantation procedure by continuing the VKA at the same or reduced dose without bridging anticoagulation with heparin (*Class IIb; Level of Evidence B*).**
3. **In patients with a transvenous pacing system and an intracardiac left-to-right shunt, long-term anticoagulation with a VKA may be considered (*Class IIb; Level of Evidence C*).**
4. **Because of the risk of paradoxical embolus, placement of transvenous intracardiac pacing systems is not recommended in pediatric patients with right-to-left intracardiac shunting unless no other options are available (*Class III; Level of Evidence C*). If a transvenous pacing system is deemed necessary in a patient with an intracardiac right-to-left shunt, long-term anticoagulation with a VKA is reasonable (*Class IIa; Level of Evidence C*).**

11.3. Electrophysiology Studies and Catheter Ablation Procedures

Radiofrequency Catheter Ablation

Electrophysiology studies have been performed in pediatric and CHD patients for several decades now. The onset of radiofrequency catheter ablation (RFCA) to treat arrhythmias in the late 1980s brought more patients to the electrophysiology laboratory than ever before because many of these patients had otherwise normal, healthy hearts except for an abnormal rhythm. In addition, many patients with CHD and arrhythmias related to their heart disease or surgical repair could have their arrhythmias addressed with RFCA. The result was that many patients who could be treated only with long-term medications before the advent of RFCA subsequently could stop taking these medications in many cases.

Many of the principles of electrophysiology studies as they relate to the presence of catheters and anticoagulation are covered

§Risk factors include previous stroke or transient ischemic attack, diabetes mellitus, history of hypertension, and heart failure.

in the section on cardiac catheterization. However, RFCA in addition to electrophysiology studies adds another set of risk factors for thrombus formation during the procedure. RFCA destroys targeted tissue by resistive heating of the tissue at the catheter tip. This results in coagulation necrosis and endothelial disruption.

Several studies have compared patients having electrophysiology studies alone with those having RFCA. Manolis et al[540] and Michelucci et al[541] separately studied activation of the clotting system, comparing patients who had routine electrophysiology studies with patients who had RFCA procedures. Spontaneous platelet aggregation, prothrombin fragment 1+2, thrombin-antithrombin complex, and d-dimer levels increased in all patients. However, patients who had RFCA had more marked elevations in prothrombotic indicators, some >2 times that for electrophysiology studies. In addition, although no significant association was found with the number of energy applications, total energy delivery time, or duration of the procedure, significance was noted with the mean duration of energy application >23.5 seconds and elevation of prothrombin fragment 1+2. Some indicators returned to normal in 24 hours, but the thrombin-antithrombin complex and d-dimer remained >2.5 times above the baseline values. Although this study was in adults, the patient age standard deviation was large. There was a positive correlation between age and hemostatic parameters at baseline and after ablation. This is in contrast to a study by Dorbala et al,[542] who compared similar groups and found no significant difference between the RFCA and non-RFCA groups but found a more prominent activation of the coagulation cascade with the length of the RFCA procedure. A study of patients having RFCA for AFL demonstrated that ablation causes release of procoagulant microparticles derived from platelets and leukocytes but not from endothelium.[543]

The thrombotic complications of RFCA reported in multiple adult studies were reviewed by Zhou et al.[544] The thromboembolic complication rate ranged from 0% to 2%. Most of these studies reported systemic heparinization during the ablations, particularly when ablating on the left side. The complications included coronary artery occlusion, cerebral embolism, PE, and femoral artery occlusion. In 1 study, intracranial microembolic signals were seen during 16 of 51 left-side ablations (32%) as detected by Doppler ultrasound.[545] Neurological symptoms were transiently observed in 2 older adult patients immediately after the onset of radiofrequency energy, but no long-term sequelae were noted.

Catheter Cryoablation

Catheter cryoablation is a relatively new catheter method to create cardiac lesions by freezing the targeted tissue. Freeze lesions to −80°C results in cellular death without damaging the connective tissue and intercellular matrix supporting the cells. Several studies in pediatric patients who have had catheter cryoablation have been reported with no thromboembolic complications.[546–549] Compared with RFCA, catheter cryoablation appears to be less thrombogenic. An in vitro study demonstrated significant damage to blood cells and platelets with RFCA compared with catheter cryoablation.[550] A comparison of catheter cryoablation with RFCA in 30 adult patients has been reported by Tse et al.[551] They found a significant increase in platelet activation in the RFCA group compared with the catheter cryoablation group. Several thrombotic parameters were elevated in both the catheter cryoablation and RFCA groups, observed immediately after sheath insertion. Finally, a study in dogs comparing RFCA and catheter cryoablation found a significantly higher incidence of thrombus formation and a greater thrombus volume with RFCA compared with catheter cryoablation.[206]

Anticoagulation and Catheter Ablation Procedures

Heparinization is commonly used during catheter ablation, especially for mapping on the left side of the heart or in patients with intracardiac shunting. Techniques for heparinization vary but often begin with a bolus (50–100 IU/kg, up to 5000 IU) after sheaths and catheters are placed and often before transseptal puncture is performed. Periodic repeat boluses or a heparin infusion is then used for the duration of the case. ACTs were used to monitor heparinization in several mostly pediatric studies.[544,552–555] However, many studies using heparin administration do not include the desired ACT during ablation or the anticoagulation monitoring methods. The benefit of heparinization administration during catheter ablation procedures is unclear, with several reports demonstrating either no benefit or no enhanced benefit with earlier heparin administration after placement of sheaths.[544,556,557] Epstein et al[558] demonstrated a low incidence of embolic complications among 758 pediatric and congenital patients from 11 centers. A wide variety of anticoagulation protocols was used, but all used heparin for left-side ablations. Despite the variety of anticoagulation protocols, there was no significant difference in the rate of embolic events. The presence of thromboembolus was also demonstrated in a study in dogs using RFCA despite pretreatment with aspirin and intraprocedural heparin administration.[206]

Aspirin is often administered after ablations, particularly on the left side. Data to support this practice are sparse. One study compared pigs that received a single preablation dose of heparin followed by 5 to 7 days of a single aspirin dose of 150 mg to controls.[559] Thrombus formation was significantly more common in the control group, with 9 of 10 pigs found to have thrombi. Nevertheless, 4 of 10 pigs in the aspirin group had thrombi.

Transseptal Catheterization

Transseptal puncture is often used for access to place ablation lesions on the left side of the heart. Transseptal puncture is generally regarded as a safe procedure. Multiple studies have demonstrated the overall safety of transseptal catheterization. A review of the Pediatric Radiofrequency Catheter Ablation Registry demonstrated no difference between transseptal, retrograde, or intracoronary sinus approaches with regard to thromboembolic complications.[560] A study in adults by De Ponti et al[561] evaluated 5520 patients and found a thrombotic complication rate of <1%. Lesh et al[562] compared groups of patients, both pediatric and adult, who had left-side ablation via the retrograde versus transseptal approach. There was no difference in the rate of complications between the 2 groups. None of the complications were thromboembolic in nature. Several pediatric ablation studies mention transseptal access, but thromboembolic complications are rare or not reported.[553,554,563]

However, transseptal catheterization itself can be an added risk for catheter ablation. There are no studies in pediatric patients that look specifically at the thrombotic effects of transseptal puncture. Two separate adult studies prospectively studied their ablation patients, isolating the effects of transseptal catheterization and the risk of thrombotic complications.[555,564] Maleki et al[555] demonstrated thrombus formation at the end of the transseptal sheath by intravascular ultrasound within 15 minutes in 9% of a group of patients who had their transseptal sheath prepared before intravenous access with a standard heparin solution of 2 U/mL and received a bolus of 5000 IU heparin followed by 1000 U/h with an ACT >250 seconds. Another similar group of patients had the same heparin bolus and heparin infusion but had their transseptal sheath flushed with 1000 U/mL. In this second group, only 1% of the patients had thrombus on the transseptal sheath. The thrombi from both groups were successfully aspirated back into the sheath. Thrombus was withdrawn from the sheath and confirmed visually. No patient had a clinically evident thromboembolic event.

Cauchemez et al[564] demonstrated a difference in the rate of transseptal sheath perfusion. Five patients (6%) had cerebrovascular embolic complications when their transseptal sheaths were perfused with heparinized saline (1000 U/L) at a standard flow rate of 3 mL/h compared with no patients having cerebrovascular embolic complications when the transseptal sheath was perfused at 180 mL/h. Although many adults can tolerate this volume of infusion, small pediatric patients or those with congestive heart failure may not.

Although heparinized saline solutions are often used to perfuse transseptal sheaths with some evidence of benefit, there is also good reason to be concerned about infusing air or thrombus into the left side of the heart during catheter exchanges. Therefore, the infusion should be discontinued during catheter exchanges, and the operator must be very careful that air or thrombi are not in the sheath or introduced during catheter exchanges or when the infusion is restarted.

Recommendations for Anticoagulation During Catheter Ablation Procedures in Children

1. **Pediatric patients having catheter ablation procedures on the left side of the heart, regardless of transseptal or retroaortic approach, should have procedural systemic anticoagulation with UFH (*Class I; Level of Evidence B*).**
2. **It is reasonable to use UFH when a transseptal sheath is placed into the left side of the heart for as long as the transseptal sheath is in the left side of the heart. In addition, it is reasonable to monitor the ACT with a goal of >250 seconds. It is also reasonable to use a constant infusion of heparin at 1000 U/mL in the sheath at a minimum rate of 3 mL/h (*Class IIa; Level of Evidence B*). Care must be taken to stop the infusion and to ensure that the sheath is free of air and thrombus when exchanging catheters.**
3. **The recommended dose for UFH during left-side ablation procedures is a bolus of 50 to 100 U/kg up to 5000 IU. Heparinization can be maintained or adjusted throughout the case with either repeated boluses or a continuous intravenous infusion. Use of an ACT is reasonable to guide heparinization, with a goal for left-side ablations of >250 seconds (*Class IIa; Level of Evidence B*).**
4. **Administration of UFH is reasonable for RFCA on the right side of the heart for the duration of the case (*Class IIa; Level of Evidence B*).**
5. **Administration of low-dose aspirin is reasonable for 6 to 8 weeks after radiofrequency ablation when lesions have been placed on the systemic side of heart or when significant intracardiac shunts are present (*Class IIa; Level of Evidence C*).**
6. **Anticoagulation with UFH may be considered in electrophysiology procedures using cryoablation only (*Class IIb; Level of Evidence B*).**

11.4. Special Considerations in Adults With CHD and Arrhythmias

Adult patients with AF and AFL are at increased risk for systemic and cerebral thromboembolic complications. In adults, the risk is roughly equivalent for all 3 temporally based categories: paroxysmal, persistent, and permanent AF. Currently, long-term antithrombotic prophylaxis with either warfarin for those at highest risk or aspirin for those at lowest risk is recommended for all patients except for those with lone AF. These guidelines have been summarized in the 2006 ACC/AHA guidelines for the management of patients with AF.[511]

By definition, no patient with CHD falls into the low-risk category because it requires that the patient is <60 years of age and has no evidence of cardiopulmonary disease. The choice of antiplatelet therapy or warfarin for long-term anticoagulation depends on the relative risk for thromboembolism and an assessment of a patient's ability to be compliant with the regimen. Warfarin should be strongly considered in those at highest risk, including those with enlargement of the systemic atrium, systemic ventricular systolic and diastolic dysfunction, Fontan circulation (especially in the presence of an atrial communication), and a prior thromboembolic event.[203] The target INR is 2.0 to 3.0, except for patients with recurrent thromboembolism on warfarin and those with mechanical prosthetic valves. In these patients, the target INR should be 2.5 to 3.5, and low-dose aspirin (75–100 mg daily) may be added. If a thromboembolic event occurs in the higher therapeutic range (INR, 2.5–3.5), even higher target INRs should be considered.[317]

12. Primary Prevention and Treatment of Thrombi in Children With Acquired Heart Disease

12.1. Kawasaki Disease

12.1.1. General Guidelines

First described in 1967, Kawasaki disease is an acute vasculitis involving high fever, nonexudative conjunctivitis, inflammation of the oral mucosa, rash, cervical adenopathy, and findings in the extremities, including swollen hands and feet, red palms and soles, and later subungual peeling[565] If

untreated, coronary artery aneurysms develop in 20% to 25% of affected children and may lead to ischemic heart disease or sudden death.[566] Kawasaki disease is an immune-mediated vasculitis with a self-limited clinical course. During the acute phase, there is production of a host of inflammatory cytokines (interleukin-2, interleukin-6, tumor necrosis factor-α, etc) and cytotoxic antibodies, which contribute to injury to the vascular endothelium. The endothelium, which normally possesses anticoagulant properties, is rendered procoagulant. During the acute and subacute phases, platelets also increase in number and become activated. The prevalence of coronary artery aneurysms is reduced to <5% by administration of high-dose intravenous immune globulin within 10 days of fever onset. Aspirin is prescribed in high dose (80–100 $mg \cdot kg^{-1} \cdot d^{-1}$, divided into 4 daily doses) for its anti-inflammatory and antipyretic effects until the fever has dissipated for at least 48 hours; the dose is then lowered to 3 to 5 $mg \cdot kg^{-1} \cdot d^{-1}$ as a once-daily dose for its antiplatelet effects for 6 weeks after illness onset in patients without coronary aneurysms.[567,568] In those with persistent coronary abnormalities, low-dose aspirin is continued indefinitely.

Because ibuprofen antagonizes aspirin-induced platelet inhibition, repeated doses of ibuprofen should be avoided in patients with coronary aneurysms taking aspirin for prophylaxis of coronary artery thrombosis.[569] Finally, use of high-dose aspirin in Kawasaki disease has been associated with Reye syndrome.[570,571] Although Reye syndrome has not been associated with antiplatelet aspirin dosage, all aspirin dose regimens should be discontinued during infection with influenza or chicken pox. Antithrombotic therapy may be maintained during these intervals with clopidogrel or LMWH. In addition, the influenza vaccines should be administered annually to children on long-term aspirin therapy.

For patients with persistent coronary artery abnormalities, long-term antithrombotic management is tailored to the degree of coronary artery involvement.[567]

12.1.2. Patients With Coronary Artery Aneurysms

12.1.2.1. Prevention of Coronary Artery Thrombosis in Patients With Coronary Artery Aneurysms

The safety and efficacy of antithrombotic regimens for prophylaxis of coronary thrombosis in Kawasaki disease have not been tested in randomized, clinical trials. Indeed, such trials are unlikely to be performed in the foreseeable future because the small number of patients and thrombotic end points limits its power and hence trial feasibility. Thus, recommendations for antithrombotic therapy in Kawasaki disease are based on retrospective case series, experience in adults with atherosclerotic coronary artery disease, and consensus of experts.

Platelets are activated in acute Kawasaki disease and, among patients with coronary aneurysms, in the chronic phase of the disease. For this reason, antiplatelet agents are important in short- and long-term patient management. Specifically, low-dose aspirin therapy is standard of care in patients with small coronary aneurysms. A second antiplatelet agent that antagonizes adenosine diphosphate–mediated activation such as clopidogrel is sometimes added to aspirin for the suppression of platelet activation in patients with moderate-sized (≈4–6 mm) aneurysms. The combination of aspirin and clopidogrel has been more effective than either agent alone in preventing coronary or cerebrovascular disease in adults (Clopidogrel in Unstable Angina to Prevent Recurrent Events [CURE]).[572–575] Most experts believe that antiplatelet therapy is indicated for Kawasaki disease patients with stable, mild to moderate coronary disease.

Patients with giant aneurysms, defined as at least 8 mm in maximum dimension, are at particularly high risk for coronary artery thrombosis. Abnormal flow conditions within a giant aneurysm, with low blood flow velocities and relative stasis, together with activation of platelets, clotting factors, and the endothelium, produce a powerful stimulus for coronary thrombosis during the first months of the disease. Over time, stenoses often develop at the proximal or distal ends of giant aneurysms. Stenoses that are proximal to a giant aneurysm may stimulate thrombus formation as platelets are activated by sheer stress and then decelerate and linger within an area of turbulence and low flow of the giant aneurysm. Furthermore, endothelial activation may be caused by turbulence of flow, further augmenting the risk of thrombosis. The risk of coronary thrombosis is also increased when stenosis at the distal end of a giant aneurysm occludes flow and worsens stasis. Furthermore, the presence of chronic thrombus in an aneurysm may amplify the thrombotic cascade by presenting fibrin and clotting precursors. Because coronary thrombosis in giant aneurysms involves platelet, endothelial, and humoral clotting factors, treatment with a combination of antiplatelet and anticoagulant drugs is reasonable. Most commonly, patients with giant aneurysms, with or without stenoses, are treated with low-dose aspirin, together with warfarin, maintaining an INR of 2.0. to 3.0.[576] Therapeutic doses of LMWH may be used instead of warfarin in infants or in the occasional older child in whom warfarin is difficult to regulate.

Because patients with especially large giant aneurysms, with stasis of contrast on coronary angiography, or with a history of coronary thrombosis are at especially high risk for recurrence, some experts treat such patients with more aggressive regimens. These may include aspirin with warfarin to maintain the INR between 2.5 and 3.5, a regimen similar to that used in individuals with mechanical mitral valves. An occasional young infant at extraordinary risk of coronary thrombosis may be placed on triple therapy with aspirin, clopidogrel, and warfarin; because the risk of bleeding is high, the risk-to-benefit ratio of such a regimen should be considered on an individual basis.

Finally, the choice of antithrombotic regimen for patients with large but not giant aneurysms, eg, 6 to 8 mm, is especially challenging. The decision to add clopidogrel versus anticoagulation (ie, warfarin or LMWH) to aspirin therapy may be influenced by patient factors. For example, a 6-mm aneurysm in a 3-month-old infant is likely to have flow characteristics similar to those of a giant aneurysm in a larger child, warranting the use of anticoagulation in addition to antiplatelet therapy. In contrast, a 60-kg adolescent with a 6-mm aneurysm might be treated with only antiplatelet agents. Guidelines for use of coronary artery z scores in the choice of antithrombotic regimen are needed.

Recommendations for Antithrombotic Therapy in Children With Kawasaki Disease

1. **Long-term low-dose aspirin therapy is indicated in all patients with persistent coronary artery disease (*Class I; Level of Evidence C*).**
2. **It is reasonable to treat patients with giant aneurysms (≥8 mm), with or without stenoses, with low-dose aspirin together with warfarin, maintaining an INR of 2.0 to 3.0 (*Class IIa; Level of Evidence B*).**
3. **In infants or older children in whom warfarin is difficult to regulate, it is reasonable to treat giant aneurysms (≥8 mm) with aspirin and therapeutic doses of LMWH instead of warfarin (*Class IIa; Level of Evidence C*).**
4. **For patients with moderate-sized aneurysms, aspirin together with a second antiplatelet agent that antagonizes adenosine diphosphate may be considered (*Class IIb; Level of Evidence C*).**
5. **For young infants at extraordinary risk of thrombosis, for example, because of giant aneurysms and a recent history of coronary thrombosis, triple therapy with aspirin, a second antiplatelet agent, and anticoagulation with warfarin or LMWH may be considered (*Class IIb; Level of Evidence C*).**

12.1.2.2. Monitoring for Coronary Artery Thrombosis

The highest risk for coronary artery thrombosis occurs within the first 3 months of illness, with a peak incidence in the first 15 to 45 days of illness onset. For this reason, frequent evaluation with echocardiography and ECG is prudent for patients with giant coronary aneurysms during this time period. Myocardial infarctions in young children and infants either are silent or are associated with nonspecific symptoms such as unusual fussiness, vomiting, or shock. Sudden worsening in ventricular function or a change in ECG findings should heighten suspicion for coronary thrombosis.

Recommendation for Monitoring Coronary Arteries in Children With Kawasaki Disease

1. **Among patients with coronary aneurysms, it is reasonable to perform echocardiography for the surveillance of thrombus formation in coronary arteries at least twice a week while coronaries are rapidly expanding and at least once weekly among patients with giant coronary aneurysms in the first 45 days of illness, then monthly until the third month of disease, and then at least once every 3 months until the end of the first year after illness onset (*Class IIa; Level of Evidence C*).**

12.1.2.3. Treatment of Coronary Artery Thrombosis

For the patient presenting with coronary artery thrombosis, goals of therapy include reestablishing coronary artery patency and flow, salvaging the myocardium, and improving survival.[577] When coronary thrombosis occurs in the Kawasaki patient, thrombus size is typically much greater than that in an adult with atherosclerotic coronary artery disease.[567] Furthermore, the causes of coronary thrombosis in Kawasaki disease and in adults with atherosclerotic heart disease differ. In adults, coronary thrombosis most often derives from plaque rupture or inflammation, exposing lipids and extracellular matrix to the coagulation system. Nevertheless, because randomized, controlled trials have not been performed in children with Kawasaki disease, treatment of acute coronary thrombosis in Kawasaki disease patients is derived largely from studies in adults with acute coronary syndromes and from small pediatric case series.

The most commonly administered therapeutic regimen for occlusive or near-occlusive coronary thrombosis in children is thrombolytic therapy with tPA, administered intravenously together with oral aspirin and intravenous heparin or less commonly subcutaneous heparin LMWH if intravenous access is limited.[567] During such treatment, one must carefully monitor hemostasis to prevent bleeding diathesis. Fibrinogen is kept >100 mg/dL to minimize bleeding. Clotting studies are monitored at least daily. Specifics of management are outlined in the 2004 AHA scientific statement.[567] The reader is also directed to recommendations for the management of ST-segment–elevation myocardial infarction in adults.[578–581]

Because a large thrombus burden is often present in the child with coronary thrombosis secondary to Kawasaki disease, as well as the tendency for rebound thrombosis, reduced-dose thrombolytic therapy is sometimes administered in combination with a glycoprotein IIb/IIIa inhibitor, namely the monoclonal antibody abciximab,[567,582–584] 0.25-mg/kg bolus over 30 minutes, followed by an infusion of 0.125 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 12 hours. Inhibition of this receptor has been shown to improve outcomes, both with and without the use of thrombolytics, in adults with acute coronary syndromes.[585–587] When a small mural coronary thrombus, that is, not posing an urgent threat of occlusion, is noted by echocardiographic surveillance in the first weeks of the illness, it may be reasonable to use abciximab rather than tPA to prevent clot extension.

Mechanical restoration of coronary blood flow, that is, the use of immediate coronary angioplasty or stent placement, is effective in adults. Mechanical restoration of myocardial perfusion in the setting of acute coronary thrombosis may be used in Kawasaki disease patients large enough for the use of adult catheters. Such procedures should be performed by or with the assistance of experienced adult interventional cardiologists.

Because coronary artery perfusion should be reestablished as quickly as possible, the treatment of coronary artery thrombosis chosen is that which can be administered with the greatest expertise in a timely fashion in the patient's clinical setting.

Recommendations for Treatment of Coronary Artery Thromboses in Children With Kawasaki Disease

1. **Coronary artery thrombosis with actual or impending occlusion of the arterial lumen should be treated with thrombolytic therapy or, in patients of sufficient size, by mechanical restoration of coronary blood flow at cardiac catheterization (*Class I; Level of Evidence C*).**
2. **Thrombolytic agents should be administered together with low-dose aspirin and low-dose heparin (*Class I;***

***Level of Evidence C*) with careful monitor for bleeding as described in the text.**

3. **It may be reasonable to treat coronary artery thrombosis in patients with substantial thrombus burden and a high risk of occlusion with a combination of reduced-dose thrombolytic therapy and abciximab (see text) (*Class IIb; Level of Evidence C*).**
4. **It may be reasonable to treat a small mural coronary artery thrombosis (without an immediate threat of occlusion) that is newly noted on echocardiographic surveillance in early Kawasaki disease with abciximab rather than thrombolytic therapy (*Class IIb; Level of Evidence C*).**

12.2. Anticoagulation for Dilated and Inflammatory Cardiomyopathy

Children and adolescents with dilated or inflammatory cardiomyopathy are at risk for thrombus formation, which can contribute important morbidity and mortality. Thrombus formation in this setting may be related to low cardiac output or focal wall motion abnormalities, leading to localized stasis. Thrombosis may be further promoted by congenital and acquired abnormalities of thrombosis and fibrinolysis, endothelial and endocardial dysfunction, and arrhythmias. Thrombus is most commonly located in the left ventricle, particularly near the apex and on the free wall, but can occur in the atria and right ventricle, as well as vascular structures. Thrombus and embolism may be present at the time of presentation of cardiomyopathy or develop early during follow-up. Of note, thrombus can develop in the setting of cardiomyopathy even when prophylactic antithrombotic therapy is given. The prevalence is incompletely known because large-scale pediatric cohort studies have not been performed and may be higher when autopsy findings are included.

McCrindle et al[588] reviewed 66 pediatric patients with dilated or inflammatory cardiomyopathy and noted 4 patients with thrombus at presentation, 4 who developed thrombus during follow-up (15 days–2.8 months; all patients were on anticoagulation, only 1 patient with a therapeutic INR), and an additional patient who died who had thrombus noted at autopsy. Only 1 patient had an embolic stroke. Patients with versus without thrombus had lower ejection fractions (21% versus 29%, respectively; $P<0.05$), but 2 of the 8 patients with thrombus had ejection fractions >25% at the time of their thrombus detection. Patients with low ejection fractions were more likely to be given prophylactic systemic anticoagulation. Thrombus was not related to age at presentation, initial ejection fraction, ventricular dimension, use of anticoagulation at presentation, or duration of follow-up. They estimated a 9-year period prevalence of 14%, with the risk highest at presentation and within the first few months. A review of 130 pediatric patients by Gunthard et al[589] noted thrombus/embolism in 17 patients, 14 at initial presentation, for a prevalence of 14%. Patients with versus without thrombus had significantly lower shortening fraction (10% versus 17%; $P<0.001$). They recommended that patients with a shortening fraction <20% receive prophylactic systemic anticoagulation. A pediatric review by Chang et al[590] noted a prevalence of 16% in children with dilated cardiomyopathy. Hsu et al[591] reported a prevalence of 14% for PE for pediatric patients with dilated cardiomyopathy listed for heart transplantation. Other studies have been reviews of patients presenting with intracardiac thrombus, which have included some patients with cardiomyopathy.[592,593]

Data on management and outcomes are derived from case reports and small case series. A recent pediatric review of intracardiac thrombus with heterogeneous origins showed resolution with medical therapy including heparin, warfarin, and aspirin in 63% (55% for those with dilated cardiomyopathy), sometimes used in combination.[593] Surgical thrombectomy is rarely performed as a primary therapy, and experience with thrombolytic therapy is very limited. A recent review of anticoagulation in adult patients with heart failure concluded that although clinical trial evidence was lacking, the risk-to-benefit ratio for anticoagulation was likely favorable for patients with an ejection fraction <20%, those with left ventricular dysfunction and history of previous stroke, and patients with known thrombus in the left or right ventricle.[594]

Recommendations for Anticoagulation in Children With Dilated and Inflammatory Cardiomyopathy

1. **Children and adolescents with dilated or inflammatory cardiomyopathy should receive transthoracic echocardiographic assessment for intracardiac thrombus at the time of presentation and with follow-up transthoracic echocardiogram (*Class I; Level of Evidence B*).**
2. **For patients with embolism but no transthoracic echocardiographic evidence of thrombus or those with inadequate visualization from transthoracic echocardiographic windows, use of additional imaging modalities, including transesophageal echocardiography, is recommended (*Class I; Level of Evidence B*).**
3. **Patients with evident thrombus should be treated with systemic anticoagulation for at least 3 months (*Class I; Level of Evidence B*).**
4. **Patients with thrombus causing important hemodynamic abnormalities (obstruction to flow with symptoms or signs, interference with valve function) or at high risk of embolization (poorly adherent or mobile thrombus, thrombus located in an area of high flow) should receive thrombolytic therapy or surgical thrombectomy (*Class I; Level of Evidence B*).**
5. **Ongoing systemic anticoagulation therapy is reasonable for cardiomyopathy patients with arrhythmias, previous thrombosis/embolism, thrombophilic conditions, or shortening fraction ≤10% or ejection fraction ≤25% (*Class IIa; Level of Evidence B*).**
6. **For patients presenting with shortening fraction ≤20% or ejection fraction ≤45%, systemic anticoagulation (warfarin with or without aspirin) to maintain an INR of 2.5 (range, 2.0–3.0) for 3 months may be reasonable (*Class IIb; Level of Evidence: B*). UFH may be reasonable for patients unable to tolerate oral therapy, and LMWH may be reasonable in younger patients (*Class IIb; Level of Evidence B*).**
7. **It may be reasonable to consider assessment for thrombophilia abnormalities for those patients with evident thrombus (*Class IIb; Level of Evidence C*).**
8. **In patients with thrombi who have been treated for 3 months, ongoing antithrombotic therapy may**

be reasonable for those with ongoing indications (*Class IIb; Level of Evidence C*).

13. Primary Prevention and Treatment of Thrombi Related to Diagnostic and Interventional Cardiac Catheterization

13.1. Thromboprophylaxis During Diagnostic and Interventional Cardiac Catheterization

Known risks of cardiac catheterization in children include vascular thrombosis and thromboembolism. Significant variability in the incidence of vascular thrombosis related to cardiac catheterization in children has been reported. Definitions and surveillance methods for diagnosis of the problem are highly variable. Still, it is generally accepted that venous or arterial thrombosis is one of the most frequent adverse events after cardiac catheterization in children[595–597] and that this risk can be reduced by procedural anticoagulation.[160,598,599]

13.1.1. Arterial Access Site Thrombosis

Incidence and Significance of the Problem

The true incidence of procedure-related femoral artery thrombosis is unknown because in pediatrics femoral arterial damage can be clinically undetected. Studies in the 1970s reported an incidence as high as 40%,[160] but this significantly decreased to ≈5% in the 1980s,[600–602] when the use of thromboprophylaxis with UFH for arterial studies in pediatrics became a common practice. Recent studies indicate a much lower incidence of vascular compromise from cardiac catheterization, reaching <5%.[595,603,604] However, almost no report includes risk stratification (age, size, procedural duration, size of catheter/introducer, efficiency and monitoring of thromboprophylaxis during the procedure, patient predisposing factors). In addition, there is no standard surveillance methodology used regularly after the procedure to seek clinically silent events.

With technological advances in catheter technique (ie, cut downs are almost never used currently; reduced catheter and introducer size profile is necessary for diagnostic and interventional procedures), the incidence of vessel trauma related to large introducer size has decreased.[602] Still, there has not been any further decrease in the reported complication rate,[597] which likely can be explained by a simultaneous increase in the complexity of transarterial interventions and patient-related risk factors (ie, prematurity).

Clinical manifestations of femoral arterial thrombosis vary from silent vessel occlusions to severe limb ischemia. The consequences of femoral thrombosis include threatened limb viability, leg-length discrepancies and muscle wasting, claudication, and loss of arterial access for future interventions. Because surveillance for late outcomes related to this adverse event is not standard, the true incidence of this occurrence is unknown.[605]

The implications of limited access for future cardiac catheterizations include the potential inability to perform certain transcatheter interventions, limiting therapeutic options; prolonged access time and procedure duration; and potential increase in patient discomfort. Risk factors have included smaller patient size, compromised patient hemodynamic status, operator technique, larger introducer size, and longer procedural duration.[606]

Intense surveillance can indeed identify a higher incidence of vascular compromise after the procedure. A 33% incidence of arterial occlusion after cardiac catheterization was demonstrated by Taylor et al[607] in 58 children >5 years of age using arterial duplex scanning and lower-extremity radiographs of bone length 5 to 14 years after arterial studies. In addition, leg growth retardation was present in 8% of children.

Using 2-dimensional and Doppler sonography in 22 infants before and after undergoing cardiac catheterization, Kocis et al[608] demonstrated 32% complete occlusion of the common femoral artery despite standard procedural thromboprophylaxis. It is common to identify occluded vessels at the time of cardiac catheterization in children who have undergone prior studies. The cause is, however, likely multifactorial (prior cardiac catheterization, arterial or venous monitoring lines in the intensive care unit or operating room).[608] Hurwitz et al[609] reported complete occlusion of the femoral artery with extensive collateralization as diagnosed by angiography in 4 of 48 patients (8%) who were recatheterized 6 months to 9 years after their initial procedure.

Burrows et al[610] demonstrated that obstructive lesions of the iliofemoral arteries are common after transfemoral balloon angioplasty of arch obstructions (58%). Catheter size and manipulation were the main contributing factors.

13.1.2. Venous Access Site Thrombosis

Incidence and Significance of the Problem

Venous thrombosis at the site of access for cardiac catheterization is a well-known complication. Celermajer et al[611] reported that >30% of children and adolescents who had a history of prior cardiac catheterizations presented later with access problems at subsequent catheterizations caused by an occluded vessel, a stenosed vessel, or scar tissue. Keane et al[612] documented a 4% incidence of occlusion of the iliac vein or inferior vena cava after single catheterization of the femoral vein in patients <6 months of age.

Most cardiac catheterizations in children involve the use of both arterial and venous access. Because thromboprophylaxis with UFH is used for all arterial studies, it is therefore used in the vast majority of cardiac catheterization procedures in children. No studies have specifically addressed the efficacy of UFH in venous thromboprophylaxis alone in pediatric cardiac catheterization studies.

The implications of venous thrombosis can be substantial in patients with CHD. Very rarely is this symptomatic, manifesting lower-extremity ectasia or prominent lower abdomen superficial veins.[613] The deep femoral veins remain patent, and venous collaterals will drain blood, bypassing the stenosis, often via the internal iliac vein and paravertebral venous system. Because femoral venous thrombosis is most often clinically silent, the true incidence is unknown. Lacking lower-extremity venous access can limit therapeutic options because access to certain cardiac structures may be almost impossible from alternative routes. Trans-hepatic access, which has higher risk than peripheral access, may be required. The lack of venous access can have major secondary implications. For instance, it may eliminate heart transplantation as an option in end-stage disease because having reliable venous access is a requirement for future surveillance biopsies.

It is common practice not to use thrombosis prophylaxis for studies of the right side of the heart in patients who do not have a source of right-to-left shunting. Exceptions include patients undergoing prolonged studies, those with predisposing factors for thrombosis, or those undergoing certain transcatheter interventions (eg, pulmonary artery angioplasty and stenting). There are, however, no studies specifically addressing this issue. The practice is variable.

13.1.3. Thromboprophylaxis for Arterial and Venous Thrombosis

Several clinical trials clearly indicate the benefits of antithrombotic therapy with UFH during pediatric cardiac catheterization.[160,599,614–617] Freed et al[160] demonstrated that anticoagulation therapy with 100 to 150 U/kg UFH reduced the incidence from 40% to 8% in a double-blind, controlled study with and without systemic heparinization. Although a small randomized study suggested that a 50-U/kg bolus of heparin may be as efficacious as 100 U/kg when given immediately after arterial puncture,[599] this study was underpowered. Thus, there is not enough evidence to recommend a bolus of 50 U/kg as optimal prophylaxis at this time.

A study by Bulbul et al[617] evaluated patients weighing <10 kg, undergoing cardiac catheterization, and receiving 100 versus 150 IU/kg heparin in a double-blind, randomized manner. The incidence of significant arterial complications was 5% and did not appear to be preventable by a higher dose of heparin.

Following the initial bolus of UFH, additional boluses or a constant infusion is used in prolonged procedures (ie, >60 minutes), aiming to keep the ACT >200 seconds, especially during interventional catheterizations. However, the risks/benefits of this practice are not known.

The study by Grady et al[618] demonstrated that increasing the ACT with heparin resulted in a dose-related decrease in fibrinopeptide A levels. A single heparin bolus of either 50 or 100 U/kg elevated the ACT above baseline and reduced fibrinopeptide A levels below baseline. Heparin flush alone did not increase the ACT above baseline and failed to suppress an increase in fibrinopeptide A levels. A bolus dose of 100 U/kg heparin is preferred because it most consistently reaches the target ACT of >200 seconds.

Few other medications for thromboprophylaxis have been studied in children. Freed et al[598] demonstrated that prophylactic anticoagulation therapy with aspirin does not significantly reduce the incidence of femoral artery thrombosis.

The use of subcutaneous LMWH for thromboprophylaxis during cardiac catheterization has not been generally accepted as a standard alternative in pediatrics. There are, however, limitations for the use of UFH; thus, other anticoagulants have been investigated, especially in adults undergoing coronary intervention.[619] In a pediatric study by Roschitz et al,[620] 40 children received a 100 U/kg body weight bolus of UFH, administered after arterial or venous access, and 25 children were treated with 1 to 1.6 mg/kg enoxaparin subcutaneously. The prophylactic levels of anti-FXa activity were achieved in all patients at the end of catheterization. They concluded that LMWH may be considered an alternative for thromboprophylaxis during cardiac catheterization in children. However, the study lacked sufficient power to show a beneficial effect of LMWH. In addition, there are several issues that make LMWH impractical for use during routine cardiac catheterization. For example, procedure schedules may change. Because LMWH reaches full plasma effect 2 to 6 hours after administration, a change in the schedule may render the patient inappropriately anticoagulated. In addition, children with early-morning heart catheterization would need to be awakened in the middle of the night for LMWH administration. Difficult access is common in pediatrics, and having anticoagulation effect during placement of catheters may be unsafe, increasing the risk of bleeding and access site hematomas. Plus, there would be an increased bleeding risk if trans-hepatic or subclavian venous access was necessary in a fully anticoagulated patient. Because the duration of the anticoagulation effect of LMWH is longer than with UFH, short procedures would end at the time of peak anticoagulation, which could impede and prolong access site hemostasis and enhance potential site-related bleeding, hematomas, and other access-related complications. Thus, routine anticoagulation with LMWH for thromboprophylaxis during cardiac catheterization is not recommended.

Reports on the use of other more novel agents such as direct thrombin inhibitors have been scarce in children until recently, mainly case reports and limited patient series.[438,439,621] These agents, however, have potential advantages over UFH and LMWH. HIT is a potentially life-threatening, adverse effect of heparin therapy. Patients with this complication require an alternative approach to anticoagulation. Bivalirudin is a direct thrombin inhibitor with an efficacy comparable to that of heparin, a short half-life, and reduced bleeding complications in adults. Therefore, it has become an alternative to UFH as adjunctive anticoagulant therapy during percutaneous coronary interventions.[622]

In adults, 2 direct thrombin inhibitors, argatroban and lepirudin, are approved for the management of HIT in the United States,[623] and bivalirudin is approved for use in patients with HIT who are undergoing percutaneous coronary intervention (section 3.1, Heparin-Induced Thrombocytopenia and section 10.1.4, HIT and Alternatives to Heparin for Anticoagulation for CPB in Children With CHD). In children, case reports on the use of bivalirudin for catheterization-specific indications have been published.[438,621] A multi-institutional study on the use of bivalirudin in children as thromboprophylaxis for cardiac catheterization procedures evaluated the safety, pharmacokinetics, pharmacodynamics, and dosing guidelines of bivalirudin when used as a procedural anticoagulant in pediatric percutaneous intravascular procedures.[623a] Patients received a weight-based dose similar to that used in percutaneous coronary interventions (0.75 mg/kg bolus, 1.75 mg/kg/hr infusion). The study demonstrated that activating clotting time response was prolonged in all age groups, consistent with that seen in adult studies. There was reasonable correlation between activating clotting time and bivalirudin plasma concentrations across all age groups. There were few major bleeding (1.8%) or thrombotic events (8.2%) reported. The study concluded that bivalirudin safely provided the expected anticoagulant effect in the pediatric population undergoing intravascular procedures for CHD. However, the use of bivalirudin as procedural anticoagulant in children continues to be limited.

Using a fixed-dose UFH in pediatric cardiac catheterization without monitoring efficacy may result in significant overcoagulation or undercoagulation. A bedside, practical, and rapid test is necessary that provides quick information on the level of anticoagulation. ACT is a quantitative assay for monitoring heparin anticoagulation during various medical procedures. ACT is influenced by many constituents of the clotting system, but the degree of anticoagulation can be estimated with this test.[618] It is standard of care to aim for an ACT >200 seconds. However, for certain procedures at high risk of thrombosis, a higher ACT (250–300 seconds) may be advantageous.

Recommendations for Procedural Anticoagulation in Children Undergoing Cardiac Catheterization

1. **Procedural anticoagulation initiated with a UFH bolus of 100 U/kg (up to 5000-U maximum dose) is recommended in children undergoing cardiac catheterization with arterial access (*Class I; Level of Evidence B*).**
2. **Monitoring of anticoagulation during cardiac catheterization is recommended with determination of ACTs 1 hour after bolus and every half-hour for longer procedures. Additional 50 to 100 U/kg heparin should be administered to keep the ACT >200 seconds (*Class I; Level of Evidence C*).**
3. **Procedural anticoagulation initiated with a bolus of UFH 100 U/kg (up to 5000-U maximum dose) is reasonable in children undergoing cardiac catheterization via only venous access if there is a right-to-left shunt, if the procedure is interventional, or if the procedure is expected to be prolonged (*Class IIa; Level of Evidence C*).**
4. **LMWH may be considered for procedural thromboprophylaxis but offers no practical advantages over UFH (*Class IIb; Level of Evidence B*). Limitations of LMWH during cardiac catheterization are discussed in the text.**
5. **Procedural thromboprophylaxis with aspirin alone is not recommended (*Class III; Level of Evidence B*).**

13.2. Management of Catheterization-Related Vascular Thrombosis

13.2.1. Post–Cardiac Catheterization Arterial Thrombosis

Despite the generalized use of UFH for thromboprophylaxis, femoral artery thrombosis remains a well-known complication after cardiac catheterization. Its treatment is controversial. Options considered include continuation of intravenous anticoagulation for 12 to 72 hours with UFH or the initiation of thrombolytic therapy. Unfortunately, limited studies have explored these management options.

Wessel et al[603] demonstrated the efficacy of fibrinolytic therapy with streptokinase use in children with femoral pulse loss after cardiac catheterization. This was a prospective study aimed at determining the safety and efficacy of systemic fibrinolytic therapy for treatment of femoral artery thrombosis. Among 771 patients who underwent retrograde arterial catheterization, including transarterial balloon dilation procedures, there was an overall incidence of femoral artery thrombosis of 3.6%, including 39% of all patients undergoing transarterial balloon dilation procedures. All patients were given heparin 100 U/kg at the time of arterial cannulation. Patients who had a pulseless extremity 4 hours after catheterization continued to receive heparin therapy for 24 to 48 hours. If the extremity continued to have no palpable pulse and the systolic blood pressure was <50% of that in the contralateral leg, intravenous streptokinase infusion was begun. After an average treatment period of 33 hours with intravenous UFH, 16 patients continued to have a pulseless extremity and were treated with streptokinase for an average duration of 13 hours. Normal pulses and systolic blood pressure returned in 88% and were nearly normal in 6%. The incidence of bleeding at the arterial puncture site was 25% and was highest in the patients who had a transarterial balloon dilation procedure. No serious complications occurred. After this experience, systemic thrombolysis became standard practice in pediatric patients who have pulse loss after arterial cardiac catheterization in some centers, especially for those children who are likely to need future additional transcatheter procedures.

Brus et al[624] reported in 1990 the use of systemic infusion of streptokinase after retrograde arterial catheterization in 9 patients with signs of impaired arterial circulation despite heparinization. Arterial perfusion became normal in all patients. Hematological monitoring showed lengthening of the thrombin time and a decrease in the fibrinogen concentration during streptokinase treatment. There were no serious complications. They concluded that systemic infusion of streptokinase may be a safe and useful treatment in children with persistent femoral artery thrombosis after arterial cardiac catheterization.

Gupta et al[58] studied safety and outcomes of thrombolysis with tPA of intravascular thrombus in 80 children, 65 of whom had arterial thrombosis, most of which occurred after cardiac catheterization. They received an average dose of 0.5 $mg \cdot kg^{-1} \cdot h^{-1}$ tPA for a median duration of 6 hours. Clot resolution was complete in 65% of children and partial in 20%, and there was no effect in 15%. There were major complications in 40% (including cerebral ischemia in 2 patients and intracranial hemorrhage in 2 patients), minor complications in 30%, and no complications in 30%. Clot resolution was not related to patient age or weight, dose, duration of tPA therapy, or fibrinogen levels. However, complications were more likely in patients who weighed less, had a longer duration of therapy, had a greater decrease in fibrinogen levels, and failed to have resolution of their clot. They concluded that tPA therapy can be effective in the thrombolysis of intravascular thrombus in children but is associated with a low margin of safety and an unknown risk-to-benefit ratio. This study supports the need for further multicenter testing of the use of thrombolytic therapy for arterial catheter–related thrombosis in children. tPA has several advantages over streptokinase and urokinase, including being thrombus specific and acting on the plasminogen-fibrin complex, leading to a minimal decrease in systemic fibrinogen, and being nonantigenic and unaffected by anti-streptococcal antibodies.[625] However, the relatively high incidence of complications reported is concerning. Of note, the reported complication rates appear higher with the use of tPA than those observed with streptokinase. However, no study comparing the safety and efficacy of these treatment methods has been performed.

Zenz et al[59] reported 17 patients treated with tPA after 24 hours of heparin infusion that was administered at 0.5 $mg \cdot kg^{-1} \cdot h^{-1}$ for 1 hour, followed by 0.25 $mg \cdot kg^{-1} \cdot h^{-1}$ until improvement was observed. Pulse returned in 16 patients after 4 to 11 hours (mean,

7.1 hours). Bleeding complications were seen in 9 patients, restricted to the arterial puncture site in all but 1 patient.

Levy et al[626] reported 12 patients treated with tPA after 24 hours of heparin administered at 0.5 $mg \cdot kg^{-1} \cdot h^{-1}$ intravenously or 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$ intra-arterially, with return of pulse after 2 hours to 3 days in 8 patients and return of diminished pulse in 3 patients. Such late return of pulse may be attributable to the development of effective collaterals. Long-term patency of the target vessel was not documented.

Almost all reports on thrombolytic therapy using streptokinase,[603,624,627] urokinase,[628] or tPA[59,626,629–631] have demonstrated effective restoration of extremity pulse but have not assessed long-term patency. Most reports on tPA[59,626,629,630] were based on a small number of patients receiving a variety of doses given after the initial 24 hours.

A retrospective study by Balaguru et al[625] reported the experience in 21 patients using a uniform dosing protocol of tPA that began 4 to 6 hours after cardiac catheterization following an initial infusion of UFH. All patients who had absent or significantly diminished lower-extremity pulse at the conclusion of cardiac catheterization were initially placed on a 4-hour UFH drip at 17 $U \cdot kg^{-1} \cdot h^{-1}$. If no significant improvement was seen, the patients were transferred to the intensive care unit and treated with tPA as a bolus of 0.1 mg/kg followed by an infusion of 0.5 $mg \cdot kg^{-1} \cdot h^{-1}$ for 2 hours. This was followed by reinstitution of UFH infusion at 17 $U \cdot kg^{-1} \cdot h^{-1}$ for 4 hours. If pedal pulses became easily palpable during this period, heparin was continued for 6 hours. Otherwise, a second course of tPA was given again with a bolus of 0.1 mg/kg followed by an infusion of 0.5 $mg \cdot kg^{-1} \cdot h^{-1}$ for 2 hours with subsequent heparin infusion at 17 $U \cdot kg^{-1} \cdot h^{-1}$ for 6 hours. The use of tPA in this study differed from that in other studies in the institution of treatment early and the short duration of the infusion. Pedal pulses were restored in all patients, and long-term patency of the target vessel was achieved in 95% of patients. Bleeding from the cannulation site occurred in 29% but was clinically inconsequential with local compression.

When fibrolytics are used, almost all published experience advocates for a specific observation protocol in a monitored setting with specifically trained personnel, given that delayed recognition of bleeding can be life-threatening.

In conclusion, studies on the use of fibrinolytics for femoral pulse loss after cardiac catheterization in children tend to support their use, but the studies are limited by small study size, their retrospective nature, and underpowered design. However, although significant controversies persist about indications, drug selection, onset, and duration of therapy among the pediatric interventional cardiology community, the use of fibrinolytic agents for post–cardiac catheterization arterial thrombosis has become an accepted therapeutic option. Further studies are necessary to determine specific indications, optimal drug choices, dosing, duration of therapy, and follow-up.

Depending on individual institutional expertise, some advocate the use of either transcatheter or surgical mechanical thrombectomy to treat femoral arterial thrombosis. The study by Ino et al,[606] undertaken to assess the efficacy of thrombolytic therapy for this complication, included a total of 526 consecutive infants and children prospectively evaluated after cardiac catheterization and 42 patients evaluated retrospectively who required femoral artery thrombectomy between 1975 and 1985. There were no serious complications of surgery. In the prospective study, patients were given a bolus injection of 150 U/kg UFH at the time the artery was entered. Patients with persistently absent or diminished pulse 2 hours after catheterization received a second bolus injection of 50 U/kg followed by an infusion of 20 $U \cdot kg^{-1} \cdot h^{-1}$ UFH for a maximum of 48 hours. If the affected leg pulse was absent or reduced and the systolic Doppler blood pressure was less than two-thirds that of the unaffected leg, thrombolytic therapy was begun. Decreased or absent pulse after catheterization was present in 45 of 526 patients (8.6%), 32 of whom (71.1%) improved with systemic heparinization only. Thirteen patients (28.9% of those requiring therapy for pulse loss) had a persistently absent pedal pulse, suggesting femoral artery thrombosis. Among these, thrombolytic therapy was successful in 11 patients, whereas 2 patients required surgical thrombectomy. Prothrombin time was prolonged and fibrinogen levels were significantly reduced during therapy. The complication observed was bleeding from the entry site in 4 patients (30.8%). During follow-up, persistence of pedal pulses was noted in all patients. The study concluded that systemic thrombolytic therapy can be used effectively in the management of complications of femoral artery thrombosis after cardiac catheterization without serious complications and with results comparable to those of surgical intervention. They also recommended careful observation and hematologic monitoring during administration of the fibrinolytic agent.

Surgical repair of arterial injuries in the very young represents a technical challenge because of the small size of the vessels and the presence of arterial spasm. Therefore, medical management is more commonly recommended.[577] Some, however, advocate surgical treatment[39,632–635] and report good results. No study has compared the various management approaches prospectively.

Peuster et al[636] reported a small number of patients with arterial thrombosis who were treated with transcatheter recanalization and subsequent balloon dilation of the occluded vessel. Repeat angiography or duplex sonography 3 to 14 months after intervention showed completely patent arteries without restenosis in 7 patients; there was residual narrowing of the vessel in the 2 remaining patients. Use of this therapeutic option can be considered only in older patients because cannulation of the contralateral artery is typically needed for transcatheter intervention, which in infants would in itself be a significant risk for thrombosis of the unaffected artery.

In conclusion, optimal management of postprocedural femoral artery thrombosis, especially the indication for thrombolytic therapy or interventional or surgical treatment, remains controversial. Published studies are retrospective, not randomized, and are underpowered.

Recommendations for the Management of Catheterization-Related Vascular Thrombosis in Children

1. **Patients with lower-extremity arterial pulse loss and evidence of limb ischemia after cardiac catheterization should initially be treated with intravenous UFH**

for at least 12 to 48 hours (*Class I; Level of Evidence B*). Dosing and length of therapy should be individualized according to degree of perfusion impairment (*Class I; Level of Evidence C*).

2. **Surgical consultation is indicated if limb ischemia persists despite therapeutic heparinization (*Class I; Level of Evidence C*).**
3. **It is reasonable to transition to fibrinolytic therapy if limb ischemia persists after therapeutic heparinization (*Class IIa; Level of Evidence C*). Vascular ultrasound for diagnostic confirmation is reasonable before the initiation of fibrinolytic therapy (*Class IIa; Level of Evidence C*).**
4. **Surgical or transcatheter intervention may be considered if thrombolytic therapy is contraindicated or if limb loss is imminent (*Class IIb; Level of Evidence C*).**

13.2.2. Post–Cardiac Catheterization Venous Thrombosis

Because venous thrombosis after cardiac catheterization is often subclinical, undiagnosed until a later time when vascular access becomes necessary,[611,612] management of the condition is rarely necessary in the acute setting. Clinical signs of venous thrombosis after cardiac catheterization such as venous congestion warrant the consideration of anticoagulation with intravenous UFH. However, little has been reported on the efficacy of this approach. Although seen in the postoperative patient secondary to indwelling CVLs, obstruction of the large veins (ie, superior vena cava syndrome) is unlikely after cardiac catheterization.

Ing et al[613] have reported successful late transcatheter rehabilitation of femoral vein thrombosis identified at a follow-up cardiac catheterization with implantation of stents in 24 patients. Although guidewires were easily passed across the stenotic vessels, occluded vessels required puncture through the thrombosed sites with a stiff wire or transseptal needle. Once traversed, the occluded site was dilated serially before stent implantation. At follow-up, 87% of the vessels remained patent.

There is currently a lack of studies addressing the problem of post–cardiac catheterization venous thrombosis; therefore, specific recommendations cannot be formulated.

13.3. Interventional Procedures

In general, thromboprophylaxis is recommended in children who undergo cardiac catheterization using arterial access whether or not the catheterization procedure is interventional or just diagnostic. Because certain interventional procedures have a higher risk of thrombosis, it is common that the operator may aim to achieve higher ACT values (250–300 seconds).

When a transvenous catheter intervention is performed without the use of arterial access, thromboprophylaxis with UFH can be considered, but there is significant variability in the practice. Such is the case in balloon atrial septostomies or pulmonary valve balloon dilation procedures (see below). Procedural thromboprophylaxis is not routinely used in patients undergoing cardiac catheterization of the right side of the heart only or endomyocardial biopsies.

13.3.1. Thromboprophylaxis of Endovascular Stents in Children

The use of stents in children with CHD was first demonstrated in the early 1990s.[637,638] Since then, their use in children has expanded considerably, now playing a major role in the management of almost all stenotic vascular lesions in children,[639–641] including branch pulmonary artery stenosis,[641,642] systemic venous obstructions,[643] systemic arterial stenosis such as coarctation of the aorta,[644–646] pulmonary vein stenosis, patent ductus arteriosus,[647] and surgical conduits or homograft prostheses.[648–650] Stents are also used to maintain vascular patency of the ductus arteriosus in selected conditions.[647,651]

Although for most of these lesions in-stent restenosis and thrombosis are very rare,[641,652] specific lesions are considered to be at higher risk of thrombosis, especially those associated with passive nonpulsatile flow, very small vessels, or lesions at recanalization of previously thrombosed vessels. No studies have assessed the role of anticoagulation or antiplatelet therapy to avoid stent thrombosis in children, but overall, its incidence in pediatrics is quite low. It is common practice to administer UFH at the time of stent insertion, followed by aspirin therapy for a variable period of time until the stent is assumed to be completely endothelialized. Further studies are required to determine the optimal prophylactic anticoagulation after such procedures.

The reported experience with the use of stents in CHD has included variable use of thromboprophylaxis during and after the procedure.[638,639,650] The most common anticoagulation regimen includes intravenous administration of 100 U/kg UFH (maximum, 5000 U) at the start of the procedure, redosed as needed to maintain the ACTs >200 seconds, although some have reported the use of 150 U/kg to achieve ACTs of 250 seconds.[653] At the conclusion of the procedure, patients are often placed on a continuous heparin infusion to achieve systemic heparinization and a therapeutic PTT for a minimum of 12 hours and are started on an oral antiplatelet agent that they continue for a minimum of 6 months. If patients have stents in the venous circulation or nonpulsatile flow pattern (such as a pulmonary artery stent in the Fontan circulation), warfarin or LMWH is often initiated for 6 months followed by low-dose aspirin for an additional 6 months or longer. However, it has not been shown whether warfarin is superior to aspirin alone in this setting. Variable use of aspirin with or without additional dipyridamole has been reported.[639] The role of combination therapies using antiplatelet therapy in addition to clopidogrel or other agents has not been studied. Regardless of the anticoagulation management approach, the incidence of stent thrombosis reported has been exceedingly low.

Recommendations for Anticoagulation in Children During the Placement of Endovascular Stents

1. **Procedural anticoagulation initiated with a UFH bolus of 100 U/kg (up to 5000-U maximum dose) is recommended in children undergoing placement of endovascular stents (*Class I; Level of Evidence C*).**
2. **Postprocedural thromboprophylaxis with low-dose aspirin is recommended in children undergoing placement of endovascular stents for noncoronary lesions for at least 6 months after stent implantation (*Class I; Level of Evidence C*).**
3. **In children undergoing stent implantation for higher-thrombotic-risk lesions (ie, nonpulsatile flow, previous complete occlusion, thrombophilic abnormality)**

and in the absence of contraindications, it is reasonable to use warfarin or LMWH with or without antiplatelet therapy for 3 to 6 months after implantation and then continue or institute the antiplatelet therapy alone (*Class IIa; Level of Evidence C*).

13.3.2. Thromboprophylaxis of Cardiac Transcatheter Closure Devices

13.3.2.1. Transcatheter Closure of Atrial Septal Defects

The first device procedure for atrial septal defect closure in children was performed >30 years ago.[654] Device technology matured in the 1980s and 1990s so that now most atrial septal defects are closed by transcatheter device placement, although the procedure can be potentially complicated with thrombus formation on the device during or after implantation. Two devices are currently approved by the FDA for closure of atrial septal defects and variants: the Amplatzer Septal Occluder (AGA Medical Corp, Plymouth, MN) and the Helex Occluder (W.L. Gore Associates, Newark, DE). The CardioSEAL device (NMT Medical, Boston, MA) is also available in the United States but is not approved by the FDA specifically for this indication. Subacute thrombus formation on the device has been a very rare complication reported for every device used for this purpose.[655–661]

In the larger series using multiple devices that have been published, the incidence of device thrombosis is particularly low or nonexistent.[656,659,662,663] The study by Chessa et al[663] reports only 1 device thrombotic complication among 417 patients, and this patent was an adult. All patients in this study were placed on aspirin 5 $mg \cdot kg^{-1} \cdot d^{-1}$ for 6 months after the procedure.

There appears to be a higher incidence of device-related thrombotic complications reported in adults series,[657,660] although these typically also include patients with closure of the PFO after a history of cryptogenic stroke, a population very different from children with simple atrial septal defects.

In general, antithrombotic prophylaxis with antiplatelet agents after device implantation is believed to be necessary, but current practice is variable and remains controversial.[664] To date, no randomized studies have been published assessing the optimal anticoagulation strategy or whether any prophylaxis is necessary. Thus, therapy is based on empirical data, standard-of-care practices, local experience, and case reports from the literature.

For antithrombotic prophylaxis, most centers currently use low-dose aspirin alone for 6 months,[662] or in adults or older patients, some use a combination of aspirin and clopidogrel initially (75 mg) for a variable duration followed by aspirin to complete a total of 6 months.[657,660,664] Often, aspirin therapy is initiated 1 to several days before device implantation. In higher-risk patients such as those with a history of stroke, inherited thrombophilic disorders should be excluded before device implantation so that antithrombotic prophylaxis can be adapted accordingly. The duration of thromboprophylaxis theoretically should extend until complete device endothelization is achieved. Limited data exist on this process from human device explantations, however.[665] It has become standard of care to provide thromboprophylaxis for 6 months. When this approach is used in pediatrics, device thrombosis continues to be an extremely rare event. If complete defect closure is not achieved (ie, residual defect after device implantation), complete endothelialization may not occur. In such cases, many elect to continue thromboprophylaxis beyond 6 months because there is an ongoing risk of paradoxical embolus.

Recommendations for Thromboprophylaxis of Transcatheter Atrial Septal Defect Devices in Children

1. **Patients undergoing device closure of atrial septal defects should receive at least 100 U/kg UFH (up to 5000-U maximum dose) at the time of implantation (*Class I; Level of Evidence C*).**
2. **Children undergoing device closure of atrial septal defects should receive oral antiplatelet therapy with low-dose aspirin for at least 6 months after implantation (*Class I; Level of Evidence C*).**
3. **For older children and adults, after device closure of atrial septal defect, another anticoagulant may be considered in addition to aspirin for 3 to 6 months after implantation (*Class IIb; Level of Evidence C*).**

13.3.2.2. Transcatheter Closure of Ventricular Septal Defects

Over the past decade, several occluding devices have been developed to offer a transcatheter closure alternative to surgery. Two such devices are available in the United States for closure of certain types of ventricular septal defects (the CardioSEAL and the Amplatzer muscular ventricular septal defect occluder). Patients undergoing device closure systematically receive 100 U/kg UFH intravenously at implantation and are discharged on an antiplatelet agent such as low-dose aspirin for 6 months.[666–668] Among the multiple series published on transcatheter closure of ventricular septal defects, device-related thrombosis has not been reported as a procedural complication.[666–671] Thus, it appears that the common practice of using aspirin therapy for 6 months is effective thromboprophylaxis, although there are no studies addressing the safety and efficacy of aspirin.

Recommendations for Thromboprophylaxis of Transcatheter Ventricular Septal Defect Devices in Children

1. **Children undergoing device closure of ventricular septal defects should receive UFH 100 U/kg (up to 5000-U maximum dose) at the time of implantation (*Class I; Level of Evidence C*).**
2. **It is reasonable to treat children undergoing device closure of ventricular septal defects with oral antiplatelet therapy with low-dose aspirin for at least 6 months after implantation (*Class IIa, Level of Evidence C*).**

13.3.3. Thromboprophylaxis of Transcatheter Embolization Procedures

Coil and device embolization of abnormal vascular lesions has been performed routinely in children since the late 1980s and early 1990s.[672,673] Variable use of procedural anticoagulation has been reported, depending on operator preference and site of embolization. It is standard practice to treat patients

undergoing closure of collateral vessels or coronary artery fistulas with at least 100 U/kg UFH at the time of implantation. However, procedural anticoagulation for other lesions such as patent ductus arteriosus closure is highly variable. Some publications report routine use of procedural UFH for closure of the patent ductus arteriosus,[674] whereas other series do not comment on the use of thromboprophylaxis at all[675] or refer to variable use according to operator preference.[676] No study has evaluated the efficacy of and need for procedural thromboprophylaxis for patent ductus arteriosus device or coil closure. Many centers use a lower dose of procedural thromboprophylaxis (ie, 50 U/kg heparin).

After coil or device closure of patent ductus arteriosus or collaterals, no specific postprocedural thromboprophylaxis is typically recommended. Device thrombotic complications have not been reported in series published on the use of the Amplatzer occluder device or coil for patent ductus arteriosus. There is 1 case report in the literature of thrombus formation on a Rashkind device immediately after implantation,[677] although the current relevance of this is limited because this device is no longer available anywhere in the world for any indication.

Recommendations for Thromboprophylaxis of Transcatheter Embolization Procedures in Children

1. **Patients undergoing coil or device closure of collateral vessels or coronary fistulas should receive procedural anticoagulation with UFH 100 U/kg (up to 5000-U maximum dose) (*Class I; Level of Evidence C*).**
2. **Procedural anticoagulation with UFH 50 to 100 U/kg (up to 5000-U maximum dose) may be considered in patients undergoing transcatheter closure of the patent ductus arteriosus (*Class IIb; Level of Evidence C*).**

13.3.4. Thromboprophylaxis for Valvuloplasty and Angioplasty Procedures

Variable procedural thromboprophylaxis is used for pulmonary balloon valvotomy, depending on operator preference. The first reported patient to receive a pulmonary balloon valvotomy received 100 U/kg UFH for the procedure.[678] There is a lack of information with this regard because almost all articles on the subject exclude any information on the thromboprophylaxis used for the procedure. In pediatrics, the decision about the use of thromboprophylaxis commonly is based on the need for arterial access, estimated length of the procedure, and patient individual risk factors and may not be intervention specific. Thus, if femoral arterial access is obtained, anticoagulation with UFH would be standard to minimize the risk of femoral artery thrombosis, regardless of the intervention planned.

Given the need for arterial access at the time of aortic balloon procedures, thromboprophylaxis with UFH is routinely given. A specific recommendation would be redundant because all aortic balloon procedures would have to involve cardiac catheterization of the left side of the heart and thus procedural anticoagulation.

For angioplasty procedures (pulmonary arteries, systemic and pulmonary veins, aorta, etc), procedural anticoagulation is generally performed with at least 100 U/kg UFH. Reports on pulmonary angioplasty procedures in pediatrics, however, lack information on procedural thromboprophylaxis. This may be attributable to the fact that the decision to use procedural anticoagulation in pediatrics is made at the start of the procedure (based on venous access alone or combined arterial/venous access) and is not necessarily based on the angioplasty procedure itself.

13.3.5. Thromboprophylaxis for Balloon Atrial Septostomy and Transseptal Puncture

In pediatric patients, transseptal punctures are commonly performed after prior administration of intravenous UFH for procedural thromboprophylaxis at the start of the procedure. The indications for transseptal cardiac catheterization typically include conditions for which cardiac catheterization with arterial access for the left side of the heart is used for the diagnostic component of the study (ie, mitral stenosis, single ventricle with restrictive atrial septal defect, failing unfenestrated Fontan procedure, severe PH). The decision of whether to proceed with transseptal puncture often is made well into the procedure. The risk of perforation and bleeding, however, is very low.[679–682]

There is significant practice variability in the use of thromboprophylaxis with regard to the creation of atrial septal defects, including balloon atrial septostomy. Balloon atrial septostomy is typically performed without the use of procedural heparinization.[683] Other interventions such as the creation of atrial communications with the use of various techniques are typically done with full heparinization because most of these patients do need femoral arterial access, as well as catheterization of the left side of the heart. Specific recommendations in this regard cannot be formulated because there is a paucity of published information.

13.4. Special Considerations for Cardiac Catheterization in Adults With CHD

For patients with atrial septal defect closure devices, aspirin and clopidogrel are usually recommended for the first 6 months after device closure. Warfarin anticoagulation should be given to patients with atrial arrhythmias, especially AF, and bridging with enoxaparin should be considered. Other patients who should be considered for a minimum of 6 months of warfarin therapy are those with thrombophilic disorders, previous stroke, and suspected aspirin or clopidogrel resistance. Patients with AF should continue warfarin indefinitely.[203]

14. Pulmonary Hypertension: Primary Prevention and Treatment of Thrombi

The rationale for anticoagulation in patients with PH associated with heart disease, congenital or acquired, is based on the presence of thrombotic lesions and platelet dysfunction in patients with pulmonary vascular disease.[684] In situ pulmonary artery thrombosis can be initiated or aggravated by abnormalities in the clotting cascade, endothelial cells, or platelets. Biological evidence shows that intravascular coagulation is a continuous process in patients with pulmonary vascular disease. At the present time, it is widely accepted that shear stress itself or injury of the pulmonary vessels generates a thrombogenic surface with subsequent

thrombotic lesions in many forms of pulmonary vascular disease, including PH associated with CHD and with acquired heart disease.

Moreover, an increasing body of evidence also suggests that enhanced interaction between platelets and the pulmonary arterial wall may contribute to the functional and structural alteration of pulmonary vessels. Vascular abnormalities in pulmonary vascular disease may lead to release by platelets of various procoagulant, vasoactive, and mitogenic mediators. In addition to rationale based on the pathobiology of pulmonary vascular disease, rationale for anticoagulation in patients with PH associated with heart disease is based on retrospective analyses from 7 studies in patients with idiopathic, heritable, or anorexigen-associated pulmonary arterial hypertension (formerly called primary PH), of which 5 were positive and 2 were negative.[685–688] By definition, pulmonary arterial hypertension (PAH; formerly called pulmonary vascular obstructive disease; recent classification, PH group I PAH) is an increased mean pulmonary artery pressure ≥25 mm Hg at rest, with a concomitant mean pulmonary capillary wedge pressure, mean left atrial pressure or left ventricular diastolic pressure ≤15 mm Hg, and a concomitant increased pulmonary vascular resistance, that is, >3 Wood units·m^2. In addition to meeting the hemodynamic definition (requires catheterization of the right side of the heart) above, all potential causes of secondary PH, including PH resulting from pulmonary venous hypertension (PH group II), for example, disease of the left side of the heart, PH caused by chronic lung disorders such as cystic fibrosis (PH group III), PH resulting from chronic thromboembolic disease (PH group IV), and PH associated with miscellaneous conditions (PH group V), must be excluded before the diagnosis of PAH can be confirmed.[238,689] The survival of anticoagulated patients, selected on the basis of clinical judgment, was improved compared with a concurrent population that was not treated with oral anticoagulants. Three-year survival improved from 21% to 49% in the series reported by Fuster et al,[685] and the 3- and 5-year survival rates increased from 31% to 47% and from 31% to 62%, respectively, in the series reported by Rich et al.[686] These studies were not randomized, and one can argue that the lower survival of the control groups could be related to comorbidity that precluded the use of anticoagulation in the untreated patients. In addition, only patients with idiopathic PAH, heritable PAH, and anorexigen-related PAH were included in the studies. In recent randomized, controlled trials in patients with various forms of PAH, ≈70% of patients were treated with oral anticoagulants. Interestingly, the highest prevalence of oral anticoagulant treatment was seen in the trials involving patients with mainly idiopathic PAH and heritable PAH in World Health Organization functional classes III and IV, whereas the lowest prevalence was observed in a trial of patients with scleroderma. It should be emphasized that there is no evidence of any difference in the efficacy of oral anticoagulant therapy based on functional class severity.

From the data above, the need for routine anticoagulation and its preferred mode for patients with CHD and acquired heart disease in the setting of pulmonary vascular disease remain unclear. Histological changes in the pulmonary vascular bed resemble those in patients with idiopathic or heritable PAH and those seen in patients with various other forms of PAH such as PAH associated with connective tissue diseases, HIV, or portal hypertension. However, recent evidence suggests large intrapulmonary thrombi in up to one third of adult patients with Eisenmenger physiology, particularly Eisenmenger patients with large secundum atrial septal defects.[239,690,691] These in situ thrombi are not thromboembolic and appear to be related to disease severity.[237] Whether pulmonary thrombi in this setting should be treated as arterial or venous and whether routine prophylactic anticoagulation with warfarin, a common practice for patients with pulmonary vascular disease of various origins, or other antiplatelet therapy should be recommended for all patients with pulmonary vascular disease associated with CHD or acquired heart disease remain unknown and clearly warrant urgent investigation. For the older patient with CHD and pulmonary vascular disease, other indications such as sustained arrhythmia or ventricular dysfunction may be present and thus dictate anticoagulation therapy independently.

In addition to the reasons discussed above for patients with other forms of pulmonary vascular disease, patients with Eisenmenger syndrome, in particular, are at risk for thrombotic events for several reasons: a sedentary lifestyle resulting from self-limitation in the setting of venous insufficiency, a dilated right side of the heart, sluggish pulmonary blood flow, and the demonstration of thrombophilic predisposition[692,693] and thrombotic changes in the pulmonary microcirculation[694,695] and the elastic pulmonary arteries.[696]

Even a small PE can be life-threatening in patients who cannot vasodilate or recruit additional pulmonary vessels normally; postmortem examinations of patients with pulmonary vascular disease who died suddenly often demonstrate fresh clot in the pulmonary vascular bed. Although no adequate studies have demonstrated the efficacy of anticoagulation for patients with the Eisenmenger syndrome, these observations suggest there may be an important role for anticoagulation. In addition, although patients with pulmonary vascular disease associated with CHD with intracardiac shunts are at increased risk of hemoptysis, they may also be at increased risk for paradoxical embolism in pulmonary artery and central vein thrombosis. Furthermore, patients with pulmonary vascular disease receiving therapy with long-term continuous intravenous prostacyclin analogs are anticoagulated in the absence of contraindications, owing in part to the additional risk of central venous catheter–associated thrombosis. If anticoagulation is agreed on, the involvement of the hematologist or a specialist clinic is advisable because special titrating containers, correcting for erythrocytosis in patients with Eisenmenger syndrome, for monitoring INR and slow, careful titration of warfarin dose are essential. The target INR in patients with pulmonary vascular disease varies somewhat, between 1.5 and 2.5 in most centers in North America and 2.0 to 3.0 in European centers.

Recommendations for Anticoagulation in Children and Adults With CHD and PH

1. **The use of anticoagulation may be reasonable in children and adults with pulmonary vascular obstructive**

disease associated with CHD (repaired or unrepaired) (*Class IIb; Level of Evidence C*). However, the efficacy remains unclear. This recommendation is based on consensus opinion from uncontrolled studies in adult patients only with idiopathic or heritable PAH or anorexigen-associated PAH.

2. **Low-dose anticoagulation may be reasonable in children and adults with PAH, that is, pulmonary vascular obstructive disease associated with CHD (repaired or unrepaired), and an indwelling CVL for PAH drug administration (*Class IIb; Level of Evidence C*).**

15. Nursing Considerations in the Identification and Treatment of Thrombi in Infants and Children

The advantages of using a CVL in the pediatric population are many and include that the fact that it is a painless method for sampling blood and administering medications, blood products, and nutritional support.[697] Despite these advantages, the incidence of thrombi is a common complication. In a study done in 1990, catheters that had optimal tip placement had a 16% incidence of thrombi, whereas those with suboptimal placement had an incidence of 62%.[698]

Because CVLs are not without risk, especially in the neonate who has limited access sites, the nurse can be a valuable member of the team in terms of maintaining patency of the line and identifying contraindications for thrombolytic therapy such as the presence of abnormal clotting studies, presence of active bleeding, or major surgery within the last 10 days.[58,697] Early diagnosis of the presence of a thrombus by the nurse may be based on observations such as a sluggish or absent blood return, difficulty flushing the catheter, or the inability to infuse or withdraw fluid. In a 5-year study by Robinson and colleagues,[699] the most common presenting symptoms of a thrombus were cyanosis and systemic venous congestion. Nurses are often the first to notice signs of superior vena cava syndrome such as facial, neck, or upper arm swelling; prominent neck veins; and cyanosis. As a member of the healthcare team who works with the CVL on a daily basis, the nurse plays a valuable role. He or she maintains the patency of the CVL with heparin flushes per hospital protocol,[700] identifies problems with either the infusion or withdrawal of fluids related to the CVL, and communicates any symptoms or signs of potential thrombus to other members of the care team.

Concerning anticoagulation and thrombolytic therapy, neonates may be the most difficult age group in which to safely administer anticoagulation or thrombolytics. The risk of intracranial hemorrhage during thrombolytic therapy is highest in the neonatal period. In a review of the literature, Gupta and colleagues[58] found that 6 of 7 infants who were <1 week of age and weighed <3.5 kg were positive for intracranial hemorrhage. Bleeding as a symptom in the neonate may be either subtle or obvious. For the neonate undergoing anticoagulation or thrombolytic therapy, the nurse must observe for guaiac-positive stools, the presence of petechiae, and oozing from the gums or old puncture sites. An altered level of consciousness, hypotonia, and a change in the quality or spontaneity of movements should also alert the nurse to the possibility of an intracranial hemorrhage.

Although tPA has been used safely in children for central venous catheter occlusion, complications are higher when it is used as a thrombolytic in situations other than catheter occlusion. In a study of 32 pediatric patients, 39% of the group had bleeding episodes that required blood transfusions.[58] In contrast, Fisher et al[701] did not observe any adverse events in a study that included 22 infants and children. A study involving 14 neonates also concluded that tPA was a safe and effective method of thrombolysis for this age group.[702] According to a study by Skinner et al,[703] there was an absence of standardized practice in regard to the management of central venous catheter occlusion and central venous catheter–related thrombosis. In a more recent publication,[21] guidelines have been recommended that include the use of UFH, LMWH, and tPA. These recent recommendations have also established different practice guidelines for the neonate versus the child.

Regardless of which anticoagulant or thrombolytic agent is used, the nurse must remain a keen observer for possible signs of bleeding, venous congestion, or intracranial hemorrhage during anticoagulation and thrombolytic therapy. The nurse can play a vital role in ensuring that institutional guidelines are followed and that the appropriate care teams are involved. In addition, the nurse needs to track coagulation laboratory results such as fibrinogen, activated PTT, or anti-FXa levels at the start of and during treatment, as appropriate (Table 9).

Table 9. Signs or Symptoms Indicative of Thrombus Formation or Complications of Anticoagulation/Thrombolytic Therapy Often First Identified by the Nurse That Should Be Brought to the Immediate Attention of the Medical Team

Possible signs of thrombus
Sluggish or absent blood return from catheters
Difficulty flushing the catheter
Inability to infuse or withdraw fluid from the catheter
Inappropriate or change in transduced waveforms from the catheter
Edema, plethora, or venous congestion of an extremity (possible venous thrombus)
Increased chest wall veins or caput medusa; increased abdominal veins (possible superior or inferior vena cava thrombus)
Loss of pulse, decreased perfusion, coldness of an extremity, signs of emboli to toes or fingers (possible arterial thrombus)
Signs of superior vena cava syndrome (facial, neck, or upper arm swelling; prominent neck veins; and cyanosis)
Signs of bleeding
Guaiac-positive or bloody stools
Presence of petechiae
Oozing from the gums or old puncture sites
Nosebleed
Respiratory distress, desaturation (possible hemothorax especially in postoperative children with chest tubes)
Abdominal distension, pain, or tenderness (possible retroperitoneal bleed)
Signs of intracranial hemorrhage (altered level of consciousness, hypotonia, and a change in quality or spontaneity of movements)

16. Special Circumstances Related to Thromboprophylaxis

16.1. Air Travel, Immobilization

Long periods of immobilization in a cramped position during travel by air, bus, or car are associated with an increased leg volume and a moderate activation of the coagulation system.[704,705] After air travel, this results in a 2- to 4-fold increased risk in the incidence of venous thrombosis, especially after long flights.[706] Although this may occur in people with normal cardiac anatomy and function, children and adults with CHD may be at higher risk for thrombosis during periods of immobilization because of their cardiac malformations, potential propensity to coagulopathy, or impaired myocardial function (section 4.1, Propensity to Coagulopathy in Children With Heart Disease).

16.2. Oral Contraceptives

Oral contraceptives have a complex interaction with hemostasis and are associated with procoagulant and antifibrinolytic effects. Estradiol and conjugated equine estrogen decrease fibrinogen and plasminogen activator inhibitor levels, whereas estrogen and progestin can create a procoagulant environment with a decrease in AT III and protein S.[707] There is an important dose-response relationship between estrogens and progestins and the risk of venous thrombosis.[708] The route of administration was initially thought to be significant, with less thrombotic risk associated with transdermal contraceptives. However, in a recent randomized, investigator-blinded, crossover clinical trial of 24 women 18 to 35 years of age, transdermal and oral contraceptives had similar statistically significant adverse effects on vascular risk markers.[709] Recent assessment of the etonogestrel-releasing implant suggested that these implants did not induce a prothrombotic state during the first 6 months of use.[710] Confounding factors such as vascular health, timing of medication administration, route of delivery, smoking, diabetes mellitus, insulin resistance, obesity, and genetically increased risk for thromboembolism affect the risk of thrombosis in individual patients.[707] Although guidelines have been published on relative contraindications for contraceptive use, there are no data to support recommendations on the use of antithrombotic therapy in patients on contraception who have never experienced a thromboembolic event.[711]

16.3. Pregnancy

Pregnancy induces significant changes in the coagulation system. Most coagulation factors are increased during normal pregnancy, and the balance of hemostasis is shifted toward a more hypercoagulable state.[712] Hemostatic changes in preeclampsia are shifted even more prominently toward a hypercoagulable state.[713] Anti-phospholipid antibodies in the anti-phospholipid syndrome are associated with increased thrombosis in the uteroplacental circulation and are a marker of potential fetal demise. Impaired FXIIa-dependent activation of fibrinolysis appears to be key in the hemostatic complications in this syndrome.[712] Obesity and gestational diabetes mellitus also are expected to contribute to the risk of thrombosis during pregnancy and in the postpartum period.

Guidelines for the use of anticoagulation in pregnancy are well outlined in the recently published update of the ACC/AHA valvular heart disease guidelines[317] and in the 2004 guidelines from the American College of Chest Physicians.[714] The aim is to maximize the therapeutic efficacy of anticoagulation to counter the hypercoagulability of pregnancy and to minimize the teratogenic effects and risk of maternal and fetal hemorrhagic complications. A reasonable strategy for women with prosthetic heart valves is outlined in guidelines from the American College of Chest Physicians.[714] Women with other rhythm disorders or congenital cardiac disease have additional compelling indications for anticoagulation (eg, AF, Fontan circulation with atrial shunt, Ebstein anomaly with atrial shunt, and prior thromboembolic events), and these patients can use a similar regimen.

16.4. Obesity

The Multiple Environmental and Genetic Assessment (MEGA) Study was a population-based case-control study of 3834 consecutive patients with venous thrombosis and 4683 controls assessed between March 1999 and September 2004 in the Netherlands.[715] In this study, being overweight or obese resulted in a 2- to 3-fold increased risk for thrombosis. Tall patients were at high risk of venous thrombosis compared with short men. Overweight or obese women were also found to be at significantly greater risk for thrombosis than men, although they also used oral contraceptives, which is likely a confounding factor. Multiple other studies have also indicated an increased risk for thrombosis in obesity, particularly in individuals with a concomitant factor V Leiden mutation.[715] The current obesity epidemic in the United States has resulted in a marked increase in the incidence of type 2 diabetes mellitus. This health risk is now extending to the pediatric age group[716,717]; therefore, the incidence of thrombosis in this young population is also likely to increase significantly.

16.5. Children and Adults With Developmental Delay

A few reports indicate coagulation abnormalities in patients with developmental delay resulting from syndromes or chromosomal abnormalities, including Down syndrome[718] and Lesch-Nyhan syndrome.[719] Patients with chromosome 8 deletions or duplications may also demonstrate coagulation abnormalities related to aberrations in the regulation of FVII.[720] Some of these genetic abnormalities and syndromes may be associated with a significant incidence of CHD (eg, Down syndrome), putting these patients at increased risk for thrombosis and bleeding or clotting complications if they need cardiac or other surgery. In addition, children and adults with developmental delay may require special assistance in maintaining adherence to long-term anticoagulation regimens.

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*Modest.

†Significant.

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KEY WORDS: AHA Scientific Statement ■ anticoagulants ■ antiplatelet agents ■ heart defects, congenital ■ heart diseases ■ pediatrics ■ thrombolytic agents ■ thrombosis

Correction

In the article by Giglia et al, "Prevention and Treatment of Thrombosis in Pediatric and Congenital Heart Disease: A Scientific Statement From the American Heart Association," which published online November 13, 2013, and appeared with the December 17, 2013, issue of the journal (*Circulation*. 2013;128:2622–2703), a correction was needed.

The measurement "per patient per year" has been updated to "per patient year" in the following locations:

- Page 2653, right column, last paragraph, third sentence, "…between 1.4 to 2.7 per patient per year and …between 0.7 and 3.0 per patient per year."
- Page 2654, left column, first paragraph, second sentence, "…from 0% to 5.3% per patient per year."
- Page 2654, left column, first paragraph, third sentence, "…and 5.3% per patient per year."
- Page 2654, left column, first paragraph, fourth sentence, "…to 1.3% per patient per year."
- Page 2654, left column, first paragraph, penultimate sentence, "…2.3% per patient per year."
- Page 2654, left column, first paragraph, last sentence, "…<1% per patient per year."
- Page 2654, left column, second paragraph, third sentence, "…and 3% per patient per year."
- Page 2654, left column, second paragraph, eighth sentence, "…and 1.2% per patient per year, …and 1.4% per patient per year."
- Page 2654, left column, second paragraph, last sentence, "…of 1% per patient per year,…"
- Page 2654, right column, first paragraph, second sentence, "…of 5.7±2.1% per patient per year."
- Page 2654, right column, first paragraph, seventh sentence, "…was 22% per patient per year."
- Page 2654, right column, first paragraph, eighth sentence, "…a 12% per patient per year risk…"
- Page 2655, left column, last paragraph, penultimate sentence, "…a 2.9% per patient per year risk…"

The authors regret the error.

These corrections have been made to the print version and to the current online version of the article, which is available at http://circ.ahajournals.org/content/128/24/2622.full.pdf.

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Prevention and Treatment of Thrombosis in Pediatric and Congenital Heart Disease: A Scientific Statement From the American Heart Association

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on behalf of the American Heart Association Congenital Heart Defects Committee of the Council on Cardiovascular Disease in the Young, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, and Stroke Council

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