

2026 American Association for Thoracic Surgery (AATS) expert consensus statement: Antithrombotic management of neonates/infants undergoing cardiac interventions

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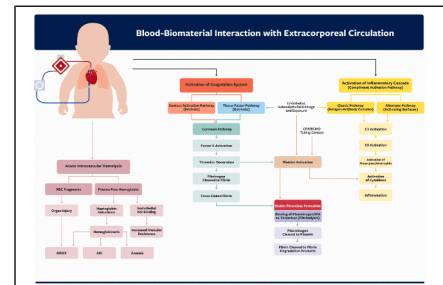
ABSTRACT

Objectives: The hemostatic system in neonates and infants with congenital heart disease is distinct as a result of developmental and disease-specific factors, necessitating population-specific periprocedural evaluation and antithrombotic management. Ongoing practice variation reflects limited evidence and highlights the need for structured guidance and further study.

Methods: To develop a more unified management strategy for periprocedural antithrombotic testing and therapy in this vulnerable population, a group of experts (cardiac surgeons, cardiologists, interventionalist, hematologists, intensivists, and pharmacologists) commissioned by the American Association for Thoracic Surgery was convened to define the basic differences in the hemostatic systems of neonates and infants compared with older children and adults and develop a framework for periprocedural antithrombotic management in neonates and infants undergoing congenital cardiac interventions using the modified Delphi methodology.

Results: Consensus was reached on all 34 statements and related figures and tables. These provide information specific to neonates and infants with congenital heart disease on the coagulation cascade; testing for congenital, acquired, and therapy-related abnormalities in the hemostatic system; and commonly used antithrombotic (anticoagulant and antiplatelet) agents and their monitoring. Recommendations were made on pre-, intra-, and postprocedural antithrombotic management, including procedure and device-specific recommendations both in the short and long term.

Conclusions: The hemostatic system in neonates and infants with congenital heart disease is distinct from that of older children and adults and warrants focused periprocedural evaluation and therapy. These recommendations guide understanding of the complex interactions during antithrombotic management in this patient population during cardiac surgical and catheter-based interventions. (J Thorac Cardiovasc Surg 2026;■:1-45)



The response of the hemostatic system to endothelial injury and foreign material exposure.

CENTRAL MESSAGE

Developmental/disease-specific factors make hemostatic system in neonates/infants with CHD distinct. Variations in antithrombotic management exist. Focused periprocedural evaluation/therapy is needed.

PERSPECTIVE

The initiation, intensity, and duration of antithrombotic therapy for neonates and infants undergoing intervention for congenital heart defects should be guided by an individualized assessment that considers patient-specific factors, surgical/procedural details, and the overall clinical condition, with attention to the dynamic risk of both bleeding and thrombosis.

See Commentary on page XXX.
See Discussion on page XXX.

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Abbreviations and Acronyms

AATS	= American Association for Thoracic Surgery
ACT	= activated clotting time
AHA	= American Heart Association
AT	= antithrombin
CHD	= congenital heart disease
CoR	= class of recommendation
CPB	= cardiopulmonary bypass
CTS	= cardiothoracic surgery
CVC	= central venous catheter
DOAC	= direct oral anticoagulant
DTI	= direct thrombin inhibitor
FFP	= fresh-frozen plasma
HMS	= Hemostasis Management System
INR	= international normalized ratio
LMWH	= low molecular weight heparin
LoE	= level of evidence
PICO	= Patients/Population, Intervention, Comparison/Control, Outcome
POC	= point-of-care
PCC	= prothrombin complex concentrate
ROTEM	= rotational thromboelastometry
STS	= Society of Thoracic Surgeons
TEG	= thromboelastography
TXA	= tranexamic acid
UFH	= unfractionated heparin
VKA	= vitamin K antagonist
VWF	= von Willebrand factor



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According to the Centers for Disease Control and Prevention, congenital heart disease (CHD) affects 1% of births (40,000 babies/year) in the United States, 25% (~10,000) of whom require interventions for CHD in the first year of life.¹ The coagulation cascade and the hemostatic balance in neonates

and infants are distinct from those of adults.²⁻⁷ Neonates exhibit developmental hemostatic differences when compared with adults. In neonates and infants with CHD, additional disease-related pathophysiologic factors—particularly in cyanotic or low-cardiac-output states—further alter coagulation compared with age-matched healthy peers.⁸⁻¹⁴

Neonates and infants with CHD require anticoagulation or antiplatelet therapy (collectively known as antithrombotic therapy) for numerous reasons. The population is heterogeneous with respect to anatomy, physiology, and bleeding/thrombotic risk. Variation in antithrombotic strategy, intensity, duration, and monitoring across centers further complicates interpretation of the literature and limits comparative effectiveness assessments.¹⁴

To address the widespread variation and develop a more unified management strategy for periprocedural antithrombotic management and testing in this vulnerable and high-risk group, a group of experts (cardiac surgeons, cardiologists, interventionalist, hematologists, intensivists, and pharmacologists) commissioned by the American Association for Thoracic Surgery (AATS) was convened to define the basic differences in hemostatic system of neonates and infants compared with older children and adults and develop a framework for periprocedural antithrombotic management in neonates and infants undergoing congenital cardiac interventions using the modified Delphi methodology.

METHODS

The AATS Congenital Heart Surgery Evidence-Based Medicine Taskforce identified the need for a consensus statement on antithrombotic management in neonates and infants undergoing intervention for CHD. Consistent with the AATS harmonized methodology manual, this document was developed as a consensus-based clinical practice guidance statement, not a full systematic Grading of Recommendations Assessment, Development, and Evaluation guideline.¹⁵ A panel of experts from 10 centers that included pediatric cardiac surgeons, cardiologists, interventionalists, intensivists, hematologists, and pharmacists was convened. Search strategy and key terms were prespecified on the basis of the PICO Framework (ie, Patients/Population, Intervention, Comparison/Control, Outcome). A literature review using PubMed, EMBASE, SCOPUS, and Web of Science revealed more than 1000 abstracts. Important related abstracts were chosen and reviewed by the expert panel and pared down to 574 for full manuscript review. The group was split into

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4 groups for full manuscript reviews to answer key questions on 4 specific sections related to the care of neonates and infants with CHD: (1) mechanistic or physiologic studies relevant to developmental hemostasis and neonate and infant population-specific changes in the hemostatic system, available antithrombotic agents, and their monitoring; (2) pre- and intraprocedural antithrombotic management and testing; (3) immediate postprocedural antithrombotic therapy management; and (4) long-term antithrombotic management. The quality of evidence and language for each statement was chosen to be consistent with that recommended in the harmonizing guidelines consensus document by the AATS,

European Association for Cardio-Thoracic Surgery, European Society of Thoracic Surgeons, and Society of Thoracic Surgeons (STS).¹⁵ Expert consensus statements with class (strength) of recommendation (CoR) and level (quality) of evidence (LoE)¹⁶ (Figure 1)¹⁵ and tables and figures were developed using a modified Delphi method. To consider the statement having reached consensus, 80% of the members needed to vote, with 75% of the members “agreeing” or “strongly agreeing.” Each statement or group of statements thus developed has an associated discussion section to highlight important elements of the statement(s). Additional information is detailed in [Appendices 1 and 2](#).

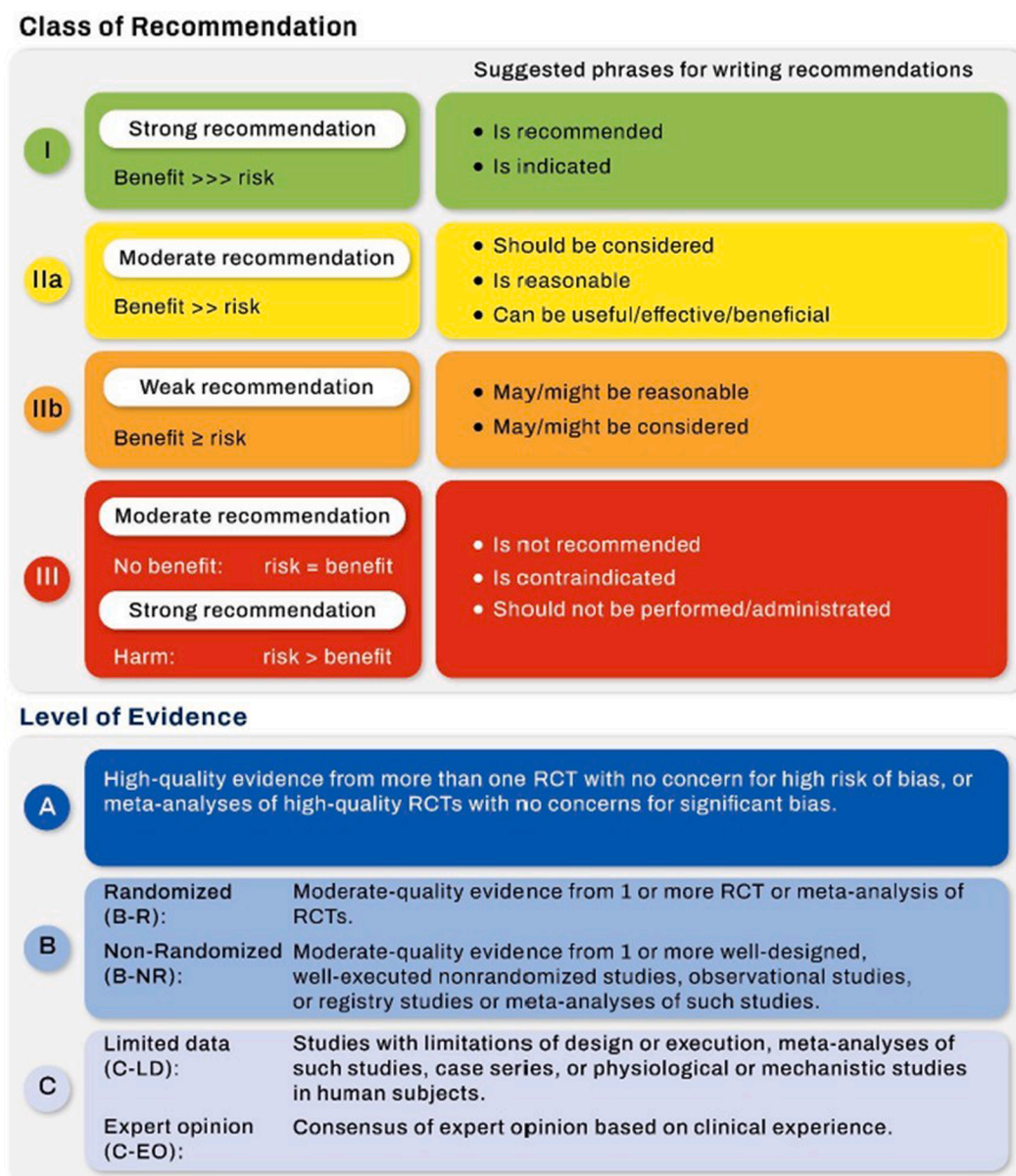


FIGURE 1. Definitions of classes of recommendation and levels of evidence. RCT, Randomized controlled trial. Adapted from the Milojevic and colleagues.¹⁵

PICO STATEMENTS

Hemostatic System in Neonates and Infants

S1. Because the hemostatic system in neonates and infants differs significantly from that of older children and adults, it is recommended that providers should understand these normal differences and the implications of these differences for coagulation testing, antithrombotic monitoring, and drug effects. (CoR I, LoE C-EO)

Developmental hemostasis refers to age-related changes in coagulation factor levels, platelet function, and regulatory pathways that are most dynamic during the neonatal and infant period but continue across the lifespan (Figure 2).² Despite lower levels of several procoagulant factors, neonates maintain effective primary hemostasis through

compensatory mechanisms, including elevated von Willebrand factor (vWF) and factor VIII levels and greater hematocrit.³ There is no evidence that routine correction of these abnormal laboratory factors is of any benefit in reducing the risk of bleeding or thrombotic events in infants who are otherwise stable. Interventions should be considered in infants experiencing clinically significant bleeding or thrombosis.

Infants born premature experience a reduced hemostatic reserve as a result of immature hepatic function, fragile vasculature, and the influence of maternal antibodies, placing them at increased risk for complications such as intraventricular hemorrhage, an outcome reduced by antenatal maternal steroids.^{2,4} As organ systems mature, the

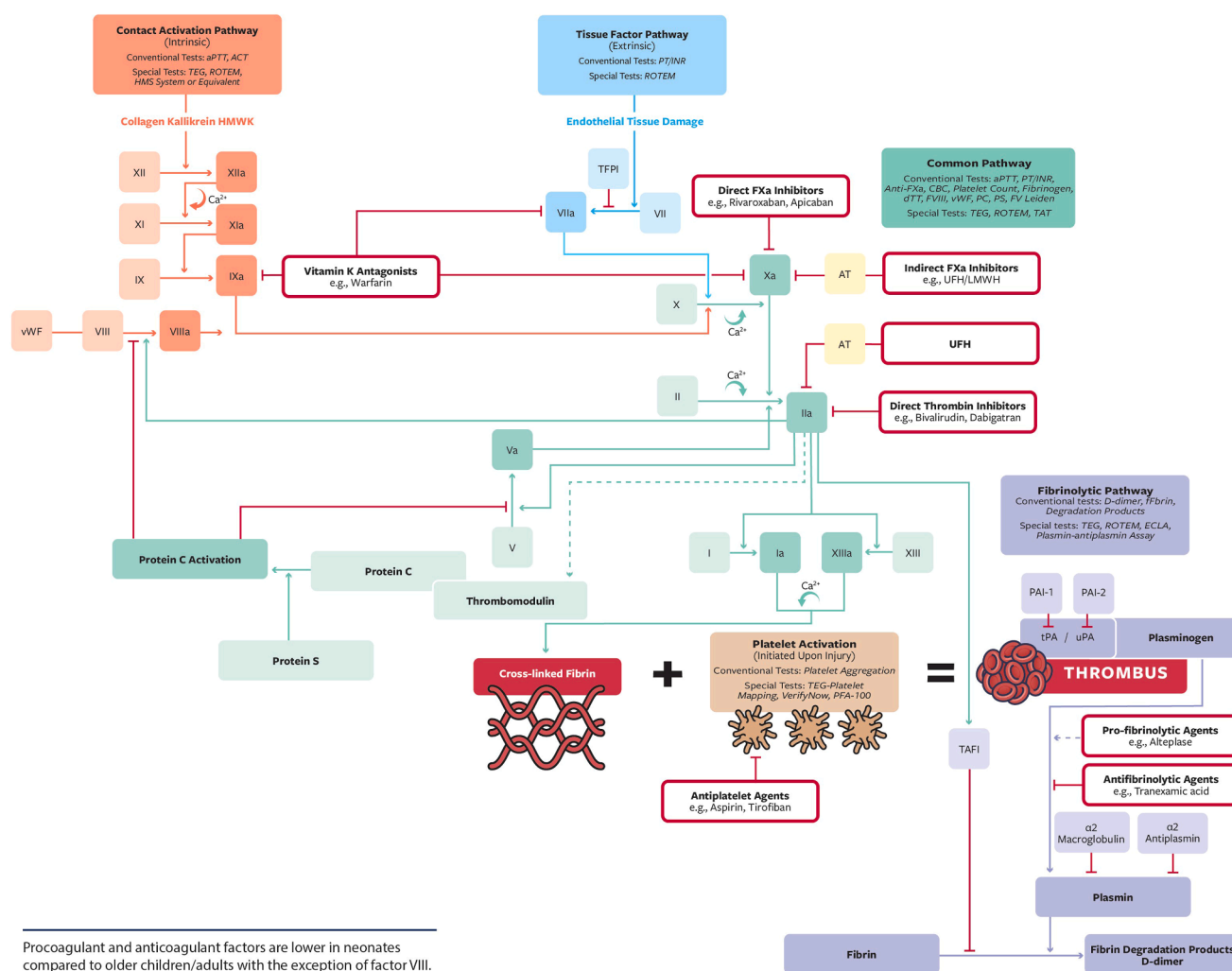


FIGURE 2. The hemostatic system of neonates and infants, and testing for various components of the hemostatic system, is presented. *aPTT*, Activated partial thromboplastin time; *ACT*, activated clotting time; *TEG*, thromboelastography; *ROTEM*, rotational thromboelastometry; *HMS*, Hemostasis Management System; *PT*, prothrombin time; *INR*, international normalized ratio; *HMWK*, high-molecular-weight kininogen; *CBC*, complete blood count; *dTT*, direct thrombin time; *vWF*, von Willebrand factor; *PC*, protein C; *PS*, protein S; *TAT*, thrombin-antithrombin; *AT*, antithrombin; *UFH*, unfractionated heparin; *LMWH*, low molecular weight heparin; *ECLA*, euglobulin clot lysis assay; *PFA-100*, Platelet Function Analyzer 100; *PAI*, plasminogen activator inhibitor; *tPA*, tissue plasminogen activator; *uPA*, urokinase plasminogen activator.

hemostatic profile gradually evolves, approaching adult reference ranges by approximately 6 months of age in infants born at term. Hemostatic maturation continues throughout childhood and adolescence, and further changes occur across adulthood. These developmental variations have direct implications for clinical care. Age-specific laboratory reference ranges are essential for accurate interpretation, and antithrombotic agents often require adjusted dosing and close monitoring, given altered pharmacokinetics (Figure 2).^{5,6} Awareness of these physiological differences is crucial to avoid misdiagnosis and inappropriate management in neonates and infants.

S2. Neonates and infants with congenital heart disease, particularly those with cyanotic congenital heart disease, demonstrate coagulation profiles that differ from age-matched healthy controls; therefore, preoperative coagulation testing may be reasonable in select patients because of their increased risk of baseline coagulation abnormalities. (CoR IIB, LoE B-R)

Neonates with CHD and patients with cyanosis exhibit more pronounced hemostatic abnormalities compared

with healthy newborns and patients without cyanosis, including greater reductions in procoagulant factors and natural anticoagulants as well as greater levels of vWF.⁸⁻¹⁰ Elevated plasminogen activator inhibitor-1 and low antithrombin (AT) levels described in neonates and infants may contribute to altered thrombosis and bleeding risk during cardiac procedures; however, direct evidence linking these laboratory findings to procedural thrombosis is limited. These differences are most significant in neonates and young infants; whereas acyanotic CHD profiles typically normalize by age 5 years, cyanotic CHD often leads to ongoing coagulopathy.¹¹ Recent studies highlight markedly greater rates of coagulation differences in cyanotic CHD (57%) compared with acyanotic CHD (17%) and healthy controls (7%), with rotational thromboelastometry (ROTEM) demonstrating impaired clot firmness and reduced prothrombin activity that correlate with increased perioperative bleeding and transfusion needs.^{12,13} Although age-related and CHD-specific coagulation differences are well described, data linking these laboratory findings to clinical outcomes are limited, and preoperative correction

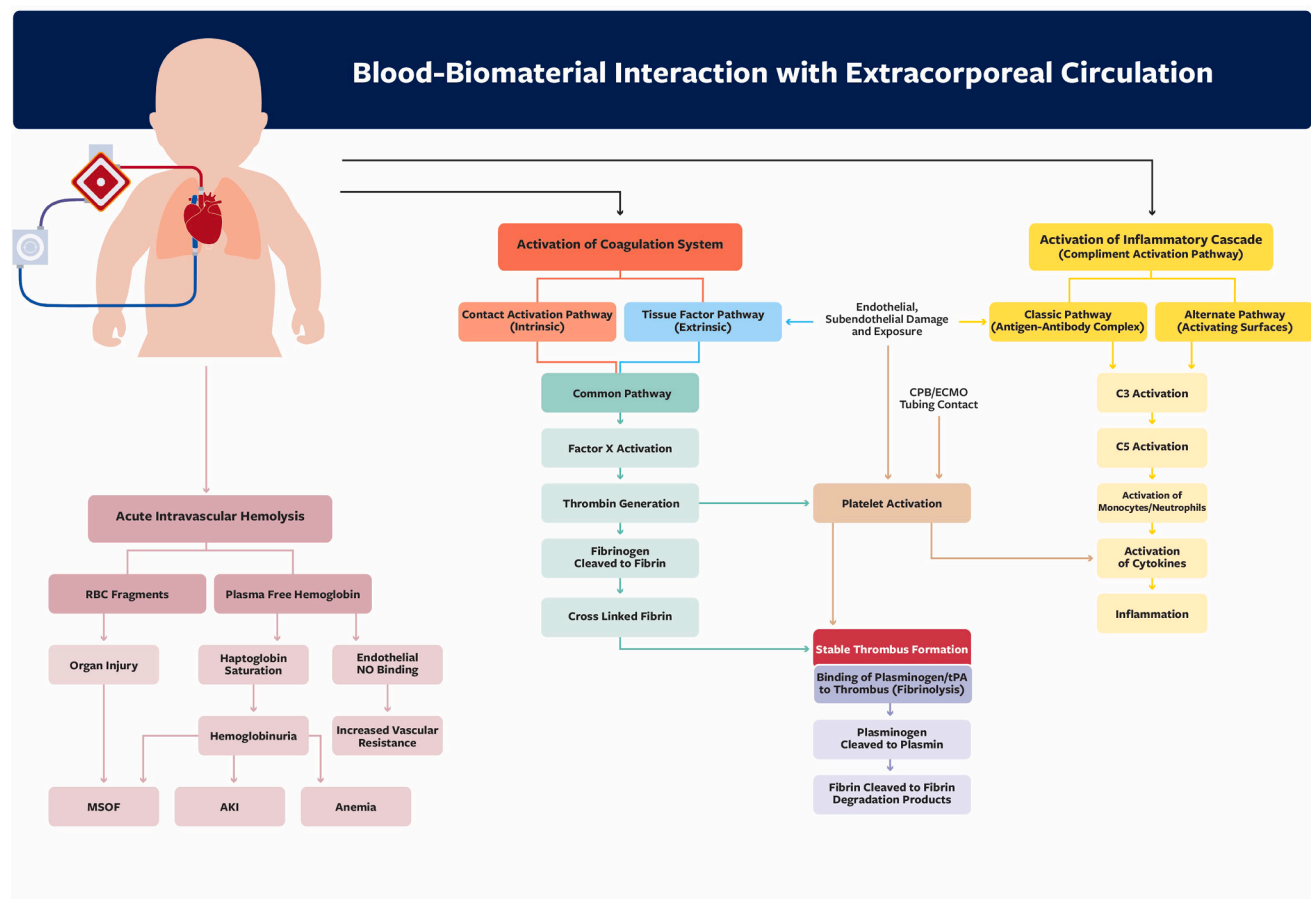


FIGURE 3. Blood-biomaterial interaction with extracorporeal circulation. A description of the response of the hemostatic system to endothelial injury and biomaterial exposure is presented. *RBC*, Red blood cell; *NO*, nitric oxide; *MSOF*, multiple system organ failure; *AKI*, acute kidney injury; *CPB*, cardiopulmonary bypass; *ECMO*, extracorporeal membrane oxygenation; *tPA*, tissue plasminogen activator.

TABLE 1. Perioperative hematologic abnormalities, diagnostic testing, and management strategies

Perioperative hematologic abnormalities	Diagnostic evaluation and/or monitoring	Indications for evaluation (preoperative, intraoperative, postoperative)	Management
Anemia	CBC, reticulocyte count, and iron studies as appropriate on the basis of clinical history and/or red cell indices	Preoperative workup Postoperative monitoring	Preoperative iron supplementation for documented deficiency (oral or intravenous infusions). Epogen (epoetin alfa) may be considered as an adjunct therapy to help minimize the need for blood transfusions perioperatively in special clinical instances. pRBCs should be transfused as warranted to achieve and maintain hemoglobin or hematocrit target (as per institutional protocols and in consideration of patient factors) to ensure adequate oxygen delivery, especially in neonates and in cyanotic heart disease.
Heparin unresponsiveness (“resistance”)	ACT, anti-factor Xa, AT activity levels	Inability to prolong ACT	Measurement of AT levels should be considered in patients with poor heparin response. This is particularly relevant in neonates with suspected AT deficiency.
Residual heparin effect	aPTT, ACT, thrombin time, anti-factor Xa activity, TEG reaction time (R) compared with and without heparinase, ROTEM-CT of the INTEM compared with HEPTTEM	Unexplained bleeding after coming off CPB (prolonged clotting times may be attributable to persistent anticoagulant activity of heparin that remains in the patient’s circulation after protamine reversal)	Consider additional administration of protamine sulfate.
Thrombocytopenia	Platelet count, CBC, TEG, ROTEM, HIT testing (PF4 ELISA, SRA), peripheral smear ADAMTS13 activity assay (suspected thrombotic thrombocytopenia purpura)	Excessive postoperative bleeding	Platelet transfusion may be used to treat thrombocytopenia or qualitative platelet dysfunction, guided by clinical context (eg, presence and severity of bleeding), platelet count, and viscoelastic assays (TEG, ROTEM), with targets based on institutional protocol and patient factors.
Coagulopathy (abnormal plasma-based coagulation tests)	PT, aPTT, fibrinogen, D-dimer, platelet count, TEG, ROTEM, individual clotting factor assays (eg, factor VIII, IX, XIII)	Excessive postoperative bleeding (nonsurgical, diffuse hemorrhage caused by impaired coagulation)	Management targeted at the etiology of coagulopathy based on conventional testing: – Low fibrinogen with prolonged PT and prolonged aPTT: suspect hypofibrinogenemia ($\pm$ dysfibrinogenemia) and give cryoprecipitate or fibrinogen concentrate; in the case of dysfibrinogenemia, exercise caution regarding simultaneously increased thrombotic risk

(Continued)

TABLE 1. Continued

Perioperative hematologic abnormalities	Diagnostic evaluation and/or monitoring	Indications for evaluation (preoperative, intraoperative, postoperative)	Management
		pathways, platelet dysfunction, or hyperfibrinolysis)	– Prolonged PT with normal aPTT and normal fibrinogen, and PT corrects with a mixing study: suspect FVII deficiency. Consider PCC/aPCC vs low-dose rFVIIa (exercise caution with use of rFVIIa in trauma or postoperative settings, given increased thrombotic risk) – Prolonged aPTT with normal PT and normal fibrinogen, and aPTT corrects with mixing study: Suspect a deficiency of factor VIII, IX, XI, or XII, and correct with FFP or factor VIII, or factor IX replacement. (NOTE: If isolated aPTT prolongation preoperatively, the diagnosis could be congenital FXII deficiency, which is one of the most common reasons for a nonartifactual isolated aPTT prolongation that does not correct on mixing study, and yet FXII deficiency is not associated with bleeding and therefore does not warrant any intervention other than education of the family and treating team). – Normal PT, aPTT, and fibrinogen: Consider von Willebrand disease (low von Willebrand factor antigen and/or activity) or factor XIII deficiency. In the former case, give von Willebrand factor products, and in the latter, give FFP or factor XIII concentrate (if available). – Prolonged PT with normal aPTT and normal fibrinogen, and PT does not correct with a mixing study: suspect an acquired antibody to FVII and give corticosteroid, with PRBC transfusion support as needed. – Prolonged aPTT with normal PT and normal fibrinogen, and aPTT does not correct with mixing study: Suspect an acquired antibody to factor VIII, IX, XI, or XII, and in the case of a diagnosis of all but antibody-mediated XII deficiency, give corticosteroid, with pRBC transfusion support as needed. – Desmopressin (DDAVP) may be considered in patients with known or suspected type 1 von Willebrand disease and associated platelet dysfunction (caution in postoperative setting due to fluid shifts that may result). – rFVIIa may be considered in post-CPB patients with coagulopathic bleeding after correction of other factor deficiencies and exclusion of a surgical source of bleeding (Caution regarding thrombotic risk; off-label in pediatrics; monitor response via viscoelastic diagnostic tests if feasible as per institutional protocol). Multi-factor products include the following: PCC, anti-inhibitor coagulant complex, such as FEIBA (for life-threatening bleeding unresponsive to conventional transfusion and coagulation support).

(Continued)

TABLE 1. Continued

Perioperative hematologic abnormalities	Diagnostic evaluation and/or monitoring	Indications for evaluation (preoperative, intraoperative, postoperative)	Management
Thrombosis	D-dimer, PT, aPTT, thrombophilia panel (protein C, protein S, AT, factor V Leiden, homocysteine, prothrombin gene mutation, lupus anticoagulant, anticardiolipin titers [IgG, IgM, beta-2-glycoprotein-1-antibody])	Arterial (including arterial ischemic stroke)/venous (including cerebral venous sinus thrombosis)/intracardiac/shunt/stent/valve thrombosis	Consider unfractionated heparin, low molecular weight heparin, or intravenous direct thrombin inhibitor in the acute phase. Beyond the acute phase, consider LMWH, DOAC (apixaban, rivaroxaban, edoxaban, dabigatran), or vitamin K antagonist for venous event; aspirin, and/or clopidogrel for arterial event after 2 wk of anticoagulation if reduction/resolution of thrombus.

Consider multidisciplinary discussion with hematology and/or transfusion medicine. *CBC*, Complete blood count; *pRBC*, packed red blood cell; *ACT*, activated clotting time; *AT*, antithrombin; *aPTT*, activated partial thromboplastin time; *TEG*, thromboelastography; *ROTEM*, rotational thromboelastometry; *CT*, clotting time; *INTEM*, Intrinsic Rotational Thromboelastometry; *HEPTEM*, heparinase thromboelastometry/heparin-modified thromboelastometry; *CPB*, cardiopulmonary bypass; *HIT*, heparin-induced thrombocytopenia testing; *PF4*, platelet factor 4; *SRA*, serotonin release assay; *FVII*, factor VII; *rFVIIa*, recombinant activated factor VII; *PT*, prothrombin time; *PCC*, prothrombin complex concentrate; *aPCC*, activated prothrombin complex concentrate; *FXII*, factor XII; *FFP*, fresh-frozen plasma; *DDAVP*, 1-deamino-8-D-arginine vasopressin; *FEIBA*, factor eight inhibitor bypass activity; *LMWH*, low molecular weight heparin; *DOAC*, direct oral anticoagulants.

algorithms are lacking. Standard preoperative testing (complete blood count, partial thromboplastin time, prothrombin time, international normalized ratio [INR], and fibrinogen) should therefore be interpreted in clinical context and trended across the peri- and postoperative period rather than used in isolation to guide intervention. Additional testing can be considered and includes D-dimer, platelet function assays, AT activity, VWF antigen, VWF GP1b activity, viscoelastic testing, and individual factor assays. Table 1 provides details of perioperative hematologic abnormalities, diagnostic testing, and management strategies.

S3. Routine thrombophilia testing is not recommended in neonates and infants with congenital heart disease undergoing cardiac intervention. (CoR III, LoE B-NR)

S4. Targeted evaluation may be considered in the setting of unprovoked or recurrent thrombosis or a strong family history, in consultation with pediatric hematology. (CoR IIb, LoE C-LD)

Perioperative thrombosis in neonates and infants with CHD is predominantly driven by clinical factors including exposure to cardiopulmonary bypass (CPB), presence of central venous catheters (CVCs), altered flow dynamics, inflammation, and low cardiac output. The contribution of inherited thrombophilia in this setting remains uncertain. Some papers have suggested an increased prevalence of inherited prothrombotic mutations and thrombophilic polymorphisms.⁷ A history of unprovoked thrombotic events and/or family history of thrombosis may warrant further

investigation for genetic thrombophilia. Thus, targeted testing, including genetic alterations in Factor V Leiden, prothrombin G20210A, and methylenetetrahydrofolate reductase, deficiencies in protein C and S, and other known prothrombotic conditions such as single-nucleotide polymorphisms and prothrombotic mutations, may be considered. Interpretation of functional studies may be challenging in the neonatal/infant population as the result of developmental differences and/or the presence of active thrombosis. As such, consultation with hematology is recommended to assist in ordering and interpreting results, taking into consideration age-related differences and the impact of active thrombosis on the results. Impacts of genetic polymorphism on thrombosis risk, as well as recommendations for short- and long-term anticoagulation management should be made in conjunction with hematology, and consultation with genetics is recommended to evaluate the risk in other family members and for future pregnancies.¹⁷ The American Heart Association (AHA) recommends individualized thrombophilia testing, guided by pediatric thrombosis specialists, particularly when a thrombotic event has occurred or when additional perioperative risk factors are present.¹⁴ This tailored approach balances thorough evaluation with the avoidance of unnecessary testing and optimizes management in this high-risk population. Of note, testing in neonates may not return in time to impact intraoperative decisions but may help with postoperative and long-term decision-making.

Periprocedural Antithrombotic and Bleeding Management During CPB and Catheter-Based Interventions

S5. In neonates and infants, perioperative comprehensive blood-conservation strategies may be considered to minimize exposure to allogenic blood products and to attenuate the inflammatory coagulopathic response during and after cardiopulmonary bypass surgery. (CoR IIb, LoE B-NR)

The acute inflammatory response to cardiopulmonary bypass (CPB) is complex and multifactorial, including contact activation of blood components by the nonendothelial surface of the CPB circuit, ischemia-reperfusion injury, hemodilution, endotoxemia, and response to operative trauma (Figure 3).¹⁸ Dilutional thrombocytopenia on CPB is more profound in neonates and infants, and platelet activation on CPB results in activated yet hyporesponsive platelets.¹⁸⁻²⁴ A comprehensive approach that implements multiple interventions should be used to attenuate the contact, shear stress, and inflammatory response related to complex congenital heart surgery. Miniaturization of contemporary CPB circuits has been shown to reduce contact activation and hemodilution, resulting in an attenuated inflammatory response and reduced transfusion requirements.²⁴ Use of biocompatible coated circuits (eg, heparin coating, alternating hydrophilic/hydrophobic domains, etc) may further attenuate the inflammatory response and coagulation cascade activation seen with CPB.²¹⁻²⁴ Priming and bypass techniques, including pre-bypass zero balance ultrafiltration, continuous ultrafiltration on bypass, and modified ultrafiltration post-bypass, may further attenuate the inflammatory response and associated coagulopathy to CPB.¹⁹ In addition, antifibrinolytics attenuate post-CPB bleeding by inhibiting fibrinolysis and preserving platelet function.^{14,18,24} Antifibrinolytics may be efficacious in neonates, neonates/infants with cyanosis, and neonates/infants undergoing repeat sternotomies.^{14,18,24} Blood-conservation strategies, including cell salvage during CPB for neonates and infants, may minimize the use of blood and blood products in the periprocedural period.²⁵

It has been demonstrated that bloodless neonatal cardiac surgery may not only be feasible but may also be associated with improved outcomes.^{18,25} Achieving transfusion-free surgery in 25% of neonates, even in complex single-ventricle cases, challenges long-held assumptions about unavoidable blood product use.²⁵ Limiting donor exposure is especially valuable for patients who may later need cardiac transplantation, because it helps preserve human leukocyte antigen-matching options and reduces allo-sensitization risk.²⁶

S6. Intraprocedure heparinization is recommended in neonates and infants undergoing cardiac interventions to reduce the incidence of thrombosis and thromboembolic complications. (CoR I, LoE B-NR)

Neonates and infants undergoing cardiothoracic surgery (CTS), especially those requiring CPB, experience greater surgical morbidity and mortality compared to older children and adults.²⁷ Lower physiologic AT levels in neonates and infants may influence heparin responsiveness and the relationship between dose and anticoagulant effect during CTS.^{27,28} Unfractionated heparin (UFH) is most commonly used for anticoagulation during CTS, not only to prevent thrombosis of the bypass circuit but also to prevent more subtle activation and consumption of coagulation system components.^{27,28} Additional procedural benefits of UFH include full reversal of effect with protamine administration. UFH should be the standard of care for patients undergoing CTS.

With the use of larger or longer sheaths and prolonged procedure times, the risk of arterial and venous thrombosis is increased in small children and infants undergoing cardiac catheterization.²⁹ Marked reduction in the incidence of thrombosis and thromboembolism can be achieved with heparinization, which should be standard practice during almost all cardiac catheterization, as explicitly recommended by clinical expert guidelines.²⁹ Heparin dosing should be carefully monitored via activated clotting time (ACT) to ensure that the target ACT is maintained with monitoring goals established by multidisciplinary team discussion at institutions. Table 2 provides information on procedural antithrombotic and reversal agents, whereas Table 3 provides details on post-operative antithrombotic medications and reversal agents for antithrombotic medications. Table 4 describes diagnostic tests for coagulation abnormalities.

S7. In neonates and infants undergoing cardiac interventions (cardiac surgery and/or cardiac catheterization), where unfractionated heparin cannot be used, direct thrombin inhibitors are appropriate as an alternative anticoagulant strategy. (CoR I, LoE B-NR)

In situations in which heparin cannot be used for cardiac interventions (eg, heparin-induced thrombocytopenia), although there are limited data that can guide substitution with direct thrombin inhibitors (DTIs), clinical expert guidelines specifically recommend bivalirudin as a reasonable option for urgent cardiac operations requiring CPB in patients with heparin-induced thrombocytopenia.³⁰⁻³³ DTIs directly inhibit thrombin without requiring AT, making them effective even in patients with heparin resistance or heparin-induced thrombocytopenia. The main challenge with procedural use of bivalirudin is the lack of a reversal agent; however, its short half-life (~20 minutes with normal renal function) allows for rapid clearance through proteolytic degradation. Bivalirudin has been compared with heparin for children without cyanosis who are undergoing CTS. Monitoring was with ACT in both groups. Overall, transfusion requirements and adverse events were similar; however, neonates and infants were not included in the studies.^{30,31} More robust studies have been

TABLE 2. Procedural antithrombotic and reversal agents

Agent name (route of administration)	Mechanism	Half-life	Metabolism and excretion	Monitoring	Side effects	Pediatric FDA-approved applications	Comments (including common off-label uses)
Indirect factor Xa and/or thrombin inhibitor UFH (intravenous)	A heparinoid that forms a UFH-AT complex, binds to FXa and thrombin with high affinity, thus inhibiting thrombin generation	Neonates: ~35-41 min Infants: ~60-90 min	Primarily through the liver and spleen (desulfation); rapidly excreted through nonrenal mechanisms (small amounts of unchanged drug in urine)	Routine monitoring: ACT or aPTT Special monitoring if feasible: Hepcon HMS system (or equivalent emerging anti-FXa platforms)	Hemorrhage, heparin-induced thrombocytopenia	Not FDA approved for pediatric use	In neonates and infants during CPB, dosing is individualized on the basis of ACT response or the newer point- of-care testing, with consideration of AT activity in neonates. Consider AT supplementation in cases of heparin unresponsiveness ("resistance") or inadequate ACT (or aPTT) prolongation. Reversal: protamine sulfate given at the end of CPB; dosage proportional to total UFH administered
Direct factor Xa and/or thrombin inhibitors Bivalirudin (intravenous)	Direct inhibition of free and clot-bound thrombin	Neonates: ~15-25 min Infants: ~20-30 min	Proteolytic cleavage; excreted in the urine, glomerular filtration, tubular secretion, and tubular reabsorption	Routine monitoring: aPTT, dTT, ACT. Special monitoring where applicable and feasible: TEG or ROTEM	Hemorrhage, antibody development, anaphylaxis	Not FDA approved for pediatric use	Alternative to heparin for anticoagulation in neonates and infants, particularly those with heparin-induced thrombocytopenia or AT deficiency. When drug is being discontinued for bleeding or urgent procedure, FFP or 4-factor PCC/ aPCC can be used to correct laboratory abnormalities and presumably reduce bleeding risk. Dose adjustment in renal impairment. Dosing not yet established for pediatrics.
Argatroban (intravenous)	Direct, reversible inhibition of free and clot-bound thrombin	Neonates: ~ 15-35 min Infants: ~ 25-45 min Hepatic impairment: 181 min	Hepatic through hydroxylation and aromatization through CYP3A4/5; primarily excreted in the feces and urine	Routine monitoring: aPTT, dTT, ACT	Hemorrhage, hypotension, hematuria	Not FDA approved for pediatric use	Alternative to heparin for anticoagulation in neonates and infants, particularly those with heparin-induced thrombocytopenia or AT deficiency. When drug is being discontinued for bleeding or urgent procedure, FFP or 4-factor PCC/ aPCC can be used to correct laboratory abnormalities and presumably reduce bleeding risk. Dose adjustment in hepatic impairment. Dosing not yet established for pediatrics.

(Continued)

TABLE 2. Continued

Agent name (route of administration)	Mechanism	Half-life	Metabolism and excretion	Monitoring	Side effects	Pediatric FDA-approved applications	Comments (including common off-label uses)
Pro-/antifibrinolytic agents							
TXA (intravenous)	An antifibrinolytic synthetic lysine analog that competitively inhibits the binding of plasminogen and plasmin to fibrin, thereby preventing fibrin degradation and stabilizing formed clots	Neonates: ~2-3 h Infants: ~1.5-3 h	Minimally metabolized; excreted unchanged in the urine via glomerular filtration	Routine monitoring: none. Special monitoring if feasible: TEG/ROTEM fibrinolysis (Ly30) can be considered, but viscoelastic testing is relatively insensitive (ie, sensitive mostly to extremes of fibrinolysis).	Seizures (especially at high doses during CPB), hypotension (if infused rapidly), nausea, visual disturbances, thromboembolic events (rare)	Not FDA approved for use in neonates and infants	In neonates and infants undergoing CPB, TXA is commonly used off-label to reduce fibrinolysis and transfusion requirements. Dose adjustment in renal impairment due to predominant renal excretion. Reversal: None; discontinue drug, supportive care.
tPA (intravenous)	A fibrinolytic recombinant human tissue plasminogen activator binds to fibrin in a thrombus and converts plasminogen to plasmin, which breaks down fibrin and reduces the clot burden	Neonates: ~ 20-40 min (alpha-phase 3-6 min; beta-phase prolonged) Infants: ~ 20-40 min	Primarily hepatic metabolism via rapid clearance by liver and plasma proteases; minimal renal excretion of inactive metabolites	Fibrinogen level, PT/aPTT, and CBC (for bleeding assessment), D-dimer trend for thrombosis resolution	Major bleeding (including intracranial hemorrhage), orolingual angioedema (esp. with ACE inhibitors), hypotension	Not FDA-approved for pediatric use.	Use is off-label and may be considered after multidisciplinary discussion. No established neonatal dose. Avoid if recent surgery or high bleeding risk Reversal: None; management is supportive (cryoprecipitate, antifibrinolytics).

Consider multidisciplinary discussion with hematology and/or transfusion medicine. Fibrin sealants/topicals are biological adhesives such as fibrin glue used in surgery for their hemostatic, chemotactic, and mitogenic properties. They replicate the final step of the coagulation cascade by converting fibrinogen to fibrin via thrombin, forming a stable clot that helps seal tissues and control bleeding. These agents act locally and are not systemically absorbed, making them effective for targeted bleeding control. However, their effectiveness is assessed subjectively by the clinical team, and they should serve only as adjuncts and not substitutes for surgical correctable bleeding or proper systemic coagulation management. *FDA*, Food and Drug Administration; *UFH*, unfractionated heparin; *FXa*, factor Xa; *ACT*, activated clotting time; *aPTT*, activated partial thromboplastin time; *CPB*, cardiopulmonary bypass; *AT*, antithrombin; *FFP*, fresh-frozen plasma; *PCC*, prothrombin complex concentrate; *aPCC*, activated prothrombin complex concentrate; *TXA*, tranexamic acid; *TEG*, thromboelastography; *ROTEM*, rotational thromboelastometry; *tPA*, tissue plasminogen activator; *PT*, prothrombin time; *CBC*, complete blood count; *ACE*, angiotensin-converting enzyme.

TABLE 3. Postoperative antithrombotic and reversal agents

Agent name (route of administration)	Mechanism	Half-life	Metabolism and excretion	Monitoring	Side effects	Pediatric FDA-approved applications	Comments (including common off-label uses)
Indirect factor Xa and/or thrombin inhibitors							
UFH (intravenous)	A heparinoid that forms a UFH-AT complex, binds to FXa and thrombin with high affinity, thus inhibiting thrombin generation	Neonates: ~35-41 min Infants: ~60–90 min	Primarily through the liver and spleen (desulfation); rapidly excreted through nonrenal mechanisms (small amounts of unchanged drug in urine).	Anti-Xa assay, aPTT	Bleeding, heparin-induced thrombocytopenia	Not FDA approved for pediatric use	Initiated in the postoperative period once surgical hemostasis is achieved and maintained for thrombosis prophylaxis/treatment where indicated. Frequent monitoring and dose adjustments are often needed due to variable heparin sensitivity and immature anticoagulation pathways in neonates. Consider AT supplementation in cases of heparin unresponsiveness (“resistance”) or subtherapeutic target. Consider transition to bivalirudin if requiring frequent AT supplementation or unable to achieve the therapeutic target despite high doses. Reversal: Protamine sulfate
Enoxaparin (subcutaneous)	A heparinoid that forms a LMWH-AT complex, binds to FXa with high affinity, thus inhibiting Thrombin generation	Neonates: ~3-4 h Infants: ~2.5-3.5 h	Hepatic, through desulfation to lower-molecular-weight molecules with little activity, and depolymerization; primarily excreted in the urine	Anti-Xa assay	Hemorrhage, spinal or epidural hematomas, heparin-induced thrombocytopenia	Not FDA approved for pediatric use	For thrombosis prophylaxis/treatment. Dosing varies depending on age and indication, and renal function. Reversal: Protamine sulfate can only partially reverse (~40%) the heparin effect.
Fondaparinux (subcutaneous)	Indirect, selective factor Xa inhibitor	Neonates: ~8-12 h (limited data; prolonged due to renal immaturity) Infants: ~6-10 h	Direct renal excretion without metabolism; Primarily excreted in the urine	Anti-Xa assay	Hemorrhage, anemia, hypotension	Not FDA-approved for pediatric use	For thrombosis prophylaxis/treatment. Reversal: No reversal agent. Component blood products and/or 4-factor PCC/aPCC can be used to correct laboratory abnormalities.
Dalteparin (subcutaneous)	LMWH – Anticoagulant—potentiates AT, inhibiting factor Xa (and to a lesser extent IIa)	<3 mo: ~2.25 h 3 mo-1 y: ~ 4.9 h	Partially hepatic metabolism; primarily renal excretion	Anti-Xa assay	Hemorrhage, thrombocytopenia, osteoporosis (rare), injection-site reactions	FDA-approved for VTE treatment/secondary prevention in pediatric patients ≥1 mo	For thrombosis prophylaxis/treatment. Dose adjustment in renal impairment. Reversal: Protamine sulfate can only partially reverse (~25-50%) the heparin effect

(Continued)

TABLE 3. Continued

Agent name (route of administration)	Mechanism	Half-life	Metabolism and excretion	Monitoring	Side effects	Pediatric FDA-approved applications	Comments (including common off-label uses)
Direct FXa and/or thrombin inhibitors							
Bivalirudin (intravenous)	Direct inhibition of free and clot-bound thrombin	Neonates: ~15-25 min Infants: ~20-30 min	Proteolytic cleavage; excreted in the urine, glomerular filtration, tubular secretion, and tubular reabsorption	aPTT, dTT ACT Special monitoring where applicable and feasible: TEG or ROTEM	Hemorrhage, antibody development, anaphylaxis	Not FDA approved for pediatric use	Alternative to heparin for anticoagulation in neonates and infants, particularly those with heparin-induced thrombocytopenia or AT deficiency. When drug is being discontinued for bleeding or urgent procedure, FFP or 4-factor PCC/aPCC can be used to correct laboratory abnormalities and presumably reduce bleeding risk. Dose adjustment in renal impairment. Dosing not yet established for pediatrics.
Argatroban (intravenous)	Direct, reversible inhibition of free and clot-bound thrombin	Neonates: ~ 15-35 min Infants: ~ 25-45 min Hepatic impairment: 181 min	Hepatic through hydroxylation and aromatization through CYP3A4/5; primarily excreted in the feces and urine	aPTT, dTT Special monitoring where applicable and feasible: TEG or ROTEM	Hemorrhage, hypotension, hematuria	Not FDA-approved in pediatrics	For thrombosis prophylaxis/treatment. Alternative to heparin for anticoagulation in neonates and infants, particularly those with heparin-induced thrombocytopenia or AT deficiency. When drug is being discontinued for bleeding or urgent procedure, FFP or 4-factor PCC/aPCC can be used to correct laboratory abnormalities and presumably reduce bleeding risk. Dose adjustment in hepatic impairment. Dosing not yet established for pediatrics.
Dabigatran (oral)	Direct, reversible inhibition of clot-bound and free thrombin	Neonates: Data limited; estimated ~8-12 h Infants (>2-3 mo): ~6-8 h	Rapidly and completely hydrolyzed to the active form by plasma and hepatic esterases, then undergoes hepatic glucuronidation, primarily eliminated in the urine; P-glycoprotein transportation	None In emergencies (overdose or bleeding): aPTT, dTT, ECT	Bleeding, GI adverse reactions	Treatment of pediatric VTE after treatment with UFH or LMWH for at least 5 d, secondary prophylaxis of pediatric VTE (3 mo to <12 y)	For thrombosis prophylaxis/treatment. Prevention/therapeutic dose is determined on the basis of age and weight. Should not be used in infants with mechanical valves or antiphospholipid syndrome (APS). Must check organ function and drug interactions and enteral feeding status before initiation. Reversal: May consider 4-factor PCC/aPCC to correct laboratory abnormalities and presumably reduce bleeding risk. Idarucizumab as a reversal agent has been studied

(Continued)

TABLE 3. Continued

Agent name (route of administration)	Mechanism	Half-life	Metabolism and excretion	Monitoring	Side effects	Pediatric FDA-approved applications	Comments (including common off-label uses)
Rivaroxaban (oral)	Direct, reversible inhibition of free and prothrombinase-bound factor Xa	<6 mo: 1.6 h 6 mo-1 y: 1.9 h	Hepatic oxidative degradation (CYP3A4/5, CYP2J2), excretion - urine and GI; P-glycoprotein transportation	Rivaroxaban level (chromogenic anti-Xa assayed to rivaroxaban). Limited data on the utility of routine monitoring in infants and children	Bleeding, coughing, vomiting, gastroenteritis	Treatment of pediatric VTE after treatment with UFH or LMWH for at least 5 d. Thromboprophylaxis in pediatric patients >2 y of age after Fontan surgery	in adults, but data on use and outcomes in infants are limited to case reports. For thrombosis prophylaxis/treatment. Should not be used in infants with mechanical valves or APS. Must check organ function and drug interactions and enteral feeding status before initiation. Reversal: May consider 4-factor PCC/ aPCC to correct laboratory abnormalities and presumably reduce bleeding risk.
Apixaban (oral)	Direct, reversible inhibition of free and clot-bound factor Xa, prothrombinase	Neonates: No direct data; estimated ~6-8 h Infants (>3-6 mo): ~4-6 h	Hepatic oxidative degradation (mainly CYP3A4), excretion - urine and feces; P-glycoprotein transportation	Apixaban level (chromogenic anti-Xa level assayed to apixaban). Limited data in children on utility of routine monitoring.	Bleeding, abnormal LFTs, leukopenia	Treatment of pediatric VTE after treatment with UFH or LMWH for at least 5 d.	For thrombosis prophylaxis/treatment. Should not be used in infants with mechanical valves or APS. Must check organ function and drug interactions and enteral feeding status before initiation. Reversal: May consider 4-factor PCC/ aPCC to correct laboratory abnormalities and presumably reduce bleeding risk.
Edoxaban (oral)	Direct, reversible inhibition of factor Xa	Neonates: No direct PK data; estimated ~6-10 h Infants (>6 mo): ~4-7 h	Minimal hepatic oxidative metabolism through CYP3A4, clearance - urine; P-glycoprotein transportation	Edoxaban-calibrated anti-Xa assay. No data on the utility of routine monitoring in infants and children	Bleeding, rash, abnormal LFTs, anemia, and interstitial lung disease	Not FDA-approved in pediatric patients	For thrombosis prophylaxis/treatment. Should not be used in infants with mechanical valves or APS. Must check organ function and drug interactions and enteral feeding status before initiation. Reversal: May consider 4-factor PCC/ aPCC to correct laboratory abnormalities and presumably reduce bleeding risk.

(Continued)

TABLE 3. Continued

Agent name (route of administration)	Mechanism	Half-life	Metabolism and excretion	Monitoring	Side effects	Pediatric FDA-approved applications	Comments (including common off-label uses)
Vitamin K-dependent anticoagulant							
Warfarin (oral)	An anticoagulant that inhibits hepatic synthesis of vitamin K-dependent clotting factors (II, VII, IX, X) and proteins C and S, leading to decreased thrombin generation	Neonates: ~20-40 h (wide variability) Infants: ~25-45 h	Hepatic metabolism (CYP2C9, CYP3A4); inactive metabolites excreted renally and in bile	PT/INR	Bleeding, skin necrosis (rare), teratogenicity, variable response with diet/drug interactions, osteoporosis, hair loss	Not FDA approved in pediatrics.	Long-term anticoagulant therapy in selected infants postcardiac surgery (eg, mechanical valves, conduit thrombosis). Multiple drug and food interactions, including OTC drugs; caution with concurrent use of antimicrobials, anti-arrhythmic drugs, and other anticoagulant agents. Need for frequent INR monitoring and frequent dose adjustments due to immature hepatic metabolism and dietary vitamin K fluctuations. Due to long and variable half-life, achieving the target therapeutic range can take 5-7 d. LMWH is recommended until a therapeutic INR achieved. Food interactions: foods rich in vitamin K. INR stability may be affected by developmental hemostasis and illnesses. Reversal: Vitamin K or FFP or 4 factor PCC/aPCC if bleeding.
Antiplatelet agents							
Aspirin (oral)	An antiplatelet agent, an irreversible COX1 and COX2 inhibitor, resulting in inhibition of thromboxane, thus inhibiting platelet aggregation	Half-life: not applicable, given irreversible platelet inhibition for the life of the platelet	Hydrolyzed to salicylate by esterases in the GI mucosa	Routine monitoring: typically, not required Special monitoring based on institutional preference, and if feasible: VerifyNow aspirin assay, Platelet Function Assay/analysis (PFA-100/PFA-200), TEG platelet mapping for arachidonic acid.	GI bleeding, hypersensitivity reactions	Not FDA-approved in pediatrics	Thromboprophylaxis/arterial thromboembolism treatment (after 2 wk of anticoagulation if reduction/resolution of thrombus). If concern for aspirin unresponsiveness or resistance, evaluate barriers to absorption (eg, PPIs that increase the gastric pH above what is required for aspirin absorption) or other drug-drug interactions. *Note that concomitant usage of other NSAIDs reduces aspirin's effect. *Note that aspirin may reduce the ACEi, and ARB antihypertensive effect.

(Continued)

TABLE 3. Continued

Agent name (route of administration)	Mechanism	Half-life	Metabolism and excretion	Monitoring	Side effects	Pediatric FDA-approved applications	Comments (including common off-label uses)
Clopidogrel (oral)	An antiplatelet agent irreversibly blocks the P2Y ₁₂ component of ADP receptors on the platelet surface. This prevents glycoprotein IIb/IIIa activation, which reduces platelet aggregation	Half-life: not applicable, given irreversible platelet inhibition for the life of the platelet	Hepatically hydrolyzed from a carboxylic acid derivative (inactive) through CYP (primarily CYP2C19) to a thiol metabolite (active)	Routine monitoring: typically, not required Special monitoring based on institutional preference and if feasible, VerifyNow PRU test, PFA-100/ PFA-200, TEG platelet mapping for ADP	Bleeding, hypersensitivity, thrombotic thrombocytopenic purpura	Not FDA-approved in pediatrics	Thromboprophylaxis/arterial thromboembolism treatment (after 2 wk of anticoagulation if reduction/resolution of thrombus). If concern for unresponsiveness, evaluate barriers to absorption, avoid contraindicated drugs that can reduce its efficacy (eg, omeprazole, esomeprazole), and exercise caution with other drugs that can reduce its effect (eg, NSAIDs, selexipag) Used either as an alternative agent to aspirin or as an add-on in patients unresponsive to aspirin or in case of progression of arterial thromboembolism on aspirin.
Dipyridamole (oral)	An antiplatelet agent inhibits the activity of phosphodiesterase (PDE), causing mediator accumulation, inhibiting platelet aggregation	Neonates: very limited data, ~10-12 h (estimated) Infants: ~9-12 h	Hepatic to glucuronide conjugation	None	Dizziness, hypersensitivity, bleeding	Not FDA-approved in pediatrics	Thromboprophylaxis/arterial thromboembolism treatment (after 2 wk of anticoagulation if reduction/resolution of thrombus).
Cangrelor (intravenous)	An antiplatelet agent, a direct P2Y ₁₂ platelet receptor inhibitor that blocks ADP-induced platelet activation and aggregation	Neonates: ~2-3 min Infants: ~2-3 min	Rapidly inactivated in the circulation by dephosphorylation	Routine monitoring: Platelet function, VerifyNow PRU or TEG platelet mapping	Bleeding, renal insufficiency, dyspnea	Not FDA-approved in pediatrics	Thromboprophylaxis/arterial thromboembolism treatment. Very limited data exists on dosing and monitoring. If PRU monitoring indicated, it should be performed STAT due to degradation of the drug in the tube if not run STAT (leading to falsely elevated PRUs).
Tirofiban (intravenous)	Reversibly inhibits platelet GPIIb/IIIa receptors, preventing fibrinogen crosslinking and platelet aggregation.	Neonates: very limited data, ~1.5-2 h (estimated) Infants: ~1.5-2 h	Hepatic metabolism; renal excretion of unchanged drug	Platelet count, aPTT, bleeding assessment	Bleeding, thrombocytopenia, hypotension, nausea	Not FDA-approved in pediatrics	For thromboprophylaxis/arterial thromboembolism treatment.

(Continued)

TABLE 3. Continued

Agent name (route of administration)	Mechanism	Half-life	Metabolism and excretion	Monitoring	Side effects	Pediatric FDA-approved applications	Comments (including common off-label uses)
Pro-/antifibrinolytic agents							
TXA (intravenous)	Antifibrinolytic synthetic lysine analog that competitively inhibits the binding of plasminogen and plasmin to fibrin, thereby preventing fibrin degradation	Neonates: ~2-3 h Infants: ~1.5-3 h	Minimally metabolized; ~ excreted unchanged in the urine via glomerular filtration	None. Special monitoring if feasible: ECLA if available (plasma); if point-of-care testing needed. TEG/ROTEM Fibrinolysis (Ly30) can be considered, but viscoelastic testing is relatively insensitive (ie, sensitive mostly to extremes of fibrinolysis).	Seizures (especially at high doses during CPB), hypotension (if infused rapidly), nausea, visual disturbances, thromboembolic events (rare)	Not FDA-approved in neonates and infants	Used off label in neonate/infant to reduce bleeding and transfusion during CPB and up to 6-12 h postoperatively. Reversal: None; discontinue drug, supportive care.
tPA (intravenous)	Profibrinolytic recombinant human tissue plasminogen activator that binds to fibrin and converts plasminogen to plasmin, which lyses local fibrin	Neonates: ~ 20-40 min (alpha-phase 3-6 min; beta-phase prolonged) Infants: ~ 20-40 min	Primarily hepatic metabolism via rapid clearance by liver and plasma proteases; minimal renal excretion of inactive metabolites	Fibrinogen level, D-dimer, PT/aPTT, plasminogen, and CBC (for bleeding assessment)	Major bleeding (including intracranial hemorrhage), orolingual angioedema (esp. with ACE inhibitors), hypotension	Not FDA-approved in pediatrics.	Paucity of published safety and efficacy data in neonates and infants postcardiac surgery and therefore most often considered for critical thrombosis in those settings. Hold/ reduce heparin and monitor closely for bleeding. Reversal: None; management is supportive (cryoprecipitate, antifibrinolytics such as aminocaproic acid or TXA).

The selection of an agent will depend on patient characteristics, institutional preference, and health care resources. Consider multidisciplinary discussion with hematology and/or transfusion medicine. *FDA*, Food and Drug Administration; *UFH*, unfractionated heparin; *AT*, antithrombin; *FXa*, factor Xa; *aPTT*, activated partial thromboplastin time; *LMWH*, low-molecular-weight heparin; *PCC*, prothrombin complex concentrate; *aPCC*, activated prothrombin complex concentrate; *VTE*, venous thromboembolism; *ACT*, activated clotting time; *dTT*, direct thrombin time; *TEG*, thromboelastography; *ROTEM*, thromboelastometry; *FFP*, fresh frozen plasma; *ECT*, Ecarin clotting time; *GI*, gastrointestinal; *APS*, antiphospholipid syndrome; *LFT*, liver function test; *PT*, prothrombin time; *INR*, international normalized ratio; *OTC*, over-the-counter; *COX*, cyclooxygenase; *PFA*, platelet function assay/platelet function analysis; *PPI*, proton pump inhibitor; *NSAID*, nonsteroidal anti-inflammatory drug; *ACEi*, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin II receptor blockers; *P2Y12*, purinergic receptor; *ADP*, adenosine diphosphate; *CYP*, cytochrome; *PDE*, phosphodiesterase; *TXA*, tranexamic acid; *ECLA*, euglobulin clot lysis assay; *CPB*, cardiopulmonary bypass; *tPA*, alteplase; *CBC*, complete blood count; *PRU*, P2Y₁₂ reaction units/platelet reactivity unit.

TABLE 4. Diagnostic tests for coagulation abnormalities

Test	Purpose/pathway	Out-of-range result	Clinical application	Management strategies/comments*
Common coagulation tests				
PT/INR	Coagulation status Extrinsic and common pathway	↑	Bleeding disorders, vitamin K deficiency, liver disease, warfarin therapy, coagulopathy/DIC (falsely elevated with bivalirudin and argatroban therapy)	Vitamin K administration, FFP or PCC†/aPCC for urgent reversal, adjust warfarin dose (elevated PT with bivalirudin, argatroban, not treated unless other clinical indications).
aPTT/PTT	Coagulation status Intrinsic and common pathway	↑	Hemophilia A/B, UFH or LMWH (rare), bivalirudin and argatroban effect, coagulopathy/DIC, artificial surface contact pathway (MCS/artificial material); lupus anticoagulant (may paradoxically cause thrombosis); consider antibody-mediated (inhibitor) depending on mixing study results.	Factor replacement depending on the etiology. Hold or reverse anticoagulant. DDAVP as indicated.
ACT	Measure of the time it takes to form a clot	↑	Bleeding or thrombosis risk	Adjust anticoagulant dose or reverse as indicated.
TT	Evaluate the conversion of fibrinogen to fibrin upon thrombin addition	↑	Hypofibrinogenemia, dysfibrinogenemia, heparin effect, bivalirudin and argatroban effect	Treat the underlying cause. Fibrinogen concentrate or cryoprecipitate for low fibrinogen. Protamine if secondary to heparin
dTT	Evaluate the conversion of fibrinogen to fibrin using a low concentration (diluted) of thrombin.	↑	Indicates presence or excess of direct thrombin inhibitors (bivalirudin, argatroban)	If prolonged, decrease or hold bivalirudin, argatroban. Highly sensitive to direct thrombin inhibitors but less to fibrinogen deficiency. Gold standard for DTI titration.
AT	Monitor DTIs Major natural anticoagulant, inhibits most factors in the intrinsic pathway, including thrombin; potentiated by heparin	↓	Liver disease, coagulopathy, DIC, dilutional, heparin resistance, recurrent venous thrombosis, neonates Inherited AT deficiency	AT concentrate or FFP for acute management. LMWH or direct Xa inhibitors for thrombosis prevention; address acquired causes (eg, DIC, liver disease, nephrotic syndrome). For inherited AT deficiency, use a vitamin K antagonist or DOAC for long-term for thrombosis prophylaxis/treatment.
TAT assay	Global clot formation (indirect measure of thrombin production)	↑	Hypercoagulable state, ongoing thrombin generation, early DIC	Address prothrombotic state (anticoagulate if thrombosis, treat DIC cause).
Reptilase time	Functional fibrinogen	↑	Dysfibrinogenemia, hypofibrinogenemia	Fibrinogen concentrate or cryoprecipitate if bleeding.
Fibrinogen level	Precursor to fibrin May be measured as functional fibrinogen or fibrinogen antigen: most routine laboratory tests are functional (Clauss)	↓	Bleeding, DIC, liver disease, or underlying hypofibrinogenemia	Fibrinogen concentrate or cryoprecipitate if bleeding.

(Continued)

TABLE 4. Continued

Test	Purpose/pathway	Out-of-range result	Clinical application	Management strategies/comments*
D-dimer	Fibrin degradation (therefore can be elevated when: (1) excess fibrin has formed in hypercoagulable states and is being normally broken down (normal fibrinolytic state); or (2) there are normal amounts of fibrin (non-hypercoagulable state) but excessive amounts of fibrinolysis).	↑	DVT prognosis, PE diagnosis/risk stratification, DIC; not specific	Manage underlying cause (eg, treat DIC or thrombosis); not directly treated.
Specific factor tests				
Factor I (fibrinogen) assay [see also above: routine coagulation tests])	Precursor to fibrin May be measured as functional fibrinogen or fibrinogen antigen: most routine lab tests are functional (Clauss)	↓	Bleeding disorders, liver disease, DIC, or underlying hypofibrinogenemia	Replacement therapy: Fibrinogen concentrate or cryoprecipitate if bleeding. Treat underlying cause (eg, DIC, liver disease). Avoid excessive hemodilution.
Factor II (prothrombin) assay	Precursor to thrombin	↓	Bleeding risk, liver disease, and vitamin K deficiency	Vitamin K if due to deficiency/warfarin; FFP or PCC/aPCC if bleeding or clinically indicated; specific factor concentrates if available (rare).
Factor V, VII, VIII, IX, X, XI, XII assays	Specific factor deficiencies	↓	Hemophilia (VIII = hemophilia A, IX = hemophilia B), rare factor deficiencies, bleeding disorders, consumptive factor deficiency	FV: FFP or PCC/aPCC; platelet transfusion; avoid antifibrinolytics unless indicated. FVII: Recombinant activated FVII (rFVIIa) for inherited deficiency; Vitamin K for Vitamin K deficiency or warfarin-induced FVII deficiency. FVIII: DDAVP for mild hemophilia A (if responsive); Factor VIII concentrate or cryoprecipitate for moderate-severe bleeding; Emicizumab for prophylaxis of hemophilia A; bypassing agents (PCC/aPCC, rFVIIa) if inhibitor present. FIX: Factor IX concentrate (recombinant or plasma-derived); if unavailable, PCC/aPCC. FX: specific FX concentrate if available, if unavailable FFP, PCC/aPCC. FXI: FFP pre-procedure or during bleeding; tranexamic acid for minor mucosal bleeds; specific concentrate (FXI). With factor replacement, avoid overcorrection (risk of thrombosis). If not corrected on a mixing study these factor deficiencies are likely antibody mediated and may require steroids.
Factor XIII assay	Cross-linking fibrin	↓	Delayed bleeding, wound healing defects	FXIII: FXIII concentrate (recombinant or plasma-derived).
vWF antigen/activity	vWF quantity/function	↓	vWD → mucocutaneous bleeding, increased levels in neonates as part of developmental hemostasis	DDAVP or vWF concentrate, depending on the etiology. Avoid aspirin.
vWF multimer analysis	Subtyping of vWD	Abnormal pattern	Type-specific diagnosis of vWD	Type-specific therapy (DDAVP for type 1, vWF concentrate for type 2/3).

(Continued)

TABLE 4. Continued

Test	Purpose/pathway	Out-of-range result	Clinical application	Management strategies/comments*
Platelet quantification/function tests				
Platelet count (CBC)	Quantitative platelet assessment	↓ (thrombocytopenia) ↑ (thrombocytosis)	↑ bleeding risk risk of thrombosis; iron deficiency, infection etc.	Platelet transfusion if active bleeding and thrombocytopenia. Treat underlying etiology for thrombocytosis (eg, immune-mediated, heparin-induced, inflammation, blood drawn contributing to iatrogenic anemia). Other options for thrombocytosis include plateletpheresis, aspirin (typically when platelet count >1 million). Treatment with IV/oral iron therapy for thrombocytosis associated with severe iron-deficiency anemia.
Bleeding time/PFA-100/platelet aggregometry	Platelet function (response to aspirin, P2Y ₁₂ inhibitors, GP IIb/IIIa inhibitors)	↑ BT ↑ Platelet aggregation	Platelet function disorders, vWD, aspirin/antiplatelet therapy, functional resistance	Stop antiplatelet therapy. DDAVP for vWD (type 1, non-neonate, nonpostoperative), treat underlying etiology (eg, dialysis for uremia).
VerifyNow assay	Response to aspirin or P2Y ₁₂ inhibitors	↓ platelet reactivity	High thrombotic risk if nonresponsive; ↑ bleeding risk if overresponsive	Tests for arachidonic acid pathway inhibition (aspirin), and P2Y ₁₂ inhibition via ADP pathway (clopidogrel, ticagrelor, prasugrel, cangrelor). Aspirin target range <550 ARU for aspirin responsiveness. PRU target range ~50-200 for clopidogrel, cangrelor responsiveness (target ranges extrapolated from adult studies). Assess for confounding factors (GI absorption), concomitant use of NSAIDs (ibuprofen), which displaces aspirin, concomitant use of omeprazole, which reduces the effect of clopidogrel, adjust antiplatelet therapy (dose or agent), and monitor for complications.
Flow cytometry for platelet glycoproteins	Receptor defects	Abnormal	Glanzmann thrombasthenia, Bernard-Soulier syndrome	Platelet transfusion for bleeding; recombinant factor VIIa if refractory.
Tests for inhibitors/anticoagulants				
aPTT/PT mixing studies	Distinguish factor deficiency vs presence of inhibitors (specific factor antibodies or lupus anticoagulant). Involves mixing patient plasma 1:1 with normal pooled plasma and repeating aPTT/PT immediately and after incubation	aPTT or PT not corrected	Tests for the presence of several inhibitors (nonspecific: lupus anticoagulant, heparin, or direct thrombin inhibitors; specific: factor VIII, IX inhibitors) - Correction: Suggests factor deficiency (eg, hemophilia, vitamin K deficiency). - No correction: Suggests inhibitor (eg, lupus anticoagulant). - Correction then prolongation after incubation: Suggests time-dependent factor inhibitor, especially factor VIII inhibitor (acquired hemophilia).	If factor inhibitor: immunosuppression (IVIG, steroids, rituximab). If lupus anticoagulant: anticoagulation therapy if thrombotic.

(Continued)

TABLE 4. Continued

Test	Purpose/pathway	Out-of-range result	Clinical application	Management strategies/comments*
Lupus anticoagulant panel	Evaluation for patients with thrombosis	Positive	↑ Thrombosis risk despite prolonged aPTT in some cases	Long-term anticoagulation (specifically, warfarin or LMWH) in patients who meet criteria for antiphospholipid syndrome (persistently positive APA at least 12 wk apart) with a personal history of thromboembolism; under the guidance of a hematologist ± rheumatologist; avoid unnecessary bleeding correction in circumstances where, for example, aPTT or PT is prolonged due to the effects of an APA; of note, monitoring anticoagulants with aPTT or PT can be challenging in the setting of an APA that can prolong these tests at baseline and cause a non-linear prolongation when monitoring anticoagulant effect; when an APA is known or suspected, then monitoring anticoagulants via a ratio of on-treatment aPTT (or PT) to baseline (pre-treatment) aPTT (or PT) may be more accurate than absolute aPTT (or PT) target, although still influenced to some degree by non-linear prolongation of the test in the setting of APA.
Heparin assays (anti-Xa) (UFH, enoxaparin)	Monitor heparin therapy, acquired or inherited thrombophilia, can be falsely elevated with bivalirudin	↓/↑	Under- or overanticoagulation	Adjust the heparin dose. Consider protamine if clinically indicated and bleeding from UFH.
DOAC calibrated anti-Xa assay	Chromogenic anti-Xa levels assayed to a specific DOAC, affected by heparin or bivalirudin or any drugs that impact anti-Xa	↓/↑	Under- or overanticoagulation	Refer to institutional protocols. No pediatric data in children, consider correction of laboratory coagulopathies with 4-factor PCC/aPCC. No data in pediatrics for reversal agents.
Fibrinolysis/clot stability tests				
FDP and D-dimer	Fibrin breakdown	↑	DIC, thrombolysis	Manage DIC supportively (FFP, fibrinogen concentrate, cryoprecipitate, platelets).
ELT	Fibrinolytic activity	Shortened/prolonged	Hyperfibrinolysis → bleeding Hypofibrinolysis → thrombosis	Antifibrinolytics (tranexamic acid, aminocaproic acid) for hyperfibrinolysis.
α2-Antiplasmin/ plasminogen activity	Fibrinolysis regulation	↓/↑	Bleeding or thrombosis tendency	Replace deficient components or give antifibrinolytics if hyperfibrinolysis occurs.

(Continued)

TABLE 4. Continued

Test	Purpose/pathway	Out-of-range result	Clinical application	Management strategies/comments*
Special tests				
Chromogenic factor assays	Factor activity (eg, Xa, thrombin inhibitors)	↓/↑	Bleeding or thrombosis risk	Adjust anticoagulant dose or reverse as indicated.
Genetic testing (factor V Leiden, prothrombin G20210A)	Hereditary thrombophilia	Mutation present	↑ Risk of thrombosis	Lifelong or situational anticoagulation as indicated.
Protein C, protein S assays	Natural anticoagulants	↓	↑ Thrombosis risk, DIC, liver dysfunction/hepatopathy, acquired or inherited thrombophilia	Anticoagulation for the acute and subacute periods of the thrombus or as needed for acquired deficiency; treat with replacement (FFP, protein C concentrate) if needed (in acute thromboembolism and sometimes as thromboprophylaxis for major surgeries in patients with severe deficiencies).
Homocysteine level	Hypercoagulable state	↑	↑ Risk of arterial and venous thrombosis	Vitamin B6, B12, and folate supplementation depending on the etiology; manage vascular risk factors. Testing for MTHFR mutation.
ECT	Direct measure of prothrombin → meizothrombin formation using the snake venom Ecarin. Highly specific for DTIs. Not affected by heparin, warfarin, or most factor deficiencies.	↑	Strongly suggests the presence of dabigatran (linear correlation with drug concentration). Indicates therapeutic or supratherapeutic levels of other DTIs (argatroban, bivalirudin). Not prolonged by factor deficiencies—helps distinguish DTI effect from coagulopathy.	If due to dabigatran: Stop drug; for emergent reversal, give idarucizumab. If due to bivalirudin/argatroban: Discontinue infusion (short half-life clears quickly). For bleeding with DTI: consider activated charcoal (if recent oral ingestion), supportive care. Use repeat ECT to trend DTI clearance.
Viscoelastic testing: thromboelastography (TEG), rotational thromboelastometry (ROTEM)				
TEG: R time (reaction time) ROTEM: CT (clotting Time- INTEM- intrinsic factors; EXTIM- extrinsic factors)	Time to clot initiation	↑	Clotting factor deficiency Anticoagulant effect	FFP or 4-factor PCC/aPCC. Reverse anticoagulant (TEG: improved/normalized CKH-R compared with CK-R; ROTEM: improved/normalized HEPTM CT compared with INTEM CT)
TEG: maximum amplitude (MA) ROTEM: MCF (maximum clot firmness)	Maximum clot strength	↓	Low platelet count/function or low fibrinogen → bleeding risk	Platelet transfusion and/or cryoprecipitate

(Continued)

TABLE 4. Continued

Test	Purpose/pathway	Out-of-range result	Clinical application	Management strategies/comments*
TEG: CFF (CFF_MA) ROTEM: FIBTEM	Functional fibrinogen contribution to clot strength	↓	Hypofibrinogenemia or impaired fibrin polymerization	Cryoprecipitate or fibrinogen concentrates (TEG CFF or ROTEM FIBTEM: specific for low fibrinogen)
TEG: LY30 (lysis at 30 min) ROTEM: LY30 (lysis index at 30 min)	Clot breakdown	↑	Hyperfibrinolysis → bleeding risk	Antifibrinolytic therapy (tranexamic acid, aminocaproic acid)

EXTEM is used to examine extrinsic coagulation pathway. INTEM is used to examine intrinsic coagulation pathway. HEPTEM removes the effect of heparin. FIBTEM is used to assess fibrinogen contribution to clot strength. TEG CFF: citrated functional fibrinogen-assesses fibrinogen contribution to clot strength. TEG CK-R: citrated kaolin reaction time. TEG CKH-R: citrated kaolin with heparinase reaction time. Coagulation tests included should use age-appropriate reference ranges. Consider multidisciplinary discussion with hematology and/or transfusion medicine. In the setting of inflammation (very common in children with acute and chronic illnesses who have, or are at risk of, acute thromboembolic events), many factor activity levels are altered, thereby potentially altering functional and global assays in either direction. (example: antithrombin may be inhibited by an antibody or consumed by proinflammatory hypercoagulability, whereas protein C, FVIII and others may be elevated as an acute phase response, making it difficult to predict the net effect of PT, aPTT, TEG, ECLA, and an anti-Xa assay. The clinical importance of inflammation is that in a very prothrombotic patient it may be more difficult to achieve the goal anti-Xa for a given “indication” (acute thromboembolism treatment; primary thromboembolism prevention) with a given dose (or age-appropriate dose/kg) of antithrombotic. In the most complex clotting phenotype patients (eg, thrombotic storm, catastrophic APS) where patients are having progressing and recurrent multifocal thromboembolism despite seemingly adequate doses (or even adequate levels achieved) of antithrombotics, sometimes requires titrating to the earlier of an adequately declining D-dimer level or the first evidence of bleeding occurrence at IV sites, etc. *PT*, Prothrombin time; *INR*, international normalized ratio; *DIC*, disseminated intravascular coagulation; *FFP*, fresh-frozen plasma; *PCC*, prothrombin complex concentrate; *aPCC*, activated prothrombin complex concentrate; *aPTT*, activated partial thromboplastin time; *PTT*, partial thromboplastin time; *UFH*, unfractionated heparin; *LMWH*, low-molecular-weight heparin; *MCS*, mechanical circulatory support; *DDAVP*, 1-deamino-8-D-arginine vasopressin (desmopressin); *ACT*, activated clotting time; *TT*, thrombin time; *dTt*, dilute thrombin time; *DTI*, direct thrombin inhibitor; *AT*, antithrombin; *DOAC*, direct oral anticoagulant; *TAT*, thrombin–antithrombin; *DVT*, deep vein thrombosis; *PE*, pulmonary embolism; *vWF*, von Willebrand factor; *vWD*, von Willebrand disease; *CBC*, complete blood count; *IV*, intravenous; *PFA*, platelet factor assay; *P2Y₁₂*, purinergic receptor; *ADP*, adenosine diphosphate; *ARU*, aspirin reaction units; *PRU*, *P2Y₁₂* reaction units; *GI*, gastrointestinal; *NSAID*, nonsteroidal anti-inflammatory drugs; *APA*, antiphospholipid antibodies; *FDP*, fibrin degradation products; *ELT*, euglobulin lysis time; *MTFHR*, methylenetetrahydrofolate reductase; *ECT*, Ecarin clotting time; *TEG*, thromboelastography; *ROTEM*, thromboelastometry; *CT*, clotting time; *CK*, citrated kaolin; *CKH*, citrated kaolin with heparinase; *ECLA*, modified mini-euglobulin clot lysis assay; *APS*, antiphospholipid syndrome. *Management strategies should consider the clinical status of patients and the risk of thrombosis. Any patient with an underlying hematological disease should include consultation with a hematologist. †PCC can be 3- or 4-factor concentrate: 4-factor PCC contains 4 clotting factors: II, VII, IX, and X, whereas 3-factor PCC contains factors II, IX, and X, but only a small amount of factor VII, if any. Both 4-factor PCC and 3-factor PCC also typically include protein C, protein S, and sometimes small amounts of heparin.

conducted in adults, showing similar results.³² Similarly, there are multiple reports of using both bivalirudin and argatroban in children undergoing cardiac catheterization safely and effectively.²⁹ Although the data are limited for the use of DTIs in neonates and infants undergoing cardiac interventions, DTIs are deemed an appropriate alternative anticoagulation strategy. Close monitoring should be followed to ensure safety and efficacy (Tables 2-4).

S8. In neonates and infants undergoing complex cardiac surgery with cardiopulmonary bypass, individualized unfractionated heparin titration using validated anti-factor Xa point-of-care diagnostic tests (eg, HMS Plus Hemostatic Management System [Medtronic] or equivalent anti-FXa-based platforms) may be considered as an alternative to activated clotting time (ACT)-guided weight-based dosing alone, where institutional expertise exists. (CoR IIB, LoE B-NR)

S9. Any intraoperative point-of-care coagulation testing platforms (eg, HMS Plus Hemostasis Management System or emerging anti-FXa-guided platforms) primarily developed for adult populations may require modification when applied to neonates and infants to optimize unfractionated heparin and protamine dosing during cardiac surgery. (CoR IIB, LoE C-LD)

Traditionally, pediatric anticoagulation management during CPB has relied on adult-derived, weight-based heparin and protamine dosing guided by ACT. However, ACT correlates poorly with plasma heparin concentration as the result of hemodilution, hypothermia, and assay variability. These limitations are particularly evident in neonates and infants with immature coagulation systems. For any monitoring strategy to be clinically valuable, it should correlate with anticoagulant effect across the therapeutic range and demonstrate association with improved patient-centered outcomes. Current data in neonates and infants remains limited and heterogeneous. To overcome these shortcomings, individualized UFH titration using systems such as the HMS Plus Hemostasis Management System enables direct measurement of patient-specific heparin levels, offering a more precise approach to anticoagulation. Evidence in infants demonstrates that HMS-based protocols achieve more stable anticoagulation, reduce hemostatic and fibrinolytic activation, and can improve clinical outcomes when tailored to pediatric physiology.²⁷ It has been reported that a modified HMS protocol in infants stabilized anti-Xa levels and reduced transfusion needs, ventilation time, and intensive care unit stay in addition to reductions in subtherapeutic ACT values, blood product use, and operating room time.^{27,34} Despite some variability in clinical outcomes, HMS-guided management consistently achieves greater and more stable heparin concentrations with superior suppression of thrombin generation and factor VIII consumption.³⁵

Although direct heparin monitoring with HMS offers advantages, standard HMS protocols were developed for

adults and older children and often fail to account for the distinct pharmacokinetics and hemostatic characteristics of neonates and infants. Applying adult-based protocols in this population can result in suboptimal anticoagulation, excessive bleeding, or incomplete heparin reversal.^{36,37} Limited evidence highlights the need for age-specific modifications; in one study, poor outcomes in neonates managed with manufacturer-standard HMS protocols prompted suspension of the trial pending recalibration.³⁵ Adaptations such as revised heparin targets, individualized protamine ratios, and neonatal-specific calibration curves have improved correlations between measured heparin levels and clinical hemostasis, reduced ACT variability, and decreased transfusion requirements. The AHA similarly notes that unmodified HMS-guided dosing may lead to greater heparin requirements and inadequate protamine reversal, whereas tailored protocols enhance anti-FXa stability and clinical outcomes.¹⁴ However, because the HMS system may be discontinued in the coming years, emerging intraoperative point-of-care (POC) anti-FXa assays are being explored as potential replacements. These next-generation platforms will require adaptation and validation for neonatal and infant physiology. On the basis of studies in patients of all ages undergoing CPB, guidelines from the AHA and STS support individualized heparin dosing.^{14,33} Incorporating such pediatric-specific POC technologies may ensure continued progress toward individualized, pharmacokinetically guided anticoagulation and improved perioperative outcomes in congenital cardiac surgery. Monitoring targets should be established on the basis of multidisciplinary team discussion at institutions.

S10. In neonates and infants undergoing complex cardiac surgery who demonstrate an inadequate heparin response, supplementation with antithrombin concentrate or fresh-frozen plasma may be considered to enhance heparin efficacy. (CoR IIB, LoE B-NR)

In neonates and infants undergoing cardiac procedures (requiring CPB or extracorporeal membrane oxygenation), impaired heparin responsiveness is strongly associated with low baseline AT activity.³⁸ When heparin resistance is AT-dependent, additional high doses of heparin often fail to achieve target ACT levels and may worsen postoperative bleeding, whereas inadequate anticoagulation reflected by elevated thrombin generation or low anti-Xa activity can increase thrombotic risk.³⁸ Although fresh frozen plasma (FFP) administration during CPB can partially attenuate the effects of low baseline AT activity and reduce total heparin requirements, standard FFP (1 U/mL AT) is too diluted to effectively correct AT deficiency.³⁹ In contrast, pooled AT concentrate given before heparinization reliably increases heparin sensitivity, reduces overall heparin dosing, and has been shown to lower postoperative bleeding and blood product transfusion needs.^{28,40,41} The STS and Society of Cardiovascular Anesthesiologists support

supplemental AT use during CPB for AT-mediated heparin resistance, and AT concentrates are considered safer than FFP given lower volume requirements and reduced risks of allergic reactions and transfusion-related complications.⁴² The AHA also recommends AT concentrate for children with CHD and heparin resistance (ACT <300 seconds after >600 U/kg heparin), with FFP considered a reasonable alternative when AT concentrate is unavailable.¹⁴ Multiple studies confirm that correcting AT deficiency improves heparin efficacy and anticoagulation in this population.^{28,38-41}

S11. In neonates and infants, point-of-care coagulation testing (activated clotting time [ACT], thromboelastography [TEG], rotational thromboelastometry [ROTEM]) may be considered instead of conventional laboratory tests to support timely intraoperative anticoagulant management during cardiopulmonary bypass surgery. (CoR IIB, LoE C-LD)

POC coagulation testing, including ACT, TEG, and ROTEM, offers distinct advantages over conventional laboratory assays for intraoperative anticoagulation management in neonates and infants undergoing CPB. These tests provide rapid, bedside assessment of global hemostasis, enabling timely and targeted interventions crucial in this high-risk population. Unlike conventional laboratory tests, which are limited by delayed turnaround times, large blood volume requirements, and poor correlation with real-time intraoperative changes, POC viscoelastic tests (TEG/ROTEM) provide a more comprehensive evaluation of clot initiation, propagation, and fibrinolysis by using whole blood samples that better reflect physiological conditions.^{43,44} The STS and AHA endorse incorporating POC testing in patients of all ages undergoing CPB surgery into goal-directed transfusion and anticoagulation algorithms to reduce bleeding and optimize blood product use.^{14,33,45} Studies including pediatric and adult patients undergoing cardiac surgery demonstrate that these modalities improve the precision of heparin and protamine management, expedite clinical decision-making, and may enhance hemostasis management.^{46,47} However, the use of POC testing in neonates and infants must account for age-dependent coagulation physiology and the lack of well-established pediatric reference ranges. Despite increasing clinical adoption, robust data validating the precision and outcome benefits of POC-based strategies in this age group remain limited, underscoring the need for multicenter prospective pediatric studies to confirm their safety, efficacy, and optimal integration into perioperative practice.

S12. Antifibrinolytics should be considered in neonates and infants undergoing cardiac surgery involving cardiopulmonary bypass to reduce excessive bleeding and transfusion requirements in the perioperative period. (CoR IIA, LoE B-R)

Antifibrinolytic agents, most notably tranexamic acid (TXA), ϵ -aminocaproic acid, and aprotinin, reduce bleeding by inhibiting plasminogen activation or downstream serine proteases involved in fibrin degradation.¹⁴ These agents consistently decrease postoperative blood loss and transfusion requirements.^{48,49} Evidence supports similar reductions in chest tube output and transfusion needs across all 3 agents, including neonate-specific subgroup analyses, without increases in mortality or major adverse events.⁵⁰ TXA is a commonly used agent and is considered safe in this population; however, its dosing requires careful age-specific consideration.⁵¹ Developmental pharmacokinetics during the first year of life contribute to a decreasing bolus dose requirement with increasing age to maintain target serum concentrations.⁵¹ High TXA plasma levels have been linked to postoperative seizure-like activity and potentially worse long-term neurodevelopmental outcomes, underscoring the need for individualized dosing.⁵¹ Current recommendations from the AHA support the use of TXA or ϵ -aminocaproic acid in infants at high bleeding risk during CPB, with TXA generally preferred for its safety profile, whereas aprotinin use remains limited due to renal concerns.¹⁴ Although there is wide variation in the dosing of TXA that may be used, some pharmacokinetic data suggest optimized TXA dosing of a 10 to 15 mg/kg loading dose followed by a 1 to 5 mg/kg/h infusion (to balance efficacy with seizure risk mitigation), and can be extended up to 6 to 8 hours postoperatively.⁵¹ (Table 2).

S13. Perioperative viscoelastic testing may be considered as a supplement to conventional coagulation laboratory testing to guide intraoperative blood product transfusion decisions and potentially reduce postoperative transfusion requirements in neonates and infants undergoing complex cardiac surgery. (CoR IIB, LoE B-NR)

The STS, along with the Society of Cardiovascular Anesthesiologists, the American Society of ExtraCorporeal Technology, and the Society for the Advancement of Blood Management, explicitly recommends perioperative viscoelastic POC testing (TEG/ROTEM) as a supplement to conventional coagulation assays to guide transfusion therapy in cardiac surgery, including in neonates and infants.⁴⁵ Conventional coagulation assays have limited predictive value for perioperative bleeding in cardiac surgery. Multiple randomized and observational studies, as well as meta-analyses (largely in mixed adult-pediatric populations), demonstrate that viscoelastic-guided transfusion algorithms reduce allogeneic blood product use. Evidence specific to neonates and infants remains limited and primarily single center. Goal-directed algorithms incorporating viscoelastic testing are endorsed to reduce bleeding and transfusion requirements.^{52,53} Conventional plasma-based tests have limited predictive value for perioperative bleeding. Clinical

studies and meta-analyses demonstrate that viscoelastic-guided transfusion algorithms significantly reduce allogeneic blood product use, bleeding, and cost without increasing morbidity.^{54,55} In neonates and infants who are particularly prone to coagulopathy due to immature hemostasis, hemodilution, and exposure to extracorporeal circuits, these assays allow rapid identification of specific deficits, such as hypofibrinogenemia or platelet dysfunction. Parameters such as TEG maximum amplitude/ROTEM maximum clot firmness have been shown to predict postoperative bleeding and guide individualized transfusion therapy.⁵⁵⁻⁵⁷ Collectively, growing evidence supports integrating perioperative viscoelastic testing with standard laboratory assays to optimize hemostatic management, enhance transfusion precision, and improve postoperative outcomes in neonates and infants.

S14. In neonates and infants with clinically significant bleeding after cardiopulmonary bypass and evidence of thrombocytopenia or platelet dysfunction, platelet transfusion is recommended as targeted therapy. (CoR I, LoE B-NR)

Postoperative bleeding is common in neonates and infants after CPB due to platelet dysfunction, thrombocytopenia, hypofibrinogenemia, residual heparin effect, and hemodilution. CPB induces both quantitative and qualitative platelet abnormalities through hemodilution, shear stress, and exposure to artificial circuit surfaces. This leads to platelet activation, consumption, and hyporesponsiveness that impair hemostatic function.

Platelet transfusion is the primary therapy for correcting these defects and mitigating bleeding and is often used alongside red blood cells and coagulation factors to counteract CPB-related hemodilution.^{58,59} Guidelines from the Association for the Advancement of Blood & Biotherapies and the International Collaboration for Transfusion Medicine Guidelines recommend platelet transfusion for neonates and infants with consumptive thrombocytopenia and active bleeding after CPB, with preference for cytomegalovirus-safe, gamma-irradiated, and volume-reduced products to minimize fluid overload.^{60,61} Early, targeted transfusion guided by clinical signs, laboratory testing, or viscoelastic assessment (TEG/ROTEM) enhances hemostasis while avoiding unnecessary exposure. Conversely, routine prophylactic transfusion is discouraged in patients without thrombocytopenia. Increasing evidence supports a precision-guided approach integrating platelet count, fibrinogen concentration, and viscoelastic testing to tailor transfusion decisions.⁵⁴⁻⁵⁷ Collectively, current data and expert consensus affirm that platelet transfusion is a first-line, individualized therapy for CPB-associated bleeding in neonates and infants, balancing efficacy with transfusion-related safety.^{14,60,61} Concentrated (volume-reduced) platelets are an alternate option that may be advantageous when restricting fluid volume is a priority; however, in vitro studies have

demonstrated slight alterations in platelet activation and impaired agonist-induced aggregation after volume reduction, which may impact functional efficacy, and it also necessitates additional processing resources and time compared with standard platelets.⁶² Table 5 outlines components of transfusion products used for perioperative bleeding in neonates and infants.

S15. Targeted adjuvant therapy with fibrinogen-concentrate as a pathogen-reduced alternative to cryoprecipitate may be reasonable in neonates and infants with ongoing bleeding after cardiopulmonary bypass. (CoR IIb, LoE C-LD)

Fibrinogen plays a critical role in clot formation, and hypofibrinogenemia is a common cause of postoperative bleeding in neonates and infants after CPB. Cryoprecipitate has traditionally been used to correct low fibrinogen levels; however, it carries risks of volume overload, pathogen transmission, and variable fibrinogen content with a greater risk for hypercoagulability. Current evidence in infants supports fibrinogen concentrate as a safe, effective, and pathogen-reduced alternative for targeted fibrinogen replacement in this population.⁶³ Several studies, including a randomized trial in infants and neonates, demonstrate that fibrinogen concentrate restores hemostasis as effectively as cryoprecipitate, with comparable safety profiles and no increase in bleeding or thrombotic complications.^{63,64} Notably, its use is associated with reduced allogeneic blood product exposure, which may decrease transfusion-related risks.⁶⁵ Mechanistic studies show that fibrinogen concentrate restores clot structure and strength similar to cryoprecipitate and enhances factor XIII activity, supporting its functional equivalence.⁶⁶ Studies, including the FIBrInogen REplenishment in Surgery (FIBRES) trial in adults, further demonstrate noninferiority for bleeding control after cardiac surgery while highlighting advantages of standardized dosing, rapid reconstitution, and pathogen reduction.⁶⁷⁻⁶⁹ Generally, the United States Food and Drug Administration's blood safety strategy favors pathogen-reduced products, supporting fibrinogen concentrate from an infectious risk perspective. Although cost and availability may affect use, cumulative data endorse fibrinogen concentrate as an effective, logistically advantageous alternative for managing post-CPB bleeding in neonates and infants. Further large-scale studies may help refine patient selection and dosing, but current evidence supports its use in pediatric cardiac surgery (Table 5).⁶³⁻⁶⁹

S16. Targeted coagulation factor administration may be considered as adjunct therapy for bleeding management in neonates and infants after cardiopulmonary bypass surgery, especially when laboratory or clinical indicators suggest factor deficiencies. (CoR IIb, LoE B-NR)

Targeted administration of coagulation factors has emerged as an important strategy for managing refractory bleeding after CPB in neonates and infants, particularly

TABLE 5. Components of transfusion products used for perioperative bleeding in neonates and infants

Product type	Primary components	Notable component concentrations and additional information	Storage/how supplied	Common dose*
Commonly used blood products†				
Packed red blood cells (PRBCs)	Red blood cells	Hematocrit of 55%-65% with additives Hematocrit 70%-80% after washing	Stored at 4 °C for up to 42 d Must be transfused within 4 h of start of transfusion	10-15 mL/kg (over 2-4 h)
Fresh-frozen plasma (FFP-frozen within 8 h) and PF24 (plasma frozen within 24 h)	All major coagulation factors (fibrinogen, II, V, VII, VIII, IX, X, XI, XII, XIII), vWF, antithrombin, protein C and S, plasminogen	Contains multiple plasma proteins including albumin. Not enriched for specific factors	Stored at ≤ -18 °C for up to 12 mo Supplied thawed, to be used within 24 h	10-15 mL/kg (over 2 h)
Platelets, apheresis	Platelets suspended in plasma or platelet additive solution	1 unit of apheresis platelets is 300 mL	Can be single donor (apheresis) or pooled whole blood derived. Irradiated, leukoreduced‡ and pathogen reduced. Stored at 20 to 24 °C (room temperature) and kept gently agitated. Shelf life 5-7 d	5-10 mL/kg (over 1-4 h)
Platelet, whole blood-derived	Platelets	Predominately platelets (1 unit of platelets is 50 mL)	Often requires pooling All units come leukoreduced‡ May also irradiate if needed, if units are pathogen reduced from supplier, irradiation is not needed Stored at 20 to 24 °C (room temperature) and kept gently agitated. Shelf life 4 h from time centrifuging initiated during concentration (volume reducing) process	5-10 mL/kg (over 1-4 h)
Cryoprecipitate	Fibrinogen, fibronectin, factor VIII, factor XIII, vWF	Variable fibrinogen concentration (minimum fibrinogen concentration 150mg/unit)	Stored at ≤ -18 °C for up to 12 mo Often requires pooling Shelf life is 4 h after thawing Pathogen reduced cryo (PR-Cryo) has 5-d room temperature storage limit after thawing	5-10 mL/kg or 1-2 units per 10 Kg

(Continued)

TABLE 5. Continued

Product type	Primary components	Notable component concentrations and additional information	Storage/how supplied	Common dose*
Fibrinogen concentrate (RiaSTAP, Fibryga)	Human pooled plasma containing high concentration of coagulation factor I, and a small amount of factor XIII	Purified virus-inactivated factor product	Lyophilized powder reconstituted in sterile water stored at 2-8 °C	70 mg/kg
Commonly used factor products*,§				
3-factor PCC (Profilnine)	Human plasma containing therapeutic amounts of coagulation factors (II, IX, X)	Generally, a second-choice option. Plasma needs to be coadministered with 3-factor PCC to supplement factor VII	Lyophilized powder reconstituted in sterile water	25-50 units/kg (dose on factor IX component)
4-factor PCC (KCENTRA, Balfaxar)	Human plasma containing therapeutic amounts of coagulation factors (II, VII, IX, X along with PC and PS) Additional components: KCENTRA: Heparin, antithrombin Balfaxar: Heparin	Generally considered superior to FFP for urgent reversal of warfarin and other vitamin K antagonists' effects	Lyophilized powder reconstituted in sterile water	25-50 units/kg (dosed on factor IX component)
aPCC (FEIBA)	Human plasma containing activated and non-activated coagulation factors (II, VII, IX, and X)	Key difference from PCC is that aPCC also contains greater amounts of the activated forms of these factors (eg, FVIIa and FXa)	Lyophilized powder reconstituted in sterile water	5-10 units/kg; may repeat as necessary every 30-60 min
Factor VII (Sevenfact, NovoSeven)	Recombinant factor VIIa (rFVIIa) (laboratory-derived protein)	Other forms of FVIIa include human plasma-derived FVIIa concentrate	Lyophilized powder reconstituted in sterile water	20-40 µg/kg
Antithrombin (human) Thrombate III	Human antithrombin	Prepared from pooled units of human plasma from normal donors, virus-removed and/or inactivated.	Lyophilized powder reconstituted in sterile water after warming to room temperature. Approximate AT potency 500 units/vial	Loading dose: (120% - baseline % × body weight in kg)/1.4% Maintenance dose: Loading dose × 0.6 Alternate weight-based dosage is 50 -75 unit/kg.

PRBC, Packed red blood cell; FFP, fresh-frozen plasma; PCC, prothrombin complex concentrate; vWF, von Willebrand factor; PC, protein C; PS, protein S; aPCC, activated prothrombin complex concentrate; AT, antithrombin. *Dosing for pediatric perioperative bleeding related to cardiothoracic surgery (off-label). †Available in the United States. ‡Leukoreduced have <5 million nucleated cells. Irradiated units render lymphocytes nonreplicative. §Consider multidisciplinary discussion with hematology and/or transfusion medicine, cardiac anesthesia.

when conventional transfusion therapy is insufficient. Activated (eg, recombinant activated factor VII, activated prothrombin complex concentrate [PCC]) and nonactivated factor concentrates (eg, fibrinogen concentrate, 4-factor PCC) differ substantially in mechanism and thrombotic risk

profile. Activated products directly amplify thrombin generation and therefore carry a greater potential for thromboembolic complications, warranting more restricted, rescue-based use compared with targeted replacement using nonactivated concentrates guided by documented factor

deficiency. Ex vivo studies show that both activated and nonactivated PCCs enhance thrombin generation in neonatal plasma after CPB, supporting their role in correcting factor deficiencies and restoring hemostasis.^{70,71} Clinical studies indicate that PCCs can reduce total transfusion requirements and normalize coagulation parameters more rapidly than FFP without significantly increasing thromboembolic risk when used judiciously.^{72,73} Similarly, fibrinogen concentrate is a pathogen-reduced, volume-sparing alternative to cryoprecipitate, with randomized trials in infants and children demonstrating comparable or improved hemostatic efficacy and reduced exposure to allogeneic products.^{65,67} The AHA further recommends considering recombinant activated factor VII for life-threatening bleeding unresponsive to standard therapy, though careful monitoring for thrombosis is essential.¹⁴ Current guidelines emphasize that factor replacement should be individualized and guided by laboratory data and clinical assessment, with POC viscoelastic testing helping to identify specific coagulation deficits.⁷⁴ Collectively, growing evidence supports targeted coagulation factor therapy as an effective, physiology-based adjunct for managing refractory CPB-associated bleeding in neonates and infants when used in a monitored, precision-guided framework (Table 5).

S17. Planned discontinuation of anticoagulants or antiplatelet agents several days before complex cardiac surgery in neonates and infants is reasonable when the risk of bleeding outweighs the risk of thrombosis and the risk of thrombosis is low. (CoR IIa, LoE C-LD)

In neonates and infants undergoing complex cardiac surgery, perioperative bleeding risk may be heightened by ongoing anticoagulants and/or antiplatelet therapy. Current evidence and consensus guidelines support planned discontinuation of these agents several days before cardiac surgery when the bleeding risk outweighs the risk of thrombosis and the patient's thrombotic risk is low.⁷⁵⁻⁷⁷ Although the American College of Chest Physicians recommends stopping direct oral anticoagulants (DOACs) such as rivaroxaban and apixaban in adults 1 to 3 days before high-bleeding-risk procedures (longer for those with renal impairment), DOAC elimination in neonates and infants may differ.⁷⁸ Apixaban clearance increases with age and body weight, with neonates and young infants <9 months needing decreased time for drug elimination on a per-weight basis.⁷⁹ As such, more conservative holding strategies for apixaban may be considered for procedures with greater risks for bleeding. Apixaban levels (chromogenic anti-Xa level assayed to apixaban), if available, may help determine clearance of apixaban before emergent procedures when holding is not feasible.⁸⁰ Rivaroxaban is cleared more rapidly in infants and young children compared with older children and adults, with a reported half-life of 1.6 hours in children <6 months, resulting in ~97% clearance by approximately 8 hours as evaluated in CHD

children undergoing noncardiac surgery.⁸¹ Similar to adults on DOACs, routine perioperative heparin bridging in low-thrombotic-risk pediatric patients is not recommended due to increased bleeding risk.⁷⁸ The AHA advises withholding aspirin for at least 5 days before major surgery in pediatric patients unless there is a compelling indication to continue, emphasizing individualized decision-making on the basis of the underlying cardiac lesion and clinical context.⁸² The STS also recommends discontinuing non-vitamin K oral anticoagulants for at least 2 days before elective cardiac surgery, reserving reversal agents or prothrombin complex concentrates for urgent cases on the basis of procedural bleeding.⁴⁵ Overall, a multidisciplinary, risk-based approach that accounts for drug pharmacokinetics, patient-specific thrombotic risk, and potential for surgical bleeding, is essential to balance hemostatic safety and thrombotic protection in this vulnerable pediatric population (Tables 6-9).

S18. In neonates and infants with congenital heart disease, given the risks of thromboembolism and bleeding, the heterogeneity of the patient population, and the variability in clinical practice, a dedicated multidisciplinary team with subspecialized knowledge and expertise in cardiology and thrombosis/hemostasis should be considered to help guide the assessment of bleeding and thromboembolic risks and appropriate antithrombotic therapy selection, intensity, and duration. (CoR IIa, LoE C-EO)

Neonates and infants with CHD are at an increased risk for thromboembolism because of tissue injury, platelet activation, altered blood flow, and exposure to foreign materials such as shunts, stents, and valves.^{8,83-88} In addition, many have inherited or acquired hemostatic abnormalities and undergo procedures that may increase the risk of bleeding.⁸⁹⁻⁹¹ The unique challenges of CHD create a complex, highly individualized balance between thrombosis and bleeding in this patient population. Given the complexity, optimal management of this population requires coordinated input from a multidisciplinary team that includes cardiology, hematology, cardiothoracic surgery, interventional cardiology, pharmacy, nursing, and perfusion specialists. The combined expertise of these disciplines provides the evidence-based foundation necessary to interpret hemostatic profiles, guiding antithrombotic strategies and safely balancing thrombosis and bleeding in a heterogeneous population.⁹² Nursing and pharmacy professionals are essential for caregiver education, medication reconciliation, dosing oversight, monitoring coordination, and reinforcement of adherence and safety precautions. Current evidence in pediatric populations suggests that patient outcomes improve when care is delivered under a formalized service with clear communication pathways and a shared decision-making processes.⁹²⁻⁹⁴ By combining subspecialty knowledge and scopes of care, these teams can develop comprehensive,

TABLE 6. Antithrombotic management for congenital cardiac surgery or interventional cardiology procedures

Cardiac procedure	Postprocedure*	Class/LOE	Long-term*	Class/LOE	Periprocedural planning†	Class/LOE
Systemic-to-pulmonary shunt (mBTT, central shunt)	Aspirin	I/B-NR	Aspirin indefinitely	I/B-NR	Avoid holding aspirin; if holding necessary, bridge with LMWH or UFH	IIb/C-EO
	UFH (until aspirin is initiated)	IIa/B-NR	Dual antiplatelet therapy for complex shunt scenarios	IIb/C-EO		
	Bivalirudin (until aspirin is initiated)	IIb/C-EO				
PA banding	None‡	IIa/C-EO	None‡	IIa/C-EO	None	IIa/C-EO
Atrial septectomy/septostomy	None	IIa/C-EO	None	IIa/C-EO	None	IIa/C-EO
Norwood (HLHS) (Sano)	Aspirin	I/B-NR	Aspirin indefinitely	I/B-NR	Avoid holding aspirin; if holding aspirin, bridge with LMWH or UFH	IIb/C-EO
	UFH (consider UFH if unable to initiate aspirin within 48 h)	IIa/B-NR				
	Bivalirudin (consider bivalirudin if unable to initiate aspirin within 48 h)	IIb/C-EO				
Bidirectional Glenn/hemi-Fontan	None	IIa/B-NR	Aspirin	I/B-NR	Avoid holding aspirin; if holding aspirin, bridge with LMWH or UFH	IIb/C-EO
Comprehensive stage 2	UFH (until aspirin is initiated)	IIb/C-EO	Aspirin	I/B-NR	Avoid holding aspirin; if holding aspirin, bridge with LMWH or UFH	IIb/C-EO
			Aspirin ± LMWH for 3-6 mo	IIb/C-EO		
			Aspirin ± DOAC for 3-6 mo	IIb/C-EO		
Coarctation/interrupted aortic arch repair	None (unless extensive prosthetic material)	IIa/C-EO	None	IIa/C- EO	None	IIb/C-EO
Interrupted arch repair with VSD closure	None (unless extensive prosthetic material)	IIa/C-EO	None§	IIb/C-EO	None (If on aspirin, avoid holding aspirin; if holding is necessary, hold aspirin for 5-7 d)	IIb/C-EO
Tetralogy of Fallot repair	None	IIb/C-EO	None	IIb/C-EO	None (If on aspirin, avoid holding aspirin; if holding is necessary, hold aspirin for 5-7 d)	IIb/C-EO
Pulmonary atresia/RV–PA conduit	None	IIb/C-EO	Aspirin 3–6 mo¶	IIb/C-EO	Avoid holding aspirin; if necessary, hold aspirin for 5-7 d	IIb/C-EO

(Continued)

TABLE 6. Continued

Cardiac procedure	Postprocedure*	Class/LOE	Long-term*	Class/LOE	Periprocedural planning†	Class/LOE
Arterial switch (TGA)	None	I Ib/C-EO	None#	I Ib/C-EO	None (If on aspirin, avoid holding aspirin; if holding is necessary, hold aspirin for 5-7 d)	I Ib/C-EO
ALCAPA repair	None#	I Ib/C-EO	Aspirin for 3-6 mo**	I Ib/C-EO	Avoid holding aspirin; if necessary, hold aspirin for 5-7 d	I Ib/C-EO
Coronary unroofing	Aspirin (consider UFH if unable to initiate aspirin within 48 h)	I Ib/C-EO	Aspirin for 3-6 mo	I/B-NR	Avoid holding aspirin; if holding aspirin, bridge with LMWH or UFH	I Ib/C-EO
Rastelli/Nikaidoh (RV-PA conduit)	None (consider UFH if aspirin is necessary for conduit type, and unable to initiate within 48 h)	I Ib/C-EO	Aspirin for 3-6 mo¶	I Ib/C-EO	Avoid holding aspirin; if necessary, hold aspirin for 5-7 d	I Ib/C-EO
AVSD/VSD/ASD repairs	None (unless extensive prosthetic material)	I Ib/C-EO	None§	I Ib/C-EO	Avoid holding aspirin; if necessary, hold aspirin for 5-7 d	I Ib/C-EO
Truncus arteriosus repair (RV-PA conduit)	None (consider UFH if aspirin is necessary for conduit type, and unable to initiate within 48 h)	I Ib/C-EO	Aspirin indefinitely	I Ib/C-EO	Avoid holding aspirin; if necessary, hold aspirin for 5-7 d	I Ib/C-EO
TAPVR repair	None (unless residual obstruction or extensive prosthetic material)	I Ib/C-EO	None††	I Ib/C-EO	None	I Ib/C-EO
Ebstein anomaly – Cone repair	None (unless anatomic substrate necessitates)	I Ib/C-EO	None	I Ib/C-EO	If on aspirin, avoid holding aspirin; if necessary, hold aspirin for 5-7 d	I Ib/C-EO
Ebstein anomaly – Starnes procedure	Aspirin	I/B-NR	Aspirin indefinitely	I/B-NR	Avoid holding aspirin; if holding necessary, bridge with LMWH or UFH	I Ib/C-EO
	UFH (until aspirin is initiated)	I Ia/B-NR				
	Bivalirudin (until aspirin is initiated)	I Ib/C-EO				
Ross/Konno procedures	None (consider UFH if aspirin is necessary for conduit type, and unable to initiate within 48 h)	I Ib/C-EO	Aspirin indefinitely‡‡	I Ib/C-EO	If on aspirin, avoid holding aspirin; if necessary, hold aspirin for 5-7 d	I Ib/C-EO
Infant heart transplant	None	I Ib/C-EO	None§§	I Ib/C-EO	If on aspirin, avoid holding aspirin; if necessary, hold aspirin for 5-7 d	I Ib/C-EO

(Continued)

TABLE 6. Continued

Cardiac procedure	Postprocedure*	Class/LOE	Long-term*	Class/LOE	Periprocedural planning†	Class/LOE
Mitral valve replacement (mechanical)	UFH until therapeutic with enteral anticoagulation	I/A	VKA, INR goal 2.5-3.5 + aspirin (if indication for antiplatelet therapy)	I/A	If the procedure requires bridging, consider LMWH or UFH if INR < 2 during interruption of VKA	Ib/C-EO
	Bivalirudin until therapeutic with enteral anticoagulation	Ib/C-EO				
Aortic valve replacement (mechanical)	UFH until therapeutic with enteral anticoagulation	I/A	VKA, INR goal 2-3 + aspirin (if indication for antiplatelet therapy)	I/A	If the procedure requires bridging, consider LMWH or UFH if INR < 1.5 during interruption of VKA	Ib/C-EO
	Bivalirudin until therapeutic with enteral anticoagulation	Ib/C-EO				
Catheterization procedures Lower risk of thrombosis	None (consider prophylactic UFH/LMWH for intravascular stents and hardware at lower risk of thrombosis (Table 7) if unable to initiate aspirin within 24 h)	Ib/C-EO	Aspirin for 6 mo for intravascular stents and hardware at LOWER risk of thrombosis (Table 7)	I/B-NR	Avoid holding aspirin; if necessary, hold aspirin for 5-7 d.	Ib/C-EO
Catheterization procedures Higher risk of thrombosis	Therapeutic UFH/LMWH for intravascular stents and hardware at higher risk of thrombosis (Table 7)	Ia/C-EO	Aspirin ± clopidogrel for at least 3-6 mo (Table 7)	I/B-NR	Avoid holding aspirin; if holding aspirin, bridge with LMWH or UFH	Ib/C-EO
			Aspirin ± LMWH for at least 3-6 mo	Ib/C-EO		
			Aspirin ± DOAC for at least 3-6 mo	Ib/C-EO		

LOE, Level of evidence; *mBTT*, modified Blalock-Taussig-Thomas; *UFH*, unfractionated heparin; *LMWH*, low-molecular-weight heparin; *PA*, pulmonary artery; *HLHS*, hypoplastic left heart syndrome; *DOAC*, direct oral anticoagulant; *VSD*, ventricular septal defect; *RV-PA*, right ventricle to pulmonary artery; *TGA*, transposition of great arteries; *ALCAPA*, anomalous left coronary artery from the pulmonary artery; *AVSD*, atrioventricular septal defect; *ASD*, atrial septal defect; *TAPVR*, total anomalous pulmonary venous return; *VKA*, vitamin K antagonist; *INR*, international normalized ratio; *ICU*, intensive care unit. *Postprocedure is defined as the time period post-ICU admission. Evaluate and consider additional risk factors for thromboembolism (Tables 7-9); planning should take into account each patient's bleeding and thrombotic risk, and include a multidisciplinary team discussion (eg, cardiac surgery, interventional cardiology, cardiac intensive care, cardiology, pharmacy) when determining the overall antithrombotic therapy plan. †Procedural planning and decision whether to hold antithrombotic therapy should take into account each patient's bleeding and thrombotic risk and include a multidisciplinary team discussion (eg, cardiac surgery, interventional cardiology, cardiac intensive care, cardiology, pharmacy): –high bleeding risk procedure (Tables 7,9) and high thrombotic risk: bridging should be considered. –moderate bleed risk procedure (Tables 7,9) and high thrombotic risk: bridging may be considered. ‡Discuss as a multidisciplinary team the need for aspirin in the setting of an internal PA band with a membrane and a fenestration (MPA band). §In the setting of extensive prosthetic material, may consider aspirin for 3 mo. ||Depending on the type of RV-PA conduit material used, may consider aspirin for a minimum of 3 mo. ¶May consider aspirin indefinitely, depending on conduit material used and other risk factors. #May consider aspirin for 3 mo, depending on coronary intervention. Where aspirin is indicated, consider UFH if unable to initiate aspirin within 48 h postoperation. **May consider aspirin for 6 to 12 mo, or indefinitely if residual coronary stenosis. ††In the setting of an extensive patch or residual lesion, may consider aspirin, or aspirin ± LMWH/DOAC for 3 mo. †††May consider aspirin indefinitely, depending on conduit type. §§May consider aspirin for graft vasculopathy prevention on the basis of institutional preference.

personalized, and optimized antithrombotic care plans and address the unique challenges of pediatric patients with CHD while minimizing risk. [Table 6](#) provides information on antithrombotic management for specific congenital cardiac surgery or interventional cardiology procedures.

S19. In neonates and infants with congenital heart disease requiring intervention, the initiation, intensity, and duration of antithrombotic therapy should consider patient-specific factors, surgical/procedural details, and the overall clinical condition, after carefully weighing the risk of bleeding. (CoR IIa, LoE C-EO)

Antithrombotic agents play an important role in the management of neonates and infants with CHD, given an increased risk of thrombosis compared with the general pediatric population.^{85-87,95} Antithrombotic agents are intrinsically high risk, and the use of these agents has been associated with mortality as a result of bleeding complications in this age group.^{96,97} Importantly, the vast majority of antithrombotic drugs commonly used in neonates and infants lack approval from the Food and Drug Administration for use in this age group, and dosages are extrapolated from adult dosage recommendations. A comprehensive understanding of neonatal and infant hemostasis, as well as individual thrombotic and bleeding risk factors ([Figures 2 and 3](#)), is essential for selecting safe and effective antithrombotic regimens. [Table 7](#) outlines thrombosis risk of severity after interventional cardiac procedures. Therapeutic decisions should integrate patient-specific morbidities and factors (eg, antiphospholipid antibody syndrome), procedural variations (eg, stented vs nonstented modified Blalock-Taussig-Thomas Shunt), and variable pharmacokinetic and pharmacodynamic profiles of antithrombotic drugs when formulating antithrombotic strategies and decisions. Arterial thrombosis is related to platelet activation in the

presence of high shear stress via GPIb/GPIIb-IIIa signaling and managed with antiplatelet therapy, whereas venous thrombosis is predominantly thrombin- and fibrin-mediated, necessitating anticoagulation with UFH or low molecular weight heparin (LMWH). Given these complexities, antithrombotic regimens should be individualized rather than using a uniform approach. Antithrombotic drug selection should consider various factors (eg, short-acting agents for upcoming procedures, renal function), and dosing should reflect age-specific pharmacokinetic and pharmacodynamic principles (eg, neonates may require greater doses of enoxaparin to achieve therapeutic anticoagulation compared with children).^{92,93} Ultimately, the benefits of therapy must be weighed against the potential for bleeding. [Table 8](#) describes patient, procedural and clinical risk factors for bleeding and thromboembolism.

S20. In select neonates and infants with recurrent thrombosis or concern for inadequate antiplatelet effect, platelet responsiveness testing may be considered within experienced centers, with the recognition that validation and outcome data are limited. (CoR IIb, LoE C-EO)

Antiplatelet agents are widely used in children with CHD, with aspirin being the most frequently used antiplatelet agent. Aspirin has been associated with reduced mortality and shunt thrombosis, although the dose needed to achieve clinically meaningful platelet inhibition (ie, platelet inhibition without thrombosis and/or bleeding) remains uncertain.^{85,98,99} Data guiding dosing, platelet inhibition targets, and associated outcomes for other antiplatelet agents (eg, clopidogrel and dipyridamole) are similarly limited. No consensus exists regarding the optimal monitoring strategy for neonates and infants receiving antiplatelet therapy. Although light transmission aggregometry has long been considered the gold standard in adults, it has not been clinically adopted because of the

TABLE 7. Thrombosis risk severity after interventional cardiac procedures

Low	Moderate	High
Hardware type		
■ Bare metal stent* ≥ 4 mm ■ Drug-eluting stent ≥ 4 mm ■ Intracardiac devices†	■ Bare metal stent* < 4 mm ■ Drug-eluting stent < 4 mm ■ Flow restrictor (modified Medtronic microvascular plug)	■ Covered stent
Lesion location		
■ Ductal stent for systemic blood flow ■ Pulsatile pulmonary artery ■ Systemic artery ■ Atrial or ventricular septum ■ Ventricular outflow tract ■ Ventricle-pulmonary artery conduit	■ Coronary artery ■ Nonpulsatile pulmonary artery ■ Systemic vein ■ Pulmonary vein	■ Ductal stent for pulmonary blood flow ■ Postoperative (< 30 d) nonpulsatile pulmonary artery ■ Recanalized or severely hypoplastic pulmonary vein

Refer to [Table 6](#) for evaluation of antithrombotic strategy after evaluating patient, procedural, and clinical risk factors as outlined in [Table 8](#) to determine if thrombotic risk is deemed to be higher or lower. *Includes balloon expandable and self-expanding. †Septal occluder, duct occluder, vascular plug, etc.

TABLE 8. Risk factors for bleeding and thromboembolism

Bleeding		
Category	Risk factors	Clinical implications
Patient	- Premature/low birth weight - Cyanotic congenital heart disease	- Discuss as a multidisciplinary team (eg, cardiac surgery, cardiology, cardiac anesthesia, cardiac intensivists, neonatology, hematology, and pharmacy), etiology-driven management strategies - Use blood products, factor products, and antifibrinolytics as necessary—guided by laboratory testing where appropriate and feasible
Procedural	- Prolonged surgery - Recent surgical procedure - Redo operations - Numerous suture lines - Extensive dissection or collateral vessels - Need for ECMO preoperatively or postoperatively - Procedures in highly vascular organs - Cardiopulmonary bypass (ie, deep hypothermia, circulatory arrest, hemodilution, factor consumption)	
Clinical	- Acidosis - Hypothermia - Hepatic impairment - Excessive fibrinolysis - Thrombocytopenia - Decrease in hemostatic proteins - Coagulation factor consumption - Platelet dysfunction	
Thromboembolism		
Patient	- Single-ventricle physiology - Younger age (neonates and infants) - Prior thromboembolic event - Genetic thrombophilia	- Discuss as a multidisciplinary team (eg, cardiac surgery, cardiology, cardiac anesthesia, cardiac intensivists, hematology, and pharmacy), a documented thromboprophylaxis plan - Use antithrombotic agents (anticoagulants, antiplatelets) as appropriate on the basis of etiology and indication - Reference PICO Statements Group 3 and 4 – shunts, conduits/baffles, coronaries, valves, cardiac catheter procedures
Procedural	- Prosthetic valve replacement (mechanical or bioprosthetic) - Foreign material (eg, PTFE systemic to pulmonary artery shunt) - Significant intraoperative bleeding requiring high-volume blood product transfusion or use of procoagulant medications - Need for ECMO postoperatively - Inflammation - Platelet and complement activation	
Clinical	- Infection(s) - Mechanical ventilation - Immobility - Recent hospitalization or ICU admission - Central venous catheter(s) - Atrial arrhythmias - Low cardiac output - Corticosteroids	

(Continued)

TABLE 8. Continued

Category	Bleeding	
	Risk factors	Clinical implications
	- Decreased protein C, S, and antithrombin - Antiphospholipid antibody + - Elevated fibrinogen - Thrombocytosis	

ECMO, Extracorporeal membrane oxygenation; PTFE, polytetrafluoroethylene; PICO, Population/Problem Intervention Comparison, and Outcome; ICU, intensive care unit.

need for large blood volumes, technical resources, and lack of availability.^{100,101} The VerifyNow POC assay is increasingly used across pediatric and adult cardiac centers to evaluate platelet responsiveness through platelet-induced aggregation in whole blood via fibrinogen-coated beads reported as Aspirin reaction units or P2Y₁₂ Reaction Units (PRU) for aspirin and clopidogrel, respectively.¹⁰² The benefits of VerifyNow for the pediatric population include rapid test turnaround time, small testing volume (0.5-1 mL), and expanding availability.¹⁰³ However, it is not yet fully validated in infants and neonates, with “therapeutic” cutoff targets for aspirin (<550 aspirin reaction units) and clopidogrel (~50-200 PRU) responsiveness extrapolated from adult studies using variable dosing for different clinical indications. Nevertheless, there are reports of increased rates of thrombosis and mortality in neonates and infants with inadequate platelet inhibition.¹⁰³⁻¹⁰⁶ Given the variable absorption of antiplatelet agents and the potential for reduced responsiveness or antiplatelet resistance, it is reasonable to consider platelet responsiveness testing in this population receiving antiplatelet drug(s).¹⁰⁴⁻¹⁰⁶ Testing can help determine whether the prescribed drug achieves sufficient platelet inhibition, identify patients at risk for suboptimal response or excessive bleeding, and guide individualized therapy. Although current evidence does not clearly link antiplatelet responsiveness testing results with specific dosing strategies or dose adjustments, it is reasonable to consider evaluating potential causes of poor response, such as poor absorption, drug interactions, or genetic variants affecting drug kinetics. This information can support multidisciplinary team decision-making when evaluating and selecting the antiplatelet therapy plan or modifying therapy in this patient population that is at an increased risk for thromboembolism.¹⁰⁷

Shunt-Dependent Physiology

S21. In neonates and infants with a Blalock-Taussig-Thomas or central shunt, given increased risk for thromboembolism, parenteral anticoagulation should be considered until enteral aspirin can be initiated in the immediate postoperative period. (CoR IIa, LoE B-NR)

S22. For long-term thromboprophylaxis, aspirin is recommended as first-line therapy for an indefinite duration (CoR I, LoE B-R.); dual antithrombotic

thromboprophylaxis may be considered in complex scenarios. (CoR IIb, LoE C-EO)

Shunt thrombosis is a major cause of morbidity and mortality after palliative congenital heart surgery and remains incompletely understood.^{85,87,108} Evidence to guide optimal antithrombotic strategies is limited, and significant variation exists in clinical practice regarding antithrombotic drug/agent selection and dosing. A landmark study demonstrated that aspirin reduced the risk of shunt thrombosis 7-fold compared with no thromboprophylaxis.¹⁰⁹ Given the increased risk of thromboembolism in this patient population, antithrombotic agents (ie, anticoagulant/antiplatelet drugs) should be initiated in the immediate postoperative period once the bleeding risk is acceptable and continued long term. Aspirin remains the most studied agent for shunt thromboprophylaxis, with commonly reported doses ranging from 3 to 5 mg/kg/dose, although doses as low as 1.5 mg/kg/d or as high as 12.5 mg/kg/d have been reported.^{85,110} When aspirin cannot be initiated immediately postoperatively, most studies report use of UFH at doses of 10 to 15 units/kg/h, although some centers use therapeutic UFH titrated to a targeted activated partial thromboplastin time or anti-Xa level.⁸⁵ However, these studies are largely retrospective and not designed to evaluate safety or efficacy; thus far, an optimal dose regimen for UFH has not been established. Decisions regarding intravenous agent dosing, as well as when to initiate aspirin and stop intravenous agents, require a multidisciplinary team assessment of both patient-specific bleeding and thromboembolic risks.

Additional antithrombotic agents have been reported in small retrospective studies, including bivalirudin, enoxaparin, tirofiban, and cangrelor.^{87,111-116} In clinical situations in which thrombotic risk is believed to exceed that of standard shunt-dependent physiology, dual therapy or combination regimens (eg, anticoagulant + antiplatelet, dual antiplatelet therapy) may be necessary. Complex shunt considerations include smaller shunt diameter (eg, 3.0 mm vs 3.5 mm), particularly in infants with low weight, stented shunts or hybrid procedures, history of previous shunt thrombosis, concurrent venous/arterial thrombosis, or prothrombotic comorbidities. The selection of combination therapy should follow multidisciplinary discussion, incorporating patient-specific thromboembolic and bleeding risk factors (Tables 6-9), anticipated procedural needs, and monitoring strategies.

Conduits/Baffles/Nonautologous Patch Material

S23. Neonates and infants undergoing cardiac surgery with conduits, nonautologous patch materials, or extensive intracardiac baffles may be at increased risk for thrombosis; therefore, low-dose anticoagulation with a short-acting intravenous agent may be considered until enteral antiplatelet therapy is feasible in the immediate postoperative (24-72 hours) and early (first week) period. (CoR IIB, LoE C-EO)

S24. For long-term thromboprophylaxis, aspirin monotherapy may be considered, with duration depending on the surgical procedure and thrombotic risks. (CoR IIB, LoE C-EO)

In neonates and infants undergoing cardiac surgery, the need for antithrombotic therapy, along with its intensity and duration, is influenced by the extent, location, and composition of the reconstruction, as well as patient-specific bleeding and thrombotic risks (Table 8). Surgical constructs that incorporate substantial nonautologous material within low-pressure or nonpulsatile circulations (eg, atrial baffles, pulmonary artery reconstruction in patients with single-ventricle palliations) are generally associated with a greater risk of thrombosis and therefore have a more favorable risk-benefit profile for early antithrombotic therapy.^{87,117-119} In contrast, baffles or patchwork performed in larger pulsatile outflow tracts or systemic arteries typically carry a lower risk of thrombosis and a less favorable balance between thrombosis prevention and bleeding risk.

In patients for whom thromboprophylaxis is deemed beneficial, low-dose UFH (10-15 units/kg/h) is commonly initiated once postoperative bleeding risk is acceptable, until enteral antiplatelet therapy can be started. Aspirin (3-5 mg/kg/d) is the preferred agent for early enteral therapy, with treatment often continued for up to 6 months to allow for endothelialization of prosthetic materials.^{14,120} Indefinite antiplatelet therapy is used for most single-ventricle palliations and valved conduits (Tables 6-8).

Coronary Procedures

S25. For neonates and infants undergoing procedures involving the coronary arteries, antithrombotic therapy in the immediate postoperative period and antiplatelet therapy long term may be considered depending on the surgical procedure and coronary artery anatomy. (CoR IIB, LoE C-EO)

Neonates and infants who require procedures involving coronary arteries (eg, anomalous coronary artery from pulmonary artery repair, coronary unroofing, and coronary reimplantation) may be at an increased risk of thrombosis. Although evidence is limited, contributions to this risk are likely to include small caliber of coronary arteries,

endothelial injury related to surgical manipulation, altered flow dynamics after reconstruction, and the presence of prosthetic or patch materials. Perioperative factors such as low cardiac output, hypoperfusion, and inflammation may further predispose reconstructed coronary segments to thrombosis.¹²¹ Antithrombotic management may be considered based on procedural characteristics (eg, use of patches or stents), coronary anatomy (eg, single ostium, intramural course), and patient-specific thrombotic risk factors (Tables 6-8). Aspirin is the most commonly used agent for long-term thromboprophylaxis following coronary interventions.^{14,122,123} When aspirin is indicated but cannot be initiated, a short-acting intravenous anticoagulant may be used until aspirin therapy is feasible. However, data that can be used to compare antithrombotic strategies for coronary thromboprophylaxis in neonates remain limited. Therefore, the choice of agent and intensity of therapy should be guided by institutional experience, multidisciplinary team discussion, patient-specific clinical factors, drug characteristics (eg, pharmacokinetics, monitoring, reversibility), and inherent bleeding risk.

Interventional Cardiology Procedures—Lower Risk

S26. For intravascular stents or hardware placement at a lower risk of thrombosis, parenteral anticoagulation may be considered immediately postprocedure until enteral antiplatelet therapy is feasible (Class IIB, LoE B-NR); and aspirin monotherapy is recommended for at least 6 months. (CoR I, LoE B-NR)

Interventional catheterizations, where various hardware is placed, predispose neonates and infants to the risk of thrombosis as the result of foreign materials and the vascular access required for the procedure.^{14,124} Although the overall incidence is low, the risk of thrombosis should factor in the hardware type, stent diameter, hardware location, critical nature of the location (eg, coronary arteries, ductal stent for ductal dependent pulmonary blood flow), and patient risk factors (Tables 6-8). In general, intracardiac devices or larger-diameter stents receiving pulsatile blood flow are thought to have a lower risk of thrombosis (protective if $\sim \geq 3.5$ mm, no difference between drug-eluting stents and bare metal stents in adults).^{125,126} Conversely, smaller-diameter stents receiving nonpulsatile blood flow, especially in low-flow states, may have a greater risk of thrombosis. For lower-risk interventions, enteral aspirin is recommended for at least 6 months while endothelialization occurs.¹²⁷⁻¹²⁹ Indefinite therapy may be considered for locations where endothelialization may not occur (eg, stent inside Gore-Tex shunt/conduit). If aspirin cannot be initiated within 24 hours, and the risk of thrombosis is deemed to outweigh the risk of bleeding, the use of parenteral anticoagulation at prophylaxis dosing

(eg, UFH 10-15 units/kg/h [usually no additional testing or titration performed] or low molecular weight heparin to target an anti-Xa of 0.2-0.5 U/mL, or per institutional protocol), may be considered.

Interventional Cardiology Procedures—Higher Risk

S27. For intravascular stent or hardware placement at a higher risk of thrombosis, parenteral anticoagulation should be considered until enteral therapy is feasible (CoR IIa, LoE C-EO), and a combination of antithrombotic agents (anticoagulant, antiplatelet, or dual antiplatelet) is recommended for at least 3-6 months. (CoR 1, LoE C-EO)

As discussed in the previous section, the risk of thrombosis after interventional catheterizations with hardware placement depends on factors related to hardware characteristics, anatomic location, and flow dynamics (Table 7). In general, as the risk of thrombosis increases from low to moderate to high, antithrombotic agents escalate from single antiplatelet to dual antiplatelet, to antiplatelet plus anticoagulant, respectively.¹³⁰ For instance, a 3-mm diameter drug-eluting stent could be placed in a pulsatile pulmonary artery (low risk), a coronary artery (moderate risk), or a recanalized atretic pulmonary vein (high risk). Given the multiple combinations of risk between hardware type and location, as well as the lack of data to guide antithrombotic choice, the selection of agents, dosing, and duration of therapy should involve a multidisciplinary team discussion that considers patient-specific thrombosis and bleeding risks (Tables 6-8). For scenarios in which the risk of thrombosis is greater, it is reasonable to initiate therapeutic parenteral anticoagulation immediately postprocedure until enteral therapy can be initiated. A combination of antithrombotic agents (eg, aspirin + clopidogrel, LMWH + aspirin, DOAC + aspirin) may then be recommended for at least 3 to 6 months or longer, depending on the critical nature of the location and thrombosis risk.

Procedural Bridging Therapy

S28. For neonates and infants who are at risk of thrombosis and require temporary interruption of oral antithrombotic therapy, multidisciplinary decision-making should be considered to evaluate the net clinical benefit of bridging versus no bridging, assessing risks of both bleeding and thromboembolism. (CoR IIa, LoE C-EO)

The perioperative management of antithrombotic therapy encompasses patients receiving an oral antithrombotic drug/agent, such as a vitamin K antagonist (VKA), DOAC, LWMH, or an antiplatelet drug/agent, who require an invasive procedure. The decision regarding bridging with an anticoagulant agent should include an assessment of both the patient's thrombotic risk and the procedural bleeding risk.⁷⁸ In patients with high thromboembolic risk (eg,

mechanical valves) undergoing procedures associated with a high bleeding risk (Table 9), bridging may be considered for VKAs or antiplatelet medications.^{78,131,132} Given the relatively short half-lives of the DOACs and LWMH, temporary cessation of those agents is generally sufficient, and bridging is typically unnecessary.¹³¹ When bridging is warranted, short-acting agents such as UFH or LWMH should be considered and subsequently discontinued before the procedure to allow adequate time for drug clearance to mitigate bleeding risk.¹³² For emergent procedures in patients currently receiving antiplatelet and/or anticoagulant therapy, decisions regarding reversal depend on the timing of the last dose, the drug's half-life of the drug (typically cleared in 4-5 half-lives), end-organ function, and the availability of reversal agents. Some options for a reversal may include medication-specific antidotes (eg, protamine) or the use of blood products or factor concentrates (eg, 4-factor PCC) to correct the coagulopathy.^{78,131,132} Table 9 provides information on procedural bleeding risk and pre-procedural antithrombotic medication management.

Central Venous Catheter Prophylaxis and Management

S29. Thromboprophylaxis may be considered in neonates and infants with CVCs, on the basis of patient and anatomic thromboembolic risk factors, after considering the benefit versus the risk of bleeding. (CoR IIb, LoE C-EO)

Retrospective observational studies identify CVCs as an independent risk factor for venous thromboembolism in neonates and infants.^{10,83,133,134} However, no prospective or randomized studies in neonates or infants with CHD demonstrate that thromboprophylaxis reduces the incidence of catheter-related thrombosis compared with not using thromboprophylaxis. Evidence also remains insufficient to determine whether one antithrombotic drug/agent (eg, UFH vs LMWH) or dosing strategy (eg, high-dose vs low-dose UFH) is more effective for preventing CVC-associated thrombosis.¹³⁵⁻¹³⁸ A recent prospective multicenter observational study reported a catheter-related thrombosis rate of approximately 4 per 1000 admissions among neonates and infants admitted to an intensive care unit, whereas the rate of major bleeding during anticoagulation for venous thromboembolism treatment occurred in approximately 8% of patients.¹³⁹ Whether prophylactic antithrombotic therapy improves outcomes for CVC-related thrombosis in neonates and infants with CHD remains unknown. Given the uncertainty of benefit and known bleeding risk, the decisions regarding thromboprophylaxis for patients with CVCs are often patient-specific (Table 8). Multidisciplinary evaluation should consider patient-specific and anatomic thromboembolic risk factors (eg, risk of paradoxical embolization and stroke with CVC in

TABLE 9. Procedural bleeding risk and preprocedural antithrombotic medication management

Procedures and bleeding*		
Category	Procedural characteristics	Clinical application
Minimal bleed risk procedures	- Cardiac surgery without cardiopulmonary bypass - Epicardial pacemaker placement or cardioverter defibrillator implantation - Procedures anticipated to have no transfusion requirements	- Consider continuing antithrombotic therapy with no bridging
Low-to-moderate bleed risk procedures	- Cardiac catheterization - Bronchoscopy - Abdominal hernia repair - Nonorgan biopsy (eg, lymph node, cutaneous) - Procedures anticipated to have none to minimal transfusion requirements	- Consider bridging with short-acting intravenous or LMWH anticoagulants for moderate bleeding risk and high thrombotic risk
High bleed risk procedures	- Procedures with extensive tissue injury - Major surgeries - o Highly vascular organs - o Intracranial/spinal - o Liver biopsy - o Nephrectomy/kidney biopsy - o Orthopedic - o Reconstructive plastic surgery - o Thoracic - o Tumor (cancer) - o Urologic/GI - Endoscopic gastrostomy placement - Neuraxial anesthesia/epidurals - Procedures anticipated to have moderate to high transfusion requirements - Procedures anticipated to result in significant hemostatic derangements	- Bridge with a short-acting intravenous anticoagulant when the thrombotic risk is high - Hold anticoagulation (duration depends on half-life and organ function) before surgery - In the event of emergent reversal, use reversal agents where appropriate and feasible, or correct coagulopathy with blood/factor products
Antithrombotic medications and procedures with moderate to high bleeding risk†		
Medication	Duration to hold before the procedure*	Reversal (urgent scenarios)‡
UFH	- Approximately 4-6 h	- Protamine
LMWH	- Approximately 12-24 h (may require longer depending on renal function)	- Protamine (partial reversal)
Bivalirudin	- Approximately 2-3 h (may require longer depending on renal function)	- No reversal agent; correct coagulopathy (eg, blood products)
Argatroban	- Approximately 8-10 h	- No reversal agent; correct coagulopathy (eg, blood products)
Rivaroxaban§	- Approximately 6-10 h based on pharmacokinetics (may require longer depending on renal function), although there is a paucity of data in neonates/infants, and adult guidance may be referenced.	- Correct coagulopathy (eg, 4F-PCC/aPCC)
Apixaban§	- Approximately 24 -48 h (may require longer depending on renal function)	- Correct coagulopathy (eg, 4F-PCC/aPCC)
Edoxaban§	- No half-life data in neonates/infants	- Correct coagulopathy (eg, 4F-PCC/aPCC)
Dabigatran§	- Approximately 36-72 h (may require longer depending on renal function)	- Idarucizumab (no data in neonates/infants) - Correct coagulopathy (eg, 4F-PCC/aPCC)

(Continued)

TABLE 9. Continued

Antithrombotic medications and procedures with moderate to high bleeding risk [†]		
Medication	Duration to hold before the procedure [*]	Reversal (urgent scenarios) [‡]
Warfarin	- Approximately 3-5 d	- Vitamin K - 4F-PCC/aPCC
Aspirin	- Approximately 5-7 d	- No reversal agent
Clopidogrel	- Approximately 5-7 d	- No reversal agent
Dipyridamole	- Approximately 24-48 h	- No reversal agent

LMWH, Low-molecular-weight heparin; *GI*, gastrointestinal; *UFH*, unfractionated heparin; *4F-PCC*, 4-factor prothrombin complex concentrate; *PCC*, prothrombin complex concentrate; *aPCC*, activated prothrombin complex concentrate; *DOAC*, direct oral anticoagulant. ^{*}Procedural planning and decision whether to hold antithrombotic therapy should take into account each patient's bleeding and thrombotic risk and include a multidisciplinary team discussion (eg, cardiac surgery, interventional cardiology, cardiac intensive care, cardiology, hematology, and pharmacy). For procedures with a high bleeding risk, a longer holding time period may be necessary. [†]The duration of holding is dependent on drug half-life, organ function, and risk of bleeding. [‡]For scenarios that require urgent intervention and potential reversal of anticoagulation, careful evaluation of potential thrombotic risks should be conducted and include a multidisciplinary team discussion (eg, cardiac surgery, interventional cardiology, cardiac intensive care, cardiology, hematology, and pharmacy). [§]Data in neonates and infants are limited; bridging is not typically used for DOACs.

single-ventricle or R-L shunting physiology) and weigh the potential advantages of thromboprophylaxis against the risk of bleeding.

Antithrombotic Therapy for Valve Replacement

S30. Antithrombotic thromboprophylaxis for neonate and infant valve replacement should be considered on the basis of valve characteristics, location, patient bleeding, and thrombotic risks. (CoR IIa, LoE C-EO)

Antithrombotic management after valve replacement in neonates and infants remains a high-risk, evidence-limited practice. Given small sample sizes and limited pediatric-specific data, recommendations for neonates and infants with valve replacements are largely extrapolated from adult experience and consensus guidelines. Mechanical valve replacement, although uncommon in this population, carries a substantial risk of thrombosis as the result of small prosthesis size and low-flow physiology in certain anatomic locations. Early postoperative anticoagulation with intravenous or subcutaneous agents, until enteral feeding is tolerated, may mitigate immediate thrombotic risk while balancing postoperative hemostasis and bleeding risk.¹⁴⁰ Once enteral nutrition is established, long-term anticoagulation can be transitioned to VKAs, with target INR adjusted to valve type, position, and patient-specific factors. In select patients, particularly those with mechanical mitral valves in whom an antiplatelet agent is indicated, adjunctive low-dose aspirin (3-5 mg/kg/dose) may be considered when the potential reduction in thromboembolic risk outweighs bleeding concerns. Bioprosthetic and homograft valves are increasingly favored for their lower intrinsic thrombogenicity, yet variability in valve material, size, and location may influence thrombosis risk. High-risk infants may benefit from short-term postoperative intravenous anticoagulation followed by enteral anticoagulation for 3 months before transitioning to lifelong antiplatelet therapy, mirroring adult bioprosthetic valve practice.^{141,142} Given the

complexity and limited evidence base, multidisciplinary collaboration among cardiology, cardiac surgery, hematology, and pharmacy is essential to tailor antithrombotic strategies for valve thromboprophylaxis and minimize bleeding complications.⁹²

Mitral Valve Replacement

S31. Antithrombotic therapy is recommended for infant mechanical mitral valve replacements using a vitamin K antagonist to a goal INR 2.5 to 3.5 for the life of the valve. (CoR I, LoE A)

Mechanical mitral valve replacement in neonates and infants is uncommon, and when performed, carries a significant risk of thrombosis because of the thrombogenic nature of mechanical prostheses, small valve size, and low-flow physiology in the mitral position. Anticoagulation strategies in infants and neonates are largely extrapolated from adult guidelines, and expert consensus gives the limited pediatric-specific data.^{123,140-143} Management typically includes therapeutic intravenous anticoagulation in the perioperative period with UFH or bivalirudin, followed by transition to oral VKA therapy with a target INR of 2.5 to 3.5 for the life of the valve.^{123,140-143} Maintaining VKA therapy in infants is particularly challenging because of variations in dietary vitamin K, rapid growth, fluctuating metabolic rates, and intercurrent illness, all of which may lead to INR variability.^{123,144} As a result, vigilant monitoring is essential, with frequent INR assessments recommended. Home POC INR machines have been reported to be comparable to lab testing, enhancing the quality of life for families with more flexible monitoring strategies that can be performed at home.¹⁴⁴ (Table 6). For patients unable to tolerate warfarin, a multidisciplinary team with integrated expertise should discuss an individualized patient approach.

S32. Antithrombotic thromboprophylaxis for Melody (Medtronic) mitral valve replacements in infants and

neonates should be guided by institutional care pathways and multidisciplinary team discussion. (CoR IIa, LoE C-EO)

The Melody valve in the mitral position introduces considerations distinct from both traditional mechanical and bioprosthetic surgical valves. Its bovine jugular vein conduit tissue, stent frame, and mode of implantation may lead to a variable thrombotic risk profile influenced by factors such as patient size, ventricular function, flow dynamics across the valve, and other coexisting clinical conditions.

Evidence to guide antithrombotic therapy in this age group with Melody mitral valve replacement remains limited, largely consisting of case reports and small observational series.¹⁴⁵⁻¹⁵² As a result, most centers rely on consensus-driven institutional protocols and multidisciplinary team decision-making to balance thrombotic and bleeding risks. Management strategies may include perioperative anticoagulation with UFH, followed by transition to antiplatelet therapy, anticoagulation (eg, LMWH), or combination therapy (LMWH plus aspirin). The chosen approach often reflects valve characteristics (eg, valve size and function), atrial size, postoperative hemodynamics, and patient-specific risk factors (Table 3).¹⁴⁵⁻¹⁵² A multidisciplinary team-guided decision-making in selecting antithrombotic agent(s), dosing, and duration is necessary, given the presence of patient-specific factors (eg, risk of thromboembolism or bleeding, other clinical conditions) and limited pediatric evidence to guide agent selection.

Aortic Valve Replacement

S33. Antithrombotic therapy is recommended for infant mechanical aortic valve replacements and should use therapeutic vitamin K antagonist to a goal INR 2 to 3 for the life of the valve. (CoR I, LoE A)

Mechanical aortic valve replacement in infants requires lifelong anticoagulation because of the high thrombogenic potential of mechanical prostheses and the unique hemostatic physiology of early infancy. Current guideline recommendations are extrapolated from adult data and supported by limited pediatric observational experience, endorsing therapeutic VKA with a target INR of 2 to 3 for the life of the valve. This recommendation reflects extensive adult data and consistent pediatric observational evidence demonstrating markedly increased risks of valve thrombosis, systemic embolism, and mortality when mechanical valves are not adequately anticoagulated.^{123,143} Given the narrow therapeutic window of VKAs, developmental differences in drug metabolism, and frequent clinical variability in this population, careful monitoring and multidisciplinary management integrating cardiology, cardiac surgery, hematology, and pharmacy expertise are essential to maintaining safe and effective anticoagulation.^{92,94,153}

Concomitant Aspirin Therapy for Mitral and Aortic Valve Replacement

S34. Aspirin, in addition to vitamin K antagonist, may be considered in infants with a mechanical mitral or mechanical aortic valve who have an indication for antithrombotic therapy, when the risk of bleeding is low. (CoR IIb, LoE C-EO)

In select cases in which an indication for antiplatelet therapy exists, and the bleeding risk is low, aspirin at a low dose (3-5 mg/kg) in addition to VKA therapy may be considered. Factors that may prompt considerations of combination therapy include a history of thromboembolism or stroke, associated prothrombotic conditions, or valve or patient-specific characteristics that increase shear stress or reduce effective flow. Given limited pediatric data and heightened susceptibility to bleeding in neonates and infants, decisions regarding adjunctive aspirin must be individualized.^{92,94,123,143,153}

Limitations and Future Research

Given the lack of sufficient number of neonate/infant-specific randomized control trials, particularly those related to CHD, much of the evidence to support these consensus statements is collected from single-center or multicenter cohort studies, with randomized controlled trials included where available. Some important studies in young children and adult were included as references, particularly related to antithrombotic management of mechanical valves, with the caveat that neonate and infant hemostatic system and its responses are quite different from adults.¹⁴⁰⁻¹⁴³ Expansion of similar work to understand antithrombotic therapy in older children and adults is planned. Development of quality metrics to monitor appropriate use, efficacy, and safety of antithrombotic therapy in this population will be an important next step.

CONCLUSIONS

The hemostatic system in neonates and infants with CHD is a complex interconnected system of checks and balances. Although cardiac interventions in this population will involve perturbations in this system, appropriate antithrombotic therapy and monitoring can attenuate complications associated with iatrogenic alterations. Our consensus statements provide details on how the hemostatic balance in neonates and infants is distinct from that of adults. The normal differences found in healthy neonates when compared with adults are exaggerated in neonates with CHD, particularly those with cyanotic heart disease.

Neonates and infants with CHD require antithrombotic therapy for numerous reasons related to their cardiac interventions. There is considerable heterogeneity of the patient population and variability in clinical practice, which

underscores the importance of a dedicated multidisciplinary team with expertise in both congenital heart disease and thrombosis/hemostasis to guide the assessment of bleeding and thrombotic risk, and to determine the appropriate intensity and duration of antithrombotic therapy. The initiation, intensity, and duration of long-term antithrombotic therapy should be guided by an individualized assessment that considers patient-specific factors, surgical/procedural details, and the overall clinical condition, with attention to the variable risk of both bleeding and thrombosis.

Conflict of Interest Statement

See [Appendix E3](#). C.V. receives consulting fees from Merck, Scientific Oversight Committee. M.M. and M.N. received grants from the National Institutes of Health unrelated to this work. C.Y. has submitted patents but not yet issued. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: neonates and infants, congenital cardiac interventions, coagulation cascade, perturbations of the coagulation system, antithrombotic therapy

APPENDIX E1. LITERATURE SEARCH CRITERIA

Four major research domains related to antithrombotic therapy in neonates and infants after congenital cardiac interventions were first developed with related subquestions

Domain 1: Developmental and disease-specific hemostasis and antithrombotic pharmacology and monitoring strategies

Domain 2: Pre- and intraprocedural management of bleeding and thrombosis through antithrombotic management and testing

Domain 3: Immediate postprocedural management of bleeding and thrombosis through antithrombotic management and testing

Domain 4: Long term management of bleeding and thrombosis through antithrombotic management and testing

With the assistance of a medical librarian, PubMed, EMBASE, SCOPUS, and Web of Science were searched for relevant articles published in 1990 or later and limited to English language. For some of the questions related to the normal coagulation cascade, and age and disease-based differences, earlier literature was reviewed. This literature review process was iterative. Additional articles of interest were identified by reviewing the references in initially identified high-quality articles.

Review articles, commentaries or meta-analysis were considered if appropriate in the overall composition of the consensus document, although not necessarily used for development of the actual statements. Meta-analyses were considered when evaluating the level of evidence. All manuscripts were compiled into Excel spreadsheets for group review. Greater importance was given to more recent studies, those with larger patient populations, and those using comparison groups, especially with randomization or propensity score matching. The 2 chairs read each abstract. Authors within writing sections then reviewed in full every pertinent article related to the section they were assigned to.

Each of the 4 domains was reviewed separately and synthesized by content experts before Delphi consensus integration.

After a systematic manuscript review, clinical statements were formulated in accordance with the Patient, Intervention, Comparison, Outcome (PICO) framework. Consensus-based recommendations, each assigned a Class of Recommendation (CoR) and Level of Evidence (LoE), were derived through a modified Delphi process.^{E1} Iterative group review and revision of each statement preceded formal validation by blind vote. Consensus was defined as $\geq 80\%$ member participation with $\geq 75\%$ concordance (responses of “agree” or “strongly agree”). Blinded voting was accompanied by an open comment period to facilitate clarification of dissenting perspectives and inform subsequent statement revisions. Statements that failed to achieve consensus after 3 successive voting rounds were excluded.

CoR was assigned principally on the basis of the magnitude and estimated size of the treatment effect, weighed against the benefit-to-harm ratio. LoE was determined by the degree of certainty in the treatment effect supportable by available evidence, independent of effect magnitude; however, higher LoE was permitted to justify elevated CoR designations even in the setting of marginal absolute benefit. CoR and LoE assignments were subject to the same consensus threshold and voting requirements applied to the statements themselves. Terminology was selected in accordance with nomenclature recommended by the American College of Cardiology and the American Heart Association, with correlating language informing CoR determination where appropriate.^{E2}

Upon finalization of each recommendation and its corresponding CoR and LoE, an accompanying discussion was constructed to elucidate the intent and interpretive context of each statement, with explicit reference to the supporting evidence base underlying each recommendation.

ANTICOAGULATION ECD-SEARCH

Search Description

The PubMed search strategies were developed using a combination of controlled vocabulary (MeSH terms) and key words to ensure comprehensive retrieval of relevant literature. The search strategy incorporated Boolean operators, truncation, and proximity searching to capture variations in terminology and relationships between key concepts. Searches were structured around key concepts including population (eg, neonate, infant, pediatric), coagulation and thrombosis (eg, coagulation, thrombosis, thrombin), anticoagulant and antiplatelet therapies (eg, heparin, aspirin, anticoagulant, antiplatelet), cardiac conditions and procedures (eg, cardiac surgery, ventricular assist device, congenital heart), and perioperative context (eg, preoperative, postoperative). Searches were limited to studies published in English and excluded case reports and comments. Searches were last conducted on April 4, 2025.

Core Search Terms

1. Population: Neonates, Infants, and Children
Controlled Vocabulary:

- “Infant, Newborn”[Majr]
- infant[Majr]
- child[Majr]
- adolescent[Majr]

Key words:

- neonate*
- neonatal
- newborn*
- infant/infants

- pediatric*/paediatric*
- child*
- boy/boys
- girl/girls
- juvenile*
- adolescen*
- teen/teens/teenager*
- youth/youths

Filters:

- newborn[Filter]
- allinfant[Filter]
- child[Filter]
- adolescent[Filter]

2. Coagulation and Thrombosis (Core Anticoagulation Concept)

Controlled Vocabulary:

- “Blood Coagulation”[Majr]

Key words:

- coagulation
- coagulat*
- coagulopath*
- blood clot*
- thrombos*
- thrombin
- clot* AND blood

3. Anticoagulants and Antiplatelet Agents

Controlled Vocabulary:

- “Platelet Aggregation Inhibitors”[Majr]
- “Platelet Aggregation Inhibitors”[Pharmacological Action]
- “Heparin”[Majr]
- “Aspirin”[Majr]
- “Dipyridamole”[Majr]
- “Pentoxifylline”[Majr]
- “Ticlopidine”[Majr]
- “Trapidil”[Majr]
- “Iloprost”[Majr]
- “Disintegrins”[Majr]
- “Milrinone”[Majr]
- “Prasugrel Hydrochloride”[Majr]
- “Clopidogrel”[Majr]
- “Resveratrol”[Majr]
- “Abciximab”[Majr]
- “Cilostazol”[Majr]
- “Tirofiban”[Majr]
- “Ticagrelor”[Majr]
- “Eptifibatide”[Majr]
- “Warfarin”[Majr]

Key words:

- antiplatelet*
- anticoagul*
- platelet inhibitor*
- platelet antiaggregant*
- platelet antagonist*
- prevent* blood clot*

Drug Name Key words (Title field variants):

- heparin
- aspirin
- dipyridamole
- pentoxifylline
- ticlopidine
- trapidil
- iloprost
- disintegrins
- milrinone
- prasugrel hydrochloride
- clopidogrel
- resveratrol
- abciximab
- cilostazol
- tirofiban
- ticagrelor
- eptifibatide
- warfarin

4. Cardiac Surgery and Interventions

Controlled Vocabulary:

- “Cardiac Surgical Procedures”[Majr]
- “Heart-Assist Devices”[Majr]

Key words:

- surg*
- bypass*
- stent*
- mechanical circulatory support
- ventricular assist device*
- heart

5. Congenital and Cardiac Conditions

Controlled Vocabulary:

- “Heart Defects, Congenital”[Majr]
- “Heart Diseases”[Mesh]
- “Heart”[Majr]

Key words:

- congenital heart
- cardiac
- heart
- coronary
- cardio*

- ventricular

6. Perioperative Timing (Pre- and Postoperative Contexts)

Preoperative

Controlled Vocabulary:

- “Preoperative Period”[Mesh]

Key words:

- preoperative*
- pre-operat*
- before surg*

Postoperative

Controlled Vocabulary:

- “Postoperative Period”[Mesh]

Key words:

- postoperative
- post-operat*
- post-surg*
- after surg*

7. Healthy Population Comparator (Q1.2 Specific)

Key words:

- healthy

8. Study Limits

- English language
- Exclusion:
 - case reports
 - comments

APPENDIX E2. ANTITHROMBOTIC MANAGEMENT OF NEONATES/INFANTS UNDERGOING CARDIAC INTERVENTIONS: DELPHI WORKSHEET

Statement number	Statement	Delphi results
Hemostatic system in neonates and infants		
1	As the hemostatic system in neonates and infants differs significantly from that of older children and adults, it is recommended that providers should understand these normal differences and the implications of these differences for coagulation testing, antithrombotic monitoring and drug effect. (CoR I, LoE C-EO)	100%
2	Neonates and infants with congenital heart disease, particularly those with cyanotic CHD, demonstrate coagulation profiles that differ from age-matched healthy controls; therefore, preoperative coagulation testing may be reasonable in select patients due to their increased risk of baseline coagulation abnormalities. (CoR IIb, LoE B-R)	100%
3	Routine thrombophilia testing is not recommended in neonates and infants with CHD undergoing cardiac intervention. (CoR III, LoE B-NR)	100%
4	Targeted evaluation may be considered in the setting of unprovoked or recurrent thrombosis or a strong family history, in consultation with pediatric hematology. (CoR IIb, LoE C-LD)	100%
Periprocedural antithrombotic and bleeding management during cardiopulmonary bypass and catheter-based interventions		
5	In neonates and infants, perioperative comprehensive blood conservation strategies may be considered to minimize exposure to allogenic blood products and to attenuate the inflammatory coagulopathic response during and following cardiopulmonary bypass surgery. (CoR IIb, LoE B-NR)	100%
6	Intra-procedure heparinization is recommended in neonates and infants undergoing cardiac interventions to reduce the incidence of thrombosis and thromboembolic complications. (CoR I, LoE B-NR)	100%
7	In neonates and infants undergoing cardiac interventions (cardiac surgery and/or cardiac catheterization), where unfractionated heparin cannot be utilized, direct thrombin inhibitors are appropriate as an alternative anticoagulant strategy. (CoR I, LoE B-NR)	92%
8	In neonates and infants undergoing complex cardiac surgery with cardiopulmonary bypass, individualized unfractionated heparin titration using validated anti-factor Xa point-of-care (POC) diagnostic tests (eg, Hemostasis Management System or equivalent anti-Fxa-based platforms) may be considered as an alternative to ACT-guided weight-based dosing alone, where institutional expertise exists. (CoR IIb, LoE B-NR)	100%
9	Any intraoperative POC coagulation testing platforms (eg, Hemostasis Management System or emerging anti-FXa-guided platforms) primarily developed for adult populations may require modification when applied to neonates and infants to optimize unfractionated heparin and protamine dosing during cardiac surgery. (CoR IIb, LoE C-LD)	100%
10	In neonates and infants undergoing complex cardiac surgery who demonstrate an inadequate heparin response, supplementation with antithrombin or fresh frozen plasma may be considered to enhance heparin efficacy. (CoR IIb, LoE B-NR)	92%
11	In neonates and infants, point-of-care (POC) coagulation testing (ACT, TEG, ROTEM) may be considered instead of conventional laboratory tests to support timely intraoperative anticoagulant management during cardiopulmonary bypass surgery. (CoR IIb, LoE C-LD)	83%
12	Antifibrinolytics should be considered in neonates and infants undergoing cardiac surgery involving cardiopulmonary bypass to reduce excessive bleeding and transfusion requirements in the perioperative period. (CoR IIa, LoE B-R)	100%
13	Perioperative viscoelastic testing may be considered as a supplement to conventional coagulation laboratory testing to guide intraoperative blood product transfusion decisions and potentially reduce postoperative transfusion requirements in neonates and infants undergoing complex cardiac surgery. (CoR IIb, LoEB-NR)	92%
14	In neonates and infants with clinically significant bleeding following CPB and evidence of thrombocytopenia or platelet dysfunction, platelet transfusion is recommended as targeted therapy. (CoR I, LoE B-NR)	100%
15	Targeted adjuvant therapy with fibrinogen-concentrate as a pathogen-reduced alternative to cryoprecipitate may be reasonable in neonates and infants with ongoing bleeding likely related to hypofibrinogenemia following cardiopulmonary bypass. (CoR IIb, LoE C-LD)	92%

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Periprocedural antithrombotic and bleeding management during cardiopulmonary bypass and catheter-based interventions		
16	Targeted coagulation factor administration may be considered as adjunct therapy for bleeding management in neonates and infants after cardiopulmonary bypass surgery, especially when laboratory or clinical indicators suggest factor deficiencies. (CoR IIB, LoE B-NR)	100%
17	Planned discontinuation of anticoagulants or antiplatelet agents several days before complex cardiac surgery in neonates and infants is reasonable when the risk of bleeding outweighs the risk of thrombosis and the risk of thrombosis is low. (CoR IIA, LoE C-LD)	100%
18	In neonates and infants with congenital heart disease, given the risks of thromboembolism and bleeding, the heterogeneity of the patient population, and the variability in clinical practice, a dedicated multidisciplinary team with subspecialized knowledge and expertise in cardiology and thrombosis/hemostasis should be considered to help guide the assessment of bleeding and thromboembolic risks and appropriate antithrombotic therapy selection, intensity, and duration. (CoR IIA, LoE C-EO)	100%
19	In neonates and infants with congenital heart disease requiring intervention, the initiation, intensity, and duration of antithrombotic therapy should consider patient-specific factors, surgical/procedural details, and the overall clinical condition, after carefully weighing the risk of bleeding. (CoR IIA, LoE C-EO)	92%
20	In select neonates and infants with recurrent thrombosis or concern for inadequate antiplatelet effect, platelet responsiveness testing may be considered within experienced centers, recognizing that validation and outcome data are limited. (CoR IIB, LoE C-EO)	100%
Shunt-dependent physiology		
21	In neonates and infants with a Blalock-Taussig Thomas or central shunt, given increased risk for thromboembolism, parenteral anticoagulation should be considered until enteral aspirin can be initiated in the immediate postoperative period. (CoR IIA, LoE B-NR)	100%
22	For long-term thromboprophylaxis, aspirin is recommended as first-line therapy for an indefinite duration (CoR I, LoE B-NR.); dual antithrombotic therapy may be considered in complex scenarios. (CoR IIB, LoE C-EO)	100%, 91%
Conduits/baffles/nonautologous patch material		
23	Neonates and infants undergoing cardiac surgery with conduits, non-autologous patch materials, or extensive intracardiac baffles may be at increased risk for thrombosis; therefore, low-dose anticoagulation with a short-acting intravenous agent may be considered until enteral antiplatelet therapy is feasible in the immediate postoperative (24-72 h) and early (first wk) period. (CoR IIB, LoE C-EO)	100%
24	For long-term thromboprophylaxis, aspirin monotherapy may be considered, with duration depending on the surgical procedure and thrombotic risks (CoR IIB, LoE C-EO)	100%
Coronary procedures		
25	For neonates and infants undergoing procedures involving the coronary arteries, antithrombotic therapy in the immediate post-operative period and antiplatelet therapy long term may be considered depending on the surgical procedure and coronary artery anatomy. (CoR IIB, LoE C-EO)	92%
Interventional cardiology procedures—lower risk		
26	For intravascular stents or hardware placement at a lower risk of thrombosis, parenteral anticoagulation may be considered immediately post-procedure until enteral antiplatelet therapy is feasible (CoR IIB, LoE B-NR); and aspirin monotherapy is recommended for at least 6 mo. (CoR I, LoE B-NR)	100%, 100%
Interventional cardiology procedures—greater risk		
27	For intravascular stent or hardware placement at a higher risk of thrombosis, parenteral anticoagulation should be considered until enteral therapy is feasible (CoR IIA, LoE C-EO), and a combination of antithrombotic agents (anticoagulant, antiplatelet, or dual antiplatelet) is recommended for at least 3-6 mo. (CoR I, LoE C-EO)	92%, 100%
Procedural bridging therapy		
28	For neonates and infants who are at risk of thrombosis and require temporary interruption of oral antithrombotic therapy, multidisciplinary decision-making should be considered to evaluate the net clinical benefit of bridging versus no bridging, assessing risks of both bleeding and thromboembolism. (CoR IIA, LoE C-EO)	100%

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Central lines prophylaxis and management		
29	Thromboprophylaxis may be considered in neonates and infants with central venous catheters, on the basis of patient and anatomic thromboembolic risk factors, after considering the benefit versus the risk of bleeding. (CoR IIB, LoE C-EO)	92%
Antithrombotic therapy for valve replacement		
30	Antithrombotic thromboprophylaxis for neonate and infant valve replacement should be considered on the basis of valve characteristics, location, patient bleeding, and thrombotic risks. (CoR IIA, LoE C-EO)	100%
Mitral valve replacement		
31	Antithrombotic therapy is recommended for infant mechanical mitral valve replacements using a vitamin K antagonist (VKA) to a goal INR 2.5-3.5 for the life of the valve. (CoR I, LoE A)	100%
32	Antithrombotic thromboprophylaxis for Melody (Medtronic) mitral valve replacements in infants and neonates should be guided by institutional care pathways and multidisciplinary team discussion. (CoR IIA, LoE C-EO)	92%
Aortic valve replacement		
33	Antithrombotic therapy is recommended for infant mechanical aortic valve replacements and should use therapeutic vitamin K antagonist (VKA) to a goal INR 2-3 for the life of the valve. (CoR I, LoE A)	100%
Concomitant aspirin therapy for mitral and aortic valve replacement		
34	Aspirin, in addition to VKA, may be considered in infants with a mechanical mitral or mechanical aortic valve who have an indication for antithrombotic therapy, when the risk of bleeding is low. (CoR IIB, LoE C-EO)	100%

APPENDIX E3. AUTHOR CONFLICTS OF INTEREST

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E-References

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- E2. Otto CM, Abdullah AR, Davis LL, et al. 2025 ACC/AHA clinical practice guidelines core principles and development process: a report of the American college of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2025;152(18):e359-e370. <https://doi.org/10.1161/CIR.0000000000001383>