



Thrombosis and Modern Anticoagulation Options for the Adult with Congenital Heart Disease

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28.1 Propensity to Thrombosis in Adults with Congenital Heart Disease

It has long been recognized that adults with congenital heart disease (CHD), in particular cyanotic congenital heart disease (CCHD), are prone to thrombosis whether or not they have Eisenmenger physiology [1–3]. Although cerebrovascular events and pulmonary embolism (PE) are the most widely discussed, thrombosis of additional sites in the single-ventricle population, namely, the Fontan pathway [3–19] and deep veins of the lower extremities [20], may be equally devastating.

It is not surprising that adult congenital heart disease (ACHD) patients are prone to thrombosis. Throughout their lifetime, they have been exposed to the triad of risk factors for thrombosis initially described by Virchow in 1856 [21], namely, (a) stasis of blood, (b) hypercoagulability, and (c) endothelial injury. As in pediatric heart disease [14, 22, 23], an expansion of Virchow's triad [24] appears warranted:

1. Altered blood flow (an expansion of “stasis of blood”)

In addition to stasis of blood, ACHD patients have the potential to be exposed to “altered blood flow”:

- (a) **Stasis of blood** may occur in dilated heart chambers as well as in dilated native or prosthetic outflow tracts. These areas of stasis may serve as a nidus for thrombus formation.
- (b) **Turbulent flow** may occur across stenotic native or prosthetic heart valves, intracardiac devices/leads, stents, and/or obstructed native or prosthetic outflow tracts activating platelets either directly [25, 26] or by increasing shear

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stress that can result in platelet activation independent of endothelial damage [27]. Activated platelets adhere to these “abnormal,” artificial vascular surfaces and may result in thrombus formation. The same mechanisms are involved in the turbulent flow of mechanical support (cardiopulmonary bypass (CPB), extracorporeal membrane oxygenation (ECMO), ventricular assist devices (VAD)) where thrombosis can occur despite systemic anticoagulation. Platelets are activated. Thrombin generation is increased via the extrinsic system in response to cytokines, ischemia, sheer stress, and activated platelets and via the contact system in response to contact of blood with the circuit. A profound derangement in the coagulation/fibrinolytic balance occurs with an ineffective counterbalance by anticoagulant factors such as antithrombin III. The procoagulant state may persist well past decannulation [28–31]. Although children, especially infants with their immature coagulation system, may be more prone to such effects, it seems most likely that at least some of these factors are at play in ACDH patients as well.

2. **Blood component abnormalities (expansion of hypercoagulability)**

Blood component abnormalities have been described in children with acyanotic, acquired, as well as single-ventricle heart disease and include altered anticoagulation protein levels, increased thrombin generation potential, decreased endogenous inhibitors of coagulation, and decreased fibrinolytic proteins, among others. Such coagulopathies were first identified in children and adolescents with a Fontan circulation but more recently have been described through all stages of single-ventricle palliation, i.e., even before the Fontan completion [32–41]. Coagulopathies in Fontan patients are further described in the section on Fontans below.

As is well known to physicians caring for adults with CHD, erythrocytosis and hyperviscosity associated with chronic cyanosis are risk factors for thrombosis as well. This may be exacerbated by iron deficiency anemia which makes red cells more rigid and less deformable as well as by dehydration [3, 14, 34, 42].

3. **Endothelial injury and dysfunction**

Turbulent flow along normal vascular endothelial surfaces results in endothelial injury and dysfunction which is a precursor to thrombosis. Endothelial injury exposes tissue factor and subendothelial collagen-stimulating platelet aggregation and coagulation at the site of injury. Altered levels of endothelial markers in plasma have been found to precede intravascular coagulation and thrombosis in one study of patients with functionally univentricular hearts [43]. In addition, adults with CHD most likely have had numerous cardiac catheterizations, exposure to CPB, and central lines throughout their medical history that have the potential of further damaging an already compromised endothelium.

4. **Inflammation and bloodstream infection**

Adults with CHD are at risk for exposure to inflammation and blood stream infections which pose further risk for thrombosis. In addition to creating turbulent flow and endothelial disruption, mechanical support (CPB, ECMO, VAD) results in an inflammatory state [29–31], activating platelets and exposing tissue factor by cytokine release [26]. Recent pediatric studies have implicated sepsis

with increased thrombus formation especially in the presence of an indwelling central venous line [44–46].

Patients with CHD often have one or more of these thrombosis risk factors at play, while during mechanical circulatory support (CPB, ECMO, VAD), all four of these conditions coexist.

28.1.1 Eisenmenger Physiology

A special note should be made about patients with Eisenmenger physiology who have a well-known risk of bleeding as well as clotting, thereby making anticoagulation controversial and often contradicted [Giannakoulas 2015]. In addition to the four factors described above, pulmonary hypertension in and of itself may result in endothelial dysfunction in the pulmonary arteries increasing the risk of pulmonary emboli. Cell aggregation secondary to decreased pulmonary blood flow may also be a thrombotic risk [10, 47]. On the other side of the spectrum, pulmonary hemorrhage from rupture of one of the pulmonary vessels is often the cause of death in this patient population [48–50].

This chapter will discuss common thrombotic concerns in the adult with CHD, namely, deep venous thrombosis (DVT), pulmonary embolism (PE), arrhythmias as a risk factor for stroke, and special concerns in the Fontan patient. We will conclude with a discussion of both currently available and “under-investigation” antithrombotic therapies.

28.2 Deep Venous Thrombosis and Pulmonary Embolism in Adults with Congenital Heart Disease

A recent editorial by Giannakoulas and Boutsikou [51] reviewed the prevalence of thrombosis in adults with CCHD from ten studies over the past 25 years. The prevalence of arterial cerebral thrombosis ranged from 0 to 47%, whereas the prevalence of pulmonary thrombosis ranged from 13.2 to 35%. Only two studies looked at both cerebral and pulmonary thromboses, and as expected, the studies differed in whether they were prospective/retrospective and most importantly in whether the thrombosis was clinically evident or clinically silent and documented on screening studies only. The most recent of the included studies by Jensen [52] documented cerebral thrombosis at 47% and pulmonary thrombosis at 31% in a prospective study and commented that the large discrepancy between clinical history and imaging findings suggests a high prevalence of silent thrombotic events.

Although single-ventricle anatomy and cyanosis are significant risk factors for early postoperative thrombosis in infants and children (especially DVT associated with central venous lines) [53, 54], there is limited data on the significance of these risk factors in the adult with CHD.

It is estimated that just over half of all medical patients in US acute care hospitals are at risk for venous thromboembolism (VTE) including DVT and PE [55] with

those in the critical care setting at particularly increased risk [56]. Pulmonary embolism is considered the most common preventable cause of hospital death [57], and the Institute of Medicine defines the failure to provide adequate thromboprophylaxis to hospitalized, at-risk patients a medical error [58]. Although the prevalence of VTE in critically ill adults with CHD in the ICU is not known, based on the propensity for thrombosis in adults with CHD and the increased risk of VTE with age, it can be inferred that adults with CHD incur as much or more risk for VTE than those without CHD.

28.2.1 Risk Assessment and VTE Prophylaxis in Hospitalized Patients

Hospitalized patient characteristics considered high risk for VTE are malignancy, stroke, major general surgery and orthopedic surgery, trauma and fractures, spinal cord injury, obesity, pregnancy, heart failure, myocardial infarction, sepsis, respiratory failure, renal disease, older age, prolonged immobility >3 days, hypercoagulable states, and history of previous VTE [59, 60]. Although there are a number of schemes devised to assess thrombosis risk in the non-congenital heart disease population [61–63], they are not validated in those with CHD, and in general, we recommend that all adults with CHD in the ICU receive prophylactic anticoagulation unless they are at increased risk for bleeding (i.e., acute gastrointestinal or intracerebral bleed, profound thrombocytopenia).

Pharmacologic VTE prophylaxis is recommended over mechanical means (i.e., sequential compression devices) with the agent of choice being low molecular weight heparin (LMWH), though unfractionated heparin (UFH) can be used for those with renal failure. If the patient is at high risk for bleeding, sequential compression devices and elastic graduated compression stockings are recommended over no prophylaxis. Thromboprophylaxis should continue until the patient is ambulatory or discharged.

In the general population, prophylaxis has been found to decrease the risk of VTE in acutely ill medical patients, but there is no proven mortality benefit in medical patients [64]. In contrast, mortality benefit has been seen in surgical patients [65], although the reasons for this difference are not known. Outcomes for VTE prophylaxis in the adult with CHD are yet to be defined.

28.2.2 Management of Deep Venous Thrombosis and Pulmonary Embolism in ACHD

The mainstay of deep vein thrombosis treatment is anticoagulation in the absence of contraindications (i.e., active hemorrhage, recent intracerebral bleed, trauma, thrombocytopenia). The purpose of anticoagulation is to prevent complications such as clot extension, acute pulmonary embolism, and recurrent DVT. Anticoagulation is specifically indicated for proximal DVT which has a higher risk of embolization and

death compared to distal (e.g., below the knee) DVT [66] as well as for symptomatic distal DVTs. Other factors should be considered when deciding between surveillance and anticoagulation of asymptomatic distal DVTs such as high D-dimer levels, clot burden and extent, prior DVT, prolonged immobility, as well as bleeding risk. Inferior vena cava filter can be considered for those with a lower extremity proximal DVT and an absolute contraindication to anticoagulation [67]. Thrombolytic therapy or catheter-based extraction is reserved for rare cases such as those with massive iliofemoral DVT (phlegmasia cerulea dolens).

The diagnosis of PE in the single-ventricle patient by conventional means such as computed tomography with contrast or ventilation-perfusion scans is limited by the alteration in pulmonary arterial blood flow (lack of a systemic venous mixing chamber), and thus the diagnosis may rely on pulmonary angiography. The treatment of acute PE is guided by severity, hemodynamic stability, and bleeding risk. Therapeutic anticoagulation is indicated for patients with confirmed PE and no contraindications to anticoagulation. In general, those with hemodynamic instability with concern for massive PE should be considered for more aggressive therapies such as thrombolysis and/or mechanical embolectomy [68, 69].

The choice of anticoagulation for the treatment of VTE must take into account a number of factors including liver disease, renal disease, route of administration and dosing, compliance, and reversibility, keeping in mind that the critically ill patient in the ICU may have a predisposition toward hemorrhage. Direct oral anticoagulants (DOACs) are safe and effective alternatives to standard anticoagulation (heparin and warfarin). Table 28.1 summarizes factors to consider in selecting anticoagulation for patients with acute VTE [68]. Extensive discussion regarding diagnosis and treatment of VTE is beyond the scope of this chapter, and management should follow recommendations from clinical guidelines [68, 69].

28.3 Arrhythmia and Thromboembolic Stroke in Adults with Congenital Heart Disease

Atrial arrhythmias such as intra-atrial reentry tachycardia, typical atrial flutter, and atrial fibrillation occur in 15% of adult patients with congenital heart disease [70]. The incidence of atrial arrhythmias increases with age and underlying disease complexity, representing a major source of morbidity for adults with CHD including thromboembolic stroke [70, 71]. In the critical care setting, there is an increased risk of atrial tachyarrhythmias due to inflammation, surges in catecholamines, ischemia, volume shifts, and atrial stretch [72]. Additional superimposed risk factors include immobility, presence of prosthetic material, indwelling leads, intracardiac shunts or septal patch margin defects, sluggish flow and venous stasis, cyanosis, and hypercoagulability [3, 12], making the risk of stroke considerable.

The presence of atrial fibrillation increases the risk of thromboembolic stroke by fivefold, but stroke risk also depends on the presence of other risk factors [73]. The anticoagulation management of atrial fibrillation or atrial flutter in the critically ill adult with CHD must balance the risk of bleeding against the risk of stroke. The

Table 28.1 Factors affecting choice of treatment for acute VTE [68]

Factor	Preferred anticoagulant	Qualifying remarks
Cancer	LMWH	More so if: just diagnosed, extensive VTE, metastatic cancer, very symptomatic; vomiting; on cancer chemotherapy
Parenteral therapy to be avoided	Rivaroxaban; apixaban	VKA, dabigatran, and edoxaban require initial parenteral therapy
Once daily oral therapy preferred	Rivaroxaban; edoxaban; VKA	
Liver disease and coagulopathy	LMWH	NOACs contraindicated if INR raised because of liver disease; VKA difficult to control, and INR may not reflect antithrombotic effect
Renal disease and creatinine clearance <30 mL/min	VKA	NOACs and LMWH contraindicated with severe renal impairment. Dosing of NOACs with levels of renal impairment differs with the NOAC and among jurisdictions
Coronary artery disease	VKA, rivaroxaban, apixaban, edoxaban	Coronary artery events appear to occur more often with dabigatran than with VKA. This has not been seen with the other NOACs, and they have demonstrated efficacy for coronary artery disease. Antiplatelet therapy should be avoided if possible in patients on anticoagulants because of increased bleeding
Dyspepsia or history of GI bleeding	VKA, apixaban	Dabigatran increased dyspepsia. Dabigatran, rivaroxaban, and edoxaban may be associated with more GI bleeding than VKA
Poor compliance	VKA	INR monitoring can help to detect problems. However, some patients may be more compliant with a NOAC because it is less complex
Thrombolytic therapy use	UFH infusion	Greater experience with its use in patients treated with thrombolytic therapy
Reversal agent needed	VKA, UFH	
Pregnancy or pregnancy risk	LMWH	Potential for other agents to cross the placenta
Cost, coverage, licensing	Varies among regions and with individual circumstances	

CHA₂DS₂-VASc score and the HAS-BLED score are means of assessing stroke and bleeding risk, respectively. The CHA₂DS₂-VASc score is a risk stratification scheme for adults with non-valvular atrial fibrillation to assess stroke risk which considers the following: age, gender, heart failure, hypertension, history of stroke or transient ischemic attack, vascular disease, and diabetes [74] (Table 28.2). Those with CHA₂DS₂-VASc score ≥ 2 are considered at high risk for stroke and in whom benefit from anticoagulation exceeds bleeding risk. Though not necessarily meant to be used in the ICU setting, it can potentially help determine overall stroke risk. HAS-BLED is a risk score intended to assess bleeding risk which must always be considered when placing a patient on anticoagulation therapy [74]. The HAS-BLED

Table 28.2 CHA₂DS₂-VASc score and stroke risk [145]

	Risk factor	Points
C	Congestive heart failure (or left ventricular dysfunction)	1
H	Hypertension	1
A ₂	Age ≥ 75 years	2
D	Diabetes	1
S ₂	Stroke or transient ischemic attack history	2
V	Vascular disease (e.g., peripheral arterial disease, myocardial infarction)	1
A	Age 65–74 years	1
Sc	Sex category (i.e., female gender)	1

CHA ₂ DS ₂ -VASc score	Unadjusted ischemic stroke rate (% per year)
0	0.2%
1	0.6%
2	2.2%
3	3.2%
4	4.8%
5	7.2%
6	9.7%
7	11.2%
8	10.8%
9	12.2%

score assigns 1 point for the presence of each of the following bleeding risk factors: **h**ypertension, **a**bnormal renal and/or liver function, **p**revious **s**troke, **b**leeding history, **l**abile INR, **e**lderly and concomitant **d**rugs, and/or alcohol abuse with a score of ≥3 indicating a high risk of bleeding (Table 28.3).

The applicability of both schemes in ACHD has been examined [75–77]. The Anticoagulation Therapy in Congenital Heart Disease (TACTIC) study was a retrospective multicenter trial examining the incidence of thromboembolic events in adults with CHD and atrial arrhythmias and the predictive capacity of the CHA₂DS₂-VASc and HAS-BLED scores [75]. There were 482 patients managed on a variety of antiplatelet/anticoagulation schemes, including no therapy. The thromboembolic event rate was 8.7% over an average follow-up time of 11.3 ± 9.4 years after the qualifying arrhythmia. The CHA₂DS₂-VASc score was not predictive of thromboembolism, but higher congenital heart lesion complexity correlated with higher thromboembolic risk. Bleeding events occurred in 8.3% of patients, and HAS-BLED was an independent predictor of major bleed on multivariable analysis.

That the CHA₂DS₂-VASc score did not adequately predict thromboembolic risk in adults with CHD may be a reflection of a distinct, heterogeneous patient population with wide variation of underlying lesions and younger age. The average age of ACHD patients who experience atrial arrhythmias and the age at which they present with stroke are significantly younger than that of the general population [70, 78, 79]. The authors suggest the CHA₂DS₂-VASc score could be modified to include disease complexity as defined by the Bethesda criteria [80] which is consistent with recent guidelines on arrhythmia management in ACHD that recommend disease complexity be considered in guiding anticoagulation strategy. In this document, long-term

Table 28.3 HAS-BLED score and risk of bleeding [146]

	Risk factor	Points
H	Hypertension	1
A	Abnormal renal and/or liver function	1 or 2
S	Stroke	2
B	Bleeding predisposition or diathesis	1
L	Labile INR	2
E	Elderly age > 65 years	1
D	Drugs (aspirin or NSAIDs) and/or excessive alcohol	1 or 2

HAS-BLED score	Bleeds per 100 patient-years
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5–9	Insufficient data

INR international normalized ratio, *NSAIDs* nonsteroidal anti-inflammatory drugs

Hypertension is defined as systolic blood pressure >160 mmHg. Abnormal renal function is defined as the presence of chronic dialysis, renal transplantation, or serum creatinine ≥ 200 micromol/L. Abnormal liver function is defined as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin more than two times the upper limit of normal, plus one or more of aspartate transaminase, alanine transaminase, and/or alkaline phosphatase more than three times the upper limit normal). Bleeding predisposition includes chronic bleeding disorder or previous bleeding requiring hospitalization or transfusion. Labile INRs for a patient on warfarin include unstable INRs, excessively high INRs, or <60% time in therapeutic range

anticoagulation is a Class I recommendation for intra-atrial reentry tachycardia or atrial fibrillation in patients with highly complex CHD and Class IIA recommendation for those with moderate forms of CHD. For patients with simple non-valvular forms of CHD with intra-atrial reentry tachycardia or atrial fibrillation, anticoagulation, aspirin, or no thromboprophylaxis is a Class IIB recommendation [81].

In practice, there is no risk stratification scheme that completely captures stroke risk for adults with CHD and atrial arrhythmias, especially in the ICU setting, but underlying disease complexity and risk factors as described by the CHA₂DS₂-VASc score as well as HAS-BLED score can be used in guiding therapy especially as the patient transitions out of the ICU setting and into ambulatory care. In general, if a new-onset atrial fibrillation or flutter continues for more than 48 h in the ICU, anticoagulation is recommended, and any attempt at rhythm control should be preceded by transesophageal echocardiography to rule out intracardiac thrombosis. Anticoagulation should be instituted and continued for at least 4–6 weeks afterward. However, bleeding risk in the ICU patient may be prohibitive due to platelet dysfunction from renal failure, thrombocytopenia, liver disease/cirrhosis, coagulopathy, etc., and benefit must be balanced against risk.

Patients who are admitted to the ICU on anticoagulation for stroke prophylaxis in the setting of atrial arrhythmias should have anticoagulation continued. Consideration should be made to switching to a reversible short-acting agent

such as intravenous heparin if invasive procedures are anticipated. Gaps in anticoagulation can be managed for short periods of time as day-to-day stroke risk is relatively low.

28.4 Prosthetic Valves in Adults with Congenital Heart Disease

Valve replacement surgery is one of the most common types of cardiac surgery in ACHD [82]. Thromboembolic complications and anticoagulation-related bleeding are major contributors to morbidity and mortality after valve replacement surgery [83].

Management of patients with prosthetic valves in the ICU may involve the post-operative management of those who undergo valve replacement or long-term complications such as valve thrombosis, embolic phenomenon, or infective endocarditis. Furthermore, the anticoagulation management of patients with mechanical valve prostheses can pose special challenges for patients in the ICU who are admitted for noncardiac reasons, and interruption of anticoagulation may be necessary.

28.4.1 Thromboembolism Prophylaxis

The highest risk of thromboembolic complications occurs within the first 3 months of surgery for both bioprosthetic and mechanical valve prostheses [84]. Atrial arrhythmias, a common comorbidity found in conjunction with valvular heart disease, can further increase the risk of thromboembolic stroke. After implantation of a mechanical prosthetic valve, anticoagulation with warfarin, a vitamin K antagonist, is recommended which has been proven to decrease risk of thrombosis and thromboembolism [85]. The addition of antiplatelet therapy can decrease the risk of systemic embolism or death in patients with mechanical heart valves [86]. The American College of Cardiology (ACC)/American Heart Association (AHA) recommends anticoagulation in patients with mechanical valve prostheses with warfarin at a target INR of 2.5 in the aortic and 3.0 in the mitral positions in the absence of other risk factors (Class I Ib) as well as a low-dose antiplatelet agent (Class IA) [87]. The On-X mechanical prosthesis (On-X Life Technologies Inc., Austin, Texas) in the aortic position can be maintained at a lower target INR 1.5–2.0 (Class I Ib) after 3 months of standard therapy [88]. Direct oral anticoagulants (DOACs) should not be used in patients with mechanical valves. A recent trial investigating dabigatran vs. warfarin after aortic or mitral mechanical valve replacement was terminated early after demonstrating excess thromboembolic events and bleeding in the dabigatran arm [89].

The risk of thromboembolism after bioprosthetic valve surgery is not as high as mechanical valve replacement surgery, but there is an increased risk of events in the first 3–6 months after surgery [84, 90]. Early thrombogenicity of bioprosthetic valves can be attributed to incomplete endothelialization [91], so therefore some form of antiplatelet and/or antithrombotic therapy is recommended after

bioprosthetic valve surgery. Anticoagulation with a warfarin for 3 months after bioprosthetic mitral or aortic valve replacement surgery with a target INR 2.5 is considered a reasonable strategy (IIa recommendation) to address risk of early postoperative thrombotic risk [88]. The role of DOACs in the anticoagulation management of patients with bioprosthetic valves is not yet defined.

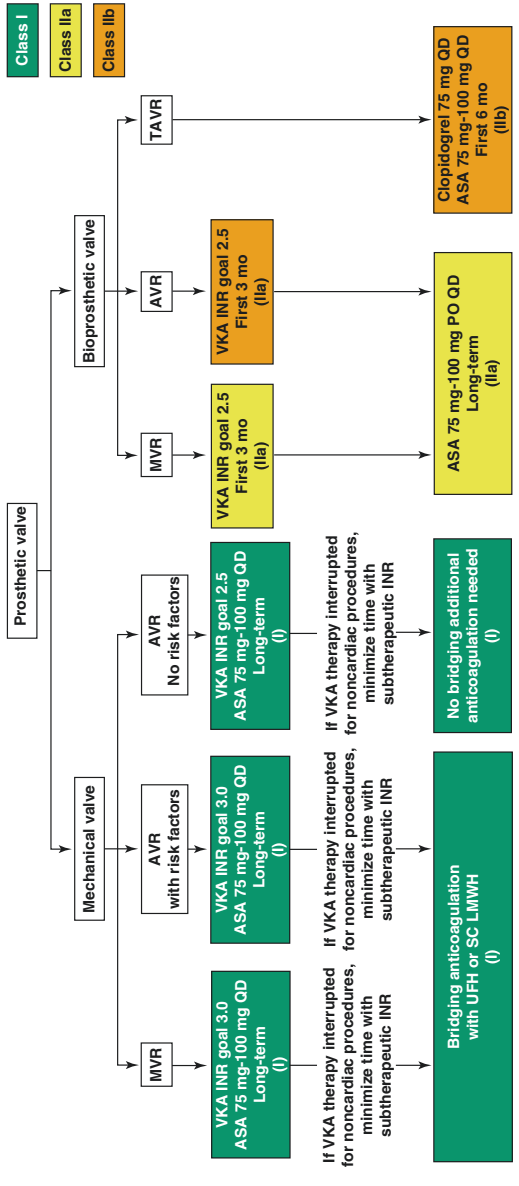
28.4.2 Bridging Anticoagulation Therapy

Anticoagulation management including cessation and bridging therapy when there is interruption should take into account the type of procedure for which interruption is being considered, bleeding risk, as well as type, location, and number of prosthetic heart valves [88]. Minor procedures such as cataract removal, cutaneous biopsy, or dental procedures generally do not require cessation of anticoagulation. Critically ill patients in the ICU may have predisposition toward hemorrhage as discussed above including sepsis, thrombocytopenia, and renal and/or liver failure. The ACC/AHA guidelines do not recommend bridging when anticoagulation is interrupted in patients with mechanical aortic valves and no other risk factors for thrombosis [87].

When oral anticoagulation with warfarin is temporarily interrupted, bridging therapy with intravenous UFH or subcutaneous LMWH can be considered for higher-risk patients including those with mechanical mitral valve prostheses or patients with aortic mechanical valve prosthesis and an additional risk factor (e.g., atrial fibrillation, previous thromboembolism, hypercoagulable state, older-generation mechanical valve, left ventricular systolic dysfunction, or >1 mechanical valve) [92], but decisions should be made on an individual basis. Data supports the use of LMWH for bridging as safe and effective in mechanical heart valves [93, 94] although intravenous unfractionated heparin UFH may be preferable in the ICU setting given its short half-life. Figure 28.1 summarizes the ACC/AHA recommendations for antithrombotic therapy in prosthetic valves [87].

28.4.3 Prosthetic Valve Thrombosis and Stenosis

Mechanical prosthetic valve obstruction can be caused by thrombosis, pannus, or a combination thereof and can present as progressive dyspnea or in extremis with severe pulmonary edema [95]. Transthoracic echocardiogram is the first-line imaging modality (including Doppler gradient across the valve), but transesophageal echocardiography is often necessary to assess leaflet motion. Computed tomography and fluoroscopy are useful to evaluate for thrombosis, but differentiation between thrombosis and pannus is challenging and can be difficult to distinguish [96]. Clinical history is important in the evaluation including time from surgery, history of inadequate anticoagulation, and acuity of symptoms as thrombosis more often presents acutely compared to pannus. Infective endocarditis must be excluded. Once thrombosis is diagnosed, anticoagulation should be instituted. Mechanical



Risk factors include AF, previous thromboembolism, LV dysfunction, hypercoagulable condition, and older-generation mechanical AVR. For the strength of recommendations: Class I means the procedure/treatment should be performed/administered. Class IIa means it is reasonable to perform the procedure/administer treatment. Class IIb means the procedure/treatment may be considered. Class III means that the procedure to treatment is not useful/effective and may be harmful. For the level of evidence: Level A means multiple populations evaluated; data derived from multiple randomized clinical trials or meta-analyses. Level B means limited populations evaluated; data derived from a single randomized trial or nonrandomized studies. Level C means very limited populations evaluated; only consensus opinion of experts, case studies, or standard of care.

AF: atrial fibrillation; ASA: aspirin; AVR: aortic valve replacement; INR: international normalized ratio; LMWH: low-molecular-weight heparin; MVR: mitral valve replacement; PO: by mouth; QD: every day; SC: subcutaneous; TAVR: transcatheter aortic valve replacement; UFH: unfractionated heparin; VKA: vitamin K antagonist.

Fig. 28.1 ACC/AHA recommendations for anticoagulation of prosthetic heart valves [87, 88]. *Note:* Updates in 2017 include [88]: • IIa recommendation from IIb for VKA after bioprosthetic AVR, • On-X AVR without risk factors target INR 1.5–2.0 (IIb, LOE B-R), and • IIb recommendation for VKA INR target 2.5 for 3 months after TAVR

left-sided prosthetic valve obstruction has a high mortality rate and requires urgent therapy including fibrinolysis or surgery (Class Ib) [88].

Bioprosthetic valve thrombosis usually presents in a more subacute manner with progressive stenosis and can occur years after surgery [97]. Evaluation is similar as above with the use of transesophageal echocardiography to better evaluate for thrombosis. Again, infective endocarditis must be ruled out. Bioprosthetic valve thrombosis has been shown to respond to warfarin [98] which can be considered as an initial treatment in patients who are hemodynamically stable (Class IIa) [88].

Patients with a prosthetic valve and stroke should undergo work-up for cardioembolic stroke including evaluation of the prosthetic valve by echocardiogram. Specifically, transesophageal echocardiography is recommended to better evaluate valve function, evidence of thrombosis or vegetation, or any other source of embolism including a careful interrogation of the left atrium, left atrial appendage, and aorta for atherosclerotic plaque. If thromboembolism occurred in the setting of inadequate antithrombotic therapy, institution of adequate therapy is the first step [87]. If thromboembolism occurred despite adequate antithrombotic therapy, consideration should be given to augmenting therapy which includes the addition of low-dose aspirin if maintained only on therapeutic warfarin, increasing the goal INR, or adding warfarin for those who were maintained on aspirin alone (i.e., bioprosthetic valves) [87].

28.5 Special Consideration of Thrombosis in Adult Patients with Fontan Circulation

It has long been recognized that thrombosis in the patient with Fontan circulation is associated with significant mortality and morbidity. A recent systemic review by Alsaied in 2017 of 28 studies, 6707 patients, and a mean follow-up time from Fontan of 8.23 ± 5.42 years found thrombosis and bleeding to be the fifth most common cause of death accounting for 10% of the 1000 deaths reported [19].

The overall incidence of thrombosis in the patient with Fontan circulation is about 12% in recent reports [15, 18] and 5.2% in a meta-analysis looking at extracardiac Fontans only [13]. Earlier reports describe a 3–33% incidence with stroke in 1.4–3.6% [14]. The discrepancy in reported incidence is secondary to the variability in the population studied, the time from the Fontan procedure, the method of thrombosis detection, the location of the thrombosis investigated (i.e., all thrombosis vs. pulmonary emboli vs. cerebral vascular event), and whether the study investigated clinically evident or silent thrombosis. Although these reviews are an important source of observational data, their heterogeneous designs limit the ability to draw conclusions from which clinical practice guidelines can be generated. They have, however, generated the following important observations:

- There appears to be two peaks in the incidence of thrombosis post Fontan: early (0–6 months) [99] and late (5–15 years post Fontan) [4–6, 9, 11, 16].
- Thrombosis post Fontan is most commonly found in the Fontan itself, intracardiac (systemic venous atrium, pulmonary venous atrium, hypoplastic ventricle)

and pulmonary arteries, although it has been reported as well in the ligated pulmonary artery stump, hypoplastic aortic root, and coronary arteries and associated with heparin-induced thrombocytopenia (HIT) [7, 15, 17]. Silent pulmonary emboli have also been described [8].

- Risk factors supported by focused retrospective observational studies include atriopulmonary type of Fontan connection, bilateral bidirectional cavopulmonary anastomoses, hypoplastic cardiac chambers with flow stasis, presence of a blind-ended pulmonary artery stump, and a history of previous thrombosis. Additional potential factors supported by general retrospective observational studies or expert opinion include protein-losing enteropathy, prolonged pleural effusions, prolonged immobilization, ventricular dysfunction, arrhythmia, presence of thrombogenic foreign material, atrial-level fenestration, Kawashima connection, and an abnormal thrombophilia profile [14]. Additional risk factors for stroke identified in adults with CHD that include the Fontan include systemic arterial hypertension, atrial fibrillation, iron deficiency anemia, microcytosis, and prior phlebotomy [3]. Additional risk factors for pulmonary embolus include age, female gender, low oxygen saturation, ventricular dysfunction, and low systolic flow velocities in the pulmonary arteries [10, 47].

It is not surprising that the adult with Fontan circulation has a propensity to thrombosis, especially in the ICU setting. The factors described above of altered blood flow, blood component abnormalities, and endothelial dysfunction are intrinsic to the Fontan. Several studies have evaluated coagulation proteins in single-ventricle patients and have shown an infantile pattern, namely, lower levels of both pro- and anticoagulant proteins, namely, low protein C and suppression of the thrombomodulin-protein C-protein S pathway [32, 35, 36, 40]. In addition several studies have documented elevated factor VIII after the Fontan [34, 37, 41]. Odegard in 2009 showed lower than control levels of both pro- and anticoagulation proteins from Norwood stage I up to Fontan [39]. After the Fontan protein C stayed low, and factor VIII was found to be significantly higher than controls; 42% of Fontan patients had FVIII >160%. There was no correlation with hemodynamics, hepatic synthetic function, or hepatocellular dysfunction. The speculation is that high factor VIII, low protein C plus Fontan physiology puts patients at risk of thrombosis over a lifetime.

Knowing that the Fontan patient is prone to thrombosis, what data is available regarding thromboprophylaxis? Two recent meta-analyses warrant mention. In 2011 Marrone reviewed 20 studies, 1075 patients who had extracardiac Fontans [13]. The average time from Fontan in the studies was 2 months to 12 years. The overall thrombotic rate was 5.2%, 4.5% in those who received aspirin alone and 5% in those receiving warfarin with or without aspirin. Alsaied in 2015 reviewed 10 studies, 1200 patients with all types of Fontans [15]. The average time from Fontan in the combined studies was 7.1 years. The overall thrombotic rate was 11.3%: 18.6% in those receiving no thromboprophylaxis, 8.6% in those receiving aspirin only, and 9% in those receiving warfarin. From these meta-analyses, it appears that some form of thromboprophylaxis is protective but that warfarin is not superior to aspirin. Whether or not thrombosis is less frequent in the extracardiac Fontan warrants further investigation.

When considering the adult Fontan patient, several limitations in these meta-analyses must be acknowledged. The average follow-up from the Fontan in the two meta-analyses was less than 15 years, giving little information about the risk of thrombosis and effect of thromboprophylaxis in the third and fourth decade of life. Second, the studies address neither time in therapeutic range for warfarin patients nor aspirin resistance in the patients receiving aspirin. Third, additional risk factors for thrombosis were not addressed in either meta-analysis.

Carefully considering the currently available, albeit limited, data, the American Heart Association's 2013 Scientific Statement on Prevention and Treatment of Thrombosis in Pediatric and Congenital Heart Disease makes the following recommendations regarding prevention and treatment of thrombosis in the patient with a palliated single ventricle at all stages [14]:

1. Patients with a palliated single ventricle should undergo clinical assessment for the anatomic and hemodynamic risk factors for thrombus. Risk factors for thrombus (as listed earlier in this chapter) should be ameliorated (i.e., arrhythmias, ventricular dysfunction, prolonged immobilization) and minimized (blinded pulmonary artery stump, prolonged immobilization) when possible (Class I; Level of Evidence B).
2. For patients with a palliated single ventricle, serial clinical assessment and monitoring for changes in anatomic and hemodynamic thrombotic risk factor are indicated because risk factors may change over time (Class I; Level of Evidence C). New risk factor for thrombus should be ameliorated (i.e., arrhythmias, ventricular dysfunction, prolonged immobilization) and minimized (prolonged immobilization) when possible (Class I; Level of Evidence C).
3. Patients with a palliated single ventricle should be monitored for thrombosis with periodic transthoracic echocardiography (with focused attention to the identification of thrombi) as part of routine follow-up assessments (Class I; Level of Evidence C).
4. For patients with a palliated single ventricle, if thrombosis is suspected on clinical grounds or from transthoracic echocardiography, diagnostic confirmation with transesophageal echocardiography, MRI, computed tomography, computed tomographic angiography, nuclear medicine lung perfusion scan, or venography/angiography can be useful (Class IIa; Level of Evidence C).
5. For patients with a palliated single ventricle, other imaging modalities (in addition to echocardiography) used to detect thrombosis such as transesophageal echocardiography or MRI may be considered for surveillance for patients with anatomic or hemodynamic risk factors (Class IIb; Level of Evidence C).
6. Initiation of antithrombotic therapy or an increase in the magnitude of antithrombotic therapy for prophylaxis (change in agent, i.e., from antiplatelet to anticoagulant or higher target levels) is probably reasonable if anatomic or hemodynamic risk factors become present at any stage in the single-ventricle pathway (Class IIa; Level of Evidence C).
And in addition specifically for Fontan patients:
7. Long-term antiplatelet therapy for prevention of thrombosis is reasonable after the Fontan procedure (Class IIa; Level of Evidence C).

8. Prophylaxis with warfarin or LMWH may be reasonable in infants and children for 3–12 months after the Fontan procedure (Class IIb; Level of Evidence C).
9. Long-term therapy with warfarin may be reasonable after the Fontan procedure for patients with anatomic or hemodynamic risk factors (Class IIb; Level of Evidence C).

Several additional comments are warranted regarding thromboprophylaxis in the Fontan patient. No method of thromboprophylaxis is 100% effective with a thrombosis rate of currently about 12% [15, 18]. Thrombosis prevention in the Fontan patient is more than pharmacotherapy. Understanding and mitigating risk factors as well as diagnosing and treating thrombosis as early as possible are essential. Thrombosis risk in the Fontan patient is not constant over time. As risk factors increase, antithrombotic therapy should be reassessed and readjusted. Continued assessment of risk over time [9] with adjustment of antithrombotic therapy based on current risk assessment is essential. Finally, as is well known to ACHD physicians, warfarin is a medication with a narrow therapeutic window and many drug-drug interactions. The DOACs are discussed below. They may have promise in the adult with Fontan circulation [100], but safety and efficacy have not yet been established especially in the Fontan with liver disease, thrombocytopenia, and/or protein-losing enteropathy where concerns of bleeding are real.

28.6 Anticoagulant Therapy

The following section will provide specific information regarding mechanism of action, pharmacokinetics, dosing, monitoring, and associated harms for commonly used anticoagulants. It is important to note that the predominant risk associated with anticoagulation therapy is hemorrhage. To minimize this bleeding risk, concurrent antiplatelet therapy should be avoided, if possible.

28.6.1 Unfractionated Heparin

Unfractionated heparin (UFH) is extracted from bovine lung or porcine intestine and is composed of a heterogeneous mixture of highly sulfated glycosaminoglycans [101]. UFH itself has no intrinsic anticoagulant effect but instead acts through the binding of antithrombin (AT) potentiating the AT anticoagulant activity over 1000-fold inactivating coagulant factors IIa (thrombin), Xa, XIa, and XIIa [102–105]. UFH is parentally available as either a continuous intravenous infusion or a subcutaneous injection. The half-life is short and estimated at 1.5 ± 0.5 h [106]. Unfortunately, UFH interacts with other plasma proteins, endothelial cells, and macrophages which can alter the pharmacokinetics with a resultant high inter- and intra-patient dose response.

Intravenous UFH therapy is typically started as a bolus (80 units/kg, maximum bolus 4000–5000 units) followed by the initiation of a continuous infusion (18 units/

kg/h, maximum initial infusion 1000–2000 U/h). If a patient has a low AT level (i.e., congenital deficiency, acquired deficiency secondary to losses from nephrotic syndrome, draining chylous effusion, consumption, or asparaginase therapy), higher UFH doses may be required. The two most common assays used to monitor UFH include the aPTT and the UFH anti-Xa level. Both tests have pitfalls when used to monitor UFH as well as poor correlation. The therapeutic goal for the aPTT is 1.5–2.5 times control (60–85 seconds), and the UFH anti-Xa goal is 0.3–0.7 units/mL. See Table 28.4 for the dose titration of UFH using these laboratory markers.

The aPTT is not a direct measure of the UFH effect and can be impacted by many other parameters that could result in either an over or underestimation of the true UFH effect. For example, an elevated factor VIII or fibrinogen (acute phase reactants) will shorten the aPTT making it appear that the patient is heparin resistant. Alternatively a deficiency in a coagulation factor (i.e., from liver failure or consumption) or the presence of an antiphospholipid antibody will prolong the aPTT making it appear that the patient is therapeutic on UFH. The UFH anti-Xa level provides a more direct measure that is not impacted by the above factors, although the UFH anti-Xa level does not reflect additional anticoagulant targets of UFH. The activated clotting time (ACT) is used to monitor higher heparin doses given to patients undergoing cardiopulmonary bypass or cardiac catheterization. The ACT is a whole-blood clotting time that is simple to perform with a rapid turnaround time. It is more sensitive to a wider range of heparin doses than the PTT and is impacted by the same factors as the PTT, and additionally thrombocytopenia prolongs the ACT.

Table 28.4 The 4T's clinical probability score for heparin-induced thrombocytopenia [120]

	Score = 2	Score = 1	Score = 0
Thrombocytopenia	Platelet count fall >50% and platelet nadir $\geq 20 \times 10^9/L$	Platelet count fall 30–50% or nadir $10\text{--}19 \times 10^9/L$	Platelet count fall <30% or a platelet nadir $<10 \times 10^9/L$
Timing of platelet count fall	Clear onset 5–10 days post-heparin or within 1 day with a prior heparin exposure within 30 days	Consistent with days 5–10 fall but not clear (missing data), onset post day 10; or fall within 1 day with a prior heparin exposure 30–100 days	Platelet count fall <4 days without recent heparin exposure
Thrombosis	New confirmed thrombosis can be venous or arterial, skin necrosis at heparin injection site, anaphylactic reaction to IV heparin bolus	Progressive or recurrent thrombosis, suspected thrombosis, erythematous skin lesions at heparin injection sites	None
Other causes for thrombocytopenia	None apparent	Possible	Definite

HIT probability score: low, ≤ 3 points; intermediate, 4–5 points; high, 6–8 points

Adapted from Lo GK et al. [120]

Full reversal of heparin can be obtained with the use of protamine sulfate, a basic protein that binds heparin and forms a salt [105]. Approximately 1 mg of protamine will neutralize 100 units of UFH [105]. Calculations should be made based on the total amount of heparin received in the prior 2–2.5 h [105]. Adverse events such as hypotension and bradycardia can be minimized with slow administration of protamine.

The benefits of UFH include the short half-life and the ability to completely reverse the anticoagulation effect. Additionally UFH can be used in the setting of renal failure where LMWHs cannot. In clinically unstable patients at risk for hemorrhage who require anticoagulation, UFH should be strongly considered. Transition to an alternative anticoagulant should occur once the patient is clinically stable. Nonhemorrhagic complications associated with UFH include HIT/HITT (see separate section) and osteopenia with long-term use [107, 108].

28.6.2 Low Molecular Weight Heparin

Low molecular weight heparins (LMWH) are derived from UFH by chemical or enzymatic depolymerization and contain shorter-length polysaccharide chains. Similar to UFH, LMWH exert an anticoagulant effect through binding AT and potentiating the AT anticoagulant activity, but as compared to UFH, there is a reduced inhibitory activity against factor IIa (thrombin) relative to factor Xa. LMWH are administered as a subcutaneous injection. The PK properties are more stable as compared to UFH. The half-life is 3–6 h and the LMWH anti-Xa levels peak 3–5 h after dosing. LMWH is predominantly cleared by the kidneys.

Dosing will vary based on the exact LMWH that is used. Common preparations include enoxaparin, 1 mg/kg/dose every 12 h, or 1.5 mg/kg once daily; in obesity, use ideal body weight to calculate the dose and tinzaparin 175 anti-Xa IU/kg daily. Additionally, similar to UFH if a patient has a low AT level, higher doses of the LMWH may be required.

Routine monitoring is not recommended except for extreme obesity or in the setting of renal insufficiency. When monitoring the LMWH, anti-Xa peak level is used with a goal of 0.5–1 units/mL (drawn 4–6 h postinjection). LMWH can be partially reversed (approximately 70%) with protamine. LMWH should not be used in the setting of renal failure. Nonhemorrhagic complications associated with LMWH are similar to UFH. HIT has been reported with the use of LMWH, but it is thought to be less frequent than UFH [109]. Long-term LMWH use is associated with less bone loss than UFH [105].

28.6.3 Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is an immunologic complication of heparin therapy. Antibodies are formed against complexes of heparin and an endogenous platelet protein, platelet factor 4 (PF4) [110]. It is postulated that the binding of

antibodies to the heparin-PF4 complex results in increased platelet reactivity with a resultant prothrombotic state [110]. This disorder is characterized by thrombocytopenia (HIT) and sometimes thrombosis (HITT) that can occur in any vascular bed and can be catastrophic. Interestingly, while the immune reaction is relatively common post-heparin exposure (8–50%), with the highest in those undergoing cardiac surgery (25–50%), only a small portion of patients will actually develop the clinical consequences of thrombocytopenia and thrombosis [111, 112]. Overall the incidence of HIT is estimated to be approximately 0.02–3% of patients [111–114]. The incidence is influenced by the clinical setting, type of heparin used, and dose [115]. Prophylactic dose UFH has a higher risk of HIT versus prophylactic LMWH [114]. Untreated HIT has a mortality of 20–30% [116, 117].

The diagnosis of HIT is based on clinical criteria. Multiple scoring systems have been developed [118–120]. The most commonly used is the 4T's clinical probability score (Table 28.5) [120]. Classically, HIT is characterized by symptoms appearing 5–10 days post-heparin exposure with a 50% fall in the platelet count (rarely is the platelet count <50,000/ μ L), and there can be venous or arterial thrombosis. Laboratory testing can be supportive in making the diagnosis and includes ELISA for the heparin-P4 antibodies and the serotonin-releasing assay. The ELISA is readily available with a fast turnaround time. This test is highly sensitive but has a significant false-positive rate. The ELISA is most helpful in ruling out the diagnosis with a negative assay. The serotonin-releasing assay is highly specific and sensitive; it measures platelet reactivity in the presence of the patient's plasma. Unfortunately, it is only performed in a few highly specialized laboratories so is not readily available for most clinicians.

The treatment of HIT includes the removal of all heparin from the patient including from central lines and avoidance of LMWH. Anticoagulation should be initiated (even without thrombosis) with a non-heparin anticoagulant such as a direct thrombin inhibitor (i.e., bivalirudin or argatroban) [121]. In this setting, warfarin should never be initiated by itself due to an increased risk of skin necrosis and further thrombotic events. Warfarin can be initiated once the platelet count has normalized and overlapped with the non-heparin anticoagulant until the INR is therapeutic. The median time for platelet recovery is approximately 4 days. Fondaparinux, a synthetic pentasaccharide LMWH, is also commonly used off-label for the treatment of

Table 28.5 Unfractionated heparin dose titration [147]

aPTT (s)	UFH Anti-Xa (units/mL)	Dose adjustment	Lab monitoring
<50	<0.1	Bolus: 50 IU/kg Increase infusion rate by 10%	4 h post rate change
50–59	0.1–0.29	Increase infusion rate by 10%	4 h post rate change
60–85	0.3–0.7	No change	4 h then q24 hours
86–95	0.71–0.9	Decrease infusion rate by 10%	4 h post rate change
96–120	0.91–1	Hold infusion for 30 min Decrease infusion rate by 10%	4 h post rate change
>120	>1	Hold infusion for 60 min Decrease infusion rate by 15%	4 h post rate change

Adapted from Monagle P et al. [147]

HIT. Although rarely HIT has been reported with the use of fondaparinux [122]. The direct oral anticoagulants (DOACs) have not been studied in HIT, so their use in this clinical setting would be considered off-label and without sufficient clinical supporting data.

The duration of anticoagulation in HIT is determined by the presence of thrombosis. For those patients with only thrombocytopenia, there remains a high risk of thrombosis for 2–4 weeks after developing HIT. Anticoagulation should be continued during this high-risk time [121]. For patients with a thrombosis, anticoagulation should be continued for 3 months [121]. In general, HIT antibodies are transient with a median time of disappearance of 50–85 days without clear evidence of an amnestic immune response with reexposure [123]. In general, patients with a history of HIT should not be reexposed to UFH or LMWH. The one exception is for procedures where the use of UFH is favored over other anticoagulants like CPB if repeat HIT antibody testing is negative. In those patients with a history of HIT who have demonstrated resolution of the HIT antibodies, a short exposure to UFH during CPB is considered acceptable [121]. This strategy does not apply to those patients with persistent antibodies, however.

28.6.4 Direct Thrombin Inhibitors: Argatroban or Bivalirudin

Argatroban and bivalirudin are parenteral direct thrombin inhibitors and are typically used in the setting of HIT/HITT when heparin needs to be avoided. Bivalirudin reversibly binds the active catalytic and substrate binding site of thrombin. It has a half-life of 25 min and has approximately 20% renal clearance. The initial dose is 0.15–0.2 mg/kg/h. It is typically monitored by the aPTT titrated to 1.5–3 times control, but the ACT has also been used. A limited number of laboratories are running direct thrombin inhibitor assays, although this has not yet become standard of care.

Argatroban reversibly binds the active catalytic site of thrombin. It also has a very short half-life of 45 min. It is predominantly metabolized in the liver so should not be used in the setting of hepatic failure. The initial dose is 2 mcg/kg/min. It is titrated via the aPTT to 1.5–3 times control; the ACT has also been used. No antidote exists for the reversal of bivalirudin or argatroban, but both have very short half-lives, so discontinuation of the infusion should be sufficient for most forms of bleeding.

28.6.5 Fondaparinux

Fondaparinux is a synthetic analog of the AT-binding pentasaccharide found in heparin and LMWH. The structure was modified to enhance its affinity for AT increasing the specific activity and half-life. Unlike UFH or LMWH, fondaparinux has no inhibitory activity against factor IIa (thrombin) and only inactivates factor Xa.

Fondaparinux is administered via a subcutaneous injection. The half-life is longer than LMWH at 17 h. There is minimal binding to other proteins. The clearance

is exclusively renal. A steady state is reached after the third or fourth daily dose. Dosing is guided by weight: <50 kg 5 mg daily, 50–100 kg 7.5 mg daily, and >100 kg 10 mg daily. Routine coagulation monitoring is not recommended. If a level is needed, specific assays calibrated for fondaparinux should be used [124]. Similar to LMWH, monitoring is achieved by measuring fondaparinux anti-Xa peak level with a goal of 0.5–1 mg/L (drawn 4 h post).

There are no reversal agents available for fondaparinux. Unlike other forms of heparin, protamine does not bind fondaparinux. There are reports of using various hemostatic therapies (prothrombin complex concentrates, activated prothrombin complex concentrates, or recombinant factor VIIa) to treat life-threatening bleeding secondary to fondaparinux [125]. Due to the long half-life and lack of a reversal agent, this medication should only be utilized in patients who are clinically stable with a low risk of hemorrhage. It should not be used in patients with renal insufficiency.

28.6.6 Warfarin

Warfarin is a vitamin K antagonist and interferes with the cyclic conversion of vitamin K through the inhibition of vitamin K epoxide reductase. This results in a decrease in the posttranslational γ -carboxylation of vitamin K-dependent clotting factors which is imperative for biologic function. This impacts coagulation factors II, VII, IX, and X and anticoagulant proteins C and S [126]. Warfarin absorption is primarily gastric and is complete within 4 h of administration. It has a very long half-life of 36–42 h. In general, warfarin is initiated with an anticoagulation “bridge” because patients are initially prothrombotic due to the variable half-lives of anti- and procoagulant proteins lowered by warfarin.

Initial dosing is individualized considering the patient’s cardiac function, nutritional status, prior warfarin dosing, current medications, and hepatic function. Typical maintenance dosing is 2–5 mg/day. Patients with Fontan circulation may require less warfarin. Patients >60 years of age may require less warfarin due to changes in warfarin metabolism. The warfarin dose is titrated via the international normalized ratio (INR). The INR goal is dictated by the clinical indication for warfarin but is commonly 2–3.

There are multiple choices available for warfarin reversal including vitamin K (oral, intravenous, or subcutaneous), non-activated prothrombin complex concentrate (PCC, Kcentra), or fresh frozen plasma. How warfarin reversal is completed is determined by the severity of bleeding and the patient’s thrombotic risk associated with reversal [127]. In the setting of severe, life-threatening bleeding, vitamin K replacement should be augmented with the use of either Kcentra or fresh frozen plasma. Kcentra contains concentrated non-activated coagulation factors II, VII, IX, and X and anticoagulant proteins C and S and is FDA approved for the urgent reversal of warfarin. Kcentra dosing is determined by the INR and the patient’s body weight: INR 2–<4, 25 units FIX/kg (maximum 2500 units); INR 4–6, 35 units FIX/kg (maximum 3500 units); and INR 6, 50 units FIX/kg (maximum 5000 units). The

benefit to using a Kcentra as opposed to fresh frozen plasma is that a much smaller volume is given to the patient and replaces only those coagulation and anticoagulation proteins impacted by warfarin.

28.6.7 Direct Oral Anticoagulants

The first direct oral anticoagulant (DOAC) received FDA approval in 2010. All of the DOACs bind directly to a key coagulant protein to inhibit fibrin formation. There are two broad categories for mechanism of action including direct anti-Xa inhibitors (rivaroxaban, apixaban, and edoxaban) and direct thrombin (IIa) inhibitors (dabigatran). The advantage to all of the DOACs is more predictable pharmacokinetics with a wide therapeutic window and limited drug-drug interactions as compared to warfarin. They also have a relative rapid onset of action and shorter half-lives as compared to warfarin. Dosing of DOACs varies by the specific drug.

Table 28.6 provides general dosing schema for each DOAC. For all of the DOACs, dosing needs to be adjusted in the setting of impaired renal clearance, and in significant renal impairment, DOAC use is not recommended.

The key advantage to predictable pharmacokinetics and a wide therapeutic window for DOACs is that routine therapeutic monitoring is not needed [128]. The disadvantage is that methods to monitor these medications are not readily available [128]. There are times when drug monitoring might be needed including in the setting of emergency surgery, breakthrough thrombosis, renal insufficiency, or bleeding [129]. Specialized laboratory assays for DOACs have been developed including a dilute thrombin time for dabigatran and anti-Xa assays that are drug calibrated for the anti-Xa inhibitors. The PT or PTT cannot reliably be used to monitor these medications.

In the setting of bleeding, all of the DOACs have relatively short half-lives of 10–12 h, so supportive care can be given, while the medication is wearing off in most cases. In the setting of life-threatening hemorrhage, reversal for dabigatran or consideration for other hemostatic therapies for oral Xa inhibitors needs to be considered. Currently, idarucizumab is the only FDA-approved DOAC reversal agent, and it is specific for dabigatran. Idarucizumab is a monoclonal antibody fragment

Table 28.6 Direct oral anticoagulant dosing

	Acute VTE	Atrial fibrillation	VTE prophylaxis
Rivaroxaban	15 mg twice daily for 21 days, followed by 20 mg daily	20 mg once daily	10 mg once daily
Apixaban	10 mg twice daily for 7 days, followed by 5 mg twice daily	5 mg twice daily	2.5 mg twice daily
Edoxaban	60 mg once daily after 5–10 days of initial therapy with a parenteral anticoagulant	60 mg once daily	
Dabigatran	150 mg twice daily, after 5–10 days of initial therapy with a parenteral anticoagulant	150 mg twice daily	220 mg once daily

All of the direct oral anticoagulants require dose adjustment for renal insufficiency

that binds dabigatran with an affinity that is 350 times greater than thrombin [130]. It can bind both free and thrombin-bound dabigatran and neutralizes its activity [130]. Clinically it is given as a one-time intravenous infusion with a complete reversal of the anticoagulant effect in minutes [131]. A rebound anticoagulant effect after the initial idarucizumab transfusion has been reported and needs to be considered in the setting of renal failure [132, 133]. Dabigatran can also be partially removed with hemodialysis [134]. For the Xa inhibitors, there is a reversal agent in development, andexanet alfa. It is a human factor Xa decoy protein but is not currently FDA approved [135]. There are reports of using various hemostatic therapies (prothrombin complex concentrates, activated prothrombin complex concentrates, or recombinant factor VIIa) to treat life-threatening bleeding secondary to DOACs [136, 137].

DOACs have been demonstrated to be efficacious and in the USA are approved for the use in stroke prevention from non-valvular atrial fibrillation, the treatment of DVT and PE, secondary prevention of DVT, and DVT prevention post-elective knee and hip surgery [138]. As mentioned above, at this time DOACs should not be used in the setting of mechanical heart valves. A clinical trial comparing dabigatran to warfarin in patients with either an aortic or mitral mechanical heart valve was halted early secondary to increased thrombotic and bleeding events in those patients receiving dabigatran as compared to warfarin [89]. A phase 2 clinical trial is currently underway using rivaroxaban in the setting of mechanical aortic valve replacement ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02128841) Identifier: NCT02128841). There is no data to support the routine use of DOACs for thrombosis prevention in Fontan patients though case reports have been published and a multicenter trial is underway.

28.7 Thrombolytic Therapy

The strongest indication for thrombolytic therapy includes either a life- or limb-threatening thrombotic event including stroke, prosthetic valve thrombosis, or a massive pulmonary embolism [139–144]. Significant bleeding (including intracranial hemorrhage) and thromboembolism are known complications of thrombolysis. Thrombolysis can be performed locally or systemically. Contraindications to thrombolytic therapy generally include active bleeding, an inability to maintain the platelet count $>75,000/\mu\text{L}$ or fibrinogen >100 mg/dL, a major operation or site of hemorrhage within 7–10 days, seizures within 48 h, central nervous system surgery/ischemia/trauma/hemorrhage within 30 days, or uncontrolled hypertension. These contraindications are not absolute, and the relative risks of thrombolytic therapy should be weighed against the potential benefits in each clinical situation.

When instituting thrombolytic therapy, baseline laboratory values should be obtained (CBC, PT, PTT, fibrinogen, and D-dimer) to assess for additional bleeding risks. For systemic sustained thrombolysis, these labs should be obtained prior to therapy and followed every 4–6 h during therapy. An increase in the D-dimer and a drop in the fibrinogen level are indicative of a “lytic” state. To minimize the risk of bleeding, if the fibrinogen level drops below 100 mg/dL, consider either holding

thrombolytic therapy or infusing cryoprecipitate as an external source of fibrinogen. The platelet count should be kept $>75,000/\mu\text{L}$. Tissue plasminogen activator (tPA) is currently the only thrombolytic agent available in the USA. Concomitant use of heparin has been used at either low or therapeutic dosing with therapeutic heparin usually continued after the thrombolytic is stopped. Due to the very high risk of hemorrhage during and immediately after thrombolysis, invasive procedures should be minimized.

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