Consensus Review of the Treatment of Cardiovascular Disease in People With Hemophilia A and B

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Abstract: With advances in care, increasing numbers of people with hemophilia (PWH) achieve near-normal life expectancies and present with typical age-related cardiovascular conditions. Evidence-based guidelines for medical or surgical management of cardiovascular conditions in individuals with hemophilia are limited. Published recommendations exist for the management of some common cardiovascular conditions (eg, ischemic heart disease, atrial fibrillation), but identifying optimal strategies for anticoagulant or antithrombotic therapy constitutes the primary challenge of managing nonoperative cardiovascular disease (CVD) in PWH. In general, as long as factor concentrates or other hemostatic therapies maintain adequate hemostasis, the recommended medical and surgical management of CVD in PWH parallels that in individuals without hemophilia. The presence of factor inhibitors complicates hemophilia management. Published outcomes of CVD treatment in PWH are similar to those in the general population. Specific knowledge about factor replacement, factor inhibitors, and disease-specific treatment distinguishes the cardiovascular care of PWH from similar care of individuals without this rare bleeding disorder. Furthermore, a multidisciplinary approach incorporating a hematologist with an onsite coagulation laboratory, ideally associated with a hemophilia treatment center, is integral to the management of CVD in PWH.

Key Words: hemophilia, cardiovascular diseases, cardiac surgery, atherosclerosis, atrial fibrillation

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Hemophilia A and B (hereafter collectively referred to as "hemophilia") encompass congenital deficiencies of the intrinsic pathway coagulation factors VIII (FVIII) and IX (FIX), respectively, with a variable risk for bleeding based on the type of hemophilia and the extent of factor deficiency. This risk for bleeding may complicate both medical and surgical management of congenital and acquired cardiovascular conditions in people with hemophilia (PWH), particularly those who are receiving anticoagulant or antithrombotic treatment or who require invasive measures for palliation or correction of a cardiovascular lesion.

PWH who receive repeated doses of factor as replacement may develop coagulation factor inhibitors that complicate the management of cardiovascular disease (CVD). Limited experience and a lack of evidence-based guidelines pose further challenges in the management of cardiovascular conditions in this population. As PWH are now achieving near-normal life expectancies due to advances in the management of their underlying disease, health care providers expect an increasing number of PWH presenting with typical cardiovascular conditions of the aging population.

This article examines the epidemiology and etiology of acquired CVD in PWH; summarizes the management of hemophilia, including hemostatic therapeutic options; and reviews the existing evidence and recommendations for managing various nonoperative and operative cardiovascular conditions in this unique population. Because of the specialized care required by these individuals, a multidisciplinary group of authors contributed to this work and provided a consensus set of recommendations for treating cardiovascular conditions in PWH. Other rare nonhemophilia congenital bleeding disorders lack data regarding CVD and are not considered in this consensus statement.

We performed a search of multiple sources to identify articles describing diagnoses and management of CVD in PWH. Table 1 lists the search categories and criteria used.

UNDERLYING DISEASE COURSE, LIFE EXPECTANCY, AND AGE-RELATED CARDIOVASCULAR DISEASE IN HEMOPHILIA

The clinical severity and bleeding risk in PWH depends on factor levels. Mild hemophilia is commonly defined by FVIII or FIX activity levels of greater than 5% (>0.05 IU/ml), constitutes 30–40% of hemophilia cases, and typically presents with bleeding episodes after hematologic stress (ie, surgery, vaginal delivery, or trauma).[1] Moderate hemophilia is defined by FVIII or FIX activity levels between 1% and 5% (0.01–0.05 IU/ml), occurs in 10% of PWH, and presents with spontaneous bleeds or bleeding after operation or trauma.[1] Severe hemophilia is characterized by FVIII or FIX activity levels of less than 1% (<0.01 IU/ml), occurs in 50% of PWH, and presents with spontaneous bleeding into joints and muscles and life-threatening (eg, intracranial) hemorrhage.[1] Although the majority of cases of hemophilia A and B are inherited (X-linked recessive), about one third of PWH who are newly diagnosed have spontaneous mutations without any family history of bleeding.[2]

Complications may develop because of factor replacement therapy in PWH. Importantly, up to one third of individuals with severe hemophilia A develop alloantibody inhibitors to FVIII after replacement therapy.[3] The incidence of FIX inhibitor development is much lower in individuals with hemophilia B (1–6%).[3] In hemophilia A, formation of FVIII alloantibodies is highest in individuals

Table 1. Search Categories and Criteria Used to Obtain Relevant Evidence About Cardiovascular Disease in People With Hemophilia

Search Categories	Criteria
Language	English only
Years covered by literature search	1980–2013
MESH search topics used in PubMed search	Hemophilia, cardiac disease, cardiac surgery, coronary artery bypass, factor inhibitors
Specific search subtopics	• Guidelines or consensus statements for treatment of PWH with CVD
	• Review articles
	• Stroke risk in PWH with atrial fibrillation
	• Use of antiplatelet drugs in PWH
	• Case reports of operative cardiac procedures in PWH
"Fugitive" literature not included in peer-reviewed journals*	• Article bibliographies to find reports of treatment of PWH (mostly surgical patients) not in traditional peer-reviewed journals
	• Web-based reports
	• Government publications
	• Publications in nonPubMed indexed journals
	• PhD dissertations

CVD indicates cardiovascular disease; PWH, people with hemophilia.
*The results of this search did not yield any relevant sources for inclusion in this article.

with certain gene mutations, specifically intron 22 inversions, large deletions, and nonsense mutations.[4] PWH transfused with plasma-derived factor replacement products risk development of transfusion-related viral infections, including human immunodeficiency virus (HIV) and hepatitis C virus (HCV). As of 2002, the first Multicenter Hemophilia Cohort Study found that concomitant HIV infection was present in more than half of HCV-seropositive PWH included in the study.[5] However, adoption of viral inactivation methods beginning in the mid-1980s substantially reduced the risk of HIV and HCV transmission via plasma-derived FVIII and FIX concentrates.[5]

Due to advances in care, including comprehensive management in hemophilia treatment centers (HTCs), primary and secondary prophylaxis, and improvements in factor replacement therapies, PWH achieve near-normal life expectancies. Since the 1990s, life expectancies in high-income countries exceed 70 years in HIV-negative men with hemophilia.[6,7] PWH with severe disease (very low FVIII or FIX levels), including those with HIV specifically, achieve lower life expectancies by approximately 10 years.[6] PWH with factor inhibitors previously had a reduced life expectancy; however, an analysis from the 1990s showed that the presence of inhibitors did not increase mortality rates in individuals with severe hemophilia with or without HIV.[8] An analysis of the Nationwide Inpatient Sample from 2007 found that the median age at death of hospitalized PWH in the United States (US) was 68 years, compared to 72 years in hospitalized individuals without hemophilia.[9] Leading causes of death in PWH included typical age-related conditions like sepsis (38%), congestive heart failure (30%), respiratory failure (28%), and pneumonia (25%), rather than intracranial hemorrhage or HIV (16%).[9] As the population of PWH ages, health care providers face increasing numbers of PWH presenting with typical age-related comorbidities, including ischemic heart disease (IHD), other atherosclerotic conditions, and degenerative valve disease.

The literature supporting any protective effect of hemophilia against IHD is conflicting. Some studies suggest that mortality from IHD is lower in PWH than in the general population,[7,10,11] presumably due to a "hypocoagulable" state that prevents thrombus formation and coronary arterial occlusion after rupture of an atherosclerotic plaque.[12,13] Others suggest that increased levels of various coagulation proteins, including FVIII and FIX, predispose affected individuals to atherogenesis[14,15]; however, reduced FVIII and FIX levels in PWH do not seem to ultimately protect against the development of atherosclerosis.[13] In fact, current consensus warns that the prevalence of atherogenesis[14–17] and endothelial dysfunction[14] is similar between PWH and the general population. The extent of these abnormalities correlates with traditional cardiovascular risk factors rather than

hemophilia severity.[14,16–18] When compared with a cohort of hospitalized individuals without hemophilia, hospitalized PWH had similar rates of angina, myocardial infarction (MI), and cardiovascular risk factors such as hypertension, diabetes mellitus (DM), obesity, and hyperlipidemia.[19]

Although the risk of coronary artery thrombus formation may be low in PWH, a cautionary note exists. Other events such as plaque rupture with atheroemboli, coronary vasospasm, or intra-plaque hemorrhage may lead to coronary events in PWH with coronary atherosclerosis.[16] Isolated case reports suggest that supernormal FVIII infusions, like those given for factor replacement in PWH before an invasive procedure, can induce coronary thrombosis,[20–22] as may other hemostatic therapies.[21,23] The presence of other underlying cardiovascular risk factors may contribute to such events.[20] PWH having procedures that typically employ anticoagulation such as cardiac operations or percutaneous coronary interventions (PCIs), require special considerations. Older patients with milder forms of hemophilia (mild or moderate factor level deficiencies) may be at particular thrombotic risk from factor replacement. These individuals require a delicate balance between anticoagulation or antiplatelet drugs and factor replacement.

PWH are susceptible to the same cardiovascular risk factors as individuals without hemophilia, and even more so to certain traditional risk factors such as hypertension[15,24–26] and obesity related to limited mobility from arthropathy.[18,27] In a cohort of more than 700 PWH from the Netherlands and United Kingdom, the predicted 10-year risk of fatal MI or stroke was significantly higher (8.9%) than in the general population (6.7%), based solely on typical factors determining cardiovascular risk (including age, blood pressure, total/high-density lipoprotein cholesterol, body mass index, and smoking or DM history).[28] A recent 5-year cross-sectional study of PWH older than age 35 in the US found that PWH had twice the lifetime prevalence of coronary artery disease (CAD), stroke, and MI compared to nonHispanic white men overall.[29] Nearly 40% of PWH in this study had 2 or more traditional risk factors for CVD.[29] In a review of 36 cases of confirmed MI in PWH, 11 PWH had 1 or more acquired risk factors for CVD, including smoking, obesity, hypertension, and immobility.[21] Systemic hemostatic therapies contributed to mortality in more than half (n = 22) of the PWH with MI.[21] Other unique risk factors predisposing to IHD in PWH include type and severity of hemophilia (with hemophilia B and mild disease being more likely among PWH with IHD in 1 cohort),[18] dyslipidemia, DM, and in PWH with HIV, hypertension from antiretroviral treatments.[30]

As PWH achieve longer life expectancies, their exposure to various cardiovascular risk factors increases. As a result, it is reasonable to expect greater numbers of PWH presenting with atherosclerotic disease in the future. Existing data already show a trend toward an increasing prevalence of IHD among PWH with increasing age, similar to the general population. Among more than 3000 PWH from the US in the late 1990s, the prevalence of IHD ranged from 0.05% in those younger than 30 years to 15.2% in those older than 60 years.[18] Similarly, there will likely be an increase in PWH presenting with other atherosclerotic conditions such as carotid occlusive disease and peripheral arterial disease (PAD), and other age-related cardiovascular conditions. In addition, PWH are susceptible to other acquired cardiovascular conditions, regardless of age: for example, PWH with late-stage HIV infection may be susceptible to acquired dilated cardiomyopathy.[31]

STANDARD HEMOPHILIA MANAGEMENT

Familiarity with the general management of hemophilia, particularly the options for treatment or prevention of bleeding, is an essential starting point for understanding the particular aspects of treating PWH who also have CVD. Replacement of the deficient factor using specific factor concentrates is a mainstay of therapy, especially in PWH with active bleeding or in those requiring operative interventions. Treatment for bleeding episodes consists of both on-demand regimens (ie, at onset of discrete bleeding episodes) and prophylactic regimens. In the latter, replacement factor is given on a scheduled basis with the intent of preventing bleeding, especially hemarthroses, a particularly disabling bleeding-related complication in PWH.[32] Administration of factor concentrates before, during, and after surgical or other invasive procedures limits bleeding, with the administered amounts of factor concentrates depending on hemophilia type and severity and the risk for bleeding associated with the procedure. Nonspecific blood products such as fresh frozen plasma (FFP) or cryoprecipitate contain relatively small amounts of hemophilia factors and are not viral inactivated.[33] As a result, administration of these nonspecific products risks disease transmission and may prove insufficient to control or prevent bleeding in many PWH who have severe bleeding episodes.

Hemophilia Factor Replacement

Options for factor replacement include plasma-derived and recombinant products (Table 2).[33,34] The screening of blood donors and harvested blood products along with adoption of viral inactivation methods has dramatically improved the safety of human plasma-derived factor concentrates.[35] Specifically, there have been no reports of HIV or HCV transmission from clotting factor concentrates since 1986 and 1997, respectively.[36] Still, concerns remain regarding the transmission of other pathogens, including nonenveloped viruses such as the parvoviruses and hepatitis A, or prions (variant Creutzfeldt-Jakob disease).[35,37,38]

Recombinant products developed in the wake of the 1980s HIV epidemic significantly reduce the risk of transmitting blood-borne pathogens.[33] The newest generation of recombinant products lack any human proteins in any of the production processes.[33] Accordingly, the Medical Advisory and Scientific Council of the National Hemophilia Foundation recommends recombinant factor concentrates as the treatment of choice for bleeding control and for surgical coverage in individuals with hemophilia A or B.[33] Consultation with a hematologist facilitates the choice of replacement product. Ultimately, the choice depends on several variables in addition to the potential for viral transmission, including availability, cost, and prior product exposure.[35]

Replacement factor dosing requires achievement of a pre-specified percentage of normal factor activity that varies based on the specific indication (eg, hemostatic coverage for minor vs major surgery). For example, immediately before major operations, correction of factor activity level to 80–100% of normal is preferred to optimize hemostasis.[39] Individuals with mild hemophilia (ie, with factor activity >5% of normal) require lesser amounts of factor concentrate than do those with severe hemophilia (ie, with factor activity level <1% of normal) and in some cases may not require any factor correction at all.

Complications of Factor Replacement

Currently, the most serious and costly complication of factor replacement therapy is the development of alloantibodies, or inhibitors, to the infused factor.[40] Inhibitors develop in approximately 20–30% of patients with severe hemophilia A and in 1–6% of those with severe hemophilia B.[3] Individuals with mild hemophilia typically have a low risk for developing inhibitors, but they are susceptible to developing inhibitors after receiving large amounts of factor concentrates for a surgical procedure, especially if they have had no previous exposure to exogenous factor replacement.[6] The presence of inhibitors typically makes factor replacement ineffective, complicating the management of bleeding events and coverage for surgical or other invasive procedures.

In PWH who develop inhibitors, bypassing agents are generally the first-line systemic therapy for hemostatic coverage, particularly for high-titer (>5 Bethesda units/mL) inhibitors.[41] These agents bypass the role of the inhibited factor in the coagulation cascade (Table 2). The bypassing agents consist of both recombinant activated factor VII {rFVIIa; NovoSeven RT [Coagulation Factor VIIa (Recombinant)], Novo Nordisk Inc., Bagsvaerd, Denmark} and a viral-inactivated, plasma-derived activated prothrombin complex concentrate (pd-aPCC) containing factors II, IX, and X in mostly nonactivated forms and factor VII mainly in the activated form [FEIBA NF (Anti-Inhibitor Coagulant Complex), Nanofiltered and Vapor Heated, Baxter Healthcare Corporation, Westlake Village, CA].

Concerns with the use of bypassing agents in the management of PWH with inhibitors include the lack of laboratory testing to predict efficacy[42] and a risk of thrombotic events. Case reports describe MI and disseminated intravascular coagulation in individuals with concurrent liver disease, those of advanced age, and those receiving higher-than-recommended amounts of pd-aPCC.[43–45] However, in a postmarketing survey of the use of FEIBA (pd-aPCC) in individuals with inhibitors, the incidence of thrombosis over 10 years was very low, with only 16 events occurring in the equivalent of 395,000 infusions.[46] Likewise, the incidence of thromboembolic events that were possibly or probably attributable to rFVIIa in clinical studies within approved indications for PWH with inhibitors was 0.20%.[47]

Although not relevant to the hemophilia population discussed here, the off-label use of rFVIIa outside of the approved indications is associated with higher rates of thromboembolic events than in placebo controlled trials.[48,49] Because pd-aPCC is used virtually exclusively in PWH with inhibitors,[50] comparable data regarding the risk of thrombotic events with off-label use of pd-aPCC are not available. Ultimately, in PWH with inhibitors who require hemostatic coverage, the risk for thromboembolism must be weighed against the risk for bleeding on an individualized basis.

Nonfactor Replacement Therapies for People With Hemophilia

In some instances, administration of nonfactor replacement therapies[33,34,51–59] occurs in lieu of, or in addition to, factor replacement products for surgical coverage or for management of perioperative bleeding (Table 2). Such therapies avoid the potential risks and costs associated with factor replacement.[60] PWH may benefit from either of 2 types of nonfactor replacement therapy: desmopressin or antifibrinolytic agents. Desmopressin is effective in mild hemophilia

Table 2. Therapeutic Options for Treatment or Prevention of Bleeding in Hemophilia

Type of Hemophilia	Factor Replacement Therapy		Bypassing Agents	Other Therapies	
	Recombinant Factors	Plasma-Derived Concentrates	rFVIIa, pd-aPCC	Desmopressin	Antifibrinolytics
Hemophilia A	• rFVIII recommended treatment of choice, especially in PWH not previously exposed to plasma products[33,34] • Lower risk for viral transmission compared with plasma-derived products[33,34] • No animal- or human-derived proteins used in the manufacturing of newest-generation products • Greater cost relative to plasma-derived concentrates	• Plasma-derived FVIII concentrates • Virally inactivated, in addition to improved screening of plasma donors*	• (Not indicated in the absence of inhibitors)	• Mobilizes FVIII stores from endothelial cells[54] • Multiple doses not effective because stores of FVIII are depleted[53] and not replenished for 1–2 weeks • Indicated in lieu of factor replacement for treatment/prevention of bleeding in mild hemophilia A (FVIII activity >5%)[33,34,55] • Assess response to treatment (ie, change in FVIII levels) before using desmopressin for hemostatic coverage[52] • Should not be used in pregnant women or children aged <2 years[33] • Children should be monitored for hyponatremia[34,51]	• TXA indicated for short-term use to reduce/prevent bleeding and reduce the need for replacement therapy during/after dental extraction[56] • Adjunctive use described in the setting of nondental surgeries as well[58,59] • Monitor for thromboembolic complications, particularly when used with other hemostatic agents or in persons at risk (eg, older adults, those with known thrombophilia)
Hemophilia B	• Recombinant FIX concentrate† recommended treatment of choice, especially in PWH not previously exposed to plasma products[33,34] • Lower risk for viral transmission compared with plasma-derived products[33,34] • Product available in the US is third-generation (ie, no animal- or human-derived proteins used in the manufacturing process) • Greater cost relative to plasma-derived concentrates	• Plasma-derived FIX concentrates‡ • Virally inactivated, in addition to improved screening of plasma donors and supply	• (Not indicated in the absence of inhibitors)	• (Not indicated)	• TXA indicated for short-term use to reduce/prevent bleeding and reduce the need for replacement therapy during/after dental extraction[56] • Adjunctive use described in the setting of nondental surgeries as well[59] • Monitor for thromboembolic complications
Hemophilia A or B with inhibitors	• May be able to use recombinant FVIII or FIX if inhibitor level is low (<5 BU/ml)	• May be able to use plasma-derived FVIII or FIX if inhibitor level is low (<5 BU/ml)	• Bypassing agents—rFVIIa (NovoSeven RT§) and pd-aPCC (FEIBA NF¶) effective and safe for hemostatic coverage for major and minor surgery in PWH with inhibitors[41] • First-line treatment, especially when inhibitor titer exceeds 5 BU/mL[41] • rFVIIa is generally used in individuals with hemophilia B[41] • Features impacting choice of bypassing agent include availability, prior patient response, and cost[33,41] • Monitor for thromboembolic complications		• TXA indicated for short-term use to reduce/prevent bleeding and reduce the need for replacement therapy during/after dental extraction[56] • Adjunctive use described in the setting of nondental surgeries as well[57,59] • Monitor for thromboembolic complications, particularly when using bypassing agents or factor concentrates

FIX indicates factor IX; FVIII, factor VIII; PWH, people with hemophilia; pd-aPCC, plasma-derived activated prothrombin complex concentrate; rFVIIa, recombinant activated factor VII; TXA, tranexamic acid; US, United States.
*Licensed plasma-derived FVIII concentrates in the US include Hemofil M (Baxter Healthcare Corporate; Westlake Village, CA) and Monoclate-P (CSL Behring LLC; Kankakee, IL).
†BeneFIX (Wyeth Pharmaceuticals Inc., Philadelphia, PA) is the only licensed recombinant FIX concentrate in the US.
‡Licensed plasma-derived FIX concentrates in the US include AlphaNine SD (Grifols Biologicals Inc., Los Angeles, CA) and Mononine (CSL Behring LLC; Kankakee, IL).
§NovoSeven RT (Novo Nordisk A/S, Bagsvaerd, Denmark).
¶FEIBA NF (Baxter Healthcare Corporate; Westlake Village, CA).

A and usually allows for avoidance of FVIII concentrates.[60] Desmopressin reduces blood loss[61,62] and red blood cell transfusion requirements[62] in select patients without bleeding disorders who experience bleeding after open-heart procedures. The antifibrinolytics, tranexamic acid and epsilon-aminocaproic acid, act as adjuncts in PWH who require operations. Both desmopressin[60] and antifibrinolytics[21] may predispose PWH to myocardial ischemia, so, like factor replacement therapies, they should be used with caution in PWH with potential IHD. This includes those individuals with traditional cardiovascular risk factors.[54] Desmopressin may be particularly thrombogenic in individuals with underlying CAD as it induces release of both FVIII and von Willebrand factor from endothelial cell granules.[54]

GENERAL PRINCIPLES IN THE MANAGEMENT OF CARDIOVASCULAR DISEASE IN PEOPLE WITH HEMOPHILIA

The management of common cardiovascular conditions poses unique challenges in PWH, particularly in individuals requiring anticoagulant and antiplatelet therapy, or in those requiring invasive procedures. The presence of factor inhibitors further complicates management. Because of the lack of evidence-based guidelines,[63] recommendations for the management of CVD in PWH are based on expert opinion, or on anecdotal experience from both cardiac and noncardiac procedures, mostly in patients without inhibitors. Given the relatively limited experience with managing CVD in this population, consultation with a hematologist who has experience in hemophilia management is paramount, particularly for assistance with navigating the fine balance between antithrombotic and hemostatic therapy required for many of these conditions. Furthermore, invasive cardiac procedures in PWH—particularly those with inhibitors—pose an extremely high-risk situation and require infrastructure and resources specifically aimed at treating PWH. The optimal setting for such procedures is a facility designated as an HTC, where all necessary ancillary services (eg, laboratory, blood bank, pharmacy), full-spectrum resources (eg, factor concentrates and other hemostatic therapies), and medical and surgical expertise are available.

NONOPERATIVE CARDIOVASCULAR CONDITIONS

Atrial Fibrillation and Other Cardiac Dysrhythmias

Nonvalvular atrial fibrillation (AF) is a common age-related cardiovascular condition that often requires antithrombotic therapy to prevent associated thromboembolic events, particularly stroke. The decision to initiate antithrombotic therapy is normally based on the projected risk for stroke as determined by a risk scoring system: either the $CHADS_2$ score[63] or the increasingly used CHA_2DS_2-VASc score.[68,69] The acronyms reflect risk factors for thromboembolic complications (congestive heart failure, hypertension, age ≥75 years, DM, stroke, vascular disease history) and their relative weight in the calculation of the score (ie, 2 points given for prior stroke or transient ischemic attack).[70] The CHA_2DS_2-VASc modification gives an additional point for female sex, 1 point for age of 65–74, and 2 points for age ≥75 and provides better stratification of risk. Neither scoring system has been studied extensively in PWH.

PWH who develop AF are not immune to thromboembolic complications; therefore, in high-risk cases, antithrombotic prophylaxis may be warranted, provided sufficient baseline factor levels are assured. There are no clinical trial data to support recommendations for antithrombotic therapy in PWH; therefore, therapy should be individualized, taking the comparative risks for bleeding versus thromboembolic complications into account. Whereas, in the general population, antithrombotic therapy is recommended for individuals

at intermediate risk for stroke ($CHADS_2$ or CHA_2DS_2-VASc score = 1),[71] a higher threshold ($CHADS_2$ ≥2) is proposed for initiating antithrombotic therapy in PWH.[63] Mannucci et al provided an algorithm for managing antithrombotic therapy in PWH with AF (Fig. 1).[63] However, several important changes have occurred in the options and recommendations for antithrombotic therapy for AF in the general population in the interim, including the recognition that aspirin alone does not sufficiently protect against thromboembolism in AF[71] and the introduction of left atrial (LA) appendage occlusion devices.

Pharmacologic options for antithrombotic therapy in PWH at lower risk for bleeding (ie, those with baseline factor levels >5% and those with severe hemophilia who are on clotting factor prophylaxis) include oral anticoagulants and antiplatelet agents (Table 3). Oral anticoagulant options include the vitamin K antagonist warfarin, which should be titrated to achieve an INR of 2.0–3.0, and the new oral anticoagulants, such as direct thrombin or activated factor X inhibitors.[71] New oral anticoagulants offer the benefits of shorter half-lives and lower bleeding risk than warfarin but have no specific antidotes,[72,73] and evidence of their use in PWH with AF is lacking. Oral anticoagulants offer better protection against stroke in AF than do antiplatelet agents, with a comparable risk for bleeding complications.[71] In cases in which antiplatelet therapy is used, dual therapy incorporating both aspirin and clopidogrel is advised (Table 3), because the reduction in stroke risk imparted by aspirin alone is only moderate at best.[71]

Mechanical interventions such as LA appendage occlusion or exclusion may alternatively be used to limit the duration of antithrombotic therapy in PWH with AF (Table 3). LA appendage occlusion devices reduce long-term risk of thromboembolism in AF, albeit with a trade-off of potential periprocedural complications. LA appendage occlusion may become the preferred strategy in PWH, especially those with factor levels ≤5%. This procedure has been described in a man with mild hemophilia A (FVIII level of 8%), allowing for a reduction of antithrombotic pharmacotherapy to a total of 6 weeks.[74] Implantation of a LA appendage occlusion device should be done at an experienced center with a low complication rate. Antithrombotic prophylaxis is not recommended in PWH with inhibitors and AF given the heightened risk for bleeding and the difficulty in treating any bleeding episodes that might occur in this subpopulation of PWH.[63]

If cardioversion is elected, no antithrombotic therapy is needed before or after the procedure for AF of less than 48 hours duration.[63] In PWH presenting with AF of longer duration, a transesophageal echocardiogram performed before cardioversion identifies periprocedural stroke risk related to the presence or absence of an LA thrombus. The absence of an LA thrombus permits avoidance of anticoagulation (and the attendant bleeding risk) in PWH before cardioversion.[75] Cardioversion of AF requires anticoagulation with therapeutic doses of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) during the procedure and for a period of 5 days thereafter (Table 3).[63] PWH without inhibitors undergoing cardioversion simultaneously require factor replacement with either recombinant or plasma-derived FVIII or FIX, maintaining a trough factor activity level of around 80%.[63] After discontinuation of periprocedural anticoagulation with UFH or LMWH, an additional 4 weeks of anticoagulation with a vitamin K antagonist is recommended, targeting an INR of 2.5.[63] During this time, PWH should receive factor concentrates to maintain trough factor levels of 30%.[63] Upon completion of this 4-week period of anticoagulation, PWH who remain in sinus rhythm convert to antithrombotic therapy based on basal factor level activity and stroke risk as outlined in Figure 1.[63] No specific recommendations exist for the management of AF in PWH with inhibitors. Because of the use of anticoagulants and bypassing agents for bleeding prophylaxis, respectively, PWH with inhibitors who require anticoagulation for AF are at increased risk for both bleeding and thrombosis.
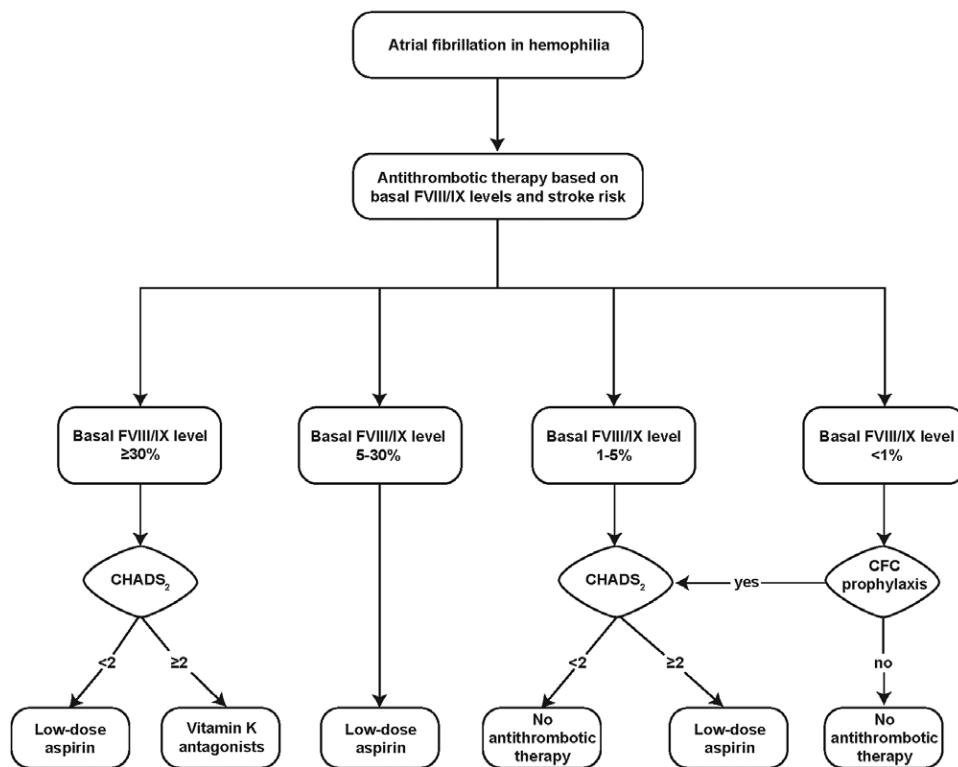
Figure 1. Recommended algorithm for management of atrial fibrillation in people with hemophilia without inhibitors.[63] The primary determinant of management of AF in PWH is the baseline FVIII/FIX level (ie, hemophilia severity). People with severe hemophilia are considered candidates for thromboprophylaxis provided they are receiving factor concentrate prophylaxis. The decision to initiate antithrombotic therapy is further based on the individual projected risk for stroke, in this case determined by the CHADS$_2$ scoring system. A score of ≥2 is considered indicative of a high risk for stroke. (See text for a description of the CHADS$_2$ score calculation.) CFC indicates clotting factor concentrate; CHADS$_2$, congestive heart failure, hypertension, age, diabetes mellitus, stroke; FVIII, factor VIII; FIX, factor IX; PWH, people with hemophilia. Republished with permission of *Blood: Journal of the American Society of Hematology*, from "How I treat age-related morbidities in elderly persons with hemophilia," Mannucci, PM, et al.,114, 26 © 2009; permission conveyed through Copyright Clearance Center, Inc.

There is little in the literature pertaining to the evaluation or management of other dysrhythmias in PWH. Reports describe a child with severe hemophilia A who underwent cryoablation for atrioventricular nodal reentrant tachycardia[76] and a 73-year-old man with severe hemophilia A who had uncomplicated diagnostic electrophysiologic studies.[77] In these 2 patients, factor levels corrected to 80–100% of normal provided adequate hemostasis.

Coronary Artery and Ischemic Heart Disease

As in the general population, efforts in PWH focus on prevention of CAD when possible. Such efforts include screening adults with hemophilia for traditional cardiovascular risk factors after the age of 40 years,[28] especially for hypertension and for obesity in PWH with arthropathy. Data suggest that screening and intervention for these traditional risk factors are currently suboptimal in PWH.[26] Aggressive management of individual cardiovascular risk factors with appropriate medications and lifestyle modifications may allow for deferment of invasive interventions and antiplatelet medications in PWH with symptomatic CAD, especially those with inhibitors.[78] Whether the benefits of low-dose aspirin prophylaxis for cardiovascular events outweigh the potential risk for bleeding in PWH is uncertain. Because of the bleeding risk, prophylactic low-dose aspirin therapy in PWH is currently not recommended as a rule.[26] Chest pain syndromes may indicate myocardial ischemia in PWH, especially in those PWH with cardiovascular risk factors

or when pain occurs after administration of factor replacement or bypassing agents.[79]

Evidence-based guidelines for the treatment of IHD in PWH are lacking, but published recommendations are available, including institutional guidelines from the Netherlands.[65] In general, the recommended management of IHD in PWH parallels that in people without hemophilia and reflects the primary clinical manifestation of IHD [ie, stable angina vs an acute coronary syndrome (ACS)], with factor replacement as needed to maintain adequate factor levels (Fig. 2, Table 3).[6,63,65,66] Specific recommendations for PWH with inhibitors do not exist, and published anecdotal experience with the management of IHD in this population is extremely limited.

In all forms of IHD, antiplatelet or antithrombotic pharmacotherapy is a mainstay of treatment. In PWH, the provision of antiplatelet or antithrombotic therapy requires concomitant maintenance of minimum factor levels to reduce bleeding risk (Fig. 2, Table 3). Some PWH (especially with mild hemophilia) achieve recommended trough factor levels on their own without ongoing factor correction.[80] In PWH with moderate or severe disease who require long-term aspirin therapy, 1 source recommends concomitant factor replacement initially, followed by bolus or continuous factor infusion as needed for bleeding complications thereafter.[81] Managing traditional cardiovascular risk factors is particularly important in PWH with severe disease who cannot receive antiplatelet agents,[82] including those who are not maintained on factor prophylaxis.[6,65]

Table 3. Management Suggestions for Nonoperative Cardiovascular Disease in People With Hemophilia*

Cardiovascular Condition	Antithrombotic Therapy	Hemostatic Therapy
Atrial fibrillation (nonvalvular)		
Cardioversion[63,64]	Therapeutic doses of UFH or LMWH × 5 days, then warfarin × 4 weeks (target INR 2.5), then low-dose ASA according to CHADS$_2$ score	CFC to FVIII/FIX levels ≥80% × 5 days then ≥30% × 4 weeks, then as below
CHADS$_2$ = 1[63,64]	Consider low-dose ASA (based on factor levels and bleeding risk)†	CFC as needed to maintain FVIII/FIX levels ≥10% (ongoing)
CHADS$_2$ ≥2	Warfarin (target INR 2.0–3.0) or new oral anticoagulants preferred over dual antiplatelet therapy (ASA plus clopidogrel); LA appendage occlusion may be preferred in PWH with FVIII/FIX ≤5% to limit duration of antithrombotic therapy	CFC as needed to maintain FVIII/FIX levels ≥30% for duration of antithrombotic therapy[63,64]
IHD[6,65,66]		
Stable angina	Low-dose ASA (ongoing)	CFC as needed to maintain FVIII/FIX levels >5–10% (ongoing)
Unstable angina/NSTEMI	UFH 70 U/kg bolus then 400 U/kg/d × 48 hours, then clopidogrel (600 mg load then 75 mg/d × 4 weeks) + ASA (325 mg load then 80 mg/d long-term)	CFC to FVIII/FIX levels of 80% × 48 hours, ≥30% × 4 weeks (during dual antiplatelet therapy), then >5–10% (ongoing)
STEMI		
>12 hours (PCI not indicated)	As for NSTEMI	As for NSTEMI
<12 hours (PCI indicated)	UFH 70–100 U/kg before PCI, then LMWH 100 U/kg SQ BID × 48 hours; antiplatelet therapy after heparin (Figure 2)	CFC to FVIII/FIX levels of 80% before PCI and for 48 hours thereafter‡
PAD with ABI <0.9[67]	Low-dose ASA OR clopidogrel 75 mg/d (ongoing)	CFC as needed to maintain FVIII/FIX levels >5–10% (ongoing)

ABI indicates ankle-brachial index (ratio of upper to lower extremity systolic pressures); ASA, aspirin; CFC, clotting factor correction; CHADS$_2$, congestive heart failure, hypertension, age, diabetes mellitus, stroke; FIX, factor IX; FVIII, factor VIII; IHD, ischemic heart disease; INR, international normalized ratio; LA, left atrial; LMWH, low-molecular-weight heparin; NSTEMI, non–S-T segment elevation myocardial infarction; PAD, peripheral arterial disease; pd-aPCC, plasma-derived activated prothrombin complex concentrate; PCI, percutaneous coronary intervention; PWH, people with hemophilia; rFVIIa, recombinant activated factor VII; STEMI, S-T segment elevation myocardial infarction; UFH, unfractionated heparin.

*Recommendations are for PWH without inhibitors, unless otherwise specified. Consultation with a hematologist is recommended for all PWH with cardiovascular disease to ensure optimal medical management.

†Long-term ASA prophylaxis may be deferred in individuals with moderate FVIII/FIX deficiency and CHADS$_2$ score <2 to avoid continuous CFC prophylaxis.

‡Bypassing agents should be used in lieu of CFC in PWH with inhibitors as follows: rFVIIa, 90 mcg/kg every 3–4 hours for 24 hours on the day of PCI and then 90 mcg/kg daily for the 4 weeks of dual antiplatelet therapy or pd-aPCC, 80 units/kg every 12 hours for the first 24 hours followed by the same daily dose for the duration of dual antiplatelet therapy.[6] Use of bypassing agents beyond the first month is discouraged given the risk for thrombogenesis.[6]

Recent articles summarize the "real-life" management and outcomes of ACS in PWH, including those managed with PCIs.[80,83] PCI is primarily indicated in cases of S-T segment elevation myocardial infarction (STEMI) presenting within 12 hours (Fig. 2) and in certain high-risk non-STEMI patients.[6,65] Prospective evaluation of the previously mentioned Dutch guidelines support the recommendations for PCI for STEMI,[66] albeit in a small number of PWH, none of whom had severe hemophilia or inhibitors at the time of their procedures. There are several important considerations for performing PCI in PWH. Radial artery access is optimal in lieu of femoral access, especially in PWH with inhibitors.[65,66,82,83] A recent study found that unselected individuals who underwent PCI for acute MI via the radial route had significantly lower bleeding rates, vascular complications, and mortality at 2 years compared with those who underwent PCI via the femoral route.[84] However, many publications document catheterization via the femoral route in PWH with negligible complications.[83,85] In cases where femoral access is used, a vessel closure device may reduce local bleeding complications.[86]

In PWH who require stenting, a bare metal stent (BMS) facilitates a shorter duration of dual antiplatelet therapy (typically 1 month) compared with a drug-eluting stent (DES, up to 12 months).[63,65] A novel BMS under clinical development designed to enhance endothelialization by "recruitment" of endothelial progenitor cells [the Genous-R stent (OrbusNeich Medical Technologies, Fort Lauderdale, FL)] may allow an even shorter (ie, approximately 2 weeks) duration of dual antiplatelet therapy[87] in PWH.[88] Although the risk for restenosis in PWH is not known,[65] expert consensus suggests that the risk of prolonged dual antiplatelet therapy outweighs any benefit that a DES offers in terms of a reduced risk for restenosis.[63] Because of the limited ability of DESs to reduce

mortality or reduce recurrent MI compared with BMSs, consensus recommendations suggest that only special circumstances like symptomatic restenosis or high risk for restenosis justify the use of DESs in PWH.[83] PWH with mild disease (specifically, factor levels exceeding 25%) are good candidates for DES in ACSs, as they may not require factor replacement for the duration of dual antiplatelet therapy.[66] Newer-generation DESs may permit shorter (ie, <6-month) periods of dual antiplatelet therapy[66,85] but experience in PWH is nonexistent.

In general, the regimen for antithrombotic therapy during and after PCI mirrors that recommended for PWH presenting with other ACSs; however, PWH undergoing PCI should additionally receive glycoprotein IIb/IIIa inhibitors in the 12 hours after PCI (Fig. 2).[6,65] The short-acting direct thrombin inhibitor bivalirudin was used in lieu of UFH during successful PCI in 4 PWH described in the literature; 3 of these individuals had severe hemophilia.[83,89–91]

Pretreatment with antiplatelet agents is recommended in the general population before PCI.[92] In contrast, consensus suggests deferring antiplatelet therapy in PWH before possible PCI to limit bleeding events,[93] especially in the minority who may require urgent operative coronary revascularization. This recommendation is somewhat controversial because withholding antiplatelet therapy in planned PCI risks the development of thrombi during PCI in PWH, especially when factor replacement is administered.[93] To avoid the burden and costs related to ongoing clotting factor correction, the recommended duration of dual antiplatelet therapy in PWH is 1 month.[66] This recommendation coincides with general guidelines for the minimal duration of dual antiplatelet therapy after placement of a BMS, the preferred stent for PWH with significant symptomatic coronary obstruction.[66]
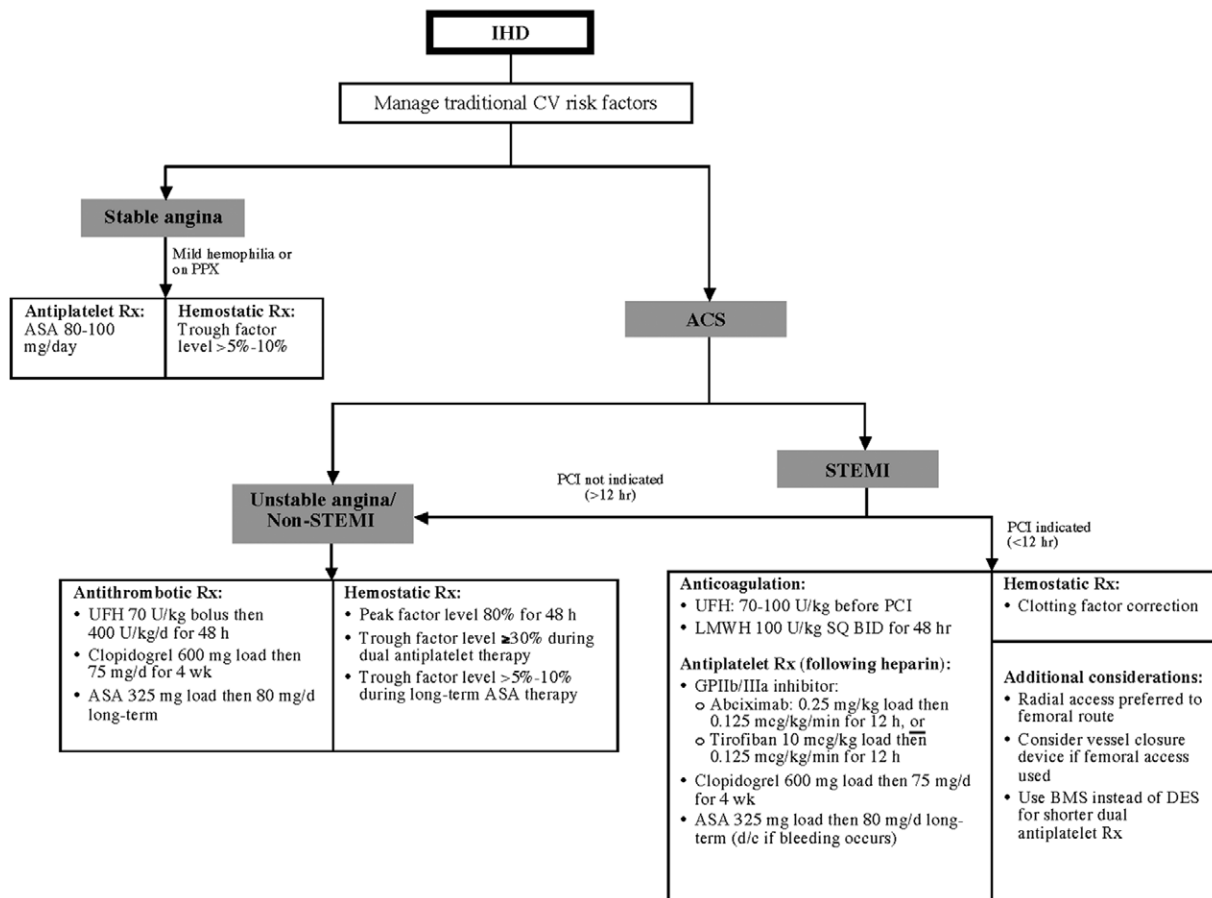
Figure 2. Suggested algorithm for management of ischemic heart disease in people with hemophilia without inhibitors.[6,65,66] ACS indicates acute coronary syndrome; ASA, aspirin; BMS, bare metal stent; CV, cardiovascular; d/c, discontinue; DES, drug-eluting stent; GP, glycoprotein; IHD, ischemic heart disease; LMWH, low-molecular-weight heparin; PCI, percutaneous coronary intervention; PPX, prophylaxis; Rx, therapy; STEMI, S-T segment elevation myocardial infarction; UFH, unfractionated heparin.

After PCI in PWH, the recommendation is for near-complete [80%[6] (Fig. 2) or 40–60%[83]] correction of clotting factor levels for at least 48 hours. This consensus includes factor correction to levels of at least 80% for the first 48 hours followed by daily dosing to a trough level of 30% for the duration of dual antiplatelet therapy.[6] In PWH with inhibitors receiving prolonged antiplatelet therapy, continuous prophylaxis with bypassing agents beyond the first month after PCI risks thrombosis and is not recommended.[6]

Because of the extreme bleeding risk, the use of fibrinolytic therapy in lieu of PCI is contraindicated; however, a recent panel of experts from Europe concluded that fibrinolysis may be justified in PWH when primary PCI is unavailable, provided there is adequate factor correction (minimum of 50% and peak ≥80%) and the capacity for serial measurement of factor levels.[94] When there is 3-vessel CAD or stenosis of the left main coronary artery, surgical coronary artery bypass grafting (CABG) is indicated.[6] In some cases, multivessel PCI provides an alternative in PWH who are deemed too high risk for CABG.[89]

Other Atherosclerotic Conditions

PWH are susceptible to other atherosclerotic conditions in addition to IHD, although there is very little in the literature describing the presentation and management of additional conditions such as carotid occlusive disease or PAD. In one study, carotid intima media thickness increased significantly in PWH concurrent with the calculated 10-year cardiovascular risk, based on traditional cardiovascular risk factors.[17]

There are currently no descriptions of the medical management of carotid occlusive disease in PWH in the literature. Surgical management is discussed in the next section ("Cardiovascular Conditions Requiring Operations in PWH").

PWH with cardiovascular risk factors are likely susceptible to PAD as well, encompassing atherosclerosis of the aorta and iliac and lower extremity arteries. A single study from 2000 found that, compared with age- and risk-matched controls, PWH had a significantly lower number of atherosclerotic plaques in the abdominal aorta and leg arteries as detected by color echo Doppler.[95] Nevertheless, similar to IHD, the prevalence of PAD in PWH may be higher than previously believed, because risk factors for the development of PAD are similar to those for CAD. In addition, some evidence suggests that PAD is a marker of other atherosclerosis-related morbidities and mortality.[67] PAD may go unrecognized in PWH for a number of reasons. PWH with severe hemophilic arthropathy may not be sufficiently mobile to manifest claudication, the classic presenting symptom of PAD.[67] Claudication-related pain may also be erroneously attributed to arthropathy or may be masked by analgesics used to treat this condition.[67] Therefore, PAD is a consideration in PWH with severe arthropathy and cardiovascular risk factors who present with atypical pain or worsening dysfunction of the lower extremities.[67,96] In addition, PWH should undergo screening for PAD in a manner similar to the general population.[96] Screening for PAD is particularly important in PWH over age 70 and in those under age 50 with a history of smoking or DM.

The ankle-brachial index (ABI), a ratio of upper to lower extremity systolic pressures, assesses the risk of PAD. In PWH with significant joint deformity precluding ABI measurement, a toe-brachial index or duplex ultrasonography are useful options for screening.[67] In individuals with an ABI less than 0.9, measures to reduce overall cardiovascular risk should be implemented.[67] To reduce the risk for peripheral ischemic events, antiplatelet therapy is typically employed, along with factor replacement as needed to maintain trough FVIII/FIX levels of more than 5% (Table 3).[67] However, data supporting the use of antiplatelet therapy in PWH with PAD are limited.[67] Individuals with mild hemophilia may tolerate low-dose aspirin without bleeding.[67] In contrast, those with moderate or severe hemophilia may require factor correction to avoid bleeding with the use of antiplatelet therapy.[67] The use of prophylactic antiplatelet therapy calls for an individualized management approach in consultation with a hematologist. Although pentoxifylline or cilostazol is generally used to manage claudication, the benefits and risk of bleeding attributable to these agents in PWH are unknown; therefore, their use should be discouraged until more information is available.[67] Individuals with limb-threatening ischemia (ie, ischemic pain at rest, ischemic ulcers, or gangrene) or with claudication that interferes with quality of life despite pharmacologic treatment are candidates for surgical intervention.

CARDIOVASCULAR CONDITIONS REQUIRING OPERATIONS IN PEOPLE WITH HEMOPHILIA

Numerous cardiovascular conditions, both acquired and congenital, require operations in PWH, including those with inhibitors. An extensive literature search revealed reports of cardiac operations in fewer than 50 PWH (Table 4). With such a small sample, assessment of clinical outcomes in this population is difficult. Results of cardiac procedures in PWH seem similar to those in people without hemophilia, but there is undoubtedly publication bias in these literature reports. A published summary of "best evidence" in this area exists,[123] but evidence-based recommendations grounded on controlled trials or even on large observational studies do not exist for PWH undergoing cardiac procedures. Consequently, recommendations for the management of cardiac procedures in PWH come from expert consensus rather than large published series.

General Perioperative Considerations

Table 5 summarizes general recommendations and considerations for surgical management of CVD in PWH. Given the challenges of ensuring hemostasis, particularly when systemic anticoagulation is required, operative intervention is a formidable undertaking in PWH, especially those with inhibitors. Accordingly, less invasive procedures—for example, PCI in lieu of CABG[89] or transcatheter correction of cardiac lesions (eg, septal defects,[124] patent ductus arteriosus[125])—seem preferable whenever possible and appropriate. In PWH for whom elective surgery is the only or best option, preoperative coordination of all necessary personnel and resources is vital. Ample supplies of factor concentrates or bypassing agents and blood products are required. Consultation with a hematologist ideally affiliated with an HTC throughout the perioperative period is paramount.

Cardiac transplantation poses a particular challenge when it comes to coordinating care, because the timing for this procedure cannot be planned in advance. Sufficient supplies of hemostatic agents are essential for this procedure, as is the ability to mobilize emergency laboratory, blood bank, and pharmacy support.[115] Not surprisingly, relative to similar procedures in the general population, cardiac operations in PWH incur substantially increased costs (primarily due to hemostatic treatments) and resource utilization.[115,123,126] Advance planning and involvement of a multidisciplinary team serves to optimize clinical outcomes while minimizing risk.

Numerous regimens exist for perioperative clotting factor correction. Most reports describe a factor activity level of 100% from immediately before operation extending to the conclusion of the procedure, using bolus dosing or continuous infusion. The latter avoids the fluctuation in factor levels that bolus dosing causes and potentially reduces the total amounts of factor ultimately consumed.[81] Consensus suggests that maintaining factor levels in the range of 80–100% of normal activity through the early postoperative period, at least to postoperative day 3, is optimal. Thereafter, standard recommendations endorse maintenance of trough factor levels of 50% until wound healing is nearly complete (postoperative day 10–14).[102] In PWH with inhibitors, unless the inhibitor titer is low (≤5 Bethesda units/mL) or there is an opportunity to eradicate the inhibitor before operation, bypassing agents substitute for clotting factor replacement (Table 2).[41] In addition to factor replacement therapies, adjunctive use of tranexamic acid for postoperative hemostatic coverage in PWH is an option.[58,125] In individuals with refractory bleeding during or after operation, acquired hemostatic perturbations, such as consumptive or dilutional coagulopathies from cardiopulmonary bypass (CPB) or deep hypothermia, are possibilities.[127] Cases complicated by acquired coagulopathy may require additional hemostatic products (eg, FFP, platelets) independent of hemophilia factor replacement.

Procedures requiring CPB in PWH constitute high-risk undertakings, given the need for systemic anticoagulation. Consequently, off-pump or minimally invasive variations of procedures that typically require extracorporeal circulatory support, such as CABG,[36,98,112] confer less risk to PWH. Anecdotal evidence suggests that minimally invasive procedures reduce the risk for bleeding and coagulopathy in PWH.[36,98,112] Published experience with management of anticoagulation and hemostasis during CPB in PWH is limited and entirely anecdotal. Ultimately, this procedure requires a highly individualized approach. In many PWH described in the literature, procedures using CPB incorporated standard heparinization protocols,[58,77,105,108,114,116,128] after 100% correction of factor levels by bolus or continuous administration of factor concentrates.[77,105,108–111,113,116,118] For 1 patient, the bypass circuit was primed with FFP in lieu of saline to minimize hemodilution.[115] However, use of this large amount of FFP (as much as 1500 mL) confers additional risk of transfusion-related complications without providing much evidence of benefit.

The monitoring of anticoagulant activity during CPB in PWH is problematic. Activated clotting time (ACT) is most often used to monitor heparin effect. Importantly, the accuracy of ACT monitoring is uncertain unless there are near-normal factor levels.[126] In addition, the utility and accuracy of ACT monitoring during CPB when using hemostatic coverage with bypassing agents is uncertain. For monitoring hemostatic therapy during cardiac surgery (with or without CPB), the measurement of PTT or factor levels is a viable option. For this purpose, it is necessary to have reliable venous access at a site separate from where factor concentrates will be administered, preferably placed in advance of the operation.[109] High heparin concentrations during CPB preclude accurate determination of FVIII levels.[105,113] To determine factor levels in this setting, a chromogenic assay with heparin neutralization should be used instead of a coagulation-based assay.[109] Point-of-care tests such as thromboelastography monitor perioperative coagulation in settings where hemostatic perturbations are likely (including cardiac operations). However, experience with thromboelastography for directing perioperative hemostatic management specifically in PWH is extremely limited,[129] especially in the setting of cardiac surgery. In PWH with factor inhibitors who require bypassing agents for hemostatic coverage, there is no reliable biochemical means of monitoring hemostatic response, other than by clinical parameters.

Table 4. Reports of Cardiac Operations in People With Hemophilia: Survey of the English-Language Literature Between 1980 and 2013

Reference	Hemophilia Type and Severity	Age (years)	Operation	Inhibitors (Yes/No)	Replacement Therapy	Complications
Fitzsimons et al (2013)[97]	A (mild, FVIII 8–22%) and IgA deficiency	53	Redo-AVR	No	Continuous rFVIII supplemented with intraoperative aminocaproic acid and IgA deficient blood products	Cardiac tamponade
Sprunck et al (2012)[98]	A (severe, FVIII <1%)	38	2-v OPCAB	No	Continuous rFVIII until POD 13	None
Kypson et al (2012)[99]	A (severity not specified); HIV positive	52	3-v CABG	No	Continuous rFVIII supplemented with aminocaproic acid intraoperatively. rFVIII continued until POD 10	None
Furutachi et al (2012)[100]	A (mild, FVIII = 17–28%)	61	Aortic arch replacement (Type A dissection)	No	Continuous plasma-derived FVIII until all wires and lines removed	32U PRBCs, 50 U FFP, and 40 U platelet concentrates given
Barillari et al (2012)[101]	A (severe, FVIII <1%) and HCV with liver disease	58	2-v CABG	No	Continuous rFVIII and tranexamic acid through POD 13	None
Zatorska et al (2012)[102]	A (mild, FVIII = 19%)	30	MV repair (SBE)	No	Bolus FVIII until POD 7. Warfarin given for 1 month postoperatively	None
Lison et al (2011)[103]	A (moderate, FVIII 3–5%)	67	2-v CABG and AVR	No	Minimal FVIII replacement and low dose heparin during CPB. Continuous plasma-derived FVIII used until POD 7 to maintain FVIII level of ~50%	None
Frías et al (2011)[104]	A (moderate, FVIII = 8%)	5	Biventricular Berlin assist device for 178 days followed by heart transplant complicated by need for 5 days of postoperative ECMO	No	Bolus FVIII to maintain levels above 50% for 2 weeks postoperatively. No anticoagulation administered after Bi-VAD once bleeding controlled	Three reoperations for bleeding after Bi-VAD. Multiple doses of rFVIIa for periprocedural bleeding (concomitant mild congenital FVII deficiency)
Rodriguez et al (2010)[105]	A (severe, FVIII <1%)	35 weeks	TOF repair	Yes	Preoperative bolus rFVIII followed by continuous intraoperative and postoperative rFVIII	Developed FVIII inhibitor 2 months after operation
Krakow et al (2009)[106]	B (moderate, FIX = 8%)	61	AVR bioprosthesis	No	Bolus and continuous rFIX until POD 10. Heparin given POD 1–7	None
Pesaro et al (2009)[36]	B (severe, FIX <1%, HIV positive)	37	Off-pump 2-v CABG	No	Continuous FIX through POD 12	Early vein-graft occlusion required PTCA and clopidogrel
Tang et al (2009) #1[58]	A (mild, FVIII = 25%)	60	AVR (biologic)	No	Bolus rFVIII through POD 14 and intraoperative and postoperative tranexamic acid	Postoperative GI bleed on LMWH
Tang et al (2009) #2[58]	A (mild, FVIII = 24%)	72	Ventricular resection and MV reconstruction	No	Bolus rFVIII intraoperatively and postoperatively through POD 13	None
Tang et al (2009) #3[58]	A (mild, FVIII = 20%)	67	3-v CABG	No	Bolus rFVIII intraoperatively and postoperatively through POD 11	None
Tang et al (2009) #4[58]	A (moderate, FVIII = 3%)	68	AVR (biologic) and 1-v CABG	No	Bolus rFVIII intraoperatively and postoperatively through POD 24 and perioperative tranexamic acid	None
Tang et al (2009) #5[58]	A (severe, FVIII <1%)	57	4-v CABG	No	Bolus rFVIII intraoperatively and postoperatively through POD 15, intraoperative and postoperative tranexamic acid	None
Tang et al (2009) #6[58]	A (mild, FVIII = 18%)	61	AVR and 1-v CABG	No	Bolus rFVIII intraoperatively and postoperatively through POD 15, intraoperative and postoperative tranexamic acid	Atrial flutter
Thankachen et al (2007)[107]	B (mild, FIX = 14%)	25	AVR, MVR (mechanical [Starr Edwards])	No	Bolus plasma-derived FIX preoperatively and continuous infusion postoperatively to maintain FIX levels 80% of normal POD 1–3, then tapered. INR maintained between 1.5 and 2.0	Postoperative cardiac tamponade on POD 4, ARF
Gasparović et al (2007)[108]	A (severe, FVIII <1.0%)	47	AVR (bioprosthesis)	No	Bolus followed by continuous infusion of FVIII along with intraoperative aprotinin. Continuous FVIII continued until POD 12	None
Murugan et al (2006) #1[109]	A (mild, FVIII = 11%)	5 weeks	Repair TAPVR	No	Continuous rFVIII until POD 8	None
Murugan et al (2006) #2[109]	A (moderate, FVIII = 5%)	11 weeks	Repair VSD and TAPVR	No	Continuous rFVIII until POD 11	None

(Continued)

Table 4. (Continued)

Reference	Hemophilia Type and Severity	Age (years)	Operation	Inhibitors (Yes/No)	Replacement Therapy	Complications
Eren et al (2006)[110]	A (severe, FVIII <1%)	62	3-v CABG	No	Bolus rFVIII given during operation along with 8 U FFP, 8 U platelet concentrates, and 7 U PRBCs. Bolus rFVIII given postoperatively through POD 14	None
Stine and Becton (2006)[111]	A (mild, FVIII = 6%)	64	1-v CABG and MV repair	No	Continuous FVIII until POD 3, then bolus FVIII for 7 days. Maintained on aspirin and warfarin for 1 month after operation	None
Grandmougin et al (2005)[112]	B (severe, FIX <1%) and HCV	52	OPCAB x 2	No	Bolus and continuous plasma derived FIX until POD 14	None
De Bels et al (2004)[113]	A (mild, FVIII = 10%)	53	3-v CABG	No	Preoperative bolus of plasma-derived FVIII combined with intraoperative continuous FVIII infusion and tranexamic acid. FVIII infusion stopped on POD 3	Postoperative bleeding. Chest tube drainage increased (1590 mL). Transfusion of 6 U PRBCs, 4 U FFP, and 6 platelet packs
Kaminishi et al (2003)[114]	A (mild, FVIII = 6.9%)	53	Aortic root replacement	No	Bolus plasma-derived FVIII continued until POD 6	Received 10U platelet concentrates
Sheth et al (2001)[115]	A (severe, FVIII <1%)	14	Heart transplant (cardiomyopathy post-MI on high-dose pd-aPCC therapy)	Yes	High-dose plasma-derived FVIII supplemented with rFVIIa on POD 6 after anamnesis developed	Seizure on POD 2 (watershed injury on MRI). Bacteremia on POD 6. Bleeding on POD 7 requiring epsilon aminocaproic acid. Maintained on rFVIIa
MacKinlay et al (2000) #1[77]	A (mild, FVIII = 15%)	56	2-v CABG	No	Continuous plasma-derived FVIII until POD 9	None
MacKinlay et al (2000) #2[77]	A (mild, FVIII = 25%)	56	5-v CABG	No	Bolus plasma-derived FVIII until POD 10	None
MacKinlay et al (2000) #3[77]	A (moderate, FVIII = 4%)	49	AVR and MVR (bioprosthetic)	No	Bolus plasma-derived FVIII until POD 16	None
MacKinlay et al (2000) #4[77]	A (moderate, FVIII = 4%)	54	Redo AVR and MVR	No	Bolus plasma-derived FVIII until POD 15	None
MacKinlay et al (2000) #5[77]	A (mild, FVIII = 7%)	58	AVR	No	Continuous plasma-derived FVIII until POD 9	Warfarin given for mechanical valve
MacKinlay et al (2000) #6[77]	B (mild, FIX = 32%)	18	ASD closure	No	Bolus plasma-derived FIX until POD 11	Drainage of postoperative pericardial effusion
Donahue et al (1999)[116]	B (moderate, FIX = 8%)	80	3-v CABG	No	Bolus rFIX intraoperatively and postoperatively. Perioperative tranexamic acid	Aortic dissection POD 2, emergency reoperation, perioperative death
Palanzo and Sadr (1995)[117]	B (moderate, FIX = 2.4%)	71	6-v CABG	No	Bolus plasma-derived FIX daily until discharge (POD 6). Aprotinin used perioperatively	None
Scharfman et al (1993)[118]	B (moderate, FIX = 5%)	52	4-v CABG	No	Bolus plasma-derived FIX complex concentrate (PCC) until POD 7. Aminocaproic acid used perioperatively	None
Wilson et al (1991)[119]	B (mild, FIX = 12%)	74	CABG	No	Bolus plasma-derived FIX complex concentrate (PCC) until POD 7	None
Mazzucco et al (1986)[120]	B (severe, FIX <1%)	7	VSD and AV repair	No	Perioperative PCC and FFP until POD 20	None
Raish et al (1985)[121]	B (moderate, FIX = 5%)	59	4-v CABG	No	Preoperative plasma exchange with FFP replacement followed by postoperative FFP	None
Roskos et al (1983) #1[122]	B (moderate, FIX =2%)	16	TGA, VSD and pulmonic stenosis repair	No	Bolus FFP until POD 7. Discharge on POD 11	None
Roskos et al (1983) #2[122]	A (severe, FVIII <1%)		TGA repair	No	Bolus cryoprecipitate until POD 10	None

1-v CABG indicates 1-vessel coronary artery bypass grafting; 2-v CABG, 2-vessel coronary artery bypass grafting; 3-v CABG, 3-vessel coronary artery bypass grafting; 4-v CABG, 4-vessel coronary artery bypass grafting; 5-v CABG, 5-vessel coronary artery bypass grafting; 6-v CABG, 6-vessel coronary artery bypass grafting; 2-v OPCAB, 2-vessel off-pump coronary artery bypass; ARF, acute renal failure; ASD, atrial septal defect; AV, aortic valve; AVR, aortic valve replacement; Bi-VAD, biventricular assist device; CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; FFP, fresh frozen plasma; FIX, factor IX; FVIII, factor VIII; GI, gastrointestinal; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IgA, immunoglobulin A; INR, international normalized ratio; LMWH, low-molecular-weight heparin; MI, myocardial infarction; MRI, magnetic resonance imaging; MV, mitral valve; MVR, mitral valve replacement; OPCAB, off-pump coronary artery bypass; PCC, prothrombin complex concentrate; pd-aPCC, plasma-derived activated prothrombin complex concentrate; POD, postoperative day; PRBCs, packed red blood cells; PTCA, percutaneous transluminal coronary angioplasty; rFIX, recombinant factor IX; rFVIIa, recombinant activated factor VII; rFVIII, recombinant factor VIII; SBE, subacute bacterial endocarditis; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

Table 5. Management Consensus for People With Hemophilia Requiring Surgical Treatment of Cardiovascular Disease

	Without Factor VIII or Factor IX Inhibitors	With Factor Inhibitors
Preoperative assessment	• Measure factor levels • Enlist multidisciplinary team (HTC, if possible) • Assess for inhibitors (inhibitor titer by Bethesda assay)	• Enlist multidisciplinary team (HTC, if possible) • Measure inhibitor levels, because some patients with low titer inhibitors can have routine factor replacement therapy
Intraoperative treatment of PWH having cardiac operations	• Continuous or bolus CFC to maintain levels above 80% at end of operation • Antifibrinolytics during operation • Minimally invasive, if possible • Tissue valve preferred for valve replacements • Low dose of heparin to match defect in intrinsic clotting cascade • Multifactorial blood conservation program that includes cell salvage, mini-circuits, microplegia, and ultrafiltration • Assay for factor levels on CPB (chromogenic assay) • Factor levels above 80% in early postoperative period	• Bypassing agents after completion of CPB • Dosing of bypassing agents is purely empiric without good guidelines • Antifibrinolytic agents during and shortly after CPB • Use bolus or continuous factor replacement in patients with low levels of inhibitors (<5 BU/ml)
Postoperative care of PWH after cardiac operations	• Continuous or bolus factor replacement (preferably with recombinant products) for 7–10 days • Factor level replacement to above 50% after POD 3 • Anticoagulation (eg, LMWH) necessary to avoid thrombosis as long as supplemental high-level factor replacement is given • Warfarin for 3 months after valve replacement but with supplemental factor replacement to maintain levels above 5% • Low-dose aspirin prophylaxis for life • Screen for inhibitor development 1–2 months after operation	• Bypassing agents at higher doses for 3 days after operation • Bypassing agents at reduced level for 7–10 days after operation • Anticoagulation during the period of use of bypassing agents

BU indicates Bethesda unit; CFC, clotting factor correction; CPB, cardiopulmonary bypass; HTC, hemophilia treatment center; LMWH, low-molecular-weight heparin; POD, postoperative day; PWH, people with hemophilia.

Valve Replacement

There are several important considerations specific to PWH undergoing valve replacement, including the need for postoperative anticoagulation. In the majority of PWH undergoing valve replacement, a bioprosthetic valve is preferred to avoid the need for prolonged anticoagulation.[58,103,128] Published reports suggest that anticoagulation strategies in the immediate postoperative period vary and include LMWH for a period of up to approximately 10 days,[58,106,107] warfarin,[77] or no therapy.[77,128] Specific institutional recommendations for anticoagulation from centers in Italy and the Netherlands advocate the use of LMWH (5000–7000 U twice daily) for 10 days after valve replacement, in conjunction with factor replacement.[6] Subsequently, in those who receive bioprosthetic valves, warfarin derivatives targeting an INR of 2.5–3.5 are recommended for a period of 3 months, during which time trough factor levels should be maintained at ≥5%.[6] In certain cases, based on age or hemodynamics,[107] PWH may receive a mechanical prosthesis because of hypothetical superior longevity. Use of a mechanical valve mandates indefinite anticoagulation and maintenance of factor levels above 30% by continuous prophylaxis.[63] One case report, however, described the initial deferment of anticoagulation after mechanical valve replacement in a man with moderate hemophilia A who developed FVIII inhibitors.[130] Instead, measurement of D-dimer levels and monitoring of echocardiography eventually pointed to evidence of thrombosis and prompted warfarin therapy.[130] Experience with annuloplasty in this population is very limited, with only 2 case reports identified in the literature.[102,111] Individuals without hemophilia who undergo annuloplasty typically receive anticoagulation for 3 months after the procedure, similar to those undergoing bioprosthetic valve replacement.[102] Whether PWH require similar anticoagulation after annuloplasty is uncertain.

Lower Extremity Peripheral Arterial Disease

To date, there is only a single description of surgical intervention for PAD in the setting of hemophilia: a 61-year-old man with mild hemophilia A who underwent femoral-popliteal bypass using an autogenous saphenous vein graft.[131] The patient received hemostatic coverage with intermittent boluses of plasma-derived FVIII. Other

details of the procedure are lacking. Stenting is a possible option in PWH who have aortoiliac disease.[132] However, the benefits of this approach in PWH are uncertain, especially in view of the need for ongoing antiplatelet or antithrombotic therapy.[67]

Acquired Aortic Conditions

A few cases of elective repair of abdominal aortic aneurysm in PWH appear in the literature. These aneurysms had the gross and histologic appearance of typical atherosclerotic aneurysms.[133,134] Two patients with mild[133] and moderate[134] hemophilia A had surgical graft replacement; 1 had a collagen-coated Dacron bifurcation graft placed to avoid the need for preclotting.[133] More recently, a man with severe hemophilia B had endovascular aneurysm repair (EVAR).[135] All individuals met the criteria for elective repair, based on aneurysm size or on a rapid increase in diameter.[136] In all cases, factor levels were corrected to ≥100% of normal for the operation using corresponding factor concentrates, followed by maintenance of factor levels at 80–100% for approximately 1 week after the procedure.[133–135] Intraoperative heparinization was employed in 2 cases.[134,135] In individuals without bleeding disorders, blood loss and transfusion requirements are significantly reduced for EVAR compared with open procedures.[135] Whereas logic supports the use of minimally invasive procedures such as EVAR in PWH,[135] given the existence of only a single reported case of EVAR in PWH, it is difficult to generalize this recommendation to the entire population.

Literature reports describe the surgical management of aortic dissection in PWH.[100,116,127,137] Because emergent intervention is necessary, the management of acute aortic dissection poses challenges beyond those of elective cardiovascular procedures in PWH. Surgical and other considerations are summarized in a recently published first-ever case report describing management of an acute type A dissection in an individual with hemophilia A.[127]

Carotid Occlusive Disease

Two reports document carotid endarterectomy after cerebrovascular events in a total of 3 PWH: 1 with mild hemophilia B,[138] 1 with

moderate hemophilia B,[139] and 1 with mild hemophilia A.[138] Two of these individuals had substantial cardiovascular risk factors, and 1 had prior CABG. These reports did not provide extensive operative details. Management of hemophilia factor replacement involved continuous intraoperative infusion of recombinant FIX in both individuals with hemophilia B,[138,139] in 1 case continuing for 48 hours postprocedure.[139] In the other case, postoperative FIX replacement was achieved by bolus dosing continued for 7 days after operation.[138] Ironically, both individuals with hemophilia B developed carotid artery pseudotumors within 8 weeks of endarterectomy, and both underwent successful excision of their pseudotumors under FIX cover.[138,139] The individual with hemophilia A received bolus dosing of FVIII during endarterectomy and for 10 days thereafter.[138] A Dacron patch was used for carotid closure in 1 of the men with hemophilia B.[139]

CONCLUSIONS

As the population of PWH ages, cardiovascular health care providers will encounter increasing numbers of PWH presenting with typical age-related cardiovascular conditions, in addition to other acquired or congenital conditions spanning all ages. The management of cardiovascular conditions in PWH may prove especially challenging when antithrombotic therapy or surgical intervention is indicated, particularly in the presence of inhibitors. Further complicating the challenges of ensuring hemostasis in PWH is the lack of evidence-based guidelines upon which to base therapeutic decisions. Accordingly, current recommendations for the medical and surgical management of common cardiovascular conditions in PWH derive from anecdotal experience and expert opinion. Most recommendations reflect guidelines and common practices for people without hemophilia. Ultimately, the rigorous, systematic investigation of management strategies for many cardiovascular conditions is unobtainable, given the relative rarity of hemophilia and even smaller numbers of PWH with any given cardiovascular condition. The utilization of data from existing global registries or from newly created registries may provide useful information regarding approaches to antithrombotic and hemostatic therapy in PWH. In the meantime, the best options include individualization of treatment protocols, with coordinated input from a multidisciplinary team. To optimize resource utilization and clinical outcome and to minimize bleeding risk and complications, close consultation with a hematologist, ideally in association with an HTC, is essential.

ACKNOWLEDGMENTS

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