The life expectancy of people with hemophilia has increased such that children with hemophilia now look forward to a normal life expectancy and excellent health-related quality of life. Median life expectancy in males with severe hemophilia was 11 years in the early 1900s and had increased to the range of 55 to 63 years in the 1970s. A more recent study of Italian persons with hemophilia found that life expectancy had increased from 64.0 years in 1990-1999 to 71.2 years in 2000-2007. This increased life expectancy results in an increasing number of individuals aged 45 to 64 years in the hemophilia population.

The two major contributors to improved quality of life, reduced morbidity, and increased life expectancy among persons with hemophilia are 1) the availability of high-quality antihemophilic factor concentrates for replacement therapy and 2) the provision of comprehensive care. As life expectancy increases, there is an associated increase in the incidence and prevalence of conditions that affect the general older population, such as cardiovascular disease (CVD), hypertension, and diabetes. The emerging clinical concerns in this population represent an important treatment area in hemophilia.

Historically, it was suggested that hemophilia had a protective effect against the occurrence of ischemic heart disease, while other more recent data suggested that hemophilia does not have a preventative effect. At least one study found an unfavorable CVD risk profile in hemophilia patients compared with the general age-matched male population. In fact, it appears that the relationship between factor VIII (FVIII) deficiency and CVD is subtle: a study of hemophilic mice found that FVIII deficiency delays but does not eliminate the early phase of atherosclerosis, the primary pathology of CVD, suggesting that coagulation protein deficiency confers a protective effect that declines with increasing age.

The number of deaths caused by ischemic heart disease in patients with hemophilia is on the rise. Circulatory disease was found to be the second most common cause of death in persons with hemophilia during the period of 1995-1998. Moreover, the Centers for Disease Control and Prevention (CDC) found an elevated risk for acute myocardial infarction (standardized mortality ratio = 3.0; 95% CI = 1.5-5.8) among persons living with hemophilia in a surveillance study of six U.S. states. The level of coronary stenosis in persons with hemophilia is reported to be similar to that of individuals without hemophilia. In addition to diabetes and hypertension, increased levels of FVIII (e.g., related to factor concentrate infusions) may increase the risk of CVD in this population.

**CVD Risk Factors and Screening in Hemophilia**

A recent study by the Indiana Hemophilia and Thrombosis Center (IHTC) and other earlier studies showed that people with hemophilia appear to have the same risk of developing heart disease as the general population, based on other cardiac risk factors, specifically age, family history of cardiac disease, smoking status, hypertension, diabetes, and hyperlipidemia (Table 1). Overall the prevalence of CVD risk factors and the associated risk of CVD were comparable between individuals with hemophilia and age-matched persons in the general population.

Moreover, various CVD risk factors related to the hemophilia population, such as administration of factor concentrates and infection with HIV, may play a role in the occurrence of heart disease in this population. For example, HIV infection and hemophilia type were significantly associated with various forms of heart disease, such as cardiac dysrhythmias, cardiomyopathy, and heart failure, which may occur as a result of HIV disease, its treatment or secondary opportunistic infections.

Thus it is reasonable to conduct screening for heart disease in patients with hemophilia and determine the presence of risk factors.
Factors. The HTCH study found that while approximately 70% of participants had their cholesterol or lipid panels checked by subspecialists, 15% of participants had never had their cholesterol levels analyzed, revealing a gap in care for persons with hemophilia. The following routine screening and evaluations for risk factors of CVD are recommended for individuals with bleeding disorders: family history and smoking status, blood pressure, body mass index (BMI) and waist circumference. Laboratory analysis to include: fasting lipid panel, complete blood count (monitoring hemoglobin, platelet count), basic metabolic panel (monitoring renal function), HIV and viral hepatitis screening if unknown.

<table>
<thead>
<tr>
<th>Type of hemophilia</th>
<th>Odds ratio</th>
<th>Lower CI</th>
<th>Upper CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilia B vs. A</td>
<td>2.5</td>
<td>0.7</td>
<td>8.7</td>
</tr>
</tbody>
</table>

Severities of hemophilia

<table>
<thead>
<tr>
<th>Severity</th>
<th>Odds ratio</th>
<th>Lower CI</th>
<th>Upper CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate vs. mild</td>
<td>1.1</td>
<td>0.3</td>
<td>4.2</td>
</tr>
<tr>
<td>Severe vs. mild</td>
<td>2.1</td>
<td>0.5</td>
<td>10.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age of the patient (years)</th>
<th>Odds ratio</th>
<th>Lower CI</th>
<th>Upper CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 45-54 vs. 35-44*</td>
<td>3.8</td>
<td>1</td>
<td>13.7</td>
</tr>
<tr>
<td>Age 55-64 vs. 35-44</td>
<td>1.2</td>
<td>0.2</td>
<td>5.5</td>
</tr>
<tr>
<td>Age ≥65 vs. 35-44</td>
<td>2.9</td>
<td>0.3</td>
<td>26</td>
</tr>
</tbody>
</table>

**Other risk factors**

- Hypertension**: 4.9, 1.4, 17.3
- Diabetes mellitus: 3.7, 0.9, 14.9
- Smoking**: 6.4, 3.4, 20.4
- Obesity: 0.4, 0.4, 1.4
- HIV infection: 1.8, 0.3, 9.4
- Hepatitis C infection: 0.5, 0.1, 1.7
- Hypercholesterolemia: 2.4, 0.8, 7.3

HIV, human immunodeficiency virus, *P = 0.05; **P <0.002.

Currently, there does not appear to be a defined role for carotid ultrasound to predict atherogenesis by measuring intima media thickness of the carotid artery. Using B-mode ultrasound for testing for intima-media thickness of the carotid artery between patients with bleeding disorders and healthy controls, Šrámek et al found that decreased coagulability has no clinically relevant effect on atherogenesis (formation of subintimal atheromatous plaques within the lining of arteries); thus the role of carotid ultrasound is not defined.

Screening for liver disease should be performed as part of a thorough medical evaluation. Liver function tests (total and direct bilirubin, albumin, total protein, along with PT/INR) and liver enzymes (AST, ALT, alkaline phosphatase) should be obtained. Additionally, there may be likelihood that older patients with hemophilia were transfused with blood products prior to 1992, potentially exposing them to viral hepatitis. Thus, if not documented, they should be appropriately screened for viral hepatitis (hepatitis B and C) based on their past exposure to blood products.

Patients where a stress test is required who have significant arthropathy should be considered for chemical stress test when deemed absolutely necessary and given no contraindications. A dobutamine or cardiolite stress test may be considered.

Alternatives to bicycle or treadmill stress tests that may cause less stress to the joints include elliptical machine or water exercise stress tests, if available.

Use of Anticoagulants in Hemophilia

Although persons with hemophilia have been reported to have decreased mortality and complications due to CVD, the cardioprotective effect of hemophilia does not preclude ischemic heart disease and its effect may diminish with advancing age. As the number of older adults with hemophilia continues to increase, antithrombotic agents (anticoagulant and antiplatelet drugs) are increasingly being considered for the management and prevention of age-related CVD and other thrombotic conditions in this population.

There are two main classes of antithrombotic agents: anticoagulants and antiplatelet drugs. Anticoagulant agents dampen the clotting process, thereby reducing fibrin formation and preventing clot propagation. Fibrin plays a more important role in clots that form in veins, although it also plays a significant role in arterial thrombosis.

The most commonly used anticoagulant agents include the following:

- **Anticoagulant Agent**
  - Oral
  - Intravenous
  - Subcutaneous
  - Heparin
  - Low molecular weight heparin (LMWH)
  - Fondaparinux
  - Warfarin
  - Bivalirudin
  - Argatroban
  - Apixaban/rivaroxaban
  - Dabigatran

Anticoagulant agents are used for the treatment or prevention of thromboembolism in a variety of conditions, including acute coronary syndrome, acute ischemic stroke, and atrial fibrillation, and in patients with risk factors for stroke or thromboembolism. Until recently, vitamin K antagonists, such as warfarin, were the only available oral anticoagulants.

In recent years, however, new oral anticoagulants have been introduced that specifically target either factor Xa (FXa) or thrombin. The most commonly used anticoagulant agents include:

- Aspirin (acetylsalicylic acid)
- ADP-receptor antagonist (eg, ticlopidine, clopidogrel)
- GPIIb/IIIa-receptor antagonists (eg, abciximab)

Anticoagulant agents are prescribed for patients with any of the following conditions:

- Coronary artery disease (CAD)
- MI
- Angina (chest pain)
- Stroke and transient ischemic attack (TIA)
- Peripheral artery disease (PAD)
- After angioplasty and stent placement
- After cardiovascular procedures (eg, heart bypass or valve replacement surgery)
- To prevent the formation of blood clots in people with arterial fibrillation

Evidence-based guidelines for the acute treatment and secondary prophylaxis of CVDs in persons with hemophilia are currently lacking. In addition, consensus has not been reached on how to manage the increased risk of bleeding associated with invasive procedures and the short- and long-term use of antithrombotic drugs.
In the absence of guidelines, recommendations for antithrombotic therapy rely on anecdotal evidence from hemophilia treatment centers (HTCs) experienced in managing such patients as well as the adaptation of general guidelines used in nonhemophilic populations.\textsuperscript{11,16-21} Given the delicate balance between bleeding and clotting in this population, management of CVD in individuals with hemophilia requires a multidisciplinary approach with close cooperation between cardiologists, hematologists, and their multidisciplinary team.\textsuperscript{12,13}

As evidence-based guidelines have not been developed, clinicians are encouraged to review the references listed below to gain a better understanding of the background of CVD in persons with hemophilia. The list of cited publications is not exhaustive yet does summarize of the management strategies utilized by various HTCs experienced in the management of individuals with hemophilia and coexisting CVD.

**Data Collection Systems**

Currently the number of older persons with hemophilia is small; therefore, the clinical problems of CVD in individuals with hemophilia cannot readily be resolved by adequately powered and controlled clinical trials. One approach to address this lack of data is to establish international registries on age-related diseases in older patients with hemophilia.\textsuperscript{14} The registries could collect data on CVD at regular intervals from large populations. To address this and other issues, the European Haemophilia Safety Surveillance (EUHASS; http://euhass.org) was initiated, and represents a prospective reporting system for adverse events in persons with hemophilia in Europe.\textsuperscript{15,26}

**Desmopressin Use**

One potential contraindication in cardiac procedures in persons with hemophilia who have CVD is the use of desmopressin acetate, a synthetic analogue of the natural antidiuretic hormone (ADH) 8-arginine vasopressin. This hormone is produced by the pituitary gland and helps to regulate water balance and renal water conservation.\textsuperscript{16} All patients receiving this agent should be observed for signs and symptoms associated with hyponatremia.\textsuperscript{36}

Desmopressin has infrequently produced changes in blood pressure causing either a slight increase or a transient fall with a compensatory increase in heart rate. The drug, therefore, should be used with caution in patients with coronary artery insufficiency and/or hypertensive CVD and in cases of severe congestive heart disease due to its antidiuretic effect.\textsuperscript{36,37} In rare cases, patients predisposed to thrombus formation have experienced thrombotic events after administration of desmopressin. No causality has been determined, but the drug should be used with caution in these patients.\textsuperscript{38}

Although desmopressin has been used in patients undergoing invasive cardiac procedures to reduce postoperative blood loss and transfusion requirements, a benefit has not been demonstrated in large randomized controlled trials.\textsuperscript{39} Therefore, the routine use of desmopressin in uncomplicated cardiac operations is not recommended\textsuperscript{39} and is considered to be contraindicated in patients with unstable CAD.\textsuperscript{40}

Because patients who are receiving desmopressin may experience hyponatremia, serum sodium levels should be carefully monitored and the desmopressin dosages should be adjusted accordingly. In patients older than 65 years using high-dose desmopressin nasal spray, fluid intake should be limited if the serum sodium levels trend downward.\textsuperscript{41}

**Invasive Interventions**

Cardiovascular surgery represents a major hemostatic challenge because of the sternotomy, the need for hemparation, extracorporeal circulation, mild hypothermia, and cardiac arrest.\textsuperscript{42} Few centers have experience in performing cardiovascular surgery in patients with hemophilia\textsuperscript{20,43} and performing randomized controlled trials in this population could collect data of the small population size.\textsuperscript{44} Therefore, only limited information exists on the efficacy and safety of hemostatic replacement regimens during and after major surgical interventions. Furthermore, postoperative thromboprophylaxis with antiplatelet drugs is problematic in patients with hemophilia.\textsuperscript{12}

Despite the lack of high-quality evidence, there are compelling data that demonstrate good surgical outcomes are possible for patients with hemophilia undergoing cardiovascular surgery.\textsuperscript{15,32,44-47} The key requirements reported to achieve successful outcomes with cardiovascular surgery include a multidisciplinary team approach, factor replacement protocols often utilizing continuous infusion to maintain a consistent factor level, and perioperative coagulation monitoring with factor levels.\textsuperscript{45,46}

Because elevated factor levels may contribute to blood clot formation, levels should be monitored carefully in the perioperative period to ensure that these are within the established range and do not exceed these thereby predisposing the patient to possible thrombotic events.\textsuperscript{48} Intravenous plasma factor levels can be easily measured before heparin and after protamine sulphate administration, whereas during cardiopulmonary bypass, measurements require a chromogenic method.

Rapid bolus factor infusions may create significant factor activity peaks and should be avoided. Some HTCs recommend slow bolus infusions, while others recommend continuous infusion of clotting factor concentrates before, during, and after surgery until wound healing is sufficiently complete.\textsuperscript{49} For valve replacement, tissue valves, which generally avoid the need for long-term anticoagulation therapy, are generally preferred over artificial valves.\textsuperscript{15}

A comprehensive written care plan by the local HTC is essential for cardiac surgery. The plan should include communication to the interventional cardiologists, cardiac surgeons, anesthesiologists, coagulation laboratory, and blood bank and/or pharmacy.\textsuperscript{42} Because hemophilia is a rare condition, personnel who deliver and their areas of care such as specialty and ward nurses, physiotherapists, and pharmacists in intensive care, high-dependency units, and postoperative ward settings, should receive education about the specific considerations for a patient with hemophilia undergoing cardiac surgery.

Among patients with hemophilia B, no data from prospective randomized trials are available to inform the decision to use bolus or continuous infusion of factor replacement product, yet largely the same principles for hemophilia A apply to hemophilia B. Consensus is also lacking on the minimal target FIX level before, during, and after surgery, the duration of replacement therapy, or the use of antibrinolytic agents. The bleeding risk for patients with different severities of hemophilia B requiring dual antiplatelet therapies or vitamin K antagonists after angioplasty and stent insertion, or after valve surgery, is not well elucidated. To avoid the need for long-term use of such drugs, the health care team should carefully consider the type of stent and valve prosthesis used when planning the patient’s procedure.\textsuperscript{42}

No standard-of-care or formal guidelines exist regarding the use of aspirin and clopidogrel (or similar medications) before, during, and after invasive procedures for patients with hemophilia. Aspirin should not be used in patients with severe hemophilia not receiving clotting factor prophylaxis.\textsuperscript{42} According to Mackinlay et al.,\textsuperscript{48} standard heparinization and reversal with protamine appear to be safe when the patient is appropriately replaced with factor concentrate. In general, the use of these medications should be discussed on a case-to-case basis weighing the individual risks and benefits of each medication.\textsuperscript{15,22,40}

As with any intervention in any population, there are risks and complications associated with cardiac catheterization in the hemophilia population. These risks, most of which are similar to those in the nonhemophilic population, include bleeding during the procedure or from the sheath site following the procedure, wound infection, thrombosis, bleeding secondary to antithrombotic agents administered in association with acute coronary syndromes, and other complications from the procedure that could result in bleeding – for example, coronary vessel injury, cardiopulmonary arrest requiring CPR and/or central line placement.

Of primary importance to the hemophilia population, optimal clotting factor replacement therapy should be tailored to the increased risk of bleeding associated with invasive procedures and antithrombotic therapies, particularly during the acute phase of the acute coronary syndrome.\textsuperscript{23} Secondly, if stents are placed during the catheterization, bare metal stents are preferable from the hematologic standpoint, as dual oral antiplatelet therapy with clopidogrel or similar agents are required for a short duration after stent placement.\textsuperscript{42,48,49,62} Thirdly, antithrombotic agents with shorter half-lives that are reversible or have an antidote are recommended for these patients.\textsuperscript{24}

Wound infection is a serious consideration in patients with bleeding disorders. It has been demonstrated experimentally in animal models that impaired coagulation results in delayed wound healing.\textsuperscript{63} In a study of hemophilia B, impaired thrombin generation leads to impaired tissue factor expression following an injury.\textsuperscript{64} Cutaneous wounds heal slowly and show histological abnormalities, even after wound closure.\textsuperscript{65} In all bleeding disorders, to prevent rebleeding and additional tissue damage, it is important to normalize hemostasis until the process of angiogenesis and vascular remodeling has fully resolved.\textsuperscript{41} The HTC hemotologist should be consulted for optimal management of hemostasis.

In percutaneous interventions in the general population, up to 70% of all major bleeding events are related to femoral artery access.\textsuperscript{25} Radial artery access has been shown to reduce bleeding by 73% as compared with femoral artery access (0.05% vs 2.3%, OR 0.27 [95% CI 0.16, 0.45], P < .001).\textsuperscript{46} The relative safety of radial access is well-established\textsuperscript{41} and it is thus recommended in one institutional guideline for treatment of ischemic heart disease in hemophilia patients to reduce bleeding during the procedure.\textsuperscript{41}

**Inhibitor Patients**

Finally, patients with hemophilia and inhibitors who develop ischemic heart disease present a formidable challenge. Very
little experience with this patient population has been described in the literature, even by large tertiary care centers.

Some centers advocate testing for inhibitors before all surgical procedures, while other test inhibitors peripheratively for inhibitors in patients with a history of inhibitor development. Given the complexity of managing patients with inhibitors, cardiac surgery in this subpopulation should be carried out only by an experienced team in collaboration with the multidisciplinary team of health care providers at HTCs.

Conclusion

The Indiana Hemophilia and Thrombosis Center (IHTC) is the only federally recognized comprehensive hemophilia treatment center in Indiana and one of the largest centers in the nation. The IHTC is a 501(c)3 nonprofit entity that is dedicated to providing the best, most comprehensive care to people in Indiana with bleeding or clotting disorders and to their families. The IHTC is both nationally and internationally distinguished as a Center of Excellence for its leadership in bleeding disorder care and research. The IHTC has coordinated 70 cardiopulmonary procedures in bleeding disorders patients with greater than 90% having achieved an adequate hemostatic outcome. Our comprehensive team and its extended services ensure that your referrals will receive the best management available for the bleeding disorder and its related complications in Indiana.

References


The IHTC, Indiana's Center of Excellence for bleeding and clotting disorders

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