



REVIEW ON CARDIOVASCULAR RISK IN PATIENTS WITH HEMOPHILIA

Dr. Manish Kumar^{1*}, Dr. Rajesh Kumar Sharma², Dr. Akhilesh Patel³, Shivam Singh⁴ and Himanshu Kumar⁵

^{1,5}PHARM.D, NIMS Institute of Pharmacy, NIMS UNIVERSITY Jaipur Rajasthan.

²Associate Professor, Department of Pharmacology, NIMS Institute of Pharmacy, NIMS UNIVERSITY Jaipur Rajasthan.

³Assistant Professor, Department of Pharmacy Practice, NIMS Institute of Pharmacy, NIMS UNIVERSITY Jaipur Rajasthan.

⁴Assistant Professor, Department of Pharmacology, NIMS Institute of Pharmacy, NIMS UNIVERSITY Jaipur Rajasthan.



*Corresponding Author: Dr. Manish Kumar

PHARM.D, NIMS Institute of Pharmacy, NIMS UNIVERSITY Jaipur Rajasthan.

Email ID: kmanishkr4@gmail.com

Article Received on 28/04/2024

Article Revised on 18/05/2024

Article Accepted on 08/06/2024

ABSTRACT

Beyond its core signs, hemophilia—a hereditary bleeding illness defined by clotting factor shortage or dysfunction—presents special problems. There appears to be a correlation between hemophilia and cardiovascular risk, which calls for a thorough examination. In order to clarify the relationship between hemophilia and cardiovascular health, this study summarizes recent research and looks at probable causes, risk factors, and clinical consequences. Important discoveries demonstrate the complex relationship between cardiovascular risk and hemophilia patients, including comorbidities, inflammation, coagulation irregularities, and physical inactivity. Moreover, this study emphasizes the significance of customized treatment approaches and interdisciplinary care to reduce cardiovascular risk and improve outcomes in this susceptible group. This study seeks to enlighten physicians, researchers, and policymakers on the cardiovascular implications of hemophilia. This will facilitate the development of tailored therapies and improve the overall health outcomes of individuals with hemophilia.

KEYWORDS: Hemophilia, Cardiovascular Risk, Clotting Factors, Inflammation, Coagulation Abnormalities, Comorbidities, Multidisciplinary Care.

INTRODUCTION

Overview of Cardiovascular Diseases (CVD)

Heart and blood vessel disorders are included in the wide category of ailments known as cardiovascular diseases (CVD). Worldwide, they constitute the primary cause of sickness and mortality.

Coronary Artery Disease (CAD)

Atherosclerotic plaque accumulation causes the coronary arteries to constrict or block, which reduces blood flow to the heart muscle and is the hallmark of coronary artery disease (CAD). Angina (chest discomfort), myocardial infarction (heart attack), and other problems may arise from this.

Stroke: A stroke happens when there is a disruption or reduction in the blood flow to a portion of the brain, depriving the brain tissue of nutrition and oxygen. This may result from either a hemorrhagic stroke (blood vessel rupture) or an ischemic stroke (blood vessel obstruction).

Peripheral Artery Disease (PAD): The illness known as peripheral artery disease, or PAD, is characterized by narrowing or blockage of the arteries supplying blood to the limbs, most often the legs. In severe situations, this may result in tissue death as well as discomfort and numbness.

Heart Failure: Heart failure happens when the heart cannot pump enough blood to fulfill the body's requirements. Numerous illnesses, such as CAD, hypertension, and cardiomyopathy, can cause it.

Hypertension (High Blood Pressure): High blood pressure, is a chronic illness that raises blood pressure in the arteries over time, raising the risk of heart attacks, strokes, and other cardiovascular problems.

Atrial Fibrillation (AFib): An irregular, frequently fast heart rhythm known as atrial fibrillation (AFib) can result in blood clots, strokes, heart failure, and other heart-related problems.^[1,2,3,4,5]

HEMOPHILIA: AN OVERVIEW

A hereditary bleeding illness called hemophilia is defined by a lack or shortage of certain clotting factors, which are blood proteins necessary for healthy blood coagulation. Prolonged bleeding episodes result from the body's inability to create stable blood clots due to this deficit. Because of its X-linked recessive inheritance pattern, hemophilia typically affects men, while female carriers may occasionally show symptoms if their levels of clotting factors are low.

Types of Hemophilia

Hemophilia A: Also referred to as classic hemophilia, this is the most prevalent kind of the illness and is brought on by a lack of clotting factor VIII. Approximately 80% of all hemophilia cases are of this kind. Hemophilia A can have varying degrees of severity; some people may have less severe symptoms, while others may have regular, severe bleeding episodes.

Hemophilia B: A lack of clotting factor IX is the cause of hemophilia B, sometimes referred to as Christmas illness. It makes up around 20% of instances of hemophilia, which is less prevalent than hemophilia A. Much like hemophilia A, hemophilia B can have mild to severe symptoms based on blood level factor IX concentration.^[6,7]

Pathophysiology

Genetic Basis and Inheritance Patterns: Gene mutations encoding clotting factors are the main cause of hemophilia, which is predominantly an inherited condition. Mutations in the F8 gene, which codes for clotting factor VIII, cause hemophilia A. On the other hand, mutations in the F9 gene, which codes for clotting factor IX, cause hemophilia B. Because both of the genes are found on the X chromosome, hemophilia is an X-linked recessive illness. Males are more commonly afflicted since they have only one X chromosome, whereas females have two X chromosomes and are usually carriers. However, if they have both X chromosomes containing the mutation or have dramatically decreased levels of the affected clotting factor as a result of lyonization, they may have symptoms.^[8,9,10]

Mechanisms of Bleeding and Clotting Abnormalities:

The normal blood coagulation cascade is disrupted when clotting factor VIII or IX is lacking or absent, which makes it difficult for a stable fibrin clot to form. Prolonged bleeding occurs as a result of this impairment, which inhibits the amplification of thrombin production, an enzyme essential to the clotting process. Excessive bleeding after operations or traumas and spontaneous bleeding episodes are signs of inadequate clot formation.

Clinical Manifestations

Symptoms and Severity: The blood's level of clotting factor activity is correlated with the severity of hemophilia.

- **Severe Hemophilia:** Less than 1% of normal factor levels. Individuals frequently have periods of spontaneous bleeding into soft tissues, muscles, and joints (hemarthrosis).

- **Moderate Hemophilia:** Factor concentrations between 1 and 5% of normal. Bleeding episodes are less common and frequently follow minor procedures or traumas.

- **Mild Hemophilia:** Factor levels in mild hemophilia range from 5 to 40% of normal. Usually, bleeding happens mainly following major surgeries or wounds.

Prolonged bleeding from wounds, frequent nosebleeds, severe bruises, hematuria (blood in the urine), and bleeding in the gastrointestinal tract are common symptoms. Joint hemorrhages can cause arthropathy and persistent pain, which can greatly reduce quality of life.^[11,12]

Diagnostic Criteria

- **Family History:** Examining the family history for bleeding diseases.
- **Clinical Evaluation:** History and bleeding patterns are noted.

Laboratory Tests

- Prolonged activated partial thromboplastin time (aPTT).
- Normal prothrombin time (PT) and bleeding time.
- Specific assays to measure the levels of factor VIII or IX activity to confirm the type and severity of hemophilia.
- Genetic testing to identify mutations in the F8 or F9 gene for definitive diagnosis.^[13,14,15]

Management of Hemophilia

Traditional Treatment Approaches

- **Factor Replacement Therapy:** This is the mainstay of hemophilia treatment, which is injecting clotting factor concentrates intravenously to stop or manage bleeding episodes. In patients with severe hemophilia in particular, prophylactic infusions are administered on a regular basis to maintain clotting factor levels and avoid spontaneous bleeding.

- **On-Demand Therapy:** Patients with mild to moderate hemophilia frequently get factor replacement therapy solely in reaction to bleeding episodes or before undergoing dental or surgical procedures.

Modern Therapeutic Advances

- **Extended Half-Life Factor Products:** These more recent versions of factor VIII and IX have been altered to extend their duration of activity, which lowers the number of prophylactic infusions required.

- **Gene Therapy:** This novel treatment seeks to implant functional copies of the faulty F8 or F9 gene into

the patient's liver cells, with the goal of permanently increasing the production of clotting factors. Promising outcomes have been shown in early clinical studies, when a considerable decrease in bleeding episodes and near-normal factor levels were attained by certain patients.

- **Non-Factor Therapies:** Patients with hemophilia A, especially those with inhibitors (antibodies that neutralize the infused clotting factors), might benefit from new medicines such as emicizumab, a bispecific antibody that mimics the activity of factor VIII.

In summary, sophisticated treatment alternatives including gene therapy and non-factor medicines have been added to standard factor replacement therapy, marking a substantial evolution in hemophilia care. For hemophiliac patients, these advancements mean a higher quality of life and better clinical results.^[16,17,18]

IMPORTANCE OF UNDERSTANDING CARDIOVASCULAR RISK IN HEMOPHILIA PATIENTS

Understanding cardiovascular risk in hemophilia patients is crucial for several reasons

1. Changing Demographics and Aging Population

Patients with hemophilia now live much longer because to advancements in therapy, especially the increasing use of clotting factor replacement medicines. Like the general population, these individuals are more vulnerable to age-related cardiovascular diseases (CVD) as they become older. This change calls for a more thorough comprehension of the cardiovascular hazards unique to hemophiliac individuals.

2. Unique Pathophysiological Interplay

Historically, hemophilia has been associated with a lower risk of thrombotic events because of persistent hypocoagulability. This protective effect isn't unaffected, though. Patients with hemophilia may still experience peripheral artery disease, myocardial infarction, and stroke. In clinical practice, the interaction between hypocoagulability and the risk of thrombosis must be carefully taken into account to prevent both bleeding and thrombotic consequences.

3. Increased Prevalence of Traditional Cardiovascular Risk Factors

Patients with hemophilia, like the general population, are more likely to have conventional cardiovascular risk factors such as diabetes, dyslipidemia, hypertension, and obesity. These disorders raise the risk of cardiovascular disease overall and may combine with consequences unique to hemophilia, such as joint disease and long-term effects from factor replacement treatment.

4. Impact of Hemophilia-Specific Treatments

New hemophilia medications and long-term factor replacement therapy may have an impact on the heart. Certain treatments, for example, may have an impact on

lipid metabolism or endothelial function, which may have an impact on cardiovascular health. Creating comprehensive care strategies that address bleeding and cardiovascular risks requires an understanding of these impacts.

5. Paradoxical Nature of Anticoagulation Therapy

Because anticoagulant medication raises the risk of bleeding, managing cardiovascular events in hemophiliac patients poses a special difficulty. It is difficult to strike a balance between managing bleeding risk and preventing thrombotic episodes; this calls for specific expertise and close observation. This contradiction highlights the value of interdisciplinary care teams and tailored treatment plans.

6. Need for Tailored Cardiovascular Risk Assessment and Management

Hemophiliac patients' risk profile may not be well reflected by conventional cardiovascular risk assessment instruments. Customized evaluation techniques that take into account characteristics unique to hemophilia as well as conventional cardiovascular risk factors are crucial. The creation and application of such instruments can enhance the precision of risk assessment and the efficacy of treatment and preventative measures.

7. Optimizing Clinical Outcomes

Better therapeutic results can result from a comprehensive understanding of cardiovascular risk in hemophilia patients, since this knowledge can inspire more effective interventions for CVD prevention, early identification, and therapy. In this particular demographic, this includes the potential to lower morbidity and death linked to cardiovascular problems.

8. Guiding Future Research

Future research efforts might be directed by identifying gaps in our present understanding of cardiovascular risk in hemophilia patients. This study may result in the creation of novel therapeutic strategies, improved administration of current therapies, and evidence-based protocols for the management of cardiovascular health in hemophiliac patients.

Improving the general health and quality of life of hemophilia patients requires a thorough understanding of their cardiovascular risk. To address the special demands and problems of this group, an interdisciplinary strategy including knowledge from cardiology, hematology, and other pertinent domains is necessary.^[19,20,21,22]

PREVALENCE OF CARDIOVASCULAR DISEASE IN HEMOPHILIA PATIENTS

Due to improved treatment outcomes and longer life expectancies for hemophiliac patients, there has been a growing focus on the incidence of cardiovascular disease (CVD) in this population. Even while hypocoagulability can be beneficial, hemophiliacs are not immune to CVD, according to current research. After adjusting for age and

conventional risk factors, their rates of myocardial infarctions, strokes, and other cardiovascular events are either somewhat lower or similar to those of the general population. Patients with hemophilia often have common cardiovascular disease risk factors, such as obesity, diabetes, dyslipidemia, and hypertension, which increase their risk of cardiovascular disease. Their cardiovascular health is further complicated by hemophilia-specific problems, such as joint disease that limits physical activity and the long-term consequences of factor replacement medication. Therefore, to successfully control bleeding risks and cardiovascular problems in this population, multidisciplinary treatment and routine cardiovascular screening are necessary.^[23,24]

RISK FACTORS FOR DEVELOPING CARDIOVASCULAR DISEASE IN PATIENTS WITH HEMOPHILIA

1. Age: One cardiovascular disease risk factor that cannot be changed is advanced age. Patients with hemophilia may experience an increased risk of cardiovascular events and age-related comorbidities.

2. Obesity: Patients with hemophilia are more likely to be obese, which raises their risk of insulin resistance, metabolic syndrome, dyslipidemia, and hypertension. Obesity increases the risk of atherosclerosis and cardiovascular events by causing endothelial dysfunction and persistent low-grade inflammation.

3. Hypertension: In individuals with hemophilia, hypertension is a substantial risk factor for cardiovascular disorders. High blood pressure raises the risk of myocardial infarction, stroke, and heart failure by causing endothelial damage, arterial stiffness, and an increased cardiac workload.

4. Dyslipidemia: Individuals who have hemophilia may experience dyslipidemia, which is typified by increased levels of triglycerides, total cholesterol, and low levels of HDL cholesterol. Dyslipidemia raises the risk of peripheral arterial disease, coronary artery disease, and stroke in addition to promoting atherosclerosis.

5. Diabetes Mellitus: Patients with hemophilia are more likely to develop cardiovascular illnesses if they have diabetes mellitus, type 1 or type 2. Chronic hyperglycemia raises the risk of cardiovascular events by accelerating atherosclerosis, oxidative stress, inflammation, and endothelial dysfunction.

6. Hemophilia-Specific Factors

a. Joint Disease: Osteoarthritis, cartilage degradation, and persistent synovitis are the hallmarks of hemophilia-related joint disease, which may increase the risk of cardiovascular disease. Diabetes, obesity, and cardiovascular problems are all exacerbated by joint disease-related reduced mobility and physical activity.

b. Chronic Inflammation: Subclinical bleeding, exposure to blood products, and recurrent joint hemorrhages cause hemophilic patients to endure chronic inflammation. Atherosclerosis, cardiovascular events, and endothelial dysfunction are all influenced by persistent inflammation.

c. Factor Replacement Therapy: Long-term usage of factor replacement treatment may raise the risk of thrombotic consequences, such as myocardial infarction, stroke, and venous thromboembolism. This is especially the case when using procoagulant drugs like factor VIII or IX concentrates.

7. Smoking: One important modifiable risk factor for cardiovascular disease is tobacco use. Smokers with hemophilia are more likely to experience cardiovascular events such as peripheral artery disease, myocardial infarction, and stroke.

8. Sedentary Lifestyle: A sedentary lifestyle raises the risk of obesity, hypertension, dyslipidemia, and other cardiovascular risk factors. It is linked to a lack of regular physical exercise. For certain individuals, joint problems associated with hemophilia and physical activity restrictions may be factors in their sedentary lifestyle.^[25,26,27,28]

MECHANISMS LINKING HEMOPHILIA AND CVD

Hemostatic system function, endothelial function, and conventional cardiovascular risk factors are all intricately entwined in the complicated pathways that connect hemophilia and cardiovascular disease (CVD). Because of its hypercoagulability, hemophilia has historically been associated with a lower risk of thrombotic events; however, new research points to a more complex link between hemophilia and CVD.

1. Endothelial Dysfunction: By controlling thrombosis, inflammation, and vasodilation, endothelial cells are essential for preserving vascular homeostasis. Chronic exposure to clotting factor deficits in hemophilia can cause endothelial dysfunction, which is typified by increased oxidative stress, pro-inflammatory cytokine production, and reduced nitric oxide bioavailability. Endothelial dysfunction contributes to the development of CVD by promoting thrombosis and atherosclerosis.

2. Chronic Inflammation: Patients with hemophilia frequently suffer from recurrent bouts of muscle and joint bleeding, which can cause tissue damage and chronic inflammation. In addition to making hemophilic arthropathy worse, persistent inflammation raises the risk of systemic inflammation, which is linked to atherosclerosis and cardiovascular events. In people with hemophilia, inflammatory mediators including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α) may hasten the development of endothelial dysfunction and atherosclerosis.

3. Altered Coagulation Profile: Although hypocoagulability is the hallmark of hemophilia, individuals may be at risk for thrombotic events in specific situations due to modifications in their coagulation profile. Von Willebrand factor (VWF), a glycoprotein that mediates platelet adhesion and thrombus formation, is frequently increased in hemophilic patients. A prothrombotic condition can result from increased VWF levels upsetting the delicate balance between bleeding and thrombosis when combined with lower levels of clotting factors.

4. Traditional Cardiovascular Risk Factors: Patients with hemophilia are susceptible to various common cardiovascular risk factors that are also present in the general population, including as diabetes, obesity, dyslipidemia, and hypertension. In individuals with hemophilia, these risk factors may exacerbate endothelial dysfunction, hasten atherosclerosis, and raise the chance of cardiovascular events. These risk factors may be made worse by lifestyle choices including poor eating and exercise habits.

5. Factor Replacement Therapy: The cornerstone of hemophilia therapy, clotting factor concentrates, when used over an extended period of time may have effects on cardiovascular health. Recombinant factor concentrates have the potential to cause thrombotic problems due to their capacity to induce immune responses or include procoagulant impurities. Further affecting cardiovascular health is the risk of venous thromboembolism and catheter-related infections associated with frequent venous access for factor infusions.

6. Genetic and Epigenetic Factors: The risk of hemophilia and CVD may be influenced by genetic and epigenetic changes. Hemophilia patients' vulnerability to thrombotic events may be influenced by polymorphisms in genes related to coagulation and inflammatory pathways. Histone modifications and DNA methylation are examples of epigenetic alterations that can modify gene expression patterns and aid in the pathophysiology of both disorders.^[29,30,31,32]

ASSESSMENT OF CARDIOVASCULAR RISK IN HEMOPHILIA

When evaluating cardiovascular risk in patients with hemophilia, a thorough assessment is conducted, taking into account both conventional cardiovascular risk factors and hemophilia-specific variables. Important actions in determining and diagnosing cardiovascular risk in this group are listed below.

1. Comprehensive Medical History

a. Cardiovascular History: Record any family or personal history of cardiovascular events, such as peripheral artery disease, myocardial infarction, and stroke.

b. Hemophilia History: Learn about the history of factor replacement therapy, joint disease, bleeding phenotype, and the severity of hemophilia.

2. Clinical Evaluation

a. Physical Examination: Conduct a comprehensive physical examination that includes taking blood pressure, calculating body mass index (BMI), and looking for indications of joint disease or other hemophilia-related problems.

b. Cardiovascular Symptoms: Look for signs of exertional tiredness, palpitations, chest discomfort, and shortness of breath that could indicate a cardiovascular condition.

3. Laboratory Investigations

a. Lipid Profile: To evaluate levels of total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides, obtain fasting lipid profiles.

b. Fasting Glucose: Determine your fasting glucose levels to check for diabetes mellitus, a major risk factor for heart disease.

c. Inflammatory Markers: Examine inflammatory indicators that may point to a higher risk of cardiovascular disease, such as interleukin-6 (IL-6) and C-reactive protein (CRP).

4. Coagulation Studies

a. Hemostatic Assays: Conduct coagulation tests to evaluate the degree and likelihood of bleeding associated with hemophilia. Determine the activity levels of factor VIII or IX and, if necessary, look for inhibitors.

5. Cardiac Imaging

a. Echocardiography: Examine the anatomy and function of the heart, check for abnormalities in the valves, and look for signs of myocardial infarction or heart failure.

b. Electrocardiography (ECG): Use ECG to look for signs of myocardial ischemia or infarction, arrhythmias, and abnormalities in conduction.

c. Stress Testing: If a patient has hemophilia and is at an elevated risk of cardiovascular disease, consider using stress testing to screen for inducible myocardial ischemia and assess functional ability.

6. Bleeding Risk Assessment

a. Bleeding Assessment Tool: To assess bleeding propensity and direct management decisions, use proven bleeding assessment methods, such as the International Society on Thrombosis and Haemostasis (ISTH) bleeding assessment tool.

7. Multidisciplinary Collaboration

a. Hematology: Work together with hematologists to enhance treatment plans for preventative treatment and factor replacement therapy in hemophilia.

b. Cardiology: Seek the advice of cardiologists for expert assessment and treatment of problems and risk factors related to the heart.

8. Shared Decision-Making

a. Patient Education: Inform patients with hemophilia about lifestyle changes, treatment recommendations, and their cardiovascular risk profile.

b. Shared Decision-Making: Work with patients to create customized treatment regimens that successfully strike a balance between bleeding and cardiovascular risks.

9. Follow-Up and Monitoring

a. Regular Follow-Up: Arrange for frequent follow-up appointments to track cardiovascular risk factors, evaluate the effectiveness of treatment, and modify management plans as necessary.

b. Longitudinal Monitoring: Evaluate hemophiliac patients over an extended period of time to evaluate changes in cardiovascular risk and to maximize the effectiveness of preventative measures.

Healthcare practitioners can determine cardiovascular risk in hemophilia patients and adopt interventions to decrease risk and enhance outcomes by adhering to these guidelines and including multidisciplinary teamwork.^[33,34,35,36]

CLINICAL MANAGEMENT OF CARDIOVASCULAR RISK IN HEMOPHILIA Preventive Strategies

1. Lifestyle Modifications

- **Diet:** Promote a heart-healthy diet low in sodium, cholesterol, trans fats, and saturated fats and high in fruits, vegetables, whole grains, and lean meats.

- **Exercise:** To maintain a healthy weight and enhance cardiovascular fitness, encourage consistent aerobic activity that is adapted to the patient's capacities.

- **Smoking Cessation:** In order to lower cardiovascular risk, assist and educate people with hemophilia who wish to give up.

- **Weight Management:** Provide guidance on techniques for controlling weight, such as calorie restriction, portion control, and regular.^[37,38]

2. Pharmacologic Interventions

- **Hypertension Management:** Start using antihypertensive drugs to lower blood pressure and lower the risk of cardiovascular disease.

- **Lipid-Lowering Therapy:** To control dyslipidemia and lessen the risk of atherosclerotic cardiovascular disease, use statins or other lipid-lowering medications.^[39,40]

Treatment of Established CVD

1. Balancing Anticoagulation and Bleeding Risk

- When administering anticoagulant treatment to hemophilia patients, exercise caution and weigh the danger of bleeding against the risk of thrombosis.

- Because non-vitamin K antagonist oral anticoagulants (NOACs) have a reduced bleeding risk profile than warfarin, use them as the recommended agent.

2. Use of Antiplatelet and Anticoagulant Therapies

- In patients with hemophilia who are at elevated risk of cardiovascular events, antiplatelet medication combined with low-dose aspirin may be used as a primary or secondary preventive measure.

- Use anticoagulant and antiplatelet medications sparingly, considering the risks of thrombosis and bleeding in each unique situation.

Special Considerations

1. Management During Surgical Procedures

- Hemophiliac patients should have their bleeding risk during surgical procedures properly coordinated with hematologists and surgeons.

- To reduce the risk of bleeding issues, modify factor replacement treatment and take into account additional hemostatic medications.

2. Monitoring and Follow-Up Protocols:

- Arrange for routine follow-up appointments to track cardiovascular risk factors, evaluate the effectiveness of treatment, and make any necessary adjustments to management plans.

- Evaluate hemophiliac patients over an extended period of time to evaluate changes in cardiovascular risk and to maximize the effectiveness of preventative measures.

Healthcare professionals may successfully control cardiovascular risk in hemophilia patients and enhance long-term results by putting these preventative techniques into practice, treating cardiovascular illness that has already been diagnosed, and taking particular precautions.^[41,42]

EMERGING THERAPIES AND FUTURE DIRECTIONS IN MANAGING CARDIOVASCULAR RISK IN PATIENTS WITH HEMOPHILIA

Because of the interaction between their underlying hemostatic condition and established cardiovascular risk factors, hemophiliac patients confront particular challenges in controlling their risk of cardiovascular disease. Future possibilities and developing medicines

provide interesting opportunities for improving cardiovascular outcomes in this group as our awareness of this intricate relationship continues to grow.

1. Gene Therapy

a. Potential Benefits: By providing the chance for a permanent treatment of the underlying coagulation problem, gene therapy has great promise for hemophilia patients. With the development of gene therapy technologies, hemophilia-related problems including joint disease and chronic inflammation that raise the risk of cardiovascular disease may also be addressed.

b. Cardiovascular Impact: Future versions of gene therapy strategies could include cardiovascular-specific targets to reduce thrombotic and atherosclerotic risk factors, even if the main goal of present techniques is to restore coagulation factor levels.

2. Personalized Medicine

a. Tailored Treatment Strategies: Owing to developments in precision medicine and genetic profiling, hemophilia patients may now get customized treatment plans that are based on their unique genetic composition, bleeding phenotype, and cardiovascular risk profile.

b. Risk Prediction Models: By incorporating biomarker, clinical, and genetic data into prediction models, hemophilia patients at increased cardiovascular risk can be identified early and treated with targeted therapies and preventative measures.

3. Novel Antithrombotic Therapies

a. Balancing Bleeding and Thrombotic Risks: Upcoming antithrombotic medications seek to provide hemophilia patients with minimal bleeding problems while also reducing thrombotic occurrences. New drugs with better modes of action and safety profiles could provide more effective thromboprophylaxis without sacrificing hemostasis.

b. Targeted Anticoagulation: Studies investigating techniques for targeted anticoagulation, such as tissue factor pathway inhibition or factor XI inhibition, show promise in lowering thrombotic risk and decreasing bleeding problems in individuals with hemophilia.

4. Lifestyle Interventions

a. Digital Health Solutions: Wearable technology and smartphone applications, among other digital health innovations, provide people with hemophilia with cutting-edge means of encouraging lifestyle changes and enhancing cardiovascular health outcomes. With the help of these technologies, patients may actively control their cardiovascular risk by monitoring their diet, exercise routine, and medication compliance in real-time.

b. Integrated Care Models: Hemophilia patients can receive comprehensive support from integrated care

models that address their needs for managing cardiovascular risk as well as bleeding, and which include multidisciplinary teams of hematologists, cardiologists, physiotherapists, nutritionists, and mental health professionals.

5. Longitudinal Outcome Studies

a. Real-World Data Analysis: By utilizing real-world data from extensive hemophilia registries and electronic health records, longitudinal outcome studies can offer important insights into the cardiovascular risk profile of hemophilia patients over the long term and the efficacy of current management approaches.

b. Health Economics Research: By assessing the cost-effectiveness of cardiovascular risk management strategies in hemophilia patients, health economics research may help determine the best way to allocate scarce healthcare resources and shape healthcare policy.^[43,44,45]

CONCLUSION

Conclusively, this review offers significant perspectives on the intricate relationship between hemophilia and cardiovascular risk, illuminating the growing comprehension of this crucial health issue. Due to their hypocoagulable state, hemophiliacs have historically been thought to be at lower risk for cardiovascular diseases; however, new research shows that traditional cardiovascular risk factors are becoming more common in this population, as well as the possibility of thrombotic complications. This review emphasizes the significance of customized risk assessment, multidisciplinary teamwork, and individualized care techniques to enhance cardiovascular health outcomes in patients with hemophilia through a thorough synthesis of existing research. Future research and therapeutic developments are crucial to addressing the particular difficulties hemophilia patients have due to cardiovascular risk and enhancing their general quality of life.

REFERENCES

1. Flora GD, Nayak MK. A Brief Review of Cardiovascular Diseases, Associated Risk Factors and Current Treatment Regimes. *Curr Pharm Des.*, 2019; 25(38): 4063-4084.
2. Adhikary D, Barman S, Ranjan R, et al. (October 10, 2022) A Systematic Review of Major Cardiovascular Risk Factors: A Growing Global Health Concern. *Cureus*, 2022; 14(10): e30119.
3. Pazos-López P, Peteiro-Vázquez J, Carcía-Campos A, García-Bueno L, de Torres JP, Castro-Beiras A. The causes, consequences, and treatment of left or right heart failure. *Vasc Health Risk Manag.*, 2011; 7: 237-54.
4. Yang J, Park B A scoping review key elements and effects of cardiovascular disease management programs based on community-based participatory research. *PLoS ONE*, 2023; 18(1): e0279563.

5. Maharani A, Sujarwoto, Praveen D, Oceandy D, Tampubolon G, Patel A. Cardiovascular disease risk factor prevalence and estimated 10-year cardiovascular risk scores in Indonesia: The SMARTHealth Extend study. *PLoS One*, 2019 Apr 30; 14(4): e0215219.
6. Kaufman RJ, Powell JS. Molecular approaches for improved clotting factors for hemophilia. *Blood.*, 2013 Nov 21; 122(22): 3568-74. doi: 10.1182/blood-2013-07-498261
7. Kar A, Phadnis S, Dharmarajan S, Nakade J. Epidemiology & social costs of haemophilia in India. *Indian J Med Res.*, 2014 Jul; 140(1): 19-31
8. Pezeshkpoor B, Oldenburg J, Pavlova A. Insights into the Molecular Genetic of Hemophilia A and Hemophilia B: The Relevance of Genetic Testing in Routine Clinical Practice. *Hamostaseologie*, 2022 Dec; 42(6): 390-399.
9. Sarmiento Doncel S, Díaz Mosquera GA, Cortes JM, Agudelo Rico C, Meza Cadavid FJ, Peláez RG. Haemophilia A: A Review of Clinical Manifestations, Treatment, Mutations, and the Development of Inhibitors. *Hematol Rep.*, 2023 Feb 16; 15(1): 130-150.
10. A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A|NEJM. [(accessed on 7 September 2021)].
11. Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A. Definitions in hemophilia: communication from the SSC of the ISTH. *J Thromb Haemost.*, 2014; 12(11): 1935-1939.
12. Castaman G, Matino D. Hemophilia A and B: molecular and clinical similarities and differences. *Haematologica*, 2019 Sep; 104(9): 1702-1709.
13. Palmer RL. Laboratory diagnosis of bleeding disorders. Basic screening tests. *Postgrad Med.*, 1984 Dec; 76(8): 137-42, 147-8.
14. Lollar P. Pathogenic antibodies to coagulation factors. Part one: factor VIII and factor IX. *J Thromb Haemost.*, 2004; 2(7): 1082-1095.
15. Carcao MD. The diagnosis and management of congenital hemophilia. *Semin Thromb Hemost.*, 2012; 38(7): 727-734.
16. Sahu S, Lata I, Singh S, Kumar M. Revisiting hemophilia management in acute medicine. *J Emerg Trauma Shock.*, 2011 Apr; 4(2): 292-8.
17. GN, Nikisha & Menezes, Dr. Godfred. Hemophilia and Its Treatment: Brief Review. *International Journal of Pharmaceutical Sciences Review and Research*, 2014; 26: 277-283.
18. Okaygoun, D., Oliveira, D.D., Soman, S. *et al.* Advances in the management of haemophilia: emerging treatments and their mechanisms. *J Biomed Sci.*, 2021; 28: 64.
19. Sousos N, Gavriilaki E, Vakalopoulou S, Garipidou V. Understanding cardiovascular risk in hemophilia: A step towards prevention and management. *Thromb Res.*, 2016 Apr; 140: 14-21.
20. Tuinenburg, Attie & Mauser-Bunschoten, Eveline & Verhaar, Marianne & Biesma, Douwe & Schutgens, Roger. Cardiovascular disease in patients with hemophilia. *Journal of Thrombosis and Haemostasis*, 2008; 7: 247-254. 10.1111
21. DiMarco JP, Flaker G, Waldo AL, Corley SD, Greene HL, Safford RE, Rosenfeld LE, Mitrani G, Nemeth M; AFFIRM Investigators. Factors affecting bleeding risk during anticoagulant therapy in patients with atrial fibrillation: observations from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Am Heart J.*, 2005 Apr; 149(4): 650-6.
22. Sood, Suman & Cheng, Dunlei & Ragni, Margaret & Kessler, Craig & Quon, Doris & Shapiro, Amy & Key, Nigel & Manco-Johnson, Marilyn & Cuker, Adam & Kempton, Christine & Wang, Tzu-Fei & Eyster, M & Kuriakose, Philip & Drygalski, Annette & Gill, Joan & Wheeler, Allison & Kouides, Peter & Escobar, Miguel & Leissing, Cindy & Konkle, Barbara. A cross-sectional analysis of cardiovascular disease in the hemophilia population. *Blood advances*, 2018; 2: 1325-1333.
23. Franchini M, Focosi D, Mannucci PM. How we manage cardiovascular disease in patients with hemophilia. *Haematologica*, 2023 Jul 1; 108(7): 1748-1757.
24. Badescu MC, Badulescu OV, Butnariu LI, Bararu Bojan I, Vladeanu MC, Dima N, Vlad CE, Foia LG, Ciocoiu M, Rezus C. Cardiovascular Risk Factors in Patients with Congenital Hemophilia: A Focus on Hypertension. *Diagnostics*, 2022; 12(12): 2937.
25. Shapiro S., Benson G., Evans G., Harrison C., Mangles S., Makris M. Cardiovascular disease in hereditary haemophilia: The challenges of longevity. *Br. J. Haematol*, 2022; 197: 397-406. doi: 10.1111/bjh.18085.
26. Badescu MC, Badulescu OV, Costache AD, Mitu O, Lupu VV, Dmour BA, Lupu A, Foia LG, Costache II, Rezus C. Atherosclerosis in Patients with Congenital Hemophilia: A Focus on Peripheral Artery Disease. *Life (Basel)*, 2023 Nov 18; 13(11): 2221.
27. Penotti M, Nencioni T, Gabrielli L, Massimiliano F, Castiglioni E, Polvani F. Blood flow variations in internal carotid and middle cerebral arteries induced by post-menopausal hormone replacement therapy. *Am J Obstet Gynecol*, 1993; 169: 1226-1232.
28. Knobe K, Berntorp E. Haemophilia and joint disease: pathophysiology, evaluation, and management. *J Comorb.*, 2011 Dec 27; 1: 51-59.
29. Kamphuisen, Pieter & Eikenboom, Jeroen & Bertina, Rogier. Elevated Factor VIII Levels and the Risk of Thrombosis. *Arteriosclerosis, thrombosis, and vascular biology*, 2001; 21: 731-8.
30. Solovey A, Kollander R, Milbauer LC, Abdulla F, Chen YIE, Kelm RJ, Heibel RP. Endothelial nitric oxide synthase and nitric oxide regulate endothelial

- tissue factor expression in vivo in the sickle transgenic mouse. *Am J Hematol*, 2010; 85: 41–45.
31. Wolberg A.S., Sang Y. Fibrinogen and Factor XIII in Venous Thrombosis and Thrombus Stability. *Arter. Thromb. Vasc. Biol.*, 2022; 42: 931–941.
 32. Shi Y, Zhang H, Huang S, Yin L, Wang F, Luo P, Huang H. Epigenetic regulation in cardiovascular disease: mechanisms and advances in clinical trials. *Signal Transduct Target Ther.*, 2022 Jun 25; 7(1): 200.
 33. Yu, D., Zhao, Z. & Simmons, D. Cardiovascular risks and bleeding with non-vitamin K antagonist oral anticoagulant versus warfarin in patients with type 2 diabetes: a tapered matching cohort study. *Cardiovasc Diabetol*, 2020; 19: 174.
 34. Bowyer AE, Gosselin RC. Factor VIII and Factor IX Activity Measurements for Hemophilia Diagnosis and Related Treatments. *Semin Thromb Hemost*, 2023 Sep; 49(6): 609-620.
 35. Fasulo MR, Biguzzi E, Abbattista M, Stufano F, Pagliari MT, Mancini I, Gorski MM, Cannavò A, Corgiolu M, Peyvandi F, Rosendaal FR. The ISTH Bleeding Assessment Tool and the risk of future bleeding. *J Thromb Haemost*, 2018 Jan; 16(1): 125-130.
 36. Sharathkumar AA, Soucie JM, Trawinski B, Greist A, Shapiro AD. Prevalence and risk factors of cardiovascular disease (CVD) events among patients with haemophilia: experience of a single haemophilia treatment centre in the United States (US). *Haemophilia*, 2011; 17(4): 597-604.
 37. Ghodeswar GK, Dube A, Khobragade D. Impact of Lifestyle Modifications on Cardiovascular Health: A Narrative Review. *Cureus.*, 2023 Jul 28; 15(7): e42616.
 38. Yu E, Malik VS, Hu FB. Cardiovascular Disease Prevention by Diet Modification: JACC Health Promotion Series. *J Am Coll Cardiol.*, 2018 Aug 21; 72(8): 914-926.
 39. Borghi C, Fogacci F, Agnoletti D, Cicero AFG. Hypertension and Dyslipidemia Combined Therapeutic Approaches. *High Blood Press Cardiovasc Prev.*, 2022 May; 29(3): 221-230.
 40. Obarzanek E, Sacks FM, Vollmer WM, Bray GA, Miller ER, 3rd, Lin PH, Karanja NM, Most-Windhauser MM, Moore TJ, Swain JF, Bales CW, Proschan MA, DASH Research Group Effects on blood lipids of a blood pressure-lowering diet: the Dietary Approaches to Stop Hypertension (DASH) Trial. *Am J Clin Nutr.*, 2001; 74(1): 80–9.
 41. Janardan J, Gibbs H. Combining anticoagulation and antiplatelet drugs in coronary artery disease. *Aust Prescr.*, 2018 Aug; 41(4): 111-115.
 42. Rodríguez-Merchán EC, De Pablo-Moreno JA, Liras A. Gene Therapy in Hemophilia: Recent Advances. *Int J Mol Sci.*, 2021 Jul 17; 22(14): 7647.
 43. Akhondzadeh S. Personalized medicine: a tailor made medicine. *Avicenna J Med Biotechnol.*, 2014 Oct; 6(4): 191.
 44. Santo K, Redfern J. Digital Health Innovations to Improve Cardiovascular Disease Care. *Curr Atheroscler Rep.*, 2020 Oct 3; 22(12): 71.
 45. Hay CRM, Shima M, Makris M, Jiménez-Yuste V, Oldenburg J, Fischer K, Iorio A, Skinner MW, Santagostino E, von Mackensen S, Kessler CM. Challenges and key lessons from the design and implementation of an international haemophilia registry supported by a pharmaceutical company. *Haemophilia*, 2020 Nov; 26(6): 966-974.
 46. Schopohl, Dorothee & Bidlingmaier, Christoph & Herzig, D. & Klamroth, Robert & Kurnik, Karin & Rublee, Dale & Schramm, Wolfgang & Schwarzkopf, Larissa & Berger, Karin. Prospects for research in haemophilia with real-world data—An analysis of German registry and secondary data. *Haemophilia*, 2018; 24.