

Therapeutic problems in elderly patients with hemophilia

Krystyna Zawilska¹, Maria Podolak-Dawidziak²

¹ Department of Hematology and Internal Diseases, Struś Hospital, Poznań, Poland

² Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation, Wrocław Medical University, Wrocław, Poland

KEY WORDS

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ABSTRACT

Since the introduction of clotting factor concentrates, the life expectancy of patients with hemophilia has increased from 40 years in the 1960s to 60 or even 70 years today. In Poland, almost all elderly patients with hemophilia have arthropathy, the majority are infected with hepatitis C virus (HCV), and some even with hepatitis B or human immunodeficiency virus. Liver cirrhosis associated with HCV infection develops within 15 to 20 years in 20% to 30% of these patients. Coexistent diseases related to aging and affecting the heart, kidneys, and other organs constitute another challenge. To prevent ischemic heart disease, cardiovascular risk factors should be carefully monitored.

The present paper describes the current recommendations for the use of antithrombotic therapy for acute coronary syndromes and atrial fibrillation in patients with hemophilia. Changes in the urinary system in hemophiliacs develop with age, often leading to dialysis. There is an urgent need for intensive physiotherapy and improved access to orthopedic treatment for patients with arthropathy. High-risk surgical procedures in these patients should be performed in specialized centers with an experienced team and a coagulation laboratory. Older patients with mild hemophilia are at an increased risk for inhibitor development following intensive factor replacement therapy for surgical or invasive procedures. Pain control is a particular challenge due to contraindications to the use of many effective analgesics; another concern is the quality of life of these patients. An increasing number of older patients with hemophilia requires a comprehensive diagnostic and therapeutic approach, preferably at hematological centers.

Introduction The life expectancy of patients with hemophilia has increased from 40 years in the 1960s to 60 and even 70 years at present, excluding the period of high mortality in the 1980s and 1990s due to widespread infection with human immunodeficiency virus (HIV).¹ Nowadays, an increasing number of these patients are above 65 years of age. The mean age of all 858 hemophilia patients registered in the HemoRec registry of inherited bleeding disorders in Poland in August 2009 was 26.2 years, compared with 37.3 years in the general Polish male population in 2008.² The percentage of patients with hemophilia over 40 years of age was also significantly lower than that of the general male population in Poland (20.8% for hemophilia A and 16.4% for hemophilia B vs. 40.8% for the general population).³ In our opinion, these results were due to the lack of adequate prophylactic treatment in Poland as well as increased mortality

due to viral hepatitis C. The analysis of data from 2269 hemophilia patients in the Polish registry of inherited bleeding disorders published recently showed that the mean age of patients with hemophilia A was 30.9 years and that of patients with hemophilia B – 29.2 years.⁴ In the Poznań Hemophilia Treatment Center, there are 69 patients aged 45 years and older (26% of all 261 patients). Older patients with hemophilia did not have access to replacement therapy when they were 25- to 30-years old, which led to severe arthropathy, chronic pain, deterioration of their social status, lower quality of life, and depression.^{5,6} In addition, the majority of elderly patients become infected with hepatitis B and C virus (HBV and HCV), and, in some countries, also with HIV. In Poland, the presence of RNA HCV was reported in 77.3% of selected patients with severe hemophilia, who had received intravenous infusions of fresh frozen plasma, cryoprecipitate, or

Correspondence to:

Prof. Krystyna Zawilska, MD, PhD,
Oddział Hematologii i Chorób
Wewnętrznych, Wielospecjalistyczny
Szpital Miejski im. J. Strusia,
ul. Szkolna 8, 61-833 Poznań, Poland,
phone: +48-61-858-56-36,
fax: +48-61-852-76-11,
e-mail: k.zawilska@interia.pl

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blood before 1991. The presence of hepatitis B surface antigen was reported in 9% of these patients.⁷ Compared with the Western European countries and the United States, the prevalence of HIV infection in Poland is several times lower and is limited to a dozen or so cases.

A significant challenge in elderly patients with hemophilia are coexistent diseases related to aging and including cardiac, renal, and neoplastic diseases, degenerative joint lesions, chronic pain, prostatic hypertrophy, or sexual dysfunction. In the group of hemophilia patients aged above 65 years, 77% have 2 other coexistent diseases.⁸ Recently, a retrospective chart review has been published including 63 hemophilia patients from the Gulf States Hemophilia and Thrombophilia Center (United States) who were 40 years of age and older (16% of 404 patients).⁹ The mean age of the cohort was approximately 53 years for patients with hemophilia A (71% of the patients) and 54 years for patients with hemophilia B. The review showed that all patients had at least 1 comorbid condition other than hemophilia, and the majority had between 3 and 6 comorbidities. The most common conditions were chronic hepatitis C, hypertension, HIV, chronic arthropathy, and overweight/obesity. Optimal treatment and care for hemophiliacs with multiple comorbid conditions is a challenge both for health-care providers and patients. At present, the most frequent causes of death of hemophiliacs are not hemorrhages but liver cirrhosis, ischemic heart disease, neoplastic disease, and stroke. In elderly patients with hemophilia, numerous various diseases may coexist, which requires a multispecialty assessment and treatment coordination, preferably in hemophilia treatment centers. Hemophilia is an expensive disease, and the understanding of both treatment needs and related costs among aging hemophiliacs with comorbidities is critical to provide optimal and effective care.

Hepatitis C, liver cirrhosis, and hepatocellular carcinoma related to hepatitis C virus infection in hemophiliacs

Hepatitis C is a major comorbidity in patients with inherited bleeding disorders and the leading cause of morbidity and mortality in patients with hemophilia. Once infected, about 10% to 20% of the patients are able to clear the virus spontaneously, while the others develop chronic hepatitis. Untreated HCV infection induces liver fibrosis which may lead to liver failure and/or cirrhosis. In an international multicenter cohort study, the progression to end-stage liver disease (ESLD) was investigated in patients with inherited bleeding disorders who had been infected with HCV between 1961 and 1990, and were followed up until August 2005. HCV was cleared spontaneously in 19% of the patients, while chronic hepatitis C developed in 81%. Coinfection with HIV was reported in 210 patients. After 35 years of infection, the cumulative incidence of ESLD in all patients with chronic hepatitis C was 17.1%, but it was only 2.1% in those

who spontaneously cleared HCV ($P < 0.001$). After 20 years of infection, the incidence of ESLD for HIV-negative patients with chronic hepatitis C was 0.53 per 100 person-years vs. 2.63 for patients with HIV coinfection.¹⁰

The assessment of fibrosis may require liver biopsy. Physicians still somewhat reluctantly perform biopsy in hemophiliacs due to possible bleeding complications. However, with adequate coagulation factor coverage with infused concentrate to achieve the levels of 80 to 100 U/dl prior to biopsy, then with continued factor replacement to maintain the levels above 50 U/dl for 3 to 4 days after biopsy, the rate of clinically significant bleeding can be minimized to 1%–2%.^{11,12}

The Canadians introduced transient elastography (Fibroscan) – a noninvasive alternative diagnostic method for liver fibrosis assessment in hemophilia patients.^{13,14} Due to the risk of liver cirrhosis and hepatocellular carcinoma (HCC), patients with hemophilia and chronic hepatitis should be regularly monitored. Liver tests (alanine transaminase [ALT] and γ -glutamyltranspeptidase) and platelet count should be performed twice a year, prothrombin time and α -fetoprotein once a year, transient elastography every 2 years, and ultrasound every 3 years.¹⁵ Efficacy of HCV antiviral treatment depends on hemophilia genotype. In hemophiliacs with the most common genotype 1 or genotype 4, the response rate is about 50%, but in patients with genotypes 2 and 3, it is as high as from 80% to 90%.¹⁶ Coinfection with HIV adversely affects the effectiveness of anti-HCV treatment.¹⁶ Approximately from 20% to 30% of the patients with HCV infection develop liver cirrhosis within 20 to 30 years.¹⁷ The risk of cirrhosis is greater in men, patients who are older at the time of infection, and in those coinfecting with HBV or HIV. The presence of concomitant liver diseases, obesity, diabetes, and heavy alcohol consumption additionally increase the risk.¹⁸ Patients with liver cirrhosis are at a higher risk for HCC. In 2000, from 60% to 70% of HCC incidence in Europe and from 50% to 60% in North America was related to hepatitis C.¹⁹ In Poland, the background incidence of HCC can be even higher because at the end of the 1980s, the reported hepatitis B incidence was one of the highest in Europe (45 cases per 100,000 inhabitants per year).²⁰ However, in 2004, after the implementation of a comprehensive public health program, it dropped to 4.1 cases per 100,000 inhabitants per year.²¹

Risk factors, a natural history, and possibility of curative treatment of early-detected HCC in hemophiliacs with chronic hepatitis C was assessed in an Italian prospective study in 385 patients with bleeding disorders (311 with hemophilia A, 60 with hemophilia B, and 14 with von Willebrand disease) who had been treated with blood or plasma derivatives for at least 10 years.²² All patients had persistently elevated ALT. Annual liver ultrasound and measurement of the α -fetoprotein level were performed. The majority of patients

(355 of 385) had serum antibody to HCV and 141 had serum antibody to HIV. During 48 months of follow-up, 6 HCC cases were diagnosed. Liver cirrhosis, an increase in the α -fetoprotein level, active HCV infection, and age over 45 years at diagnosis were risk factors for HCC.

Few reports have been published on liver transplantation in patients with hemophilia and inhibitor to factor VIII (FVIII).^{23–25} FVIII replacement therapy was managed by continuous infusion and could be stopped at a median of 36 hours after transplantation.²⁶ Liver transplantation is not contraindicated in HIV-positive patients with full viral suppression (HAART Study). The risk of death due to liver disease in hemophiliacs is 16.7 times higher than in the general population.²⁷

Cardiovascular disease in hemophilia Cardiovascular diseases are a growing problem in patients with hemophilia, particularly because of the aging process and because they are at a risk for vessel closure or myocardial infarction due to increased FVIII or FIX activity following factor administration.

In a review published by Girolami et al.²⁶ in 2006, of all 42 cases of myocardial infarction and other arterial occlusions in hemophilia A patients reported in the literature, in the majority of patients (22 of 36) myocardial infarction occurred during or briefly after the infusion of clotting factor concentrates (factor VIII, activated or nonactivated prothrombin complex concentrates or recombinant factor VIIa preparations). In 3 cases, the vascular complications were linked to intravenous desmopressin administration.

In the group of 100 elderly patients with hemophilia and the control group of 200 men matched for age, the prevalence of risk factors for ischemic heart disease was assessed. The analysis showed higher incidence of arterial hypertension and higher glucose concentration but lower rate of hypercholesterolemia in hemophiliacs.²⁷ Medical imaging showed that the size of atherosclerotic plaques in the aorta of patients with hemophilia or von Willebrand disease was lower by approximately 30% compared with patients without hemorrhagic diathesis. However, the coronary artery calcification score was similar in all patients.²⁹ Thus, it seems that the risk of atherosclerosis in hemophilia is similar or slightly smaller than in the remaining population. Moreover, it was demonstrated that there was a minimal mortality risk due to severe coronary event in hemophiliacs, which may result from rarer (as a consequence of coagulation disorders related to hemophilia) thrombus formation occluding the lumen of the coronary artery following atherosclerotic plaque rupture.

To assess mortality risk associated with atherosclerotic cardiovascular complications in hemophiliacs, the Framingham scale can be used. It takes into consideration mainly age, smoking, systolic arterial pressure, and total cholesterol

concentration. In order to prevent atherosclerosis in hemophilia patients, the risk factors should be carefully monitored: body weight should be within the normal range (body mass index $<25 \text{ kg/m}^2$), arterial pressure should not exceed 140/90 mmHg, low-density lipoprotein cholesterol should be below 2.5 mmol/l, and fasting glycemia below 6.1 mmol/l.³⁰ The observation of patients with ischemic heart disease demonstrated that intensive conservative treatment including the reduction of all existing atherosclerosis risk factors reduced the rate of arterial ischemic incidents from 65% to 30% in 13 years.³¹ Support from physical therapists at treatment centers may play a vital role in promoting an active lifestyle within the boundaries of a patient's abilities. A successful medical management of multivessel coronary artery disease has been reported in a 54-year-old patient with moderate hemophilia A with FVIII inhibitor, optimization of hypertension and hyperlipidemia, and intensive lifestyle changes, without antiplatelet therapy.³²

Evidence-based guidelines on the treatment of coexistent diseases in hemophiliacs are not available, but data from treatment centers for patients with hemophilia and coexistent diseases suggest that those patients should be treated, if possible, like their counterparts without hemophilia and with the same coexistent diseases, but, additionally, should be provided with suitable preventive treatment with FVIII or FIX concentrate.³³ Recently, more detailed recommendations have been published based on the data from 2 large European treatment centers (the Bianchi Bonomi Hemophilia and Thrombosis Center in Milan and Van Creveldclinic in Utrecht).³⁴

Nonvalvular atrial fibrillation Permanent nonvalvular atrial fibrillation (AF) increases the risk of embolic complications in cerebral vessels and distal arteries. It is uncertain whether patients with hemophilia are protected against these complications by their coagulation defect, so it is rational to assume that they have the same risk as patients without hemophilia. The first attempt to control rhythm should be by cardioversion together with anticoagulant therapy with vitamin K antagonists (VKAs) – warfarin or acenocoumarol (international normalized ratio [INR], 2.0–3.0). This challenge can be successfully addressed by implementing continuous prophylaxis with factor concentrate, with the goal of maintaining plasma FVIII or FIX levels of 30% or higher. It must be highlighted that such treatment is extremely expensive.

In patients who are not suitable for cardioversion or in whom this procedure fails, the choice of treatment depends on the initial activity of FVIII and on the risk of thromboembolism, measured by the CHADS₂ coefficient. It remains to be seen whether the newly proposed CHA₂DS₂-VASc score³⁵ is a better predictor of cardioembolism in patients with hemophilia.

In patients without hemophilia, the score of 2 points or higher indicates the necessity of antithrombotic therapy with the use of an anticoagulant (VKAs, direct thrombin, or FXa inhibitor). The score of 1 enables the choice between the above antithrombotic therapy and the use of acetylsalicylic acid (ASA). The score of 0 indicates that a patient may not require antithrombotic treatment. In patients with AF and severe hemophilia A with a CHADS₂ score of 1, the preferred thromboprophylaxis is low-dose ASA and maintaining trough levels of FVIII above 10%. In all patients with hemophilia and a CHADS₂ score of 2 or higher, VKAs should be introduced (INR, 2.0–3.0), together with continuous prophylaxis with factor concentrate, with the goal of maintaining plasma FVIII or FIX levels of 30% or higher. In patients with mild hemophilia B, therapy with warfarin or acenocoumarol decreases plasma FIX activity; therefore, replacement therapy should be implemented as in those with severe hemophilia (plasma FIX level, $\geq 30\%$).

So far, there have been no studies that evaluated the effectiveness and safety of new oral antithrombotic drugs, i.e., direct FXa or thrombin inhibitors, in patients with hemophilia complicated by AF.

Acute coronary syndrome The decision on the treatment of acute coronary syndrome (ACS) in hemophiliacs requires the cooperation between a cardiologist and a hematologist. In patients with severe hemophilia, it is necessary to choose less aggressive and more conservative treatment than that recommended for patients with ACS and no congenital bleeding disorder. Thrombolytic therapy for myocardial infarction is unjustified in these patients due to an unacceptable risk of hemorrhage and should be substituted by alternative methods such as percutaneous coronary intervention (PCI).⁶ Usually, primary PCI is not indicated in unstable angina pectoris and non-ST segment elevation. Anticoagulant treatment should be started with bolus intravenous dose of unfractionated heparin and continued for 2 to 3 days, together with dual antiplatelet therapy with ASA and clopidogrel (FIGURE). Daily low-dose ASA should be continued indefinitely, while clopidogrel is usually stopped 4 weeks after the initiation of treatment.

If a patient with hemophilia develops ST-elevation myocardial infarction (STEMI), every effort should be made to provide facilities for primary PCI, ideally within 12 hours from the onset of STEMI. The radial artery access is preferable because of lesser risk of hematoma. Bare-metal stents should be placed because they require shorter duration of dual antiplatelet therapy (4 weeks) and therefore shorter period of intensive prophylaxis for maintaining the factor level of 30% or higher. The early management of STEMI with inhibitors of glycoprotein IIb/IIIa is not recommended because of too high a risk of bleeding. When preparing for heparin treatment

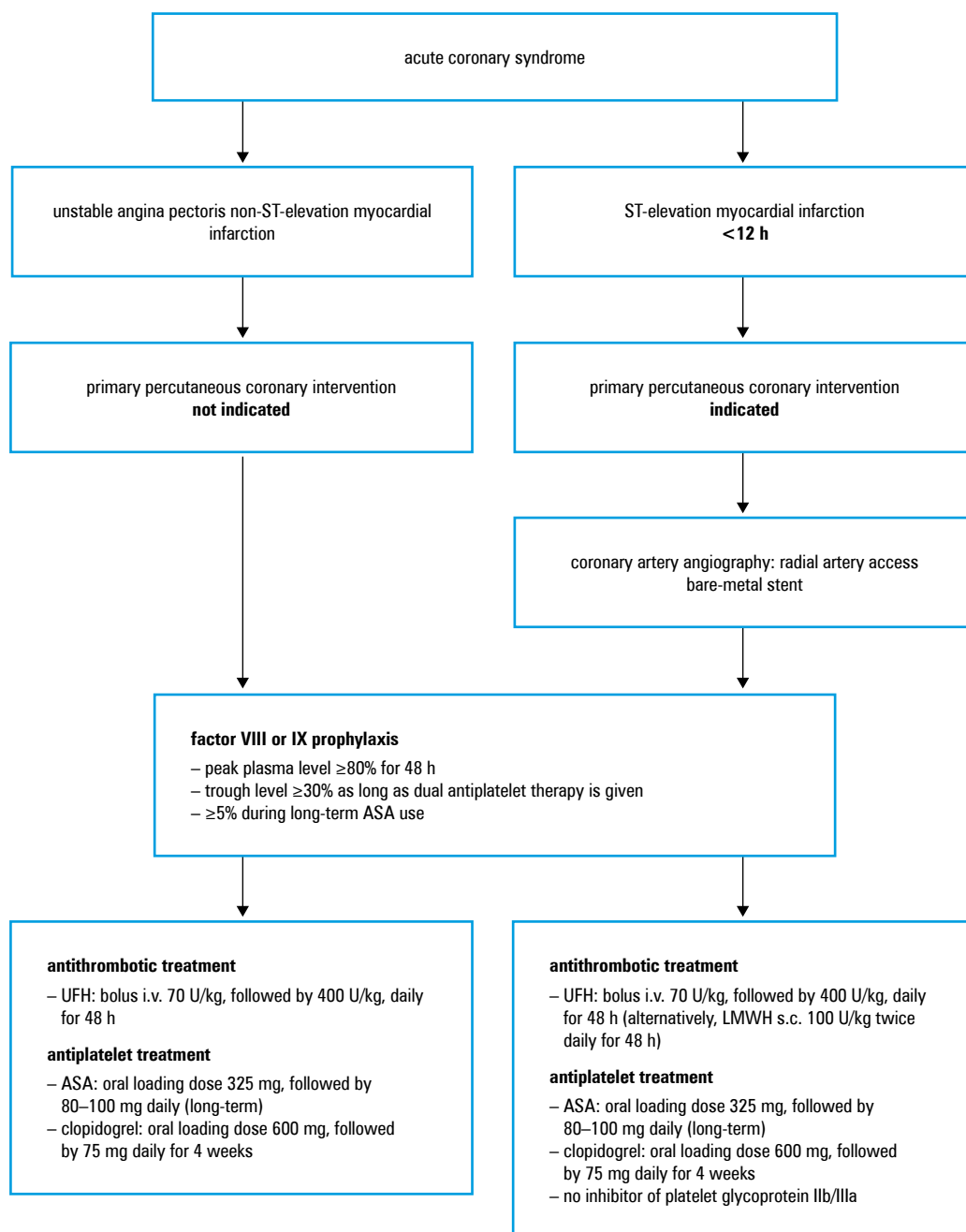
and diagnostic coronary arteriography or when implanting metal stents in hemophiliacs, it is necessary to achieve the target activity of deficient factor of 80% or higher (bolus 40 U/kg of FVIII or 80 U/kg of FIX, after 12 hours 20 U/kg of FVIII or 30 U/kg of FIX). After administration of the clotting factor concentrate, but still before the start of treatment, the factor activity should be checked. In patients treated with 2 antiplatelet drugs (ASA with clopidogrel), the activity of deficient factor should be maintained at 30% or higher (infusion 50 U/kg of FVIII or 60–70 U/kg of FIX every second day). In order to ensure the safety of ASA treatment, the activity of deficient factor should be maintained at 5% or higher (infusion 25–40 U/kg of FVIII every second day or 25–50 U/kg of FIX 2–3 times a week).^{34,36}

Lim and Pruthi³⁷ have recently described the outcomes of management of ACS in 8 patients with mild hemophilia or von Willebrand disease. Prophylactic factor concentrates were not administered for 6 of 10 coronary angiography procedures; there were no bleeding complications except groin hematoma in 1 patient. The 2 patients who were receiving dual antiplatelet therapy for 1 month without infusions of factor concentrates experienced no acute hemorrhagic complications. During a median follow-up of 8.5 years (1–11 years), 2 of 5 patients developed only minor bleeding complications while on ASA. The authors concluded that standard ACS management guidelines can be safely applied in mild hemophilia.

There are few recommendations on how to treat patients with hemophilia complicated by FVIII inhibitor, who develop ACS. Experts suggest that during PCI, these patients should receive recombinant activated FVII (rFVIIa; NovoSeven, Novo Nordisk) at a dose of 90 to 100 $\mu\text{g/kg}$ every 3 to 4 hours for 24 hours, followed by the same dose given daily for 4 weeks, or activated prothrombin complex concentrates (aPCC; FEIBA; Baxter AG; Austria) 80 U/kg every 12 hours for the first 24 hours, followed by the same daily dose during the next 4 weeks of antiplatelet therapy. They recommend only low-dose ASA, without clopidogrel, because the risk of bleeding associated with dual antiplatelet therapy is too high, and there is also a high risk of thrombosis as a potential complication of the extended prophylactic use of bypassing agents (rFVIIa or aPCC).³⁴

Arterial hypertension The results of an observational study showed that arterial hypertension occurs twice as often in hemophiliacs as in the general population and their average arterial pressure is higher.³⁸ One of the causative factors is renal failure, which is more frequent in hemophilia patients; the failure, in turn, may be caused by bleedings in the urinary system, HIV infection, and the use of antifibrinolytic drugs, e.g., tranexamic acid. Arterial hypertension increases the risk of intracranial hemorrhage (ICH). It was observed that 20 of 123 ICH episodes (16.3%) occurred

FIGURE Approach to the management of acute coronary syndrome in patients with hemophilia
Abbreviations: ASA – acetylsalicylic acid, LMWH – low-molecular-weight heparin, UFH – unfractionated heparin



in hemophiliacs over 50 years of age. Of note, the older the population of hemophiliacs who experienced ICH, the smaller the number of those with severe hemophilia.^{39,40} As long as the patient has no history of other cardiovascular risk factors, systolic pressure should be 140 mmHg or lower and diastolic pressure 90 mmHg or lower; however, in the presence of positive family history or diabetes mellitus, systolic pressure should be 130 mmHg or lower and diastolic pressure 80 mmHg or lower.⁴¹

In conclusion, evidence-based guidelines for the management of cardiovascular diseases in hemophilia are lacking. During antithrombotic therapy, there is usually a need for continuous prophylaxis with the products containing the deficient coagulation factor to control the risk of bleeding. Therefore, it is safer to use regimens of antithrombotic treatment that are less aggressive

than those recommended for patients without bleeding disorders. Anticoagulant and antiplatelet treatment should take into account the severity of hemophilia and cardiovascular disease, patient's age, inhibitor status, and comorbidities. Treatment of these patients requires a high degree of coordination between hemophilia specialists and cardiologists. Patients with hemophilia who develop cardiovascular disorders are rare, making targeted randomized clinical trials unfeasible. Thus, a well-designed registry based on an international collection of cases should provide sufficient data to create more specific and accurate recommendations in the future.

Renal failure The prevalence of changes in the urinary system in hemophiliacs increases with age. The causative factors include the coexistence of HIV infection, hypertension, diabetes; treatment

of HIV, which includes long-term use of antiretrovirals, antifungals, and antibiotics^{42,43}; as well as prostatic hypertrophy. In a meta-analysis of 3422 hemophilia records, 2975 individuals with hemophilia were documented to have chronic renal (52%) or acute renal disease (42%).⁴⁴

Hemodialysis had been successfully performed without bleeding episodes in a patient with severe hemophilia A via external arteriovenous shunt in 1977 for 1 year prior to renal transplantation.³⁸ In Wrocław, Poland, a 53-year-old man with severe hemophilia B (FIX activity, 0.1%), mild hypertension, and HCV infection who developed end-stage renal disease had been on hemodialysis for 6 months.⁴⁵ To prevent clot formation in the extracorporeal circulation and to decrease possible bleeding, the combination of heparinization and FVIII administration prior to and after dialysis was introduced.⁴⁶ Peritoneal dialysis is considered to be safer in some patients because of minimized bleeding risk.⁴⁷

Hemophilic arthropathy Hemophilic arthropathy still remains the main cause of morbidity in patients with little or no access to replacement therapy – it may coexist with osteoporosis, arthritis, and other degenerative bone diseases typical for the aging process. In addition, overweight and obesity may have more serious consequences for persons with hemophilia because increased body weight may cause additional damage to injured joints.⁴⁸ Of 62 hemophiliacs (mean age, 41 years), as many as 43.5% had decreased bone density and 25% were diagnosed with osteoporosis.⁴⁹ In a group of Italian patients with severe hemophilia aged 65 years and older, about 60% had muscular atrophy, 75% – axial deformity, 60% – flexion contractures and instability, and about 90% – impaired range of motion.⁵⁰ In a study of 92 Polish patients with severe hemophilia (median age, 26 years) who underwent on-demand therapy, only 1 patient scored 0 on the Gilbert scale and another on the Pettersson scale. Knee joints proved to be most affected. Orthopedic equipment was used, either occasionally or constantly by 37% of the patients; orthopedic surgery in history was reported in 25%; and 38% of the patients were unemployed and received social assistance. These results indicate that in Poland almost all severe hemophilia patients aged over 20 years are affected by hemophilic arthropathy.⁵¹ These patients are in urgent need for intensive physiotherapy and require improved access to orthopedic treatment. General recommendations for the management of joint disease in elderly patients with hemophilia include analgesia for pain, adjunctive therapies, prophylaxis, synovectomy to preserve joint function and reduce pain, arthroplasty and arthrodesis to relieve severe pain and prevent disability, and body weight maintenance.

Chronic pain relief Chronic pain relief is a significant challenge in patients with hemophilia. In

a group of 92 Polish patients with severe hemophilia (median age, 26 years), 84 patients (91.3%) reported pain.⁵¹ Pain is difficult to treat in this patient group because there are contraindications to the use of many effective drugs that inhibit blood platelet functions in individuals with coagulopathy. The following analgesics may be used: paracetamol, metamizole, products containing paracetamol and a small dose of tramadol in combination with a coxib, or – in case of more intense pain – higher doses of tramadol. In justified cases, morphine can be used.

Neoplastic disease The effect of hemophilia and its treatment on the incidence of malignancies and related mortality is not well known. It has been suggested that congenital disorders which decrease the thrombin level (such as hemophilia) might stimulate tumor growth and promote cancer survival.^{52,53} Human FVIII promoted invasion and growth of murine melanoma cells in the animal model,⁵⁴ but it has not been confirmed by data from observational studies. Apart from virus-associated malignancies, hemophilia does not increase the risk of other neoplastic diseases. Several analyses assessing the causes of death in hemophiliacs have shown that standardized mortality ratio (SMR) for cancer in HIV-negative cases⁵⁵ is lower than that in the general population.^{56,57} What is more, increased severity of hemophilia seems to be associated with progressive reduction of cancer incidence.¹ In the United Kingdom, the SMR for malignancies other than liver cancers or lymphomas was reported to be 0.95 in patients with mild/moderate hemophilia and 0.65 in those with severe hemophilia.¹

Inhibitor development in aging patients with hemophilia Most inhibitors occur at young age in patients with severe hemophilia, but cumulative inhibitor risk increases with age. In severe hemophilia A, it is 30% at the age of 50 and 36% at the age of 75. In moderate and mild hemophilia A, the cumulative risk is 6%, 10%, and 12% at 5, 50, and 75 years of age, respectively. For hemophilia B, the cumulative risk is much lower at the age of 75 (8%) and at all ages compared with hemophilia A.⁵⁸ Older patients with mild hemophilia are at an increased risk for inhibitor development following intensive factor replacement therapy for surgical or invasive procedures and should be monitored for the presence of inhibitor subsequent to factor exposure.⁵⁹ The role of immune tolerance induction for inhibitor eradication in this age group of patients is unknown. Desmopressin may be contraindicated in mild hemophilia with inhibitors due to the reports of acute myocardial infarction following infusion. Patients with high-titer inhibitors who experience bleeding episodes or are undergoing surgery are typically treated with rVIIa or aPCC (FEIBA). Risk of thrombotic complications associated with the use of bypassing agents should be considered in the aging population with hemophilia.

Surgical or orthopedic treatment There is a growing demand for urgent or scheduled surgical or orthopedic treatment in aging patients with hemophilia. In the case of major surgeries in patients with severe hemophilia A, a constant infusion of FVIII concentrate is recommended, which ensures retaining about 100% activity of the factor within 4 days and about 80% at 5 to 7 days. Next, FVIII can be given in injections every 12 hours with the target activity of 50% at 7 to 10 days. During rehabilitation, it is sufficient to administer FVIII daily and maintain the activity of 40%. In patients with hemophilia B, FIX activity may be about 20% lower.

In the Institute of Hematology and Transfusion Medicine in Warsaw, Poland, in the years 2003 to 2008, surgical procedures were performed in 19 patients with hemophilia A or B who were diagnosed with malignant neoplasms at various sites, most frequently colorectal. The mean age of patients was 55.8 years (range, 22–82 years); 17 patients had hemophilia A (6 severe, 4 severe with inhibitor, including 2 high-titer and 2 low-titer, 1 moderate, and 6 mild); 2 patients had hemophilia B (1 severe, 1 moderate). In factor replacement therapy for patients with no inhibitor, the strategy was to maintain the activity of the deficient clotting FVIII before the operation at 80% to 100% of the normal value, within the range of 80% to 100% on days 1 to 3 after surgery, at 60% to 80% on days 4 to 6, at 30% to 60% on days 7 to 10, and at 20% to 40% on all subsequent days until the surgical wound is healed. In patients with hemophilia B, the levels were about 20% lower. Deficient factor was injected every 8 or 12 hours or administered in continuous intravenous infusion. In patients with hemophilia A with high-titer inhibitors to FVIII (above 5 Bethesda units/ml), aPCC (FEIBA) were used at 50 to 100 U/kg every 8 to 12 hours. All patients survived surgery. Two patients with pancreatic carcinoma died in the postoperative period due to multiorgan failure. Complications occurred in 7 patients (37%) including 6 patients (32%) with bleeding complications such as hemopneumothorax, intraperitoneal bleeding, abdominal parietal hematoma, hematuria, and bleeding from esophago-pharyngocutaneous fistula following total laryngectomy. It proves that surgery of malignant neoplasms in hemophilia patients is burdened with a high risk of complications, including bleedings, despite adequate replacement therapy and administration of FVIII bypassing concentrates in patients with high-titer inhibitor. Therefore, surgical procedures involving these patients should be performed in specialized centers by an experienced team (surgeon, anesthesiologist, hematologist) and supported by a laboratory for coagulation disorders.⁶⁰ A successful long-term management of hemophilia A patient requiring heart valve surgery in Poland has also been reported.⁶¹

Sexual dysfunction Men with hemophilia reaching middle age and beyond might experience

problems with sexual functions, including loss of sexual desire, ejaculation problems, and varying degrees of erectile dysfunction. Some of these changes are caused by age-related biological changes in the hormones, nerves, and blood vessels responsible for male sexual function, while others are specific to the medical problems associated with hemophilia, such as arthropathy, chronic pain, bleeding, infection with HCV or HIV, and side effects of medications. Some sexual problems result from the psychological experience of hemophilia.⁶² Therefore, it is necessary to allow patients with hemophilia to express their sexual concerns and to be understanding, elicit their sexual history, evaluate patients with erectile dysfunction for treatable causes, and to distinguish organic from psychogenic reasons. Phosphodiesterase-5-inhibitors might be used as first-line treatment for erectile dysfunction. Pain and reduced joint motion contribute to problems with sexual function. Strategy that might be helpful is the change of sexual repertoire (e.g., alternative positions – cross position is more suitable for hemophilia patients) or the use of analgesics before sexual contact.⁶² Sometimes a referral to a sex therapist is necessary.

Quality of life In general, the literature reports an association between hemophilia and lower health-related quality of life (HRQoL). Several factors, such as increasing age, body mass index, impairment of joint function, chronic pain, bleeding frequency, presence of clinically significant FVIII inhibitors, and HIV and HCV infections, have been suggested to influence HRQoL in these individuals. It has also been suggested that the effect on HRQoL is dependent on the severity of the disease. A tool to assess specific measures relevant to hemophilia, such as Hemophilia-QoL can distinguish between different groups of disease severity. The difference in physical component summary scores aligns most closely with an index of joint damage, which is itself greater and associated with bleeding history in this population. Patients with hemophilia evaluated their health as worse than controls and believed it would deteriorate; they also had more problems with work and daily activities as a result of emotional problems compared with unaffected males.⁶³ Previous studies have also found that patients with hemophilia tend to score lower in the physical health scales but are comparable to the general population in the mental health scales.

A Polish study included 40 men with hemophilia A, and the original questionnaire of the World Health Organization Quality of Life scale was used. All patients were affected by hemophilic arthropathy and the presence of HCV was reported in 67% of the study group. The results showed that the quality of life in the study population was moderate. The degree of satisfaction with the quality of life was reported as good by 62.5% of the patients and the degree of satisfaction with health condition was reported as good

only by 30%. The most important factors affecting the quality of life were occupational activity and home treatment with factor concentrate.⁶⁴

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Problemy leczenia hemofilii u osób starszych

Krystyna Zawilska¹, Maria Podolak-Dawidziak²

¹ Oddział Hematologii i Chorób Wewnętrznych, Wielospecjalistyczny Szpital Miejski im. J. Strusia w Poznaniu, Poznań

² Katedra i Klinika Hematologii, Nowotworów Krwi i Transplantacji Szpiku, Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu, Wrocław

SŁOWA KLUCZOWE

choroby
sercowo-naczyniowe,
hemofilia, jakość
życia, niewydolność
nerek, nowotwory

STRESZCZENIE

Od czasu wprowadzenia koncentratów czynników krzepnięcia oczekiwany czas życia chorych na hemofilię wydłużył się od 40 lat w latach 60. do 60–70 lat obecnie. W Polsce prawie wszyscy starsi chorzy na hemofilię cierpią z powodu artropatii, większość z nich jest zarażona wirusem zapalenia wątroby typu C (HCV), a niektórzy także wirusem zapalenia wątroby typu B lub wirusem HIV. Marskość wątroby związana z zakażeniem HCV pojawia się w ciągu 15–20 lat po infekcji u 20–30% pacjentów. Problemem są także współistniejące schorzenia związane z procesem starzenia się, dotyczące serca, nerek i innych narządów. W celu zapobiegania chorobie niedokrwiennej serca należy u chorych na hemofilię szczególnie starannie kontrolować czynniki ryzyka.

Niniejsza praca opisuje współczesne zalecenia dotyczące stosowania terapii przeciwwskrzepowej w leczeniu ostrych zespołów wieńcowych oraz migotania przedsionków u starszych pacjentów z hemofilią. Zmiany w układzie moczowym u chorych na hemofilię postępują z wiekiem, co raz częściej prowadząc do dializoterapii. Pacjenci z artropatią hemofilową powinni mieć dostęp do intensywnej fizjoterapii i leczenia ortopedycznego. Zabiegi operacyjne, obarczone dużym ryzykiem powikłań, powinny być przeprowadzane w wyspecjalizowanych ośrodkach, dysponujących doświadczonym zespołem lekarskim i pracownią krzepnięcia. U starszych pacjentów z łagodną hemofilią intensywne leczenie substytucyjne stosowane w związku z inwazyjnymi zabiegami niesie ryzyko wytworzenia inhibitora. Kontrola bólu stanowi trudny problem u chorych na hemofilię z powodu przeciwwskazań do stosowania wielu skutecznych leków przeciwzapalnych; istotnym zagadnieniem jest też troska o jakość życia tych osób. Zwiększająca się populacja starszych chorych na hemofilię wymaga całościowego podejścia diagnostycznego i terapeutycznego, najlepiej w ośrodkach leczenia hemofilii.

Adres do korespondencji:

prof. dr hab. med. Krystyna Zawilska,
Oddział Hematologii i Chorób
Wewnętrznych, Wielospecjalistyczny
Szpital Miejski im. J. Strusia,
ul. Szkolna 8, 61-833 Poznań,
tel.: 61-858-56-36, fax: 61-852-76-11,
e-mail: k.zawilska@interia.pl
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