How I treat age-related morbidities in elderly persons with hemophilia

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ABSTRACT

In persons with hemophilia life expectancy is now approaching that of the general male population, at least in countries that can afford regular replacement therapy with coagulation factor concentrates. The new challenges for comprehensive treatment centers are thus to provide optimal health care for this aging population of patients, who often present not only with the comorbidities typically associated to hemophilia (arthropathy, chronic pain, bloodborne infections), but also with common age-related illnesses such as cardiovascular disease and cancer. There are no evidence-based guidelines on the management of these conditions, that often require drugs that interfere with hemostasis, enhance the bleeding tendency and warrant more intensive replacement therapy. At the moment, elderly patients with hemophilia affected by other diseases should be managed like their age peers without hemophilia, provided replacement therapy is tailored to the heightened risk of bleeding associated with the need for invasive procedures and drugs that further compromise the deranged hemostasis. More detailed advice is provided on the schedules of replacement therapy that are needed to tackle cardiovascular diseases such as acute coronary syndromes and nonvalvular atrial fibrillation, because these conditions will become more and more frequent challenges for the comprehensive treatment centers.
INTRODUCTION

Starting from the early 1970s a previously life-threatening and crippling condition such as hemophilia became a gratifying example of successful secondary prevention of a chronic disease.\(^1\) Owing to the increasing availability of coagulation factor concentrates (CFC), at least in high income countries life expectancy increased in persons with hemophilia (PWH) from less than 30 years to over 60.\(^2\)\(^-\)\(^7\) This favorable trend was temporarily halted in the last two decades of the 20\(^{th}\) century by the devastating impact of the infections with the human immunodeficiency virus (HIV) and the hepatitis C virus (HCV). Following the development of efficacious methods to inactivate bloodborne viruses in plasma-derived CFC and the availability of factor VIII (FVIII), factor IX (FIX) and factor VIIa produced by recombinant DNA technology, new bloodborne infections are no longer felt as a threat, and pre-existing infections can be controlled (for HIV) or cured (for HCV) with antiviral therapies in a substantial proportion of affected patients.\(^8\)\(^,\)\(^9\)

A major problem is still the acquired occurrence of alloantibodies that inhibit the activity of coagulation factors. Inhibitors develop in 20 to 30\(^{\%}\) of patients with severe hemophilia A, whereas this complication is much rarer in severe hemophilia B\(^10\)\(^,\)\(^11\) and in patients with mild hemophilia A, who develop inhibitors predominantly in adulthood or even at an old age.\(^12\)\(^-\)\(^14\) Products that bypass the coagulation defect, such as activated prothrombin complex coagulation factors and recombinant factor VIIa, are
usually effective to control bleeding episodes, and alloantibodies can be eradicated in at least 50–60% of patients with inhibitors by immune tolerance therapy based upon the prolonged administration of large doses of recombinant or plasma-derived FVIII.C13,14 On the whole, in the first decade of the third millennium, safe and effective treatment is available for PWH and life expectancy approaches that of the general population.5-7

No rose is without thorns. As a consequence of aging, the number of PWH affected with one or more age-related diseases is increasing and newer clinical concerns are emerging.15-17 At the same time, PWH born before the 1960s, who did not receive adequate replacement therapy throughout a great part of their lives, now suffer from the long-term comorbidities typically associated with hemophilia, such as arthropathy and chronic viral infections. The purpose of this How I Treat article is to advise on the management of the most frequent age-related comorbidities occurring in the elderly PWH. Particular emphasis is put on cardiovascular diseases and cancer, that often require therapeutic procedures and drugs that further compromise the already deranged hemostasis of PWH. Owing to the current paucity of data, our recommendations are not evidence-based, but stem from the available literature and the clinical experience gained in two large European hemophilia treatment centers.
HEMOPHILIA-ASSOCIATED COMORBIDITIES IN THE ELDERLY PERSON WITH HEMOPHILIA

Arthropathy is the epitome of hemophilia-associated comorbidities. Joint damage increases with aging in an almost linear fashion, not only in severely affected patients but also in moderate hemophilia.\textsuperscript{18,19} A study carried out in a cohort of 39 elderly PWH, ranging in age from 65 to 78 years, established that more than half of them had severe damage in all the 6 joints more frequently affected by bleeding (knees, elbows, ankles).\textsuperscript{17} There was also a high rate of joint instability and balance dysfunction, so that a large proportion of elderly PWH (70\%) had a high risk of falling, spontaneously or after tripping on obstacles.\textsuperscript{17} In turns, falls are likely to cause an increasing number of serious injuries and fractures, also owing to osteoporosis and osteopenia.\textsuperscript{20-22} An adverse influence on the course of arthropathy may be also due to a more sedentary lifestyle, overweight and obesity, that are commonly associated with both hemophilia and aging.\textsuperscript{23,24}

On the whole, there will be an increasing need for emergency and elective orthopedic operations with the aging of PWH. Ankle surgery is likely to match knee surgery in frequency, and there will be more revision operations (with a higher risk of bleeding) in PWH who had their first joint prosthesis implanted 10-15 years ago. More and more elderly patients with inhibitors will also need joint replacement, that are now possible and safe but at exorbitant costs using bypassing agents.\textsuperscript{25-27} Table 1 shows some
schedules of replacement or bypassing therapy recommended for these operations in PWH without and with inhibitors.

When major orthopedic operations are carried out in the elderly, venous thromboembolism is a frequent event, so that thromboprophylaxis with anticoagulants such as low molecular weight heparins should be routinely implemented also in PWH. In them, orthopedic surgeons tend to skip thromboprophylaxis on the assumption that the coagulation defect confers protection from venous thromboembolism. This assumption is not supported by evidence and venous thromboembolism does occur in patients with congenital coagulation defects, particularly in older patients.

Rather than preoperatively low molecular weight heparins should be preferably started 6-12 hours postoperatively, to minimize the risk of bleeding (Table 2). Mechanical methods of prophylaxis are advised in patients at particularly high risk of peri- and postoperative bleeding, such as those undergoing major orthopedic surgery with bypassing agents, that are less hemostatically effective than CFC. In arthroscopic orthopedic surgery, much less invasive and challenging for hemostasis than joint replacement surgery, early mobilization is usually sufficient in the absence of additional thromboembolism risk factors that, when present, demand the same schedules recommended for joint replacement. Locoregional anesthesia can be used, provided the PWH is treated with CFC at the time of this procedure that may carry a risk of spinal hematoma.

A few studies, all small and retrospective, have evaluated the effects of secondary prophylaxis based upon two- to three- weekly
infusions of CFC in adult PWH, including very few patients older than 65 years.\textsuperscript{32-34} As expected, secondary prophylaxis markedly reduced the frequency of bleeding (total bleeds from 35.8 to 4.2 and joint bleeds from 32.4 to 3.3 over 5 years),\textsuperscript{33} but while in adolescents the orthopedic status did improve, in adults the worsening of arthropathy was not halted.\textsuperscript{33} Even though the consumption of CFC for replacement therapy was much increased by the prophylactic regimen, quality of life improved and pain and need for analgesics decreased.\textsuperscript{33} Prophylaxis may also decrease the risk of intracranial hemorrhage that, owing to hypertension and traumas after falling, is increasing as the PWH gets older,\textsuperscript{35} and is one of the most frequent causes of death.

On the whole, prophylaxis in the elderly PWH is not a fully established indication in terms of health technology assessment and cost effectiveness. However, when resources are available, prophylaxis is indeed recommended, because it does dramatically improve the quality of life, particularly in frequent bleeders and during rehabilitation (Table 1). Moreover, continuous prophylaxis is going to be needed more and more frequently in elderly PWH, owing to cardiovascular disease and cancer that entail patient exposure to drugs and procedures enhancing the baseline risk of bleeding (see below).

Pain control. Chronic pain is prevalent in the elderly PWH and drug addition is not rare. The widely used paracetamol and non-steroidal anti-inflammatory drugs (NSAIDS) have adverse effects that may become more clinically significant with aging: gastroduodenal toxicity, paracetamol-associated liver dysfunction
(particularly with excessive alcohol consumption and liver disease), hypertension and renal insufficiency. Selective cyclooxygenase-2 (COX2) inhibitors are better tolerated in the gastrointestinal tract than non-selective NSAIDS, but the risk of cardiovascular disease may increase. On the other hand, traditional NSAIDS do inhibit, albeit transiently, cyclooxygenase-1 and platelet function and may cause in the elderly PWH a greater need for replacement therapy, owing not only to more musculoskeletal bleeding but also to bleeding in such dangerous sites as the central nervous system.

Upper gastrointestinal bleeding was reported to occur in 42 of 2285 PWH (incidence 1.3 per 100 patient years) and the use of NSAIDs was associated with a increased bleeding risk (hazard ratio 3.7), while the use of COX2 inhibitors was not. Hence, we prefer COX2 inhibitors to NSAIDs when paracetamol, still the drug of first choice, is not effective to control pain. An example of a pain control schedule, based upon sequential steps of more and more aggressive treatment in case of failure, is given in Table 3. For optimal management, the involvement of pain control teams in comprehensive hemophilia treatment centers may become necessary.

Chronic bloodborne infections. The long-term consequences of HCV infection are looming large on those elderly PWH, particularly with genotype 1 and HIV co-infection, who failed to achieve a sustained viral response with pegylated interferon and ribavirin. A significant proportion of them develop liver cirrhosis and carry a high risk of hepatocellular carcinoma.
The curative option of liver transplantation is made difficult by various factors: advanced age, frequent HIV co-infection and the often multifocal presentation of HCC. Periodical ultrasound screening is the only recommendation that can be made to detect HCC earlier in PWH with cirrhosis. It is also hoped that newer and more efficacious antiviral agents such as protease inhibitors may soon become safe and effective enough to eradicate HCV in a higher proportion of PWH unresponsive to pegylated interferon/ribavirin.

Due to their coagulation defect PWH with cirrhosis and portal hypertension are likely to bleed from the upper gastrointestinal tract more frequently and severely than cirrhotics without hemophilia. Therefore, preventive band ligation should be carried out as early as possible in the presence of gastroesophageal varices at high risk of bleeding.

In HIV-infected PWH, combined antiretroviral therapy (cART) has dramatically reduced the high mortality rate seen until the advent of this treatment in the middle 1990s. cART has also reduced the previously frequent occurrence of non-Hodgkin lymphomas. On the other hand, cART increases the risk of the metabolic syndrome, diabetes, renal insufficiency and atherothrombotic cardiovascular disease in non-hemophilia patients. Although there are few data on the long term clinical course of HIV infection in the elderly PWH, it is suspected that cART will induce the same long-term alterations. Monitoring serum lipid, glucose and creatinine at regular intervals is recommended.
The bleeding pattern typical of younger PWH may change with aging. Acute hemarthrosis, that accounts for 70% to 80% of hemorrhages in the young, usually becomes less frequent owing to a less physically active pattern of life. In some PWH with severe arthropathy acute painful bleedings may occur which are unresponsive to CFC. These are more likely to be arterial instead of synovial bleedings, which may require angiographic embolization for adequate control.\textsuperscript{44}

**AGE-RELATED DISEASES IN ELDERLY PERSONS WITH HEMOPHILIA**

Cancer. With the exception of HCC in HCV-infected patients and non-Hodgkin lymphomas in HIV-infected patients, it is unclear whether or not in the elderly PWH the incidence of cancer differs from that in age peers without hemophilia. Experimental data indicate that hemophilic mice form less metastasis from experimental melanomas, perhaps owing to less thrombin formation.\textsuperscript{45} It is as yet uncertain whether or not this is also true in humans.\textsuperscript{46} Two population studies found a lower incidence of cancer, particularly in patients with severe hemophilia,\textsuperscript{4,7} but the prevalence of tumors other than HCC and non-Hodgkin lymphoma was four-fold higher than in the age-matched general population in a small study of elderly PWH.\textsuperscript{47} Literature data on the treatment of cancer in elderly PWH are limited to a few case reports, so that there is no evidence-based recommendation for the optimal management of these cases. Cancer
that develops in the elderly PWH should be handled as in any other person with the same type of malignancy, but this logical approach is not without problems. The risk of bleeding inherent in the congenital coagulation defect is increased by several factors, such as the frequent use of invasive diagnostic and therapeutic procedures, chemotherapy- and radiotherapy-induced thrombocytopenia. Replacement therapy should be administered not only on an episodic basis at the time of diagnostic or therapeutic invasive procedures, but also as continuous prophylaxis when chemo- or radiotherapy are accompanied by severe thrombocytopenia. It is unknown which platelet count is safe in a PWH with cancer and hence does not entail the need of prophylaxis. In patients who develop cancer and are not already on continuous prophylaxis, there is no need to start it if thrombocytopenia is moderate (platelet count greater than 30,000/µL). On the other hand, continuous prophylaxis with CFC according to the schedule recommend in Table 1 is advised when platelet counts are lower. In patients who were already receiving continuous prophylaxis, this regimen should continue unchanged throughout the period of chemotherapy and/or radiotherapy. In some cases transfusion with platelets may be necessary. Thrombocytopenia is not itself antithrombotic, so that antithrombotic prophylaxis should be prescribed when cancer is associated with a high risk of thrombosis. After oncological surgery low molecular weight heparins should be preferably administered starting post-operatively, with dosages and treatment intervals similar or
higher than those recommended for major orthopedic surgery (see Table 2).

Cardiovascular disease. Several data indicate that in PWH mortality from coronary artery disease is lower than in the general male population. Tuinenburg et al\textsuperscript{48} showed that the standard mortality ratio (calculated by dividing the number of observed deaths by those expected in the general population) ranges from 0.2 to 0.6 in PWH in the time period spanning from 1989 to 2006.\textsuperscript{48} On the other hand, coronary artery and other atherothrombotic diseases do indeed occur in PWH, as it stems from a review on the causes of death in PWH\textsuperscript{49}, from a review article based upon 42 cases\textsuperscript{50} and the experiences gained in our large tertiary care centers. This is not unexpected, because if on one hand PWH may be protected from thrombus formation by their hypocoagulability, on the other hand they are exposed at least as normal males to such risk factors for atherosclerosis as aging, smoking and overweight.\textsuperscript{51} Other risk factors such as hypertension, physical inactivity and chronic renal disease\textsuperscript{52} may be even more frequent in PWH than in the general aging population. Finally, HIV infection and cART may per se increase the risk of the metabolic syndrome, diabetes, renal insufficiency and hence of atherothrombotic diseases.\textsuperscript{53}

Evidence-based guidelines for the acute treatment and secondary prophylaxis of cardiovascular diseases in PWH are currently lacking, nor is known how to handle the increased risk of bleeding associated with invasive procedures and the short- and long-term
use of antithrombotic drugs. Our general principle is to treat PWH like their age peers without hemophilia, provided replacement therapy is adapted to the baseline plasma factor deficiency and the added risk of bleeding carried by therapeutic procedures and antithrombotic drugs. With this as background, we elected to provide more details on the management of two cardiovascular diseases -- acute coronary syndromes and non-valvular atrial fibrillation -- that are likely to be the most frequent in the elderly PWH as in the population at large.\

Table 4 shows how replacement therapy is planned in PWH when they develop acute coronary syndromes. Peak factor levels should reach at least 80 U/dL at the time of coronary angiography and percutaneous coronary intervention (PCI) with stenting, maintaining these or higher factor levels for as long as therapeutic dosages of heparin are given. Because most PCI-related bleeding complications occur at the arterial access site, a radial access should be preferred over the femoral access. Moreover, for as long as dual antiplatelet therapy is indicated after PCI and stenting, trough plasma levels of 30 U/dL are pursued. The use of bare metal stents instead of drug-eluting stents is preferable, in order to limit to one month the period of dual antiplatelet therapy with aspirin and P2Y12 inhibitors (such as clopidogrel or prasugrel). The choice of bare metal stents, however, must be balanced against the advantage of less restenosis with drug-eluting stents. However the latter warrant up to 12 months of dual antiplatelet therapy, and hence more prolonged continuous prophylaxis, as indicated in Table 4.
For secondary antithrombotic prophylaxis in patients who recovered from an acute coronary syndrome, we recommend low-dose aspirin (100 mg) under protection with low-dose continuous CFC prophylaxis (see Table 4 for recommended dosages). Until now, continuous prophylaxis with bypassing agents was never implemented in patients with inhibitors who developed an atherothrombotic event, because the issue of thrombosis as a potential complication of the continuous prophylactic use of bypassing agents remains a concern. Fibrinolytic therapy with a tissue-type plasminogen activator is still the most frequently adopted reperfusion strategy for patients who develop ST-elevation myocardial infarction (STEMI) and cannot reach within the recommended timelines an interventional cardiology unit with expertise in PCI. Coagulation factors should be kept at normal levels (80-100 U/dL), preferably by continuous intravenous infusion, for at least 24-48 hours during and after fibrinolysis. In the presence of three-vessel coronary artery disease or stenosis of the left main coronary artery, cardiopulmonary bypass surgery should be chosen and carried out as in non-hemophilic patients, with clotting factor levels kept within normal ranges (80-100 U/dL). Continuous infusion of CFC before, during and after surgery until wound healing is enough advanced, should be preferred over bolus infusion.56,57

Despite the use of these strategies of replacement therapy, the forementioned revascularization procedures and the associated antithrombotic regimens sometime cause excessive bleeding, which may be difficult to control and increase mortality. The hemostatic
agents that are currently employed in persons without hemophilia at the time of bleeding complications should be considered also in those with hemophilia, such as recombinant factor VIIa.\(^{58}\)

Another cardiovascular disease likely to occur with increasing frequency in the elderly PWH is nonvalvular atrial fibrillation (AF). In the absence of evidence indicating that PWH are protected from cardiac embolism by their underlying coagulation defect, the occurrence of AF in PWH confronts us with the issue of how to handle antithrombotic treatment, during and after cardioversion as well as for the long-term prevention of embolic complications.\(^{49}\)

Our strategy for the long-term thromboprophylaxis in PWH with chronic AF is outlined in Fig 1. In non-hemophilia patients with AF the risk of cardioembolic stroke is stratified according to several risk factors included in the CHADS\(_2\) score\(^{60}\) (Table 5). In principle, oral anticoagulation with vitamin-K antagonists should be chosen in PWH at high risk of embolization and stroke (CHADS\(_2\) score of 2 or more).\(^{59,61}\) In practice, vitamin-K antagonists are chosen only when baseline FVIII levels are at least 30 U/dL, because in severe and moderate hemophilia these drugs would require the use of continuous prophylaxis during the whole period of treatment, entailing a huge consumption of CFC and exorbitant costs. Hence, low-dose aspirin is usually preferred (100 mg daily), because this antiplatelet agent, although less efficacious than vitamin-K antagonists in persons without hemophilia,\(^{59}\) warrants much lower trough levels of coagulation factors (5 U/dL) to avoid significant bleeding in PWH (Fig. 1). A huge problem is how to handle antithrombotic prophylaxis in patients with FVIII
inhibitors who develop AF. We would recommend aspirin without resorting to continuous prophylaxis of bleeding with bypassing agents, but we stop thromboprophylaxis with aspirin at the first signs of bleeding.

Pertaining to the choice of rhythm versus rate control in AF, no significant differences were seen in cardiovascular mortality between the two approaches, although a recent study found better quality of life and left ventricular function if rhythm control was chosen. In patients without hemophilia, no differences were found in the occurrence of stroke between high-risk patients in the rate control or sinus rhythm control arms, indicating the need for antithrombotic prophylaxis even after successful cardioversion in patients at high risk. It is essential that the selection of PWH with a high chance of successful cardioversion involves a cardiologist in the team of the specialized hemophilia treatment center.

A recommended strategy for cardioversion in PWH is outlined in Fig. 2. Patients with AF lasting more than 48 hours eligible for cardioversion require transesophageal echocardiography (TEE) to rule out atrial thrombi and at least 4 weeks of anticoagulation with vitamin-K antagonists (INR target 2.5; range 2.0–3.0), whichever method of cardioversion is chosen. The use of TEE avoids the need for a 4-weeks period of anticoagulation before cardioversion. This strategy was suitable and safe in our hands, provided adequate CFC prophylaxis was given, with the goal to maintain through FVIII levels of at least 30 IU/dL. After
cardioversion, long-term anticoagulant therapy is needed, as suggested in Figure 1.

In hemophilia B some particular problems are caused by FIX replacement, which may interfere with vitamin-K antagonists and spuriously affect the INR. Moreover, one must be aware that oral anticoagulant therapy converts mild hemophilia B into a more severe form, so that replacement therapy with CFC should be implemented in the majority of patients aiming at trough levels of 30 U/dL when vitamin-K antagonists are needed.

When cardiac valve replacement is indicated, a bioprosthetic valve should be the first choice to avoid the need of indefinite anticoagulation, but if necessary mechanical artificial valves can be used, provided trough factor levels are kept above 30 U/dL by means of long-term continuous prophylaxis. We have never been challenged with the formidable problem of PWH with inhibitors who needed a cardiac valve replacement, nor operations of cardiac surgery.

These general principles of replacement therapy can also be applied to other cardiovascular diseases. Our preferred antithrombotic therapies are those recommended by the American College of Chest of Physicians,\textsuperscript{64,65} individually adapted to the peculiar condition of patients with a bleeding tendency that must be corrected by short- or long-term prophylactic replacement therapy, particularly when invasive procedures and antithrombotic drugs are used. It is obvious that all the forementioned schedules of prophylaxis do dramatically increase the costs of therapy.

Other morbidities in the elderly persons with hemophilia.
Chronic renal disease is likely to develop with increasing frequency in the aging PWH, owing to multiple concomitant risk factors (HIV infection, cART, hematuria, structural renal damage, use of antifibrinolytic amino acids).\textsuperscript{52} Hence, there may be an increasing need to resort to dialysis. In theory, peritoneal dialysis is preferable to hemodialysis, because it does not require the placement of an artero-venous fistula nor the administration of heparin to prevent clot formation in the dialyzer, so that coverage with replacement therapy is only needed at the time of catheter insertion. However, this procedure entails a high risk of peritoneal infections, particularly in HCV- and HIV-infected patients. Hence we chose more often hemodialysis, using both heparin and a single dose of CFC replacement aiming at factor levels of 80 U/dL, before and after each procedure.

According to the results of a small cohort study\textsuperscript{17}, cognitive impairment is no more frequent in PWH than in their age peers, but it must be pointed out that 78 years was the oldest age.\textsuperscript{17} In cases with severe depression, serotonin reuptake inhibitors (SSRI) are frequently used. However, interference of these drugs with primary haemostasis was reported\textsuperscript{66}, and their use might increase the risk of upper gastro-intestinal bleeding.\textsuperscript{67} To bypass these uncertainties, we usually use drugs other than SSRI to treat depression.

An important aspect of aging is erectile dysfunction, due not only to the normal aging process with the related biosocial problems, but also to such comorbidity as painful arthropathy affecting sexual desire, and to conditions that affect erectile function.
such as arteriosclerosis and hypertension. The use of multiple drugs to treat the latter may also compromise sexual function. On the whole, living with hemophilia often strains the relationship with the sexual partner, and approximately half of the PWH complained about their limitations during sexual intercourses, specially when they had painful joints and contractures in hips and knees. The oral phosphodiesterase-5 inhibitors (sildenafil and tadalafil) slightly inhibit platelet aggregation in vitro. Yet they are being used satisfactorily by some of our elderly PWH without an apparent increase in the incidence of bleeding, despite no prophylactic CFC therapy. As seen in normal persons, a few PWH develop previously unnoticed epistaxis during the intake of these drugs, that cause some degree of nasal congestion.

Prostatic hypertrophy is a common problem in elderly PWH and alpha-reductase inhibitors, such as finasteride or alpha blockers such as tamsulosin, are commonly used. There are no reports of clinically relevant hemostatic changes while using these drugs, so that they can be safely used in PWH. Genitourinary diseases and prostatic hypertrophy would facilitate the onset of hematuria, and upper gastrointestinal bleeding may become more frequent due to concomitant cirrhosis or malignancies in the gastrointestinal tract. The use of multiple drugs for the treatment of multimorbidity is another potential reason for an increased bleeding tendency.

Cataract surgery needs replacement therapy with CFC. However, we give only a single injection one hour before cataract extraction, more with the goal to cover the risk of bleeding associated with
local anesthesia than to avoid blood loss due to cataract extraction.

CONCLUSIONS

Owing to a life-expectancy approaching that of the general population, PWH develop more and more age-related clinical conditions never experienced before, so that treatment centers must enlist the expertise of specialists rarely needed before, like cardiologists and oncologists. Integrated expertise can usually be offered only by large centers specialized in the comprehensive management of PWH, because they can provide at the same time proficiency in coagulation laboratory, hemophilia care and other surgical and medical subspecialties that are unlikely to be available to the general hematologist.

In general, our recommended approach is to treat the diseases occurring in the elderly PWH as they would be treated in age peers without a bleeding disorder. Hence, in this How I Treat article we mainly suggested when and how replacement therapy should be changed and adapted when the baseline risk of bleeding is heightened by the use of invasive procedures and/or drugs that, as antithrombotics and chemotherapeutics, cause per se a bleeding tendency. We are aware of the limits of these general recommendations, owing to the presence of many interacting clinical variables: the strength of the indication for antithrombotic therapy, the magnitude of the risk of thrombosis if antithrombotic therapy is withheld but, on the other hand, the
risk of bleeding if therapy is continued. Hence, very often clinical decisions are ultimately made on a case-by-case basis. What can be done to improve this situation of lack of evidence-based recommendations? Owing to the current relative rarity of elderly PWH, the forementioned clinical problems cannot be readily answered by adequately powered and controlled clinical trials. Perhaps the best approach is to establish international registries on age-related diseases in elderly PWH, in order to collect at regular intervals information from large populations on the events of interest (such for instance as cardiovascular disease and cancer), on how they are handled and on the corresponding outcomes. This endeavor is being tackled by EUHASS (http://euhass.org), a prospective system of reporting adverse events in PWH in Europe. The 46 hemophilia treatment centers involved in the EUHASS network represent 26 countries and care for more than 14,500 PWH, severe von Willebrand disease and other rare bleeding disorders. Every three months each participating center is asked to report whether or not there were new adverse events, including cardiovascular disease and malignancies. More details on treatment and outcome are requested when events develop. Among other purposes, this registry is meant to facilitate a more evidence-based approach to the management of comorbidities and age-related diseases in the aging PWH and to establish improved guidelines. These are particularly needed because the intensive replacement therapy that we recommend in many of the clinical situations depicted in this article, do dramatically increase the usage of CFC and will create in the elderly PWH a second period of
intensive consumption, which adds to the early peak of consumption for prophylaxis in children and adolescents with severe hemophilia. It cannot be ruled out that this second peak in the elderly PWH might produce an increase in inhibitor incidence, particularly in patients with mild disease.
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Contribution. PMM wrote the first draft and the revision of the manuscript, REGS, ES and EPM-B reviewed the first draft and revision and made significant additions and contributions to the final version.
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Table 1: Prophylaxis schedule for indications other than cardiovascular diseases in elderly persons with severe hemophilia

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosage</th>
<th>Period</th>
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<tr>
<td>Frequent bleeding, i.e., at least 2 per month</td>
<td>3 x/week 15 U/kg FVIII 2 x/week 30 U/kg FIX</td>
<td>1 year, then stop and restart if bleeding frequency increases again</td>
</tr>
<tr>
<td>Rehabilitation after severe bleeding, for severe arthropathy or after orthopedic surgery</td>
<td>3 x/week 15 U/kg FVIII 2 x/week 30 U/kg FIX</td>
<td>During the whole period of rehabilitation</td>
</tr>
<tr>
<td>Medications increasing the underlying bleeding tendency</td>
<td>3 x/week 15 U/kg FVIII 2 x/week 30 U/kg FIX</td>
<td>During the medication period</td>
</tr>
<tr>
<td>Platelet count &lt; 30,000/μL</td>
<td>Daily 10 U/kg FVIII 20 U/kg FIX every other day</td>
<td>Until platelet count &gt; 30,000/μL</td>
</tr>
<tr>
<td>Major surgery in patients without inhibitors (specially orthopedic surgery)</td>
<td>Day of surgery: FVIII or IX 50 U/kg, followed by bolus injections 2 x day 25 U/kg, or continuous infusion with 3-4 U/kg/hr aiming at trough levels &gt; 60U/dL, followed by prophylaxis aiming at trough levels of 25 IU/dL Temporary prophylaxis: 3 x week 15 U/kg FVIII 2 x week 30 U/kg FIX</td>
<td>1 week 1 week 1 week depending of type of surgery</td>
</tr>
<tr>
<td>Major surgery in patients with inhibitors (specially orthopedic surgery)</td>
<td>Day of surgery: rFVIIa 100 μg/Kg every 2 h for 24-48 h, every 3 h until day 5, every 4 h until day 7-10, every 6 h until day 14-21</td>
<td>At least 2-3 weeks, depending on the type of surgery</td>
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Table 2

**Antithrombotic prophylaxis in persons with hemophilia undergoing orthopedic surgery**

<table>
<thead>
<tr>
<th>PATIENT CHARACTERISTIC</th>
<th>RECOMMENDED METHODS</th>
</tr>
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<tr>
<td>Without inhibitors, undergoing joint arthroplasty</td>
<td>Subcutaneous low molecular weight heparin, started 6 to 12 hours after the end of the operation (for instance, enoxiparin 40 mg), continued daily for no less than 10 days and preferably up to 35 days</td>
</tr>
<tr>
<td>With inhibitors, undergoing joint arthroplasty and treated with bypassing agents</td>
<td>Mechanical methods of thromboprophylaxis (graduated compression stocking or intermittent pneumatic compression), for no less than 10 days postoperatively</td>
</tr>
<tr>
<td>With or without inhibitors, undergoing arthroscopic surgery</td>
<td>Early mobilization, as the only method of thromboprophylaxis</td>
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Table 3: Guidelines for the use of analgesics in patients with hemophilic arthropathy.

<table>
<thead>
<tr>
<th>Step</th>
<th>Medication Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Paracetamol (500-1000 mg orally, no more than 6 times a day) is the initial medication of choice; if not effective,</td>
</tr>
<tr>
<td>2.</td>
<td>Celecoxib (COX2 inhibitor), 100-200 mg orally, 1-2 times a day or, if not effective, paracetamol plus codeine (10-20 mg orally, no more than 6 times a day), or</td>
</tr>
<tr>
<td>3.</td>
<td>Paracetamol plus tramadol 50-100 mg orally, 3-4 times a day), or, if not effective</td>
</tr>
<tr>
<td>4.</td>
<td>Morphine: use a slow release product, starting with 20 mg 2 times a day, with an escape of a rapid release product 10 mg 4 times a day. Increase the slow release product if the rapid release product is used more than 4 times a day.</td>
</tr>
</tbody>
</table>
Table 4: Schedules of replacement therapy with FVIII or FIX concentrates to reach target factor levels in elderly persons with severe hemophilia during cardiac procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Dosage*</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic coronary angiography</td>
<td>bolus infusion of 40 U/kg FVIII (80 U/kg FIX), followed by 20 U/kg FVIII (30 U/kg FIX) after 12 hours</td>
<td>peak factor level at least 80 U/dL</td>
</tr>
<tr>
<td>PCI with bare metal stents</td>
<td>- before the procedure bolus infusion of 40 U/kg FVIII (80 U/kg FIX), followed by 20 U/kg FVIII (30 U/kg FIX) after 12 hours</td>
<td>peak factor level at least 80 U/dL</td>
</tr>
<tr>
<td></td>
<td>- during dual antiplatelet therapy with aspirin and clopidogrel infusions of 50 U/kg FVIII every other day (60-70 U/kg FIX) for 1 month</td>
<td>trough factor levels at least 30 U/dL</td>
</tr>
<tr>
<td></td>
<td>- during single antiplatelet therapy with aspirin infusions of 30-40 U/kg FVIII every other day or 50 U/kg FIX 3 times/week for 1 year or indefinitely</td>
<td>trough factor levels at least 5 U/dL</td>
</tr>
<tr>
<td>Fibrinolysis</td>
<td>bolus infusion of 40 U/kg FVIII (80 U/kg FIX), followed by continuous infusion (3 U/kg/h FVIII or FIX) or 20 U/kg FVIII (30 U/kg FIX) every 12 hours for 48 hours</td>
<td>peak factor levels at least 80 U/dL, followed by trough levels at least 50 U/dL</td>
</tr>
</tbody>
</table>

Abbreviations: PCI, percutaneous coronary intervention; FVIII, factor VIII; FIX, factor IX
Table 5. **CHADS₂ score: risk for stroke in non-hemophilia patients**

<table>
<thead>
<tr>
<th>CHADS₂ score</th>
<th>Adjusted stroke rate per 100 patient years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9</td>
</tr>
<tr>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
</tr>
<tr>
<td>3</td>
<td>5.9</td>
</tr>
<tr>
<td>4</td>
<td>8.5</td>
</tr>
<tr>
<td>5</td>
<td>12.5</td>
</tr>
<tr>
<td>6</td>
<td>18.2</td>
</tr>
</tbody>
</table>

CHADS₂ score is calculated by adding 1 point for congestive heart failure, hypertension, age ≥ 75 years or diabetes mellitus, and 2 points for prior stroke or transient ischemic attacks. Low risk = 0, moderate risk = 1, high risk ≥ 2
Figure 1: Recommendations for antithrombotic and replacement therapy with coagulation factor concentrates (CFC) hemophilia A patients with nonvalvular atrial fibrillation.

- Atrial fibrillation in hemophilia
  - Antithrombotic therapy based on basal FVIII/IX levels and stroke risk
    - Basal FVIII/IX level ≥ 30 IU/dL
      - CHADS$_2$ ≤ 2: Low dose aspirin
      - CHADS$_2$ ≥ 2: Vitamin K antagonists
    - Basal FVIII/IX level 5-30 IU/dL
      - Low dose aspirin
    - Basal FVIII/IX level 1-5 IU/dL
      - No antithrombotic therapy
    - Basal FVIII/IX level <1 IU/dL
      - No antithrombotic therapy
      - CHADS$_2$ ≥ 2: CFC prophylaxis
Figure 2: Recommendations for antithrombotic and replacement therapy in hemophilia A patients with nonvalvular atrial fibrillation

Cardioversion for atrial fibrillation in hemophilia

< 48 h after onset

- No antithrombotic therapy needed before, during or after cardioversion

> 48 h after onset

- TEE: exclusion of left atrial thrombus prior to cardioversion
- Therapeutic dosages of heparin (UFH or LMWH) and trough factor VIII/IX levels 80 U/dL during cardioversion and for 5 days
- Followed by vitamin K antagonists (target INR 2.5) and trough factor VIII/IX levels 30 U/dL for 4 weeks after cardioversion

Long-term antithrombotic therapy according to risk stratification as depicted in Figure 1
How I treat age-related morbidities in elderly persons with hemophilia

Pier M. Mannucci, Roger E.G. Schutgens, Elena Santagostino and Evelien P. Mauser-Bunschoten

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