REVIEW ARTICLE

How we manage cardiovascular disease in patients with hemophilia

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Abstract

With the striking advances in hemophilia care that have materialized particularly in the last two decades, an increasing number of persons with hemophilia (PWH) have achieved a quality of life and life expectancy very close to that of unaffected individuals. With aging, a growing number of PWH develop age-related co-morbidities, including cancer and cardiovascular disease. The latter (particularly coronary artery disease and atrial fibrillation) represent a new challenge for the hemophilia treatment centers because their management implies a delicate balance between the thrombotic risk and bleeding tendency, that is further enhanced by the concomitant use of antithrombotic agents. Because evidence from clinical trials is lacking, the management of PWH with cardiovascular diseases is mostly based on expert opinions, personal experiences, and the adaptation of the evidence stemming from studies on people without hemophilia. In this article, we focus on how to manage coronary artery disease and atrial fibrillation in patients with hemophilia.

Introduction

Hemophilia, the most common X-linked inherited disease which affects approximately 400,000 people worldwide, is characterized by reduced or unmeasurable levels of coagulation factor VIII (FVIII, hemophilia A) or factor IX (FIX, hemophilia B).[1] The phenotypic severity and bleeding tendency are generally proportional to the degree of factor deficiency. Accordingly, patients with severe hemophilia (plasma factor levels <1%) suffer from recurrent hemorrhages into muscles and joints that, if untreated or inadequately treated, lead to an invalidating arthropathy.[2] Since the early 1970s, the availability of coagulation factor concentrates (first plasma-derived and then recombinant) has dramatically improved the therapeutic approach to persons with hemophilia (PWH) by permitting home treatment and thus the early control or prevention of bleeding.[3,4] Before this period, PWH had a very short life expectancy (20-30 years) and many died at a young age due to life-threatening bleeding episodes.[5] Since the 1990s, the wider implementation of regular prophylaxis by hemophilia treatment centers (HTC) offering specialized and comprehensive care has fostered the clinical management of PWH, significantly contributing to improved clinical outcomes. In the last decade, the availability of extended half-life recombinant FVIII and FIX products and the non-replacement product emicizumab administered subcutaneously has improved patient adherence to prophylaxis, further personalizing this therapeutic approach.[5] Thus, with the availability of safe and effective treatments, both quality of life and life expectancy of PWH have progressively increased, approaching those of the general male population, at least in high-income countries. As a result, hematologists are now confronted with a growing population of older PWH who develop age-related diseases, including cardiovascular disease (CVD), malignancies, and renal diseases.[6-10] In this article, based on our experience as well as on an analysis of the literature, we are focusing on the management of two frequent CVD: coronary artery disease (CAD) and non-valvular atrial fibrillation (AF).

Search methods

We reviewed the medical literature for fully published studies on the management of CVD in PWH. A literature search of the PubMed electronic database (through Med-

line) was carried out without temporal limits using English language as restriction. The Medical Subject Heading (MeSH) and keywords used were: "hemophilia", "bleeding disorders", "elderly patients", "aging patients", "co-morbidities", "management", "treatment", "mortality", "life expectancy", "factor VIII", "factor IX", "cardiovascular disease", "ischemic heart disease", "coronary artery disease", "cerebrovascular disease", "atherosclerosis", "arterial thrombosis", "atrial fibrillation", "antiplatelet agents", "antithrombotic agents" and "anticoagulation". We also screened the reference lists of the most relevant review articles for further studies not captured in our initial literature search. Figure 1 reports the results of our literature search.

Clinical case

In January 2016, a 76-year-old man with severe hemophilia A was admitted to the emergency department of the Mantova City Hospital for acute coronary syndrome. He was on prophylactic replacement therapy with a plasma-derived FVIII concentrate (Haemoctin®, Biotest Pharma, Dreieich, Germany) administered on alternate days, suffered from chronic arthropathy, and had undergone total hip arthroplasty in 1993 and transurethral prostate resection in 2011, both surgeries being performed under hemostatic coverage with the FVIII concentrate. Chronic AF was one of his comorbidities, and this was handled with low-dose aspirin as the only antithrombotic prophylaxis. He had a family history positive for CVD and several additional cardiovascular risk factors, such as hypertension, obesity (body mass index 32) and dyslipidemia. After hospital admission, he underwent percutaneous coronary angiography (radial access) that showed a critical stenosis of the interventricular anterior and right coronary arteries. Two bare metal stents (BMS) were deployed under hemostatic coverage with Haemoctin® (4000 IU) with the goal of obtaining a peak FVIII level in plasma of at least 80% prior to the revascularization procedure. Before this, an intravenous bolus of 5000 IU unfractionated heparin (UFH) had also been administered, followed by a loading dose

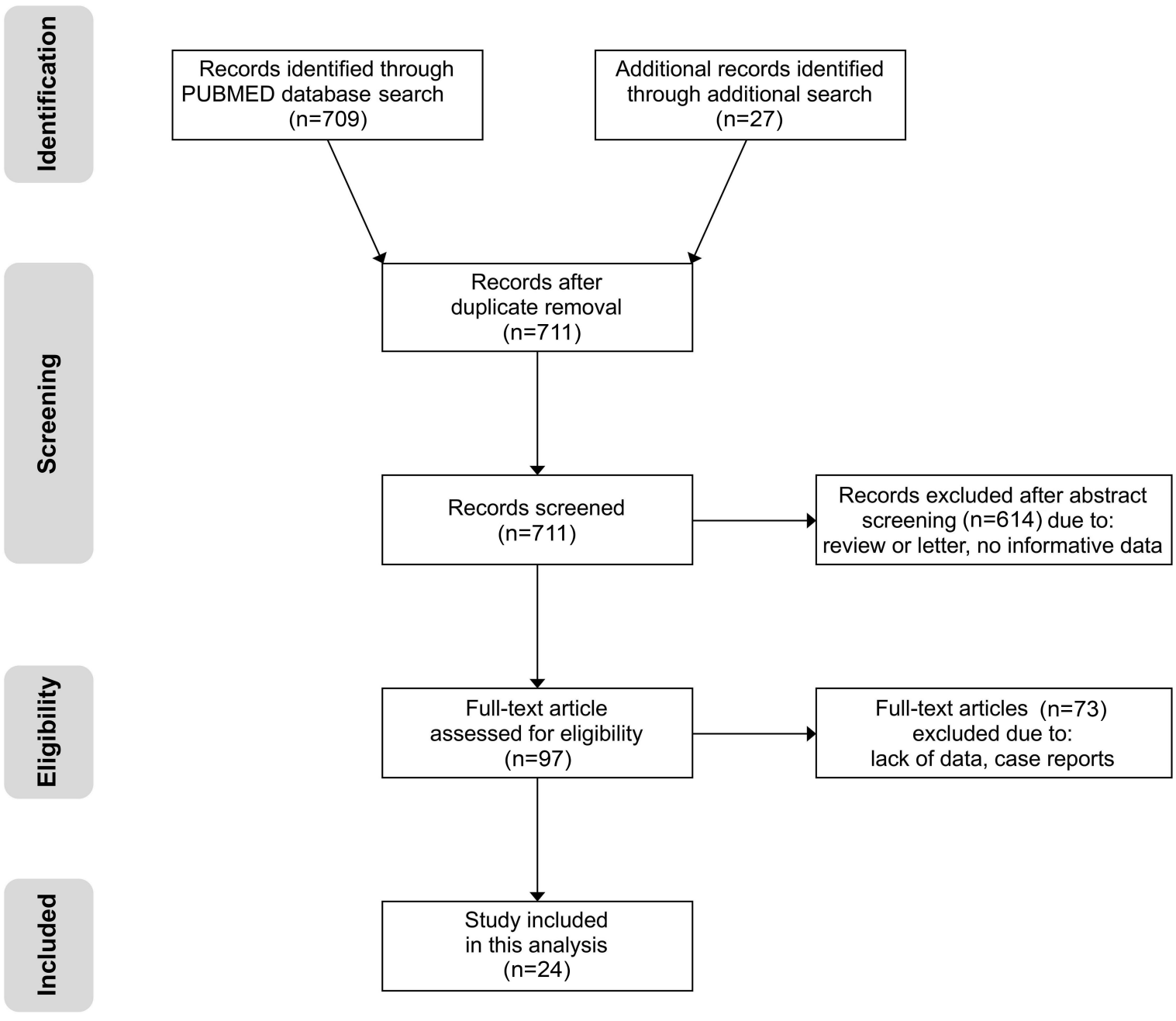

Figure 1. Flow diagram of study selection.

of 325 mg aspirin and 600 mg clopidogrel. Dual antiplatelet therapy with aspirin 100 mg daily and clopidogrel 75 mg daily was also planned. The patient was discharged after three days with no bleeding complications, the planned antithrombotic regimen was prescribed together with continued prophylaxis with daily infusions of FVIII concentrate to keep trough plasma FVIII levels above 30%. One month after the revascularization procedure the patient was switched to low-dose aspirin (75 mg daily) and prophylactic FVIII was stopped. He was again admitted to the Emergency Department of the Mantova hospital for the onset of hematuria and large hematomas in the lower trunk and limbs, and prophylaxis with the same FVIII product (3000 UI) was restarted on alternate days to maintain trough plasma FVIII above 5%. The bleeding diathesis disappeared. The patient was also re-evaluated for chronic AF. Because anticoagulant prophylaxis was deemed contraindicated by his high bleeding risk due to the coagulation disorder plus antiplatelet therapy, in March 2021 he underwent surgery for left atrial appendage closure. The procedure was followed by 30 days of dual antiplatelet therapy (aspirin 100 mg daily and clopidogrel 75 mg/daily), which again required daily treatment with FVIII (target FVIII trough level: ≥30%). The patient is currently on low-dose aspirin (100 mg daily) and prophylactic therapy (Haemoctin® 3000 UI) on alternate days with no further bleeding at the 6-month follow-up.

The burden of cardiovascular disease in hemophilia

Although hemophilia has been postulated to protect against the development of CVD due to the underlying hypocoagulability, the precise incidence of cardiovascular diseases in PWH is not known.[11-15] While a number of studies have documented that PWH have a lower mortality from CAD than the age-matched male population,[16,17] more recent data indicate that prevalence of CAD in PWH increases with age. In a single-center study conducted between 1993 and 1998 in the USA, the age-specific prevalence of CAD ranged from 0.05% in PWH under the age of 30 years up to 15.2% in those aged 60 years or older.[18] In addition, CAD-related mortality increased from 2% to 6% between 1972 and 2001, paralleling the growing life expectancy.[19] Similarly, the standardized mortality ratio (SMR) for CAD during the period 2000-2007 was approximately two-fold higher than during the years 1990-1999 (0.55 *vs*. 0.25).[20] An SMR of 3.0 for myocardial infarction, indicating an increased risk of death, was reported in a large study of PWH from the USA.[21] Despite their natural anticoagulation state, that should in principle protect against thrombus formation, older PWH have a number of factors favoring the onset of CVD, including the use of clotting factor concentrates, the presence of co-infections (i.e., HIV on antiretroviral therapy), and such other risk factors as hypertension, diabetes, overweight, poor physical activity, and chronic renal disease.[22,23] Indeed, a retrospective study from Canada observed that risk factors for CVD (i.e., hypertension, smoking, obesity, diabetes mellitus, dyslipidemia, family history, and anti-retroviral therapy), as well as such cardiovascular events as acute coronary syndrome, cerebrovascular ischemic disease and AF were common in PWH.[24] A retrospective study conducted in the USA found that among PWH the prevalence of CAD, stroke and myocardial infarction was around two-fold higher than in non-hemophilia males.[25] Furthermore, a large retrospective USA study documented an increased prevalence of CVD in PWH compared with the general male population,[26] and a report from Taiwan demonstrated that atherothrombotic cardiovascular events occurred at an earlier age, with chronic obstructive pulmonary disease, hypertension and hyperlipidemia as the main associated risk factors.[27]

All in all, evidence from the literature indicates that the prevalence of CVD in PWH is at least equal to that of their peers without hemophilia. This finding is consistent with another line of research on carotid and femoral artery intimal-medial thickness (a surrogate measure of atherosclerosis burden) which showed comparable values in PWH and the general population,[28,29] indicating that hemophilia-related hypocoagulability does not exclude atherogenesis.

Management of cardiovascular diseases

Evidence-based recommendations on how to handle CVD in PWH are lacking due to the absence of clinical trials. Thus, the few available guidelines are mostly based on those originally prepared for persons without hemophilia.[30,31] There is general consensus that PWH must be managed like their age-related peers, provided replacement therapy is adapted to the degree of plasma factor deficiency and the added risk of bleeding carried by invasive cardiac procedures and use of antithrombotic drugs.[8] The balance between bleeding and thrombosis is indeed particularly delicate in PWH, thereby representing a major challenge when these patients develop CVD.

Coronary artery disease

Both stable angina and acute coronary syndrome, the main types of CAD, can occur in PWH and need the same therapeutic approach as people without hemophilia.[13,32] However, the management of CAD is challenging because standard treatment requires antiplatelet and anticoagulant drugs, such invasive procedures as percutaneous coronary intervention (PCI), the use of bare metal stents

(BMS), drug-eluting stents (DES) or even cardiac surgery with coronary artery bypass graft (CABG).[33-35] Accordingly, particular attention must be paid to long-term antithrombotic treatments that expose PWH with CAD to a long-lasting increased risk of bleeding, as pointed out by the French registry.[36]

As far as the management of stable angina is concerned, long-term low-dose aspirin (≤ 100 mg/day) should be prescribed, but for PWH with severe disease, clotting factor prophylaxis should be given to prevent any worsening of the bleeding tendency.[10] In particular, prophylaxis is mandatory in those PWH with a phenotype of 'heavy bleeder' or at high risk of bleeding owing to comorbidities (arterial hypertension, history of intracranial bleeding, gastrointestinal disease, liver disease or other conditions increasing the bleeding tendency).[10]

With the aim of standardizing therapeutic approaches, an institutional guideline for CAD in PWH has been developed in The Netherlands[30,31] offering suggestions largely extrapolated from the guidelines for Dutch patients without hemophilia. More recently, an international group tried to apply the guidelines of the European Society of Cardiology (ESC) for the management of acute coronary syndrome to PWH.[31] Thus, by harmonizing the indications from these guidelines with our own personal experience, we recommend that PCI should be performed as soon as possible and is to be preferred over thrombolysis among the revascularization procedures due to its reduced risk of bleeding complications (Figure 2). Thrombolysis should be considered only when PCI cannot be accessed.

Regarding the choice of the stent, BMS have been the preferred approach, because of the benefit of a shorter duration of combined antiplatelet treatment (usually one month).[36,37] First-generation DES use has been reported in PWH, but these devices require more time to endothelize and dual antiplatelet therapy is required for longer.[38] Thus, BMS and short-term combined antiplatelet treatment have been the main recommendations.[30] However, second-generation DES have demonstrated a neat superiority over both BMS and early-generation DES in terms of efficacy and safety.[39] In addition, with the latest available DES, one month of dual antiplatelet therapy is not inferior to a longer treatment period in patients at high risk of bleeding.[40] Thus, we prefer to use second-generation DES and one month of dual antiplatelet therapy in PWH undergoing PCI. Regarding the access route for PCI, the radial artery is preferred to the femoral access owing to a lower risk of bleeding (local hematoma and anemia with transfusion requirement).[41] In addition, the radial artery can be more easily compressed and does not carry the risk of the retroperitoneal bleeding associated with the femoral access.

The delicate balance between coagulation and anticoagulation in PWH with acute coronary syndrome deserves special attention. Regarding heparin anticoagulation, a single intravenous bolus of UFH should be started before PCI at the dosages reported in Figure 2. According to re-

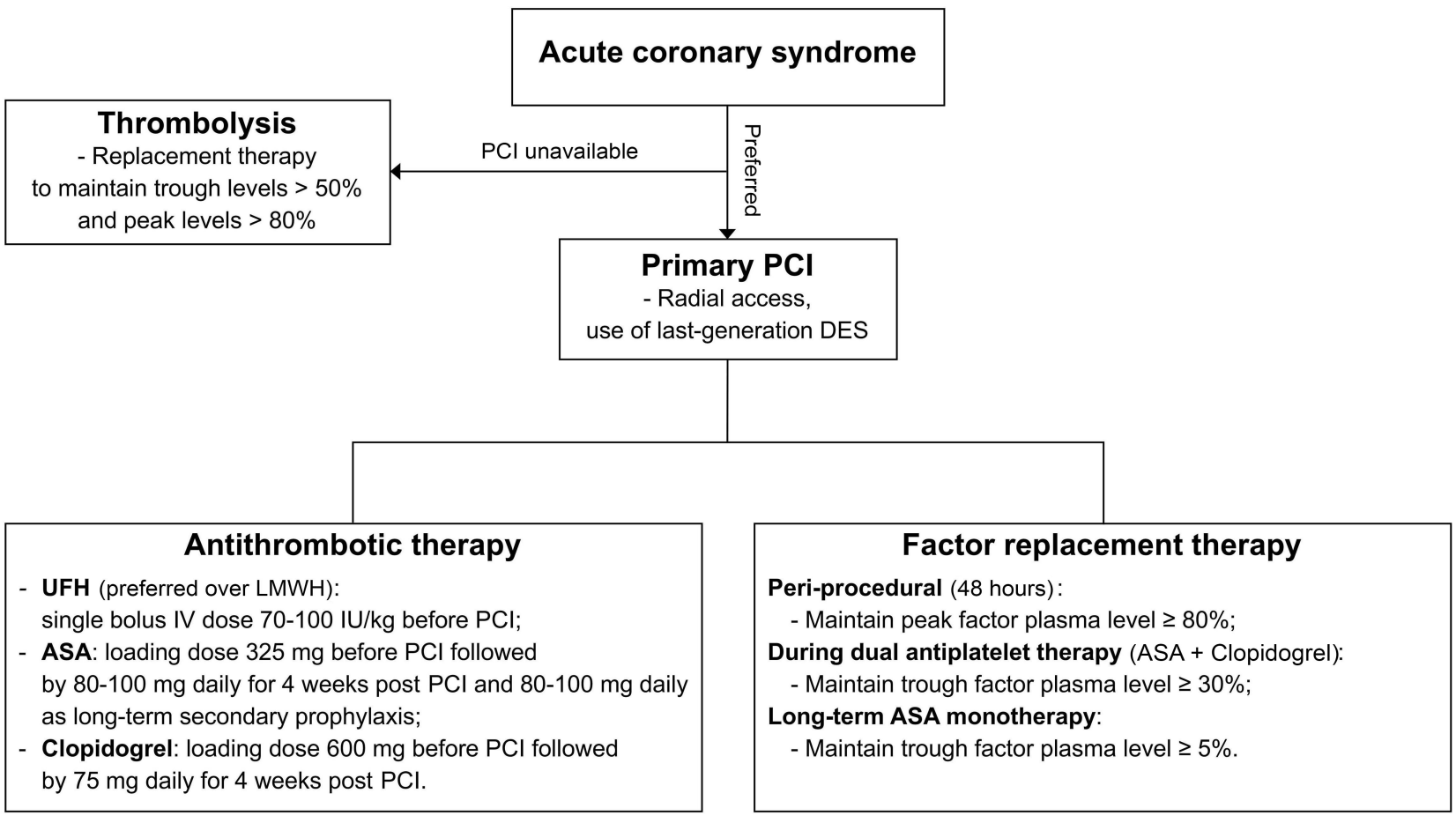

Figure 2. Management of acute coronary syndrome in persons with hemophilia. PCI: percutaneous coronary intervention; DES: drug-eluting stents; IV: intravenous; UFH: unfractioned heparin; LMWH: low molecular weight heparin; ASA: acetylsalycilic acid.

cent guidelines for non-hemophilia patients, continuous UHF infusion following revascularization is no longer required. UFH is preferable to low molecular weight heparin (LMWH) because the anticoagulant effect can be easily measured by means of a simple point-of-care test (the activated clotting time), shorter half-life (1-2 *vs*. 4-5 hours), and availability of protamine sulfate as an antidote. Along with UFH, PWH are usually treated with dual antiplatelet therapy with aspirin and clopidogrel according to general guideline recommendations and evidence from published case series of PWH.[30-32] We recommend a loading dose of 325 mg aspirin and 600 mg clopidogrel before PCI. Afterwards, PCI dual antiplatelet therapy is warranted to prevent stent thrombosis, but this is inevitably associated with an increased risk of bleeding related to the combination of the inherited coagulation defect with drug-induced platelet dysfunction. In the French registry that collected information on long-term antithrombotic treatments prescribed to PWH with CVD, bleeding was more frequent in patients treated with antiplatelet medications than in those without.[36] Therefore, in order to minimize the risk of bleeding, we recommend dual antiplatelet therapy (aspirin 80-100 mg daily and clopidogrel 75 mg daily) for the shortest possible time, i.e., only during the 4 weeks following stent deployment. Long-term single therapy with low-dose aspirin 80-100 mg daily is recommended as secondary antiplatelet prophylaxis after PCI and stent deployment in PWH.[42] Notwithstanding their higher efficacy than clopidogrel for reducing deaths and major cardiovascular events, prasugrel and ticagrelor should not be chosen for dual antiplatelet therapy due to the higher bleeding risk.[43,44] There is very little experience in PWH with glycoprotein IIb/IIIa inhibitors, but their use is discouraged because they are associated with a particularly high risk of bleeding.[32]

Obviously, PWH with CAD can be treated as above with antithrombotic agents provided their coagulation defect is adequately corrected with factor replacement therapy. Accordingly, the dosage and intervals of factor administration should be planned and tailored in order to attain a given target plasma factor level. We recommend a trough factor level of no less than 30% for the treatment of acute coronary syndrome during the dual antiplatelet period. A higher peak factor level (≥80%) is warranted during the peri-procedural PCI period, whereas trough factor levels of approximately 5% are sufficient during long-term aspirin monotherapy (Figure 2). This target level can be attained by means of factor concentrate administration every other day, or even at more spaced out intervals when extended half-life concentrates are used. In patients with severe hemophilia, factor replacement prophylaxis is indicated for as long as an antithrombotic drug is prescribed. Finally, in the rare instances when thrombolysis is used, a more intensive factor replacement (trough 50% and peak ≥80%) should be provided.

A particularly challenging situation is the management of an acute coronary syndrome in PWH who developed alloantibodies that inactivate the coagulant activity of infused coagulation factors,[45] i.e., up to 30% of cases with severe hemophilia A. There is very little information as to the best management strategy to adopt when inhibitor patients develop acute coronary syndrome. Because they fail to achieve a satisfactory hemostasis following regular replacement therapy, it is necessary to resort to plasma-derived (factor VIII inhibitor bypassing activity, FEIBA) or recombinant (activated factor VII, rFVIIa) products that contain activated coagulation factors able to bypass the inhibitor defect and thus ensure hemostasis.[45] However, both bypassing agents are potentially thrombogenic and special attention should be paid to their use in PWH who have a hypercoagulable state at the time of acute coronary syndrome.

During PCI, we suggest administering rFVIIa on the day of the procedure at a dose of 90-100 μg/kg every 3-4 hours for 24 hours, followed by the same dose given daily during the next 4-week duration of antiplatelet therapy after stent deployment. When FEIBA is chosen as bypassing medication, we suggest a dosage of 80 U/kg every 12 hours for the first 24 hours, followed by the same daily dose during the next 4-week duration of antiplatelet therapy. During this period, the use of low-dose aspirin monotherapy instead of dual antiplatelet therapy is preferable due to the increased bleeding risk caused by the concomitant presence of two antiplatelet medications and the FVIII inhibitor.[46]

More uncertainty remains as to the management of CAD in the increasing number of FVIII inhibitor patients on prophylaxis with emicizumab (a long-acting bispecific monoclonal antibody that mimics the function of activated FVIII). Because PWH on emicizumab undergoing PCI cannot be monitored in the laboratory according to activated partial thromboplastin time (APTT)-based coagulation factor assays, bovine chromogenic assays should be used to monitor and tailor FVIII levels following concentrate infusion and heparin therapy.

Cardiac surgery is feasible in PWH provided replacement therapy is adequately planned in terms of dosage and duration in the frame of a multidisciplinary specialized team that offers close clinical and laboratory surveillance and follow-up. Fortunately, in recent years the progressive increase of PCI has substantially reduced the number of CABG in general, and also in PWH with CAD.[47,48] Accordingly, indications for CABG are now limited to multi-vessel CAD or when the PCI revascularization approach is compromised.

Non-valvular atrial fibrillation

Atrial fibrillation is a leading cause of cardioembolic stroke and is a very common CVD in the aging population.[49] Thus, the frequency of this arrythmia is continuously increasing in PWH, because they are not naturally protected from AF

nor from the ensuing thromboembolic complications. As for CAD, PWH should be treated in the same way as patients without hemophilia. Considering that there are no formal clinical trial data supporting recommendations for antithrombotic prophylaxis in PWH, their therapy should be personalized, balancing the risk of bleeding with that of thromboembolic complications.[50] In the non-hemophilia population, there is a strong indication to use anticoagulation for stroke prevention if the CHA_2DS_2-VASc score with AF has a value of 1 or higher in men.[51,52] Anticoagulation, which leads to a two-thirds reduction in the risk of cardioembolic stroke, may be carried out with vitamin K antagonists (VKA) or direct oral anticoagulants (DOAC), but the latter are generally preferable, particularly in patients at high risk of bleeding, due to a lower risk of cerebral hemorrhage.[51] Scores have also been proposed to calculate the hemorrhagic risk in non-hemophilia patients who are candidates for oral anticoagulation; the HAS-BLED score is the most used.[53] However, the applicability of both the thrombotic (CHA_2DS_2-VASc) and bleeding (HAS-BLED) risk scores is questionable in PWH because, owing to the impact of the inherited hypocoagulable state on both thrombotic and hemorrhagic risk evaluation, it is difficult to ascertain whether these tools originally developed and validated for the general population do, in fact, over-estimate (CHA2DS2-VASc) or under-estimate (HAS-BLED) the corresponding risk in PWH. In particular, although the French registry reported that bleeding episodes were more frequent in PWH with HAS-BLED scores higher than 3 than in those with scores of 3 or less,[36] this tool is far from being standardized for use in congenital bleeders. Nevertheless, we and others suggest that oral anticoagulation should be considered for PWH with AF and a CHA_2DS_2-VASc score of 2 or higher.[35,46,54] When oral anticoagulation is implemented, we recommend DOAC instead of VKA due to the lower risk of cerebral hemorrhage.[55,56] However, information on the safety of DOAC, as well as their efficacy and at which dosage, is not yet available in PWH with AF owing to the lack of adequately powered trials. In practice, we prefer to use DOAC at the lower recommended daily dosages, i.e., those for older patients and for those with renal impairment. We suggest daily doses of 220 mg for dabigatran, 15 mg for rivaroxaban, 5 mg for apixaban, and 30 mg for edoxaban.

According to guidelines and expert opinions,[35,46] PWH with atrial fibrillation may be able to receive oral anticoagulation without changing their adopted therapeutic regimens when their endogenous factor levels are 20% or higher (Figure 3). According to patient experience, expert opinion and laboratory data, this cut-off value during oral anticoagulant therapy is considered to be safe enough.[35] To minimize the risk of bleeding, the continuous prophylactic use of factor concentrate is warranted in patients with FVIII/FIX levels lower than 20%, even though this approach is associated with the consumption of large amounts of concentrates and high costs. Perhaps it has been in response to these challenges that antiplatelet monotherapy has been proposed as a compromise in PWH at higher thrombotic (CHA_2DS_2-VASc score ≥2) and hemorrhagic (factor levels <20%) risk.[57] However, because antiplatelet drugs are no longer recommended to reduce the risk of stroke in the general population with AF, and yet are associated with a significant increase in bleeding risk,[51] we do not in any way support their use for PWH.

Patients with severe hemophilia (clotting factor level <1%) with AF are not usually treated with oral anticoagulation, in line with the observation that in these patients the naturally occurring, endogenous decrease in thrombin formation is similar to that of patients on the therapeutic International Normalized Ratio range during VKA therapy.[58] Thus, considering the uncertainties of the bleeding risk in PWH with FVIII/FIX levels between 1% and 20%, strategies aimed at avoiding the need for long-term anticoagulant therapy should be strongly considered. Non-anticoagulant options for AF, such as cardioversion, catheter ablation and closure of the left atrial appendage, have been successfully used not only in non-hemophilia patients at high risk of bleeding (HAS-BLED > 3), but also in PWH (Table 1).[17,59,60]

Catheter ablation

Catheter ablation after pulmonary vein isolation using a femoral vein approach can be used to interrupt the abnormal electrical activity that sustains AF, and can recover and maintain the sinus cardiac rhythm. In patients at high risk of bleeding (HAS-BLED ≥3), catheter ablation has been shown to be as effective as oral anticoagulation in the prevention of long-term thromboembolic complications, but with a lower risk of bleeding.[61] A successful single-center experience with catheter ablation in PWH was reported by van der Valk *et al.*; all patients obtained long-term sinus rhythm.[59]

Percutaneous left atrial appendage closure

Percutaneous left atrial appendage closure, non-inferior to oral anticoagulation in the prevention of thromboembolism and cardiac death,[62] is another intervention used in PWH with AF in order to limit the duration of antithrombotic therapy and the risk of bleeding, particularly in those with more severe factor deficiency.[63] The rationale for this approach lies in the fact that more than 90% of emboli originate in the left atrial appendage.[64] However, in order to prevent device-related thrombosis, antithrombotic treatment is required at least until complete endothelization of the device surface has occurred, usually for at least 3 months.[65] Factor concentrate prophylaxis is required during this antithrombotic treatment (Table 1). Although promising, experience with this technique in PWH is limited; a recent systematic literature review identified only 9 cases.[66] In

these, there was some variability in the choice of the occluding device, severity of hemophilia, as well as type and duration of antithrombotic therapy.[66] Different antithrombotic strategies in non-hemophilia AF cases at increased hemorrhagic risk have been proposed depending on their thrombotic risk profile, ranging from dual antiplatelet therapy for one month and antiplatelet monotherapy for two additional months in patients with CHA_2DS_2-VASc score of 4 or more, to up to three months of antiplatelet monotherapy in those with CHA_2DS_2-VASc score less than 4.[67] In addition, data from a recent randomized trial suggest that low-dose DOAC may be an effective alternative to antiplatelet agents for post-procedural anticoagulation.[68] Whatever the therapeutic regimen used, we suggest antiplatelet therapy for at least 3 months (the minimum period required for endothelization) following percutaneous left atrial appendage closure, together with adequate clotting factor prophylaxis (Table 1).

In summary, the CHA_2DS_2-VASc score and patient residual coagulation factor levels should first be taken into ac-

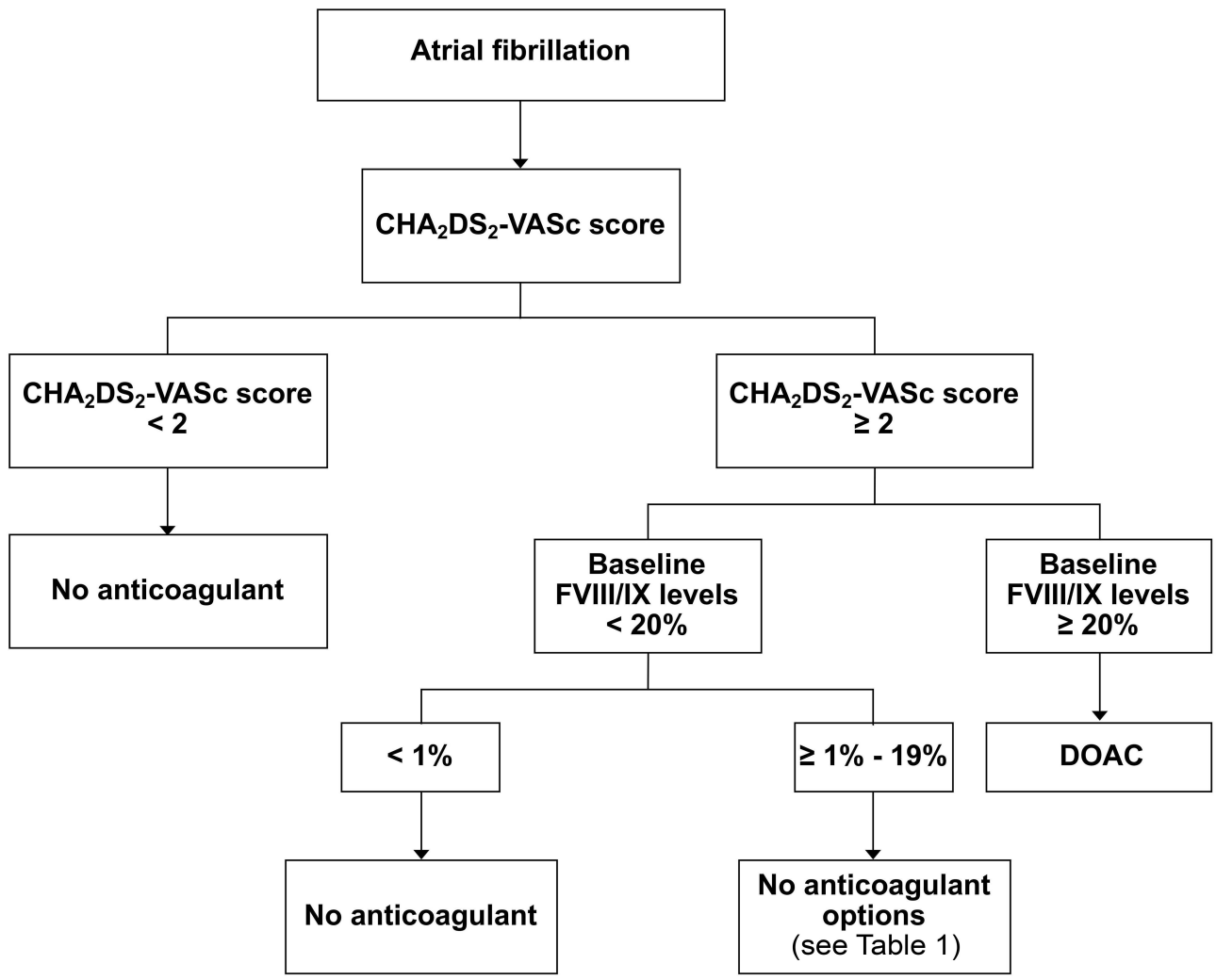

Figure 3. Management of atrial fibrillation in persons with hemophilia.

Table 1. Management of atrial fibrillation in persons with hemophilia.

Procedure	Management
Cardioversion	● AF ≤48 hours duration: no antithrombotic therapy. ● AF >48 hours duration: periprocedural (5 days) therapeutic doses of UFH and additional 4 weeks of OAC. CFC prophylaxis to maintain trough factor levels ≥80% during periprocedural period and ≥30% during the 4 weeks of OAC.
Catheter ablation	Periprocedural (2 days) therapeutic doses of UFH and additional 4-6 weeks of OAC. CFC prophylaxis to maintain trough factor levels >80% during periprocedural period and ≥30% during the 4-6-weeks of OAC.
Left atrial appendage closure	ASA and clopidogrel (preprocedural loading dose and postprocedural maintenance dose) for 1 month followed by ASA monotherapy (80-100 mg/day) for 2 months. Maintain peak factor plasma levels ≥80% during periprocedural (48 hours) period, trough factor plasma levels >30% during DAPT (1 month), and trough factor plasma levels ≥5% during ASA monotherapy (2 months).

AF: atrial fibrillation; OAC: oral anticoagulation; UFH: unfractionated heparin; DAPT: dual antiplatelet therapy; ASA: acetylsalicylic acid; CFC: coagulation factor concentrate.

count when considering the indication for oral anticoagulation in PWH with AF, although several grey areas still persist.

Conclusions

The management of CVD in PWH is complex, requiring an accurate balance between coagulation and anticoagulation. Even though we have attempted here to provide indications on the management of two main CVD, it must be emphasized once more that the approaches suggested here and published in the literature are heterogeneous, making it difficult to provide solid guidelines. Despite these limitations, some general recommendations can be offered in the light of our experience as care providers in large hemophilia treatment centers. The cardiovascular management of PWH should be individualized in order to balance the bleeding risk with the antithrombotic protection, based on the cardiovascular risk profile and the severity of factor deficiency and/or bleeding phenotype. On the whole, however, clinical choices for PWH should be the same as those adopted for non-hemophilia patients, provided factor deficiencies are corrected by adequately tailored replacement therapy. The optimization of treatment efficacy and the mitigation of bleeding can only be reached through close co-operation between hematologists and other care providers from the specialized treatment centers in a multi-disciplinary approach (cardiologists, radiologists, surgeons) including all of those involved in the management of PWH with cardiovascular diseases.

Disclosures

PMM has received honoraria from Bayer, Kedrion, Roche and Werfen for lectures at educational symposia. MF and DF have no conflicts of interest to disclose.

Contributions

All the authors collaborated in writing and reading the manuscript.

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