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Thrombosis and Hemophilia: Little More Evidence, Much More Guidance

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The deficiency in factor VIII (FVIII) or factor IX (FIX) that characterizes hemophilia in theory provides physiological protection against thrombosis. Clinical experiences, numerous publications, and several registries indicate the opposite. Thrombosis is not uncommon among patients with hemophilia (PWH), although those with severe or moderate forms are less affected. These thrombotic events are becoming more frequent, causing increasing concern and management difficulties.

PWH are more susceptible to arterial rather than venous thrombosis, which is not entirely surprising.[1] Arterial thrombosis primarily involves blood platelets and develops in atheromatous vessels (atherothrombosis). The classic arterial vascular risk factors, including hypertension, obesity, diabetes, dyslipidemia, and sedentary lifestyle, which are common in older patients, promote the development atheromatosis in PWH independently of FVIII or FIX deficiency. The high prevalence of hypertension and obesity among PWH has been well-documented.[2,3] Although the rate of atherosclerosis appears similar in PWH compared with the general population, cardiovascular mortality is reduced. It has been postulated that PWH may be protected from acute coronary syndrome and cardiovascular mortality through increased plaque stability and reduced thrombin generation following plaque rupture.[4] The other significant source of arterial thrombosis is atrial fibrillation, which hemophilia does not protect against, but FVIII or FIX deficiency intuitively reduces its thrombogenic risk.[5]

PWH are less likely to develop venous thrombo-embolic disease (VTED) due to the role of coagulation factors in their occurrence.[6] However, major orthopedic surgery in intensively substituted patients can increase the risk of VTED. The use of pharmacological antithrombotic prevention in this context is still debated for PWH. This risk of postsurgical VTED may be higher in hemophilia B patients, as FVIII levels can reach very high prothrombogenic values without restriction. Little is known about the risk of VTED among PWH exposed to other prothrombotic conditions (surgery, trauma, acute medical conditions, cancer, etc).

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FVIII or FIX substitution likely mitigates the protection against thrombosis afforded by hemophilia, especially when regular (prophylaxis) and intensive. The risk of thrombosis associated with the treatment of hemophilia may increase when physiological inhibitors of coagulation (antithrombin, tissue factor pathway inhibitor) are partially reduced or neutralized by rebalancing agents leading to more thrombin generation.[7] This risk may also be modulated by bispecific antibodies that mimic FVIII's action but are not subject to the same physiological control.[8] Additionally, gene therapy may increase this thrombotic risk if supranormal endogenous FVIII or FIX concentrations are achieved.[9]

Managing thrombosis in PWH presents a significant challenge, whether it is for acute treatment or primary and secondary prevention. The management strategy needs to carefully balance the bleeding risks associated with antithrombotic treatments (antiplatelet or anticoagulant agents) and the antithrombotic protection conferred by FVIII or FIX deficiency, which varies depending on its severity and the hemostatic treatment modalities used.

Without providing new original data, the document jointly produced by the European Hematology Association (EHA) in collaboration with the International Society on Thrombosis and Haemostasis (ISTH), the European Association for Haemophilia and Allied Disorders (EAHAD), the European Stroke Organisation (ESO), and a representative of the European Society of Cardiology (ESC) Working Group on Thrombosis should have a significant impact on the management of thrombosis among PWH. Its merits are multiple.[10] The proposed recommendations are based on a comprehensive review of the literature. The management of coronary thrombosis, the primary and secondary prevention of thrombotic events related to atrial fibrillation, the management of ischemic stroke, and the indications and methods of prevention and treatment of VTED are discussed in detail and, above all, in a practical manner. The authors have clearly attempted to provide proposals for antithrombotic management that should help clinicians address many clinical situations, even if the scientific evidence is limited.

Most of the recommendations are based on the clinical and biological observation that PWH with a basal FVIII or FIX concentration <20% are naturally anticoagulated and should not be candidates for anticoagulation (Table 1). For these patients, however, correction of the clotting factor deficiency is indicated in the case of antiplatelet therapy. For patients with an endogenous FVIII or FIX concentration >20%, antithrombotic management does not differ from that of nonhemophilic patients, although treatment must be individualized and the risk/benefit balance regularly reassessed. This document also provides recommendations for managing procedures such as coronary angioplasty, left atrial closure, and intracerebral thrombectomy.

Table 1

Main Modalities of Antithrombotic Treatments in Patients With Hemophilia According to the EHA, ISTH, EAHAD, ESO Guidance

Basal Factor VIII or IX Levels	Duration of Antithrombotic Treatment	Single Antiplatelet Therapy (Aspirin–Clopidogrel)	Dual Antiplatelet Therapy	Anticoagulation VKA DOAC (Full Dose)	Triple Therapy Dual Antiplatelet Therapy + VKA or DOAC
<20%[a]	Short and long term	Prophylaxis with FVIII or FIX Trough level: 1%–5% Or emicizumab	Prophylaxis with FVIII or FIX Trough level >20%	No anticoagulation Natural anticoagulation Avoid peak of FVIII/FIX >25% during prophylaxis	Prophylaxis with FVIII or FIX Trough level >80%
> 20%	Short and long term	Start	Start	Prefer DOAC	Prophylaxis with FVIII or FIX Trough level >80%

[a]Lowest factor level measured in case of discrepancy between 1-stage or chromogenic assays.

DOC = direct oral anticoagulant; EAHAD, European Association for Haemophilia and Allied Disorders; EHA, European Hematology Association; ESO, European Stroke Organisation; ISTH, International Society on Thrombosis and Haemostasis; VKA = Vitamin K antagonist.

If indicated, PWH should have access to these multiple procedures with precautions, namely prior appropriate correction of their clotting factor deficiency and consultation between the hemophilia expert and the other specialists.

Despite these strengths, these recommendations have some limitations. They describe the antithrombotic management of patients receiving conventional replacement therapy with intravenous FVIII or FIX concentrates. They also summarize the current limited data for patients treated with bispecific FVIII mimicking antibodies. Other new treatments that rebalance coagulation or induce endogenous synthesis (gene therapy) are not or only minimally discussed. These treatments will likely change the risk of thrombotic complications and their management. The same is probably true for an ultra-long half-life FVIII concentrate capable of maintaining near-normal FVIII concentrations for several days with weekly administrations.[11] All these treatments, which all result in more thrombin generation, should partially deprive severe and moderate PWH of their physiological protection and increase their risk of thrombosis in predisposed patients. In the future, the choice of one of these therapies should take into consideration the risk factors for thrombosis in each patient. The appropriate antithrombotic treatment modalities for patients treated with these new therapies should be carefully evaluated. Also, these recommendations do not address the management of thrombotic conditions in girls and women with hemophilia, as well as in patients with von Willebrand disease and other inherited bleeding disorders.

The complexity of the antithrombotic management of PWH reflected in these recommendations provides a strong incentive to promote strategies to increase awareness of cardiovascular diseases in PWH, evaluate and preserve their cardiovascular health, and reduce their risks of both arterial and venous thrombosis. The success and impact of these recommendations will depend on their dissemination in the community and their adoption by health professionals and all stakeholders.

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