Atrial Fibrillation in a Patient with Hemophilia A: A Case Report and Therapeutic Challenges

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Abstract

The increasing age of patients with congenital hemophilia poses new challenges for clinicians. Not only the consequences of bleeding but also age-related diseases, especially cardiovascular disorders, are of great concern. Factors such as hypertension, diabetes, or hyperlipidemia further increase the cardiovascular risk in elderly patients with hemophilia. Preventive treatment of these cardiovascular diseases may therefore also be necessary in hemophilia patients. However, determining the optimal level of anticoagulation in patients with reduced levels of coagulation factors is often difficult and requires an individualized approach. Given the absence of substantial evidence from large clinical trials, clinicians rely on case reports and expert opinions to guide the therapy. This case report details the individual risk–benefit assessment and management of a 57-year-old hemophilia A patient with atrial fibrillation.

Keywords
- atrial fibrillation
- anticoagulation
- therapy
- hemophilia A

Introduction

The development of factor concentrates made a significant contribution to reducing morbidity and mortality in patients with hemophilia, ultimately leading to increased life expectancy.[1] As hemophilia patients age, cardiovascular diseases and other aging-related diseases are increasingly observed among them. Although the prevalence of cardiovascular disease appears to be lower, risk factors for cardiovascular disease in these patients are consistent with the general population.[2] On the other hand, cardiovascular risk factors such as high blood pressure can also increase the risk of bleeding.[3] Primary and secondary prophylaxis in patients with cardiovascular diseases is a balancing act between bleeding and thrombosis. Prospective registry data indicate not only an increased risk of bleeding but also a recurrence of cardiovascular events in patients with hemophilia.[4,5] The World Federation of Hemophilia guidelines emphasize that there are no evidence-based guideline for the treatment of this patient group and call for close coordination between cardiology and hemostaseology.[6] Recently, the European Hematology Association (EHA), European Association for Haemophilia and Allied Disorders (EAHAD), and International Society on Thrombosis and Haemostasis (ISTH) released a consensus guideline, offering specific recommendations on antithrombotic therapy in hemophilia patients. According to this guideline, the decision for anticoagulation should be carefully considered in patients with low clotting factor levels.[7] However, further data are needed to improve the management and monitoring of cardiovascular disease in hemophilia patients. Treatment is therefore often based on individual risk assessment.

Atrial fibrillation (AF) is one of these increasing comorbidities of aging persons with hemophilia. The prevalence of AF is 3.4% in hemophilic patients older than 60 years, which is comparable to the normal population.[8] The CHA_2DS_2-VASc and HAS-BLED scores are utilized to evaluate the risk of thromboembolism and bleeding, respectively, in patients

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with AF. This assessment helps determine the need for therapeutic anticoagulation to prevent stroke. However, both scores are difficult to transfer to hemophilia patients.[8] A risk of stroke cannot be excluded, especially in cases of mild hemophilia.[9] Thus, long-term anticoagulation may be necessary despite bleeding tendency. There are currently no clinical studies on the standardized treatment of patients with hemophilia A and AF. Therefore, the few existing recommendations are based on registry data[4,5] or case reports.[10]

Case Report

A 57-year-old male patient with mild hemophilia A (baseline factor VIII activity 10%) and AF presented to our hemophilia center. The patient was on on-demand therapy with a recombinant factor VIII concentrate (Octocog alfa, Bayer AG, Leverkusen, Germany). The current ISTH bleeding score was 12 out of 56 (normal value for men < 4). The patient's CHA_2DS_2-VASc score was 2 with arterial hypertension and vascular disease (coronary artery disease). Symptoms associated with tachyarrhythmia were reported to be malaise and significant performance impairment (European Heart Rhythm Association score $= 2$). The patient also suffered from a 30% left anterior descending artery stenosis diagnosed by cardiac computed tomography.

The heart rate and symptoms of malaise and reduced performance were normalized with the administration of a β-blocker and flecainide. During the course of the disease, the patient received amiodarone in combination with antihypertensive therapy to control the rhythm. However, after 1 year of amiodarone therapy, AF and the associated possible stroke risk persisted, requiring further decisions.

The therapeutic options for this patient with AF were: the first option is anticoagulation with a direct oral factor Xa inhibitor, such as apixaban in usual (2×5 mg) or reduced (2×2.5 mg) doses. The second option would be pulmonary vein isolation with subsequent medium-term anticoagulation until the atrium has completely healed. The third option is a cardioversion with short-term anticoagulation. In this case, anticoagulation can be discontinued, if no thrombus is detected on transesophageal echocardiography (TEE) 4 weeks after cardioversion. Mortality remains unaffected in this procedure.[11] The final option would be left atrial appendage (LAA) occlusion (atrial occluder), which prevents thrombus formation by targeting the LAA, the primary site where clots that can lead to stroke most commonly originate.[12] It is particularly suitable for patients in whom long-term anticoagulation is contraindicated. However, long-term secondary prophylaxis with aspirin is usually indicated.

After interdisciplinary discussions and careful consideration of the benefits and risks of each option, we decided on electrical cardioversion. A key point in the decision-making process was the patient's negative attitude toward long-term factor therapy. We informed the patient about all therapy options outlining the advantages, disadvantages, risks, and benefits of each, to support his informed decision-making process.

For the procedure, the patient was given recombinant factor VIII octocog alfa (3,000 IU), which he had been receiving regularly in the past as an on-demand therapy. The target trough level was 20 to 30% factor VIII activity. The targeted peak level was between 50 and 80% (40 IU/kg). These factor levels were necessary to prevent bleeding during anticoagulation required for at least 4 weeks post-cardioversion, as thromboembolic prophylaxis is critical during this period due to the elevated risk of thromboembolic events following cardioversion.[13] Anticoagulation with apixaban 2×5 mg was started 48 hours before cardioversion. Electrical cardioversion was performed (120 J, synchronized current delivery) without complications and a stable sinus rhythm was achieved. Since the risk of stroke is highest in the first week following cardioversion,[14] an initial standard dose was administered to provide optimal protection during this critical period. After 1 week, anticoagulation with apixaban was reduced to 2×2.5 mg daily and continued for another 3 weeks (►Fig. 1). Factor VIII therapy with 3,000 IU was also continued during this time (trough level $> 20\%$) three times a week.

At the follow-up visit after 4 weeks, the sinus rhythm was present and the TEE did not show any evidence of cardiac thrombi, and the anticoagulation therapy and factor VIII substitution was stopped. Three months after the last factor VIII administration, there was no evidence of factor VIII inhibitor formation. A follow-up after 12 months showed sinus rhythm. Neither thromboembolic complications nor bleeding complications were reported during follow-up.

Discussion

AF management in the general population typically adheres to a standard protocol including pharmacological treatment (β-blockers or antiarrhythmic agents like amiodarone) and interventional approaches, including electrical cardioversion and catheter ablation. In our patient with hemophilia A, who presented with symptomatic AF, rhythm control was prioritized to alleviate symptoms of malaise and performance impairment. We carefully weighed options such as cardioversion and pulmonary vein isolation, evaluating their bleeding risks and the need for anticoagulation. In standard practice, postinterventional anticoagulation would continue based on the CHA_2DS_2-VASc score to prevent stroke. However, the CHA_2DS_2-VASc score is validated for patients with hemophilia, as it does not account for the unique bleeding risks inherent to these patients.[15] In patients with hemophilia, particularly those with mild or moderate hemophilia A without prophylactic factor treatment as presented in this case, the inherent bleeding risks associated with standard anticoagulation must be carefully weighed against thrombotic risks. In addition to clinical considerations, the patient's preferences and values regarding their bleeding and thrombotic risk tolerance should be incorporated into the decision-making process. Even in significantly more common diseases such as von Willebrand syndrome, no general recommendation for anticoagulation can be made because case studies are small and no case studies have examined the direct comparison between anticoagulation and no treatment in

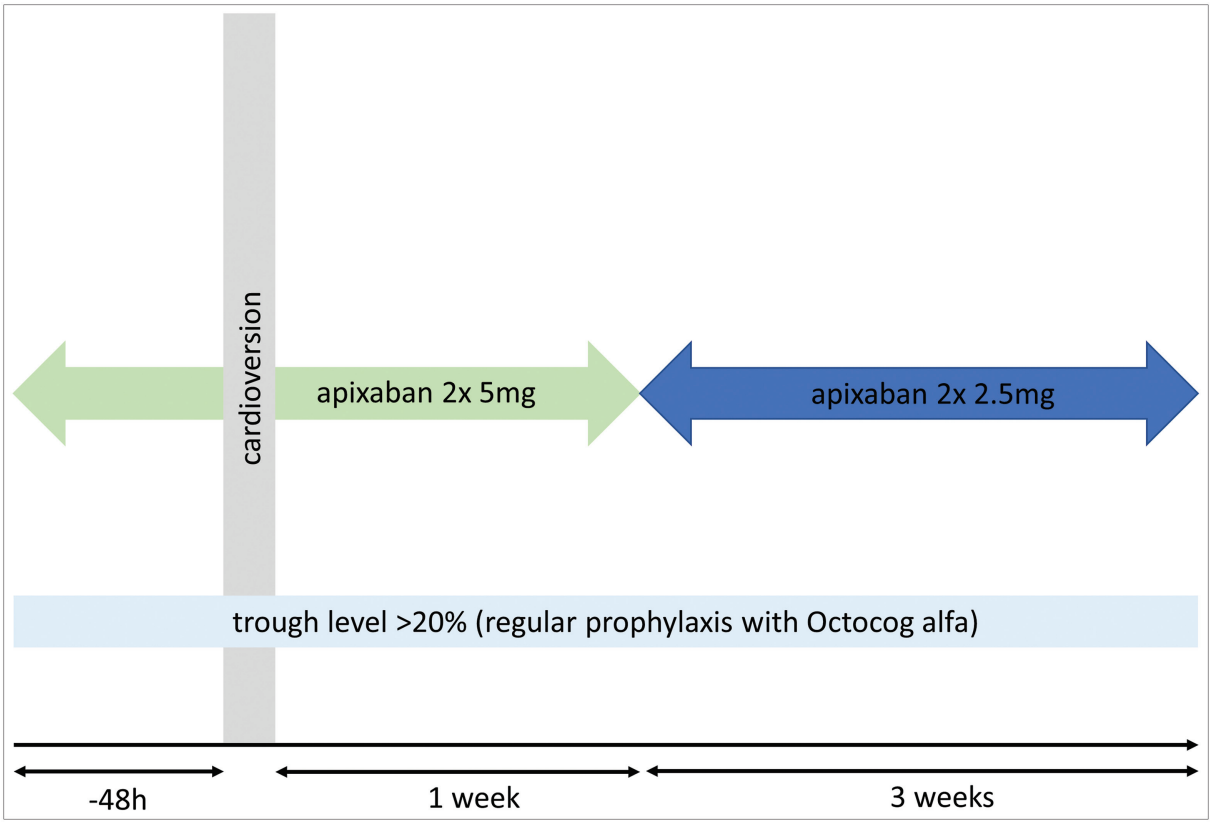

Fig. 1 Anticoagulation was started 48 hours before intervention and continued for 4 weeks after intervention. During this time, the patient received factor VIII prophylaxis. There were no bleeding complications.

patients with cardiovascular disease.[16] A comparable or reduced risk is described for hemophilia patients in the literature. A study by Fransen van de Putte et al found a lower risk of ischemic stroke in patients with severe hemophilia (0 vs. 1.5%), but there was no difference between patients with mild hemophilia and the normal population (1.1 vs. 1.5%).[17] Given the relatively low CHA_2DS_2-VASc score of 2 in our patient, we also considered the option of avoiding both anticoagulation and intervention. In hemophilia patients, particularly those with mild forms, the risk profile differs significantly from the general population due to the heightened susceptibility to hemorrhagic complications, including intracranial hemorrhage and hemorrhagic stroke. Shapiro et al[9] emphasize that while thrombotic events remain a concern in hemophilia patients, the mortality associated with hemorrhagic strokes and intracranial bleeding is considerably higher compared with the general population. In our case, however, we ultimately opted for short-term anticoagulation due to the need for cardioversion, while carefully monitoring factor VIII levels to minimize bleeding risks. Nevertheless, if AF recurrence were to occur without an increase in the CHA_2DS_2-VASc score, a conservative management approach could be re-evaluated in alignment with the patient's evolving risk factors and preferences.[7,18,19] However, since our patient has a lower residual factor VIII activity, this required a change from on-demand therapy to regular prophylaxis throughout the duration of anticoagulation. Our patient had reservations about regular prophylaxis. We therefore decided against long-term anticoagulation. This increased risk is a critical factor when determining the necessity of anticoagulation for stroke prevention in hemophilia patients with AF. The EHA/EAHAD/ISTH guidelines[7] also indicate that patients with factor VIII levels below 10 IU/dL may be naturally "anticoagulated," compared with vitamin K antagonist treatment in a therapeutic range potentially reducing the need for additional anticoagulation to prevent stroke. Given this, anticoagulation may not be strictly necessary in patients with low baseline factor levels, as their thrombotic risk may already be mitigated by their reduced clotting activity. In line with this recommendation, we carefully considered the patient's baseline factor VIII level of 10 IU/dL and discussed the option of foregoing anticoagulation. However, since the factor level was not significantly below 10 IU/dL, we ultimately decided that this approach was not feasible and opted to proceed with anticoagulation.

Another standard therapy in the treatment of AF is pulmonary vein isolation, which is a type of cardiac ablation performed in the area where the four pulmonary veins connect to the left atrium. Depending on the ablation procedure, up to 80% of patients are in sinus rhythm after 12 months.[20] Since anticoagulation should be applied for at least 2 months[21] until the ablation site has completely healed, this procedure also requires regular prophylaxis.

In addition to the therapeutic options that require short-term, medium-term, or long-term oral anticoagulation, there is also the option of an atrial occluder. It is particularly suitable for patients with contraindications to plasmatic anticoagulation. Nevertheless, antiplatelet therapy is required, which

might increase the bleeding risk in patients with hemophilia. According to the consensus recommendations and clinical practice guidance for patients with acute coronary syndrome and hemophilia, a minimum plasma factor VIII level of 3% is required.[7,18] As the patient's coronary artery disease progresses, there may be an indication for aspirin therapy even without the presence of an LAA occluder. This potential need for long-term antiplatelet therapy strengthens the case for considering an occluder despite the bleeding risks associated with antithrombotic treatment, as it would allow us to manage the patient's thromboembolic risk more effectively while potentially reducing the need for additional anticoagulation. Nevertheless, aspirin increases the relative risk of bleeding by a factor of 1.5 even in healthy people, with no effect on mortality. Therefore, an increased risk of bleeding can also be assumed in hemophilia. The COCHE study conducted by Guillet et al[5] highlighted that patients with hemophilia undergoing antithrombotic therapy have an increased bleeding risk, which varies according to the severity of hemophilia, type of antithrombotic therapy, and the presence of additional risk factors. So, we concluded that cardioversion was a safe, although not the most successful, treatment for AF, with up to 80% recurrence after discontinuation of antiarrhythmic treatment.[22]

Conclusion

Although patients with hemophilia have an increased risk of bleeding, AF is also associated with an increased risk of thrombotic events. The existing EHA/EAHAD/ISTH guidelines provide expert recommendations for antithrombotic management in hemophilia patients, offering valuable guidance for complex cases like this one.[7] However, individual considerations remain essential, as each patient's unique balance of bleeding and thrombotic risks may require a tailored approach. Joint decision-making between physician and patient is particularly valuable, enabling treatment plans that align with both guidelines and personal preferences. Collecting individual cases like this one contributes to building a broader evidence base, ultimately refining treatment strategies for hemophilia patients with cardiovascular comorbidities.

Data Availability

Data may be requested for academic collaboration from the corresponding author.

Authorship Contributions

K.A., J.S., G.U, S.H., and T.B. were responsible for the treatment of the patient. K.A. collected and analyzed the clinical data. G.U., K.A., and T.B. analyzed the data, interpreted the results, and wrote the manuscript. All authors read and approved the manuscript.

Conflicts of Interest

The case report was written in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient. All tests were performed with leftover blood samples from routine testing.

The authors have no conflict of interest related to this work. K.A. received honoraria to the Medical University Hospital of Tübingen for lectures from CSL Behring, Sobi, Meet The Experts, Expanda and Werfen, and research grants to the Medical University Hospital of Tübingen from Octapharma and Bayer. T.B. has received research funding from CoaChrom Diagnostica GmbH, DFG, Robert Bosch GmbH, Stiftung Transfusionsmedizin und Immunhämatologie e.V., Ergomed, DRK-Blutspendedienste, Deutsche Herzstiftung, Ministerium für Wissenschaft, and Forschung und Kunst Baden-Württemberg; has received lecture honoraria from Aspen Germany GmbH, Bayer Vital GmbH, Bristol-Myers Squibb GmbH & Co., Doctrina Med AG, Meet The Experts Academy UG, Schöchl Medical Education GmbH, Stago GmbH, Mitsubishi Tanabe Pharma GmbH, Novo Nordisk Pharma GmbH, Leo Pharma GmbH, and Swedish Orphan Biovitrum GmbH; has provided consulting services to Terumo; and has provided expert witness testimony relating to heparin-induced thrombocytopenia (HIT) and non-HIT thrombocytopenic and coagulopathic disorders. All of these are outside the current work.

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