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EDITORIAL

A new edition, towards better clinical care in hemostasis and thrombosis

Una nueva entrega, hacia una mejor atención clínica en hemostasia y thrombosis

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In this second issue of the journal, continuing with the assumed editorial line, we proceed with the dissemination of advances in the various fields of interest, prioritizing those with clinical impact or those that represent advances in the knowledge of the physiology or pathology of coagulation in its broadest sense.

This issue publishes a Latin American consensus on hemophilia, which addresses the gaps in the treatment and follow-up of patients with hemophilia in Latin America. It highlights the importance of international cooperation and the need to adapt to the health realities of each Latin American country, where the disparity in resources and access to treatment makes the harmonization of action protocols very complex. Employing Delphi methodology, this document establishes a total of 16 key recommendations, addressing everything from the need to improve access to specialized laboratories to the implementation of prophylactic and replacement therapies, highlighting the role of technology in monitoring joint status through ultrasound. Furthermore, continuing with hemorrhagic diseases, a clinical case on hemophilic pseudotumor complicated by femoral fracture is presented, reflecting the complexity of these complications of the disease. This work shows the importance of a multidisciplinary approach that combines the treatment of hemostasis with surgery and functional rehabilitation.

For its part, antithrombotic treatment continues to have limitations and complications, and the arrival of new generations of drugs with a better balance between safety and efficacy is still awaited. This issue reviews inhibitors targeting factor XI or activated factor XI, which are currently the most promising strategy. This review article discusses the mechanisms of action of these drugs, the currently available results, and ongoing clinical trials. These new drugs have demonstrated in preclinical and clinical studies their ability to reduce thrombotic risk with a better hemorrhagic profile than the current ones, representing an advance in the safety profile of anticoagulant therapy. In parallel, a real-world study on secondary prevention of thrombosis with direct oral anticoagulants conducted in Zaragoza (Spain) is also presented. This descriptive, observational, single-center, longitudinal, and retrospective study analyzes its safety and efficacy profile in a real-world setting. It analyzes the influence of risk factors that influence the choice of therapy and the results and complications of treatment.

This issue also publishes a study in the innovative field of artificial intelligence, in this case used as a tool for the comparative analysis of the safety and efficacy profile of treatment with pegylated factor VIII concentrates. This work shows how artificial intelligence can complement the usual methods of evaluating

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treatments in the absence of direct comparative studies and how it can mitigate, although not completely eliminate, some of the limitations of adjusted matched indirect comparisons.

The image of the quarter in this issue shows the tracing corresponding to a thromboelastometry in a patient with hyperfibrinolysis. The image shows the different thromboelastometry records in a patient with fulminant hyperfibrinolysis, highlighting the role of this methodology for the early detection of these disorders.

Finally, we want to highlight the cover of this second issue, which corresponds to a work on women carriers of hemophilia that has been awarded at the recent EAHAD (European Association for Haemophilia and Allied Disorders) congress. It develops informative materials adapted to the different stages of a woman's life as a hemophilia carrier. These materials can be accessed on the cover via the QR codes that appear there.

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Editors-in-Chief

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CLINICAL GUIDELINES AND CONSENSUS

Latin American consensus on hemophilia

Consenso latinoamericano de hemofilia

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Abstract

Hemophilia is an inherited bleeding disorder linked to the X chromosome, which is classified into type A and type B. This Latin American consensus addresses the gaps in the treatment and follow-up of patients with this disease in the region, aligning local needs with international recommendations. Nominal group and the modified Delphi Panel methodologies were used to reach consensus on 16 key recommendations, including the use of ultrasound for joint monitoring, access to specialized laboratories, patient registries, and the implementation of prophylactic and replacement therapies. Additionally, the importance of multidisciplinary teams, continuous training, and robust public policies is highlighted to improve the comprehensive care of patients with hemophilia in Latin America.

Keywords: *Hemophilia. Consensus. Latin America. Ultrasound. Prophylaxis. Multidisciplinary team. Public policies. Patient registry.*

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Resumen

La hemofilia es un trastorno hemorrágico hereditario ligado al cromosoma X, que se clasifica en tipo A y tipo B. Este consenso latinoamericano aborda las brechas en el tratamiento y el seguimiento de pacientes con esta enfermedad en la región, alineando las necesidades locales con las recomendaciones internacionales. Se utilizaron las metodologías de grupos nominales y Panel Delphi modificado para alcanzar consenso en 16 recomendaciones clave, que incluyen el uso del ultrasonido para el monitoreo articular, el acceso a laboratorios especializados, el registro de pacientes y la implementación de terapias profilácticas y de reemplazo. Además, se destaca la importancia de los equipos multidisciplinarios, la formación continua y las políticas públicas robustas para mejorar la atención integral de los pacientes con hemofilia en Latinoamérica.

Palabras clave: *Hemofilia. Consenso. Latinoamérica. Ultrasonido. Profilaxis. Equipos multidisciplinarios. Políticas públicas. Registro de pacientes.*

Introduction

Hemophilia is a severe bleeding disorder of genetic origin, characterized by a recessive inheritance pattern linked to the X chromosome. Among congenital coagulopathies, it is the second most frequent; it is estimated that up to 70% of hemophilia cases are genetic, while the remaining 30% are due to de novo mutations[1]. Hemophilia is categorized into hemophilia A and B based on the deficient clotting factor, factor VIII or factor IX, respectively[1]. Individuals with hemophilia experience spontaneous bleeding or prolonged traumatic bleeding episodes in any part of the body, with muscular and joint bleeding being the hallmark of the disease[2].

Throughout the years, the prevalence of hemophilia A has been estimated at 1 in 5,000 to 10,000 men, while hemophilia B affects 1 in 30,000 to 60,000 men[3]. The prevalence of hemophilia depends on life expectancy and access to treatment for affected individuals. Although, ideally, all hemophilia patients should be systematically registered and followed up in national health centers, this is not the case in more than 50% of countries[4,5]. A key study in this regard was conducted by Soucie et al.[6] in 1998, which identified a prevalence of 13.4 per 100,000 men for both types of hemophilia, with 10.5 for hemophilia A and 2.9 for hemophilia B.

In 2019, Iorio et al.[7] demonstrated that the current and birth prevalence of hemophilia exceeds these figures, with an estimated prevalence of 17.1 per 100,000 men for hemophilia A and 3.8 per 100,000 men for hemophilia B. Considering the global population in 2019 was 7.5 billion (3.8 billion men), there would be approximately 1,125,000 men with hemophilia, of whom 418,000 would have the severe form of the disease. These estimates were based on data from hemophilia patients in 6 developed countries and the male populations of those nations.

The treatment of hemophilia primarily focuses on prophylaxis, aiming to prevent joint bleeding and thereby avoid or delay joint damage[8].

In Latin America, significant gaps hinder timely and adequate access to treatment and follow-up regimens recommended by the World Federation of Hemophilia (WFH). These include the lack of multidisciplinary specialist teams, government-supported hemophilia treatment centers, and organized systems for continuing medical education. Additionally, timely and accurate diagnosis is often lacking, deficient, or delayed. Another major barrier is the high cost of recommended treatments, compounded by the lack of awareness among national health leaders, resulting in insufficient budgets and suboptimal care for hemophilia patients.

The goal of this consensus is to align the needs and realities of Latin America with international recommendations.

Method

This Latin American consensus of expert recommendations was developed in 2 different stages. Stage #1 involved in-person meetings using the nominal group technique to identify priority topics related to hemophilia in each country. These topics were organized into 3 broad groups, and participants joined the group of their interest. This process identified a total of 16 topics requiring consensus. Stage #2 was conducted virtually, where each group discussed and gathered scientific evidence to support the recommendations from the first stage. The work of all groups was integrated, resulting in 16 recommendations, which were shared with all participants for review.

Subsequently, a modified Delphi panel methodology was used to vote on the recommendations. A scale of 1 to 6 was used, where 1 indicated complete agreement, 2 agreement with minor reservations, 3 agreement with

major reservations, 4 disagreement with minor reservations, 5 disagreement with major reservations, and 6 complete disagreement. Consensus was defined as at least 75% agreement (combining scores of 1, 2, and 3).

In the first voting round, 22 participants responded, and all recommendations reached the agreed consensus. Of the 16 recommendations, 14 achieved 100% agreement, and the remaining 2 achieved 95%.

Laboratory and imaging, data, follow-up, access to clinical trials, and technology

Recommendation 1. Ultrasound is a useful tool and should be performed for all hemophilia patients to:
– Monitor joint health and detect subclinical bleeding.
– Manage bleeding events to ensure proper treatment.
– Perform procedures such as joint aspiration.

Agreement level: 85.71% completely agree, 4.76% agree with minor reservations, 4.76% agree with major reservations, 4.76% disagree with minor reservations.

Recommendation 2. We recommend training at least one member of the multidisciplinary team in ultrasound at each treatment center.

Agreement level: 95.45% completely agree, 4.55% agree with minor reservations.

Recommendation 3. All patients should have access to a treatment center with a laboratory capable of performing basic coagulation tests and diagnosing hemophilia A and B, including inhibitor and pharmacokinetic studies. Specific monitoring methods are recommended for extended half-life and non-replacement therapies.

Agreement level: 86.36% completely agree, 9.09% agree with minor reservations, 4.55% agree with major reservations.

Recommendation 4. Every country should have access to genetic testing to provide counseling to patients and their families.

Agreement level: 81.82% completely agree, 18.18% agree with minor reservations.

Recommendation 5. Every country should maintain an updated annual registry of carriers and individuals with hemophilia, including data such as hemophilia type, date of birth, sex, severity, inhibitors, treatment type, and deceased status. When possible, the number of bleeding episodes should also be included.

Agreement level: 90.91% completely agree, 9.09% agree with minor reservations.

Recommendation 6. Government authorities should facilitate the development of clinical studies on hemophilia, preferably through collaborative efforts.

Agreement level: 90.91% completely agree, 9.09% agree with minor reservations.

Recommendation 7. We recommend using technological tools to facilitate education, reporting, management, and follow-up of hemophilia patients. Treatment centers should promote their implementation.

Agreement level: 86.36% completely agree, 13.64% agree with minor reservations.

Discussion

The systematic use of ultrasound in hemophilia patients has been highly valuable. Its utility lies in two main objectives:
– Diagnosing acute bleeding events, whether joint or muscular (without delaying hemostatic therapy), and monitoring treatment effectiveness and duration[9-11].
– Early detection of joint damage through systematic use during consultations (point of care)[12-15].

Compared to magnetic resonance imaging (MRI)[16], the gold standard, ultrasound offers similar diagnostic capabilities with advantages such as lower cost, no need for sedation in children, rapid assessment, ability to evaluate multiple joints during a single consultation, portability, and the ability to be performed by non-radiologists, depending on national regulations[12,14,15,17]. These benefits enable clinicians to intervene early in patient management, such as optimizing primary prophylaxis[18].

The expert group believes that every hemophilia center should have, at least, 1 professional trained in point-of-care ultrasound.

Training, at least, 1 multidisciplinary team member in ultrasound is essential for diagnosing bleeding and joint health, ensuring appropriate clinical management in hemophilia[19]. This professional should undergo certified training programs, either in-person or virtual, to acquire imaging diagnostic skills, including for pediatric patients[15,19-21].

All individuals with hemophilia should have access to laboratory studies for diagnosis and monitoring, including inhibitor testing[22].

Traditional 1-stage assays for measuring factor VIII and IX levels remain fundamental, though they have diagnostic limitations in certain cases and challenges in monitoring new therapies. Therefore, combining one-stage assays with chromogenic (or two-stage) assays is recommended for more accurate evaluation[23-25].

A multidisciplinary approach, including pharmacokinetic studies, is important for monitoring therapeutic response and personalizing treatment[26].

For hemophilia A patients on non-replacement therapy, a chromogenic factor VIII assay containing bovine factor X is recommended[24,15].

Genetic evaluation of hemophilia is useful for predicting inhibitor risk, identifying female carriers, and offering prenatal diagnosis, including informed reproductive decision-making, in full compliance with national legislation[22,27].

Genetic diagnostic laboratories should follow strict protocols, including proper classification systems, accreditation, and quality control[22]. Genetic counseling, initiated with informed consent, is an essential component of comprehensive hemophilia care for affected individuals and their families[22,27,28].

Each country should maintain a registry of hemophilia patients and other congenital coagulopathies, including female carriers with factor VIII or IX levels < 50 IU/dL, who exhibit symptoms similar to mild hemophilia in men[22]. This registry serves as a lobbying tool for health authorities and insurers to improve therapies, treatment centers, and healthc are teams, ultimately enhancing patient access to comprehensive care[29].

Registries can be managed by a hematologist, nurse coordinator, or registry manager as part of the patient care team[22,30].

Registries can be web-based, in Microsoft Access, or Excel, with treatment centers having access to update information. Biannual updates are suggested[31].

Research in hemophilia documents the natural history of the disease, tests new therapies, compares treatments, documents outcomes, and informs cost-related decisions[22].

Given hemophilia's rarity, national and international collaboration in research should be encouraged[22]. This is supported by international guidelines promoting research as a core function of comprehensive care centers[4,22,28,32,33].

Accurate documentation of bleeding events and home treatment administration is crucial for evaluating treatment efficacy, as treating physicians can verify this information electronically during routine clinical follow-ups[34]. Over the years, electronic documentation tools, such as portable devices, have been developed to address these issues, enabling closer patient monitoring, better care outcomes, faster resolution of therapy administration problems, and improved adherence[35,36].

Recent studies show that health applications collecting data via mobile or wearable devices for real-time interventions have greater potential to optimize hemophilia patient care[37].

Access to treatment, prophylaxis, and new therapies

Recommendation 8. All patients in each country diagnosed with hemophilia, with or without inhibitors, should have lifelong access to treatment, including:

– Replacement therapy: plasma-derived, standard half-life, and extended half-life recombinant concentrates.
– Mimetic agents.
– Hemostasis rebalancing agents.
– Bridging agents for patients with inhibitors.

Agreement level: 90.91% completely agree, 9.09% agree with minor reservations.

Recommendation 9. Prophylaxis with hemostatic agents (replacement and non-replacement) should be initiated early and remain the standard treatment throughout the lives of patients with severe hemophilia, with or without inhibitors, and those with moderate or mild hemophilia with a bleeding phenotype (patients with more bleeding than expected for their factor level).

Agreement level: 95.45% completely agree, 4.55% agree with minor reservations.

Recommendation 10. Since hemophilia is a chronic disease requiring high-cost treatment, it is important to include it in health budgets to ensure continuous and appropriate treatment for all diagnosed patients.

Agreement level: 100% completely agree.

Recommendation 11. The inclusion of new therapies in official drug lists should be timely, based on the best available scientific evidence and pharmacoeconomic justification.

Agreement level: 95.45% completely agree, 4.55% agree with minor reservations.

Recommendation 12. The use of clinical and imaging assessment tools is recommended to document, monitor disease progression, and evaluate physical health (joint health), functional capacity, activity levels, participation, and health-related quality of life in hemophilia patients.

Agreement level: 100% completely agree.

Discussion

The foundation of hemophilia treatment is to prevent bleeding through long-term prophylaxis (prophylactic

treatment) and to manage acute bleeding episodes (episodic treatment) by replacing or supplementing clotting factors[8,22,28,38]. The available treatment options for hemophilia include[22,28]:

– Clotting factor concentrates for replacement therapy, which can be plasma-derived or recombinant, with standard or extended half-life. These are highly safe and effective for treating and preventing bleeding; however, their efficacy decreases with the development of inhibitory antibodies, which is the main complication, increasing bleeding episodes and reducing the patient's quality of life.
– Bridging therapies (activated prothrombin complex concentrates and recombinant activated factor VII), used for preventing and treating bleeding in hemophilia A or B patients with inhibitors.
– Bispecific antibody mimetics (e.g., emicizumab), a subcutaneous prophylaxis option for hemophilia A patients with or without inhibitors, offering extended half-life and high efficacy in preventing bleeding episodes.

Treatment decision-making is a challenging and multifactorial process to identify the most suitable option for each patient. Important factors to consider include the product's efficacy, safety, quality, purity, and viral inactivation. Additionally, the patient's bleeding phenotype, joint status, and preferences must be evaluated to improve hemostasis, effectively prevent joint bleeding, avoid or delay hemophilic arthropathy, and reduce emergency visits, hospitalizations, surgeries, and school or work absenteeism[22].

Scientific evidence demonstrates that prophylactic treatment in hemophilia patients should begin early to limit bleeding and reduce complications. It should be maintained throughout life to achieve the goals of prophylaxis, which are to maintain hemostasis and provide a healthy, active life that allows participation in physical and social activities[22], which contributes to improving the results of joint health[39-45]. Moreover, home-based prophylactic treatment also improves therapeutic adherence and enhances patients' quality of life[22].

As hemophilia is a rare, chronic, and high-cost disease, its treatment, particularly prophylaxis, helps prevent disease-related comorbidities and reduces long-term treatment costs.

Despite recent advances, unmet needs persist, and hemophilia patients continue to experience bleeding, functional and joint deterioration, and acute and chronic pain, even though evidence supports the cost-effectiveness of prophylactic treatments[46-50].

The expert group emphasizes the need for pharmacoeconomic studies in all countries, considering not only the product price but also the overall process costs.

Suggested tools for evaluating hemophilia patients include[22,51,52]:

– Physical examination tools:
  • WFH Physical Examination Score (Gilbert Score)[53,54].
– Pain assessment tools:
  • Wong-Baker FACES Pain Rating Scale[55,56].
  • Multidimensional Pain Questionnaire for Hemophilia[57].
– Disease and therapy efficacy assessment:
  • Laboratory tests (inhibitor measurement and factor titration).
  • Annual bleeding rate.
– Tools for measuring body structure and function in hemophilia patients:
  • Hemophilia Joint Health Score (HJHS)[54,58,59].
  • Imaging modalitiess[60,61] using MRI[62], ultrasound[12,63-65], and X-rays[66].
– Instruments for measuring activities and participation[67]:
  • Haemophilia Activities List (HAL)[68-70].
  • Pediatric Haemophilia Activities List (PedHAL)[71-73].
  • Functional Independence Score in Hemophilia (FISH)[74,75].
– Health-related quality of life instruments:
  • EuroQol-5D[76-78].
  • SF-36[79,80].

Multidisciplinary team, training, patient association empowerment, clinical guideline implementation, and public policy strengthening

Recommendation 13. The core care team for hemophilia patients should include a pediatric hematologist, a physical therapist nurse, and a psychosocial counselor trained in hemophilia, with immediate access to a specialized coagulation laboratory. A hemophilia center must have a multidisciplinary team of specialists trained in hemophilia to ensure comprehensive care for these patients.

Agreement level: 72.73% completely agree, 22.73% agree with minor reservations, 4.55% agree with major reservations.

Recommendation 14. Patient associations should organize activities to manage resources for the

comprehensive care of patients. Disease-specific training should be provided by the health care team.

Agreement level: 81.82% completely agree, 9.09% agree with minor reservations, 9.09% agree with major reservations.

Recommendation 15. Every country should have a treatment guideline, updated at least every 5 years, that includes carriers and women with hemophilia.

Agreement level: 90.91% completely agree, 4.55% agree with minor reservations, 4.55% disagree with major reservations.

Recommendation 16. Treatment decisions should include economic considerations and scientific advice from the health care team or treating physician.

Agreement level: 81.82% completely agree, 9.09% agree with minor reservations, 9.09% agree with major reservations.

Discussion

Globally, the importance of comprehensive care for hemophilia patients is recognized, addressing all medical and psychological aspects affecting patients and their families. The primary goal is to enable patients to lead daily lives like those without the disease, requiring a positive and collaborative approach among health care disciplines[81].

The WFH proposes a core team consisting of a medical director (typically a pediatric hematologist), a nurse coordinator, a physical therapist, a laboratory specialist, and a psychosocial counselor, all specifically trained in hemophilia care. Patients with severe disease or complications often require care from an extended team of specialists[22].

Advancing the specialization of hemophilia care teams, the multidisciplinary team could include specialists in hematology and pediatrics, orthopedics and physical therapy, dentistry and oral surgery, gynecology, genetic counseling, nursing, psychology and social work, emergency care, clinical technology, and clinical pharmacy[81].

In many Latin American countries, disparities in health care access are a significant challenge, often exacerbated by socioeconomic inequalities. Education and awareness initiatives are crucial to empower patients and their families through workshops, seminars, and informational campaigns.

Education and awareness initiatives are crucial for empowering patients and their families through the organization of workshops, seminars, and informational campaigns to educate the public about specific health conditions, treatment options, and preventive measures.

Conflicts between patient groups and physicians can arise from various sources, including differing expectations, communication failures, and disagreements over treatment decisions. A study by Hullur et al.[82] indicated that dissatisfaction with treatment and disagreements with doctors are common causes of conflict, often exacerbated by long wait times and rushed consultations. Understanding these conflicts is essential to fostering a collaborative healthcare environment that prioritizes patient-centered care. Proposed treatment plans should be reconciled with patients and their families, while taking into account the characteristics of each patient, family, social environment, and drug availability.

Patient groups play a crucial role in improving health care delivery, advocating for patient rights, and optimizing health outcomes across various medical conditions[83]. They are in an ideal position to provide peer-centered education tailored to patients' lived experiences. This type of education often focuses on self-care strategies, emotional support, and practical advice that empower patients to take an active role in their health care.

Health care professionals, on the other hand, are responsible for providing evidence-based medical education that includes clinical knowledge, treatment options, and the management of specific health conditions. This education often includes detailed explanations of medical procedures, medication management, and the implications of various treatment choices.

By recognizing the distinct roles of each group, healthcare systems can foster a more collaborative and effective educational environment that ultimately enhances patient care and outcomes.

Clinical practice guidelines are essential for optimizing patient care, based on systematic reviews of evidence and assessments of treatment risks and benefits[84]. Implementing guidelines for hemophilia improves care quality, ensures evidence-based approaches, and standardizes clinical practices. Benefits include[84,85]:

- Uniformity and consistency: guidelines provide a common framework for managing hemophilia, helping to standardize clinical practices and reduce variations in patient care.
- Improved decision-making: evidence-based guidelines offer up-to-date information on diagnosis, treatment, and follow-up. This enables physicians to make informed and personalized decisions, potentially improving patient outcomes.

– Resource optimization: adhering to guidelines helps prevent the inappropriate use of medical resources and maximizes efficiency in patient care.
– Patient and caregiver education and empowerment: guidelines can also serve as an educational tool for patients and their families, helping them understand hemophilia management and the importance of treatment adherence.

Studies evaluating the frequency of clinical practice guideline updates indicate that they are revised every 1 to 5 years after the last publication, depending on each institution's policies[86,87].

In many cases, regional treatment guidelines and protocols are adaptations of international guidelines individualized to the local context. Experts recommend updating them at least every 5 years, depending on new evidence that could introduce innovative therapies into health care systems and improve patient care by optimizing available resources. The latest WFH guidelines consider these aspects, recommending the preparation of medical treatment protocols to ensure continuity of care in case of changes in clinic personnel[22].

Another crucial aspect in enhancing hemophilia care is incorporating health economics tools into disease management. Cost analyses have shown that the severity of hemophilia is associated with a higher economic burden[2].

To overcome the limitations of conventional cost-effectiveness analyses—where decision-making is often influenced more by short-term budgetary impact than by long-term cost-effectiveness ratios[88]—it is essential to consider innovative health care access models. These models include the role of pharmacoeconomics in drug acquisition processes, allowing for the evaluation of new health technologies with the goal of maximizing effective resource utilization while minimizing budgetary impact.

Health technology assessment (HTA) is a systematic and multidisciplinary process aimed at identifying, evaluating, and synthesizing all available scientific evidence to support decision-making. This process applies to drugs, medical devices, vaccines, procedures, and services, guiding health policy decisions[89-91]. The following aspects are considered in HTA: characterization of the specific health problem and current treatment alternatives, description of the technology under review, evidence on safety and clinical effectiveness (comparative effectiveness), cost-effectiveness analysis, budget impact analysis, ethical considerations, and organizational, social, and legal aspects[92].

Currently, some countries are implementing innovative access models for certain health care products. These models involve agreements between healthcare technology manufacturers or producers and healthcare funders or providers, facilitating access (coverage or reimbursement) to health technologies under specific conditions[93]. One example is risk-sharing agreements, which link reimbursement or coverage to the real-world performance of a medical technology.

Conclusions

Implementing hemophilia care guidelines and recommendations contributes to more effective, safe, and patient-centered care. Hemophilia experts in Latin America are encouraged to collaborate, publish real-world evidence, and make informed decisions to provide personalized care for individuals with this condition.

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Conflicts of interest

M. Berro: speaker for Roche, Werfen, and Scienza Uruguay. M.G. Arbesú-Ponce: speaker for Novo Nordisk, Roche, Octapharma, Pfizer, CSL Behring, Bayer, and Takeda; has participated in Advisory Boards for Novo Nordisk, Roche, Pfizer, Bayer, and Takeda. A.J. Bustinza-Álvarez: speaker for Roche, Novo Nordisk, and Takeda; has participated in Advisory Boards for Novo Nordisk. M.V. Canonico-Zavalla: speaker for Novo Nordisk; has participated in Advisory Boards for Novo Nordisk and Takeda. C.P. Casas-Patarroyo: speaker for Takeda, Roche, Octapharma, Novo Nordisk, and Pfizer; has participated in Advisory Boards for Roche, Novo Nordisk, Takeda, and Biopass. D. Castillo-González: Speaker for Roche. A.R.

Estrada-Romero: speaker for Roche, CSL Behring, Novo Nordisk, and Viphor. N.E. Loayza-Urcia: speaker for Roche and Octapharma; has participated as a Clinical Investigator for Roche. K. Moreno-Peñarrieta: speaker for Roche and Takeda (Shire); has participated in Advisory Boards for Roche. C. Ochoa: speaker for Roche Ecuador; has participated in Advisory Boards for Medicamenta Ecuatoriana and Roche Ecuador. S. Oliva-Lara: speaker for Pfizer and Novo Nordisk; has participated in Advisory Boards for Bayer, Pfizer, Novo Nordisk, Roche, and Octapharma. G. Ramos-Ramos: speaker for Octapharma, Bayer, Novo Nordisk, Roche, and Takeda; has participated in Advisory Boards for Siemens and Novo Nordisk. I. Rodríguez-Grecco: has participated in Advisory Boards for Novo Nordisk, Octapharma, and CSL Behring. G.F. Rojas Alba: speaker for Roche and Octapharma. P. Sepúlveda: has participated in Advisory Boards for Roche and Novo Nordisk. The remaining participants declared no conflicts of interest whatsoever.

Ethical considerations

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The recommendations of the SAGER guidelines have been followed according to the nature of the study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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ORIGINAL RESEARCH ARTICLE

Evaluation of secondary prevention of thrombosis in patients from sector III of Zaragoza

Evaluación de la prevención secundaria de trombosis en pacientes del sector III de Zaragoza

Olga Gavin-Sebastián[1], Victoria Murillo-Cortés[2], Manuela Dobon-Rebollo[1], Neus Canal-Díaz[3], Carolina Navas[3], and María Lloret-Avellá[3]*

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Abstract

Introduction: *Venous thromboembolism (VTE) presents a significant clinical challenge, but there is currently a lack of evidence in clinical practice in Spain.* **Objective:** *To evaluate the epidemiological, clinical, and biological characteristics of patients treated with DOACs for secondary prevention of VTE.* **Material and methods:** *Descriptive, observational, single-centre, longitudinal and retrospective study of a cohort of 118 patients diagnosed with VTE in sector III of Zaragoza, who were prescribed anticoagulant treatment with direct oral anticoagulants (DOACs) for secondary prevention, from February 2012 to July 2024.* **Results:** *This study evaluated 118 patients, with 70 receiving rivaroxaban and 48 receiving apixaban. The mean age of the patients was 60.2 years, with significant differences between the treatment groups (rivaroxaban: 59.4 years; apixaban: 65.7 years; p = 0.0013). Additionally, 26.3% of patients had risk factors that justified the decision of suggesting anticoagulant treatment. Observed complications included 0.8% of thrombotic events and 9.3% of bleeding events, with no significant differences between groups. This analysis suggests that age and associated risk factors are determinants in the secondary prevention of VTE.* **Conclusions:** *DOACs administered at secondary prevention doses in selected patients represent an effective and safe alternative for patients at high risk of rethrombosis.*

Keywords: *Secondary prevention. Venous thromboembolic disease. Deep vein thrombosis. Pulmonary embolism. Direct oral anticoagulants. Risk factor.*

Resumen

Introducción: *La tromboembolia venosa (TEV) es un desafío clínico significativo con escasa evidencia en la práctica clínica española.* **Objetivo:** *Evaluar las características epidemiológicas, clínicas y biológicas de pacientes tratados con ACOD para prevenir secundariamente la TEV.* **Material y métodos:** *Estudio descriptivo, observacional, unicéntrico, longitudinal y retrospectivo en una cohorte de 118 pacientes con TEV del sector III de Zaragoza, tratados con anticoagulantes orales de acción directa (ACOD) para prevención secundaria, entre febrero de 2012 y julio de 2024.* **Resultados:** *De los 118 pacientes, 70 recibieron rivaroxabán y 48 apixabán. La edad media fue de 60,2 años, con diferencias significativas entre los grupos (rivaroxabán: 59,4 años; apixabán: 65,7 años; p = 0,0013). Un 26,3% presentaron factores de riesgo que justificaron el tratamiento anticoagulante. Las complicaciones incluyeron un 0,8% de eventos trombóticos y un 9,3% de eventos hemorrágicos, sin diferencias significativas entre los grupos. La edad y los factores de riesgo son determinantes en la prevención secundaria*

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de la TEV. **Conclusiones:** *Los ACOD en dosis de prevención secundaria son una alternativa eficaz y segura en pacientes con alto riesgo de retrombosis.*

Palabras clave: *Prevención secundaria. Enfermedad tromboembólica venosa. Trombosis venosa profunda. Embolia pulmonar. Anticoagulantes orales de acción directa. Factor de riesgo.*

Introduction

Venous thromboembolism (VTE) is a condition characterized by the formation of a blood clot in the venous or arterial circulation, disrupting normal blood flow and causing various alterations depending on the type of vessel occluded[1]. The main manifestations are deep vein thrombosis (DVT) and pulmonary embolism (PE)[2].

VTE is the most common acute cardiovascular condition after myocardial infarction and stroke[3]. In Spain, the incidence rate of DVT ranges between 53 and 162 cases per 100,000 inhabitants, while for PE, it ranges between 39 and 115 cases per 100,000 inhabitants[4,5]. On the other hand, VTE is also associated with a significant mortality rate, causing more than 370,000 deaths in six European countries[6]. In fact, nearly 20% of patients with PE die within 30 days of diagnosis[7]. Additionally, the incidence of VTE is associated with age, being eight times higher in patients aged 80 compared to those aged 50[4]. Considering that the annual costs associated with hospitalization, preventable expenses, and indirect costs related to the disease are estimated at 8.5 billion euros, it is expected that the burden of these conditions will significantly increase in the coming years for healthcare systems in the predominantly aging populations of the European Union.

DVT typically originates in the valves of the distal deep system of the lower limbs and can progressively extend to the femoropopliteal and ilio-caval regions[7]. Distal forms have less impact, while proximal forms have greater clinical relevance and a higher rate of complications. It can also occur in other areas, such as the upper limbs, the spleno-portal axis, cerebral venous sinuses, or the renal vein[2]. DVT causes partial or complete occlusion of a vein by a thrombus in the extremities and can lead to the detachment of the thrombus or clot, causing PE, infarction, or stroke[1,2,8]. Its diagnosis is based on pretest probability measured using validated scales (Wells score), D-dimer levels, and Doppler ultrasound[1,9,10].

PE is the occlusion of the pulmonary artery lumen by a thrombus formed in situ due to local damage or by a thromboembolism originating from the deep venous system of the lower extremities. The clinical presentation is heterogeneous, with symptoms such as dyspnea, tachypnea, syncope, and hypotension, and there are even cases of incidental, completely asymptomatic PE. Similar to DVT, the diagnosis is based on clinical suspicion and blood tests to evaluate D-dimer levels, requiring confirmation with imaging, preferably computed tomography angiography, although other methods such as ventilation-perfusion scintigraphy or conventional angiography can also be used[11].

VTE is a multifactorial condition that occurs when one or more predisposing factors coincide in an individual: environmental factors and patient-related factors[1]. Risk factors can be divided into: 1) identifiable or non-identifiable; 2) transient or permanent; and 3) hereditary or non-hereditary[12]. Arterial and venous thrombotic diseases are different expressions of the same disease, so cardiovascular risk factors such as obesity, smoking, dyslipidemia, hypertension, and diabetes mellitus can contribute to the event[12,13].

Recurrent VTE is the formation of a thrombus at a later time, regardless of the location of the previous episode, a phenomenon that occurs relatively frequently[2]. The incidence of recurrent VTE does not seem to depend on the clinical manifestations of the first event but often occurs in the same clinical form as the initial event. Additionally, recurrences are closely related to the factor that caused the first episode. In one study, the risk of recurrent VTE after DVT caused by an identifiable and transient risk factor, following the discontinuation of anticoagulation, was 3.3% per patient per year up to 24 months[14]. The annual risk of recurrence in cases of VTE with an unidentified risk factor after stopping treatment is 10% within the first years and increases to 50% at 10 years[15]. These patients represent 25-30% of all VTE patients[16].

The treatment of VTE is based on early and adequate anticoagulation, divided into three phases: acute (5-21 days), initial (3-6 months), and extended (> 6 months)[17,18]. Anticoagulant therapy is adjusted according to the type of event, its severity, and patient characteristics. The primary phase lasts 3 to 6 months, which is the minimum recommended duration. After completing the initial treatment, the patient should be reassessed to determine whether indefinite treatment is needed to prevent future thrombotic events, i.e., secondary prevention. However, the initiation of treatment

must always be conditioned by periodic reassessment of thrombotic and hemorrhagic risk[16].

The 2020 American Society of Hematology (ASH) clinical practice guidelines provide recommendations for selecting patients who are eligible for secondary prevention of recurrent thrombosis with extended anticoagulant therapy[19]. The criteria are based on identifying patients with VTE without an identifiable risk factor or with permanent risk factors, and in more difficult or doubtful cases, additional methods such as prognostic scales, D-dimer, or detection of residual venous thrombosis with ultrasound can be used, although these tools should not be used systematically.

Currently, there is no recommendation in clinical practice guidelines on which biological markers are indicators of re-thrombosis, but they can help in decision-making, so their determination is part of the thrombotic risk assessment of patients. D-dimer, a marker of fibrinolysis, can help evaluate the risk of recurrence along with another inflammatory marker such as factor VIII[20,21].

Anticoagulant therapy can be administered injectably with heparins or fondaparinux, or orally with vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs)[10,22].

Long-term treatment with VKAs is often associated with significant limitations, such as the need for laboratory monitoring of the International Normalized Ratio (INR), which increases the complexity of therapeutic management[23]. In contrast, DOACs represent an improvement in the treatment of these patients due to their rapid onset of action, favorable pharmacokinetics, and predictable oral bioavailability, eliminating the need for monitoring[10,24]. Additionally, compared to VKAs, DOACs have fewer interactions when administered concomitantly with other drugs[25]. In fact, current clinical practice guidelines recommend DOACs over VKAs with a level of recommendation and evidence of Ia for all phases of treatment[19,25-27].

In Spain, DOACs are only funded for stroke prevention and systemic embolism in patients with non-valvular atrial fibrillation with one or more risk factors[28], and for VTE prophylaxis in elective hip or knee replacement surgery[29]. Consequently, access to these drugs for patients with DVT or PE has been limited due to their higher short-term cost compared to the therapeutic alternative (VKAs)[30-32].

Therefore, the objective of this study is to evaluate the epidemiological, clinical, and biological characteristics of patients treated with DOACs for secondary prevention of VTE, to gain a better understanding of their safety and effectiveness in routine clinical practice in Spain.

Method

Study design

We conducted a descriptive, observational, single-center, longitudinal, and retrospective study of a cohort of 118 patients diagnosed with VTE in Sector III of Zaragoza who have an indication for anticoagulant treatment as secondary prevention.

The list of patients, as well as epidemiological, clinical, and biological data, were retrospectively obtained from the electronic medical records of patients seen at the Hospital Clínico Universitario Lozano Blesa in Zaragoza (Spain), in the hemostasis and thrombosis clinic of the hematology department. Data collection period was from February 2012 through July 2024.

Authorization for the research was obtained from the Sector Zaragoza III through the center's administration.

Study population

The study included 118 patients over 18 years of age who had suffered VTE and were undergoing treatment with DOACs for secondary prevention in Sector III of Zaragoza, with a minimum follow-up of 6 months and a 15-day window. Patients who initiated secondary prevention treatment between February 2012 and December 2023 were included. Patients who refused anticoagulant treatment and those with an identifiable VTE risk factor or a causative pathology justifying other treatment or its discontinuation were excluded.

Data collection

Data were collected from the database of the hemostasis and thrombosis clinic of the hematology department at the Hospital Clínico Universitario Lozano Blesa in Zaragoza, Spain corresponding to Sector III of Aragon. To preserve patient privacy, a pseudonymization process was implemented, replacing identifiable information with unique codes so that the data could not be directly linked to specific individuals without additional information. The data were stored in a secure environment, and only authorized personnel had access to the pseudonymization key. Additionally, all regulations established by the General Data Protection Regulation of the European Union were followed to ensure the protection and privacy of personal data.

Table 1. Description of sociodemographic variables according to the type of treatment received in secondary prevention

Variable	Apixaban	Rivaroxaban	Total	p
Age (years) at which thrombosis occurred				
Mean (SD)	65.67 (15.61)	56.39 (15.72)	60.16 (16.27)	0.0013
Valid n	48	70	1118	
Age groups (years)				
< 40	3 (6.3%)	48	11 (15.7%)	0.0015
40-49	7 (14.6%)	48	7 (10.0%)	
50-59	5 (10.4%)	48	15 (21.4%)	
60-69	8 (16.7%)	48	25 (35.7%)	
70-79	15 (31.3%)	48	8 (11.4%)	
≥ 80	10 (20.8%)	48	4 (5.7%)	
Valid n	48	70	118	
Sex, n (%)				
Male	26 (54.2%)	48	48 (68.6%)	0.1119
Female	22 (45.8%)	48	22 (31.4%)	

SD: standard deviation.

Data analysis

In the statistical analysis, the mean and standard deviation were used to present quantitative variables, and percentages were used for qualitative variables. The chi-square test was used to compare categorical variables, and the non-parametric Mann-Whitney test was used to compare continuous variables. The statistical analysis was performed using SAS Enterprise Guide, version 7.15 (SAS Institute, Cary, NC, USA). The significance level was set at $p < 0.05$ for all cases.

Results

Sociodemographic characteristics

Between February 2012 and July 2024, 118 patients meeting the inclusion criteria were evaluated, of whom 70 were treated with rivaroxaban and 48 with apixaban, both drugs aimed at secondary prevention of VTE. Table 1 summarizes the sociodemographic characteristics of the study population. The mean age was 60.2 (± 16.3) years, with a significant difference between treatment groups, being lower in patients treated with rivaroxaban (59.4 ± 15.7 years) than in those treated with apixaban (65.67 ± 15.6 years) ($p = 0.0013$). Additionally, when considering age ranges, most patients treated with rivaroxaban were between 60 and 69 years old (35.7%), compared to 16.7% in the apixaban group ($p = 0.0015$). Of the included patients, 62.7% were men, with no statistically significant differences between the groups in terms of sex ($p = 0.1119$).

Risk factors

Figure 1 shows the reasons for choosing the type of treatment for secondary prevention, with the following distributions: 33.1% of patients had recurrent thrombosis, 24.5% had proximal DVT, 19.5% had isolated PE, and 16.1% had DVT + PE concurrently. Portal thrombosis and DVT + unusual thrombosis were less frequent (4.2% and 2.5%, respectively).

Regarding treatment groups, 40% of patients with recurrent thrombosis were treated with rivaroxaban, and 22.9% with apixaban. In the case of PE, apixaban was administered more frequently to 37.5% of patients, while rivaroxaban was administered to 7.1%. For portal thrombosis, all patients received rivaroxaban (7.1%). For unusual DVT and unusual thrombosis, the distribution was similar: 2.9% of patients were treated with rivaroxaban, and 2.1% with apixaban. Similarly, in cases of DVT + PE, 14.3% of patients were treated with rivaroxaban, while 18.8% received apixaban. For proximal DVT, most patients were treated with rivaroxaban, while 18.8% received apixaban.

The statistical analyses performed were significant for the treatment groups. Among the baseline characteristics of the patients, more patients treated with apixaban had PE (37.5%), while only 7.1% of the rivaroxaban group had PE ($p = 0.0008$); the selection of the drug was based on routine clinical practice.

On the other hand, 64.6% of patients did not have any type of thrombophilia, and no significant differences were found in the presence of thrombophilia between the two groups ($p = 0.6895$). Genetic thrombophilia was

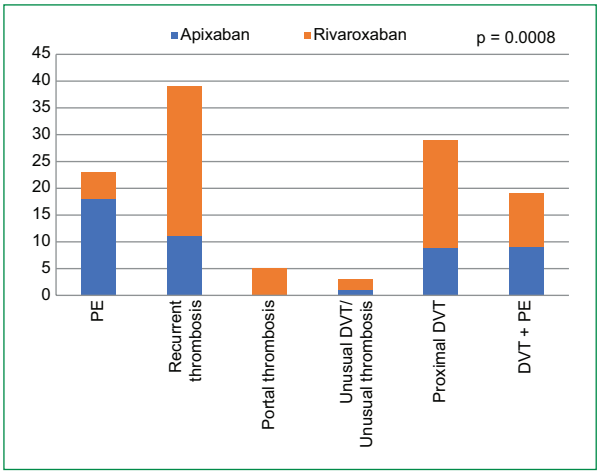

Figure 1. Type of event according to the type of treatment received.

the most common type (55.2%). There were 5 patients with plasma thrombophilia (17.2%), 4 patients with genetic and plasma thrombophilia (13.8%), 3 patients with acquired thrombophilia (10.3%), and 1 patient with genetic and acquired thrombophilia (3.4%).

A total of 26.3% of the sample had a risk factor that favored the decision to maintain anticoagulant treatment beyond 6 months. Among these, systemic disease was the most frequent clinical situation (51.6%). However, a difference was observed between the treatment groups, as 46.7% of patients treated with rivaroxaban had cirrhosis, compared to 0% with apixaban, and 6.7% had reduced mobility, compared to 43.8% with apixaban, resulting in a statistically significant difference (p = 0.0028) (Table 2).

The presence of risk factors such as hypertension and dyslipidemia was significantly higher in the apixaban group (60.4% and 58.3%, respectively) than in the rivaroxaban group (37.1% and 35.7%, respectively) (p = 0.0128 and p = 0.0152) (Fig. 2). Obesity was also more prevalent in the apixaban group (43.8%) than in the rivaroxaban group (12.9%) (p = 0.0002) (Fig. 2). Overall, patients treated with apixaban had a higher number of risk factors, with 20.8% of patients having four or more risk factors, compared to 5.7% in the rivaroxaban group (p = 0.0030) (Table 2).

Analysis of lab test results and imaging

Table 3 describes the laboratory variables according to the type of secondary prevention treatment. D-dimer levels (ngFEU/mL) measured in the interval between the end of treatment and the decision to initiate secondary prevention ranged between 29.0 and 2511.0 in the apixaban group and between 79.0 and 3711.0 in the rivaroxaban group. Specifically, the mean D-dimer levels were significantly higher in the apixaban group (691.7 ± 597.2) vs the rivaroxaban group (505.8 ± 609.3) (p = 0.0338). The results of the comparison of the remaining variables were not statistically significant.

Most imaging follow-up at 6 months, according to the type of secondary prevention treatment administered, was performed using Doppler ultrasound in 60.2% of patients.

Complications since the initiation of secondary prevention

Patients had a median of 1.8 (1.0-2.6) years of secondary prevention at the time of data extraction. Table 4 presents the different types of complications observed in patients since the initiation of secondary prevention according to the treatment received at that stage. There were 0.8% who experienced a thrombotic event during the observation period and 9.3% who experienced a hemorrhagic event; most of these were minor bleeding (54.5%) (Fig. 3). No statistically significant differences were found between the two groups in terms of the occurrence of these events, nor were there differences in the specific type of hemorrhagic event.

Regarding the mean age of patients without hemorrhagic complications, it was 61.4 (± 15.7) years, while for those with complications, it was 48.2 (± 17.3) years. The difference in mean ages between the two groups was statistically significant (p = 0.0160).

Discussion

Our study provides relevant information on the safety and efficacy profile of these drugs, as well as the clinical and demographic characteristics that may influence their selection and outcomes. The main findings focus on age differences, the incidence of PE, complications, and risk factors associated with treatment with rivaroxaban and apixaban.

The study was conducted in a retrospective cohort of 118 patients undergoing treatment with DOACs for secondary prevention. Of these, 70 received rivaroxaban (10 mg/24 h) and 48 received apixaban (2.5 mg/12 h). The mean age of the patients was 60.2 years, and 62.7% were men (with no significant differences by sex). These data are consistent with the main studies that led to the indication of these drugs, which indicate that the incidence is higher in men across all age

Table 2. Description of clinical variables according to the type of treatment received in secondary prevention

Variable	Apixaban	Rivaroxaban	Total	p
Risk factor favoring the decision to maintain treatment according to clinical situation, n (%)				
No	32 (66.7%)	55 (78.6%)	87 (73.7%)	0.1489
Yes	16 (33.3%)	15 (21.4%)	31 (26.3%)	
Valid n	48	70	118	
Type of risk factor that may have caused or precipitated the thrombotic event, n (%)				
Cirrhosis	0	7 (46.7%)	7 (22.6%)	0.0028
Systemic disease	9 (56.3%)	7 (46.7%)	16 (51.6%)	
Reduced mobility	7 (43.8%)	1 (6.7%)	8 (25.8%)	
Valid n	16	15	31	
Number of risk factors present, n (%)				
0	4 (8.3%)	20 (28.6%)	24 (20.3%)	0.0030
1	6 (12.5%)	13 (18.6%)	19 (16.1%)	
2	14 (29.2%)	24 (34.3%)	38 (32.2%)	
3	14 (29.2%)	9 (12.9%)	23 (19.5%)	
≥ 4	10 (20.8%)	4 (5.7%)	14 (11.9%)	
Valid n	48	70	118	

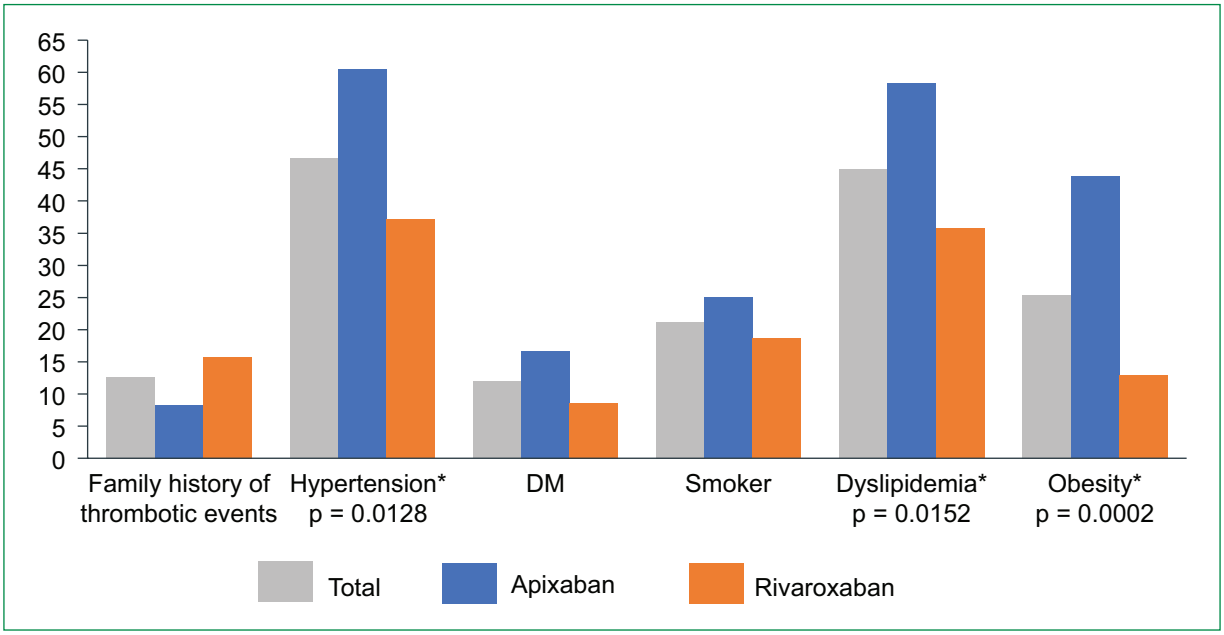

Figure 2. Type of factors that favour the decision to continue treatment.

groups when excluding specific risk factors for women, such as hormonal contraception and pregnancy[33,34].

Regarding the presentation of VTE, in our study, 33.1% of patients had recurrent thrombosis, 24.5% had proximal DVT, 19.5% had isolated PE, and 16.1% had concurrent DVT + PE. In our cohort, most patients were under secondary prevention treatment after experiencing more than one episode of VTE, and in the rest, we can conclude that DVT is more frequent than isolated PE, and the disease often manifests as a combination of DVT + PE. These data are consistent with those provided by studies on the indication of DOACs[33,34].

The utility of thrombophilia testing to predict the risk of recurrence remains a debated topic. Receiving a diagnosis and the label of thrombophilia can generate concern and lead to unnecessary interventions for the patient, especially considering that many individuals with low-risk

Table 3. Description of laboratory variables according to the type of treatment received in secondary prevention

Variable	Apixaban	Rivaroxaban	Total	p
D-dimer (ngFEU/ml) Mean (SD) Valid n	 691.65 (597.20) 34	 505.83 (609.31) 48	 582.88 (607.62) 82	 0.0338
D-dimer (ngFEU/mL) - positive/negative, n (%) Negative Positive Valid n	 23 (67.6%) 11 (32.4%) 34	 37 (77.1%) 11 (22.9%) 48	 60 (73.2%) 22 (26.8%) 82	 0.3420
Factor VIII, % Mean (SD) Valid n	 198.60 (91.38) 10	 163.29 (31.91) 41	 170.22 (50.18) 51	 0.4336
Factor VIII, % - positive/negative, n (%) Negative Positive Valid n	 7 (70.0%) 3 (30.0%) 10	 40 (97.6%) 1 (2.4%) 41	 47 (92.2%) 4 (7.8%) 51	 0.0037
PFA, n (%) No Normal Shortened Valid n	 10 (90.9%) 0 1 (9.1%) 11	 21 (61.8%) 8 (23.5%) 5 (14.7%) 34	 31 (68.9%) 8 (17.8%) 6 (13.3%) 45	 0.1489

PFA: platelet function analyzer.

Table 4. Description of complications since the start of secondary prevention according to the type of treatment received in secondary prevention

Variable	Apixaban	Rivaroxaban	Total	p
Thrombotic event, n (%) No Yes Valid n	 48 (100.0%) 0 48	 69 (98.6%) 1 (1.4%) 70	 117 (99.2%) 1 (0.8%) 118	 0.4056
Hemorrhagic event, n (%) No Yes Valid n	 45 (93.8%) 3 (6.3%) 48	 62 (88.6%) 8 (11.4%) 70	 107 (90.7%) 11 (9.3%) 118	 0.3419
Type of hemorrhagic event, n (%) Minor hemorrhage Major hemorrhage Clinically relevant hemorrhage Valid n	 2 (66.7%) 0 1 (33.3%) 3	 4 (50.0%) 1 (12.5%) 3 (37.5%) 8	 6 (54.5%) 1 (9.1%) 4 (36.4%) 11	 0.7802

thrombophilias, such as heterozygous factor V Leiden, will not develop a VTE event or have an elevated risk of recurrence. Additionally, it is important to note that research on hereditary thrombophilia has primarily focused on Caucasian populations; for example, factor V Leiden is common in this group but extremely rare in non-Caucasian populations[35].

Consequently, it is still unclear whether thrombophilia testing influences decisions on the duration of anticoagulation in clinical practice. The goal of genetic thrombophilia testing is to detect currently known hereditary or acquired prothrombotic states. In our cohort, we identified thrombophilia in 35.4% of patients. However, these findings do not allow decisions on secondary prevention to be based solely on the results of such tests, as only a proportion of patients have thrombophilia. This is consistent with the main studies cited in this discussion, which report approximately 30% of patients with a known prothrombotic state. Such results suggest the likely existence of other unidentified prothrombotic states and support the theory of a multifactorial model in the development of VTE.

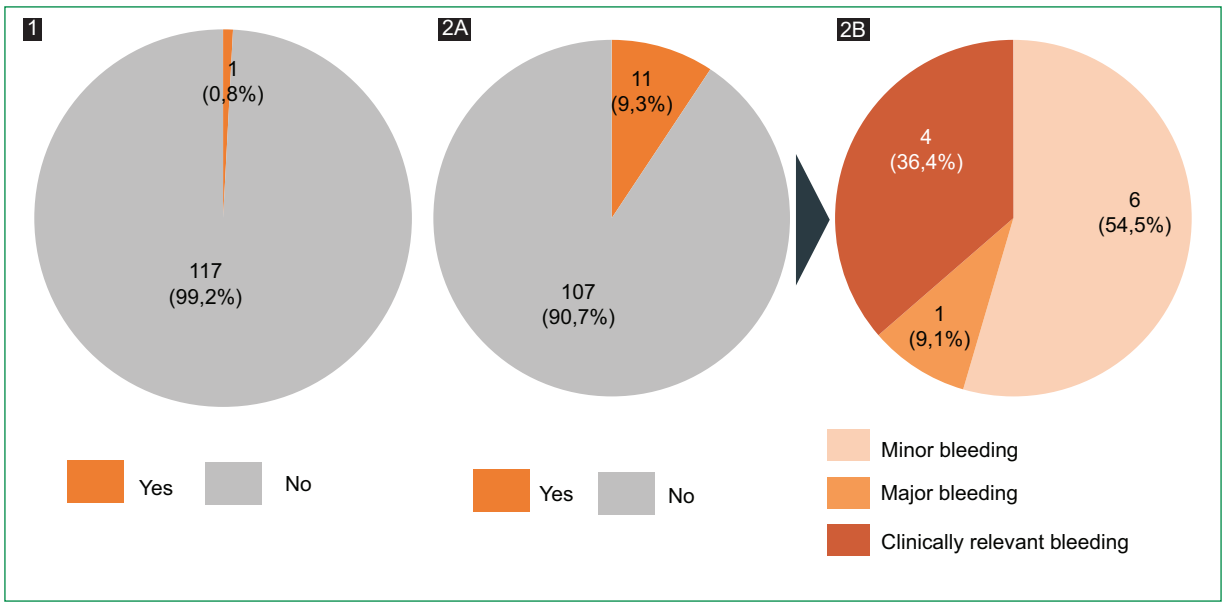

Figure 3. Presence of complications in patients according to type of event. **1:** presence of thrombotic event. **2A:** presence of haemorrhagic event. **2B:** type of haemorrhagic event.

Cardiovascular risk factors are among the causal agents of vascular wall damage that contribute to the occurrence of VTE, making it interesting to study their presence in our series of patients. Most of our patients had hypertension (46.6%) or dyslipidemia (44.9%).

One of the most notable findings was the age difference between the treatment groups, with patients treated with apixaban being significantly older than those in the rivaroxaban group (65.7 vs. 59.4 years; p = 0.0013). This could be explained by differences in tolerability or clinical preferences, as apixaban is often recommended in older patients due to its more favorable bleeding risk profile.

The higher number of patients with PE in the apixaban group (37.5% vs. 7.1%; p = 0.0008) raises important questions. It is possible that patients treated with apixaban had baseline characteristics of higher risk, such as obesity (43.8% vs. 12.9%; p = 0.0002) or hypertension (60.4% vs. 37.1%; p = 0.0128), which may predispose them to a higher incidence of PE. These results reinforce the need to individualize anticoagulant treatment, considering the thrombotic and hemorrhagic risk profile of each patient.

Regarding complications, the overall rate of hemorrhagic events was 9.3%, while recurrent thrombotic events were rare (0.8%). Although no significant differences were observed between the groups in this regard, the findings confirm that DOACs are a safe option in clinical practice, aligning with previous studies that have demonstrated their efficacy and lower need for monitoring compared to VKAs.

Patients had a median of 1.8 (1.0-2.6) years of secondary prevention at the time of data extraction. In registry studies, a duration of 24 months is tested, allowing us to confirm that the extension of anticoagulation for secondary prevention is safe and does not lead to a higher occurrence of thrombotic, hemorrhagic, or other events that would justify its discontinuation or a change in treatment[33,34].

Compared to the existing literature, the results obtained align with the 2020 ASH guidelines, which highlight DOACs as the preferred option for secondary prevention of VTE due to their safety and efficacy profile.

This study contributes to clinical knowledge by focusing on the Spanish population, whose access to these drugs has been limited by economic and funding issues. Additionally, data on risk factors such as obesity, dyslipidemia, and reduced mobility support previous research emphasizing the importance of evaluating the patient's clinical context before initiating therapy.

The main limitations of this study are the small sample size, likely due to the funding situation of these treatments in our setting, and the retrospective, single-center design, which may also limit the generalizability of the findings to other populations. Additionally, the lack of information on treatment adherence could have influenced the results. Finally, although significant differences were identified between the groups, it is

important to consider that these could be due to uncontrolled factors in the analysis, such as the initial severity of VTE or differences in clinical management.

Conclusions

DOACs at secondary prevention doses are a safe and effective alternative for patients requiring long-term treatment. The results of our study indicate that the selection of this treatment should be based on a comprehensive evaluation of the patient, considering thrombotic risk factors, demographic characteristics, and individual preferences, and its indication should be constantly reevaluated during patient follow-up.

Multicenter and prospective studies are needed to confirm these findings and address the limitations of the present study.

Funding

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Conflicts of interest

C. Navas and M. Lloret-Avellá are employees of IQVIA Information S.A.

Ethical considerations

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality, informed consent, and ethical approval. The authors obtained approval from the Ethics Committee for the analysis of routinely collected and anonymized clinical data, so informed consent was not required. Relevant recommendations were followed.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, Tables, or their corresponding captions.

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ORIGINAL RESEARCH ARTICLE

Artificial intelligence-assisted analysis of efficacy, safety, and efficiency of pegylated factor VIII concentrates in hemophilia A based on product inserts

Análisis asistido por inteligencia artificial de la eficacia, la seguridad y la eficiencia de concentrados de factor VIII pegilados en la hemofilia A basado en las fichas técnicas

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Abstract

Introduction: *There are different pegylated factor VIII concentrates, with different characteristics.* **Objective:** *To evaluate the use of basic AI, specifically ChatGPT-4o (OpenAI®), to compare different pegylated CFVIII products due to the lack of direct comparative studies and the limitations of indirect comparisons.* **Material and methods:** *Adynovi®, Jivi® and Esperoct® are compared from their data sheets, with calculations based on an average patient weighing 70 kg. ChatGPT4o performs statistical analyses to compare efficacy (annualised bleeding rate [ABR]) and factor consumption.* **Results:** *ChatGPT4o suggests that Esperoct® (50 IU/kg, 2 times/week) is the most cost-efficient regimen by annualised consumption and low ABR. Adynovi® shows a slightly favourable safety profile, with no statistically significant differences in ABR or annual factor consumption ($p > 0.05$) between regimens, suggesting similar efficacy between the options.* **Conclusions:** *Although matching-adjusted indirect comparisons are validated tools for indirect comparisons in haemophilia, they face limitations. ChatGPT4o could help address them without replacing clinical validation. Artificial intelligence, including ChatGPT4o, could improve the accessibility and accuracy of matching-adjusted indirect comparisons, but still requires ongoing validation.*

Keywords: *Generative artificial intelligence. ChatGPT. Pegylated FVIIIC. Hemophilia A.*

Resumen

Introducción: *Existen distintos concentrados de factor VIII pegilados, con características diferentes.* **Objetivo:** *Evaluar el uso de la IA básica, específicamente ChatGPT-4o (OpenAI®), para comparar los distintos CFVIII pegilados ante la falta de estudios comparativos directos y las limitaciones de las comparaciones indirectas.* **Material y métodos:** *Se comparan Adynovi®, Jivi® y Esperoct®, a partir de sus fichas técnicas, con cálculos basados en un paciente promedio de 70 kg. ChatGPT4o realiza análisis estadísticos para comparar la eficacia (tasa anualizada de sangrado [TAS]) y el consumo de factor.* **Resultados:** *ChatGPT4o sugiere que Esperoct® (50 UI/kg, 2 veces/semana) es el régimen más costo-eficiente por consumo anual y TAS baja. Adynovi® muestra un perfil de seguridad ligeramente favorable, sin diferencias estadísticamente significativas en TAS o consumo anual de factor ($p > 0,05$) entre*

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regímenes, sugiriendo similar eficacia entre las opciones. **Conclusiones:** *Aunque las comparaciones indirectas emparejadas ajustadas son herramientas validadas para comparaciones indirectas en hemofilia, presentan limitaciones. ChatGPT4o podría ayudar a abordarlas sin sustituir la validación clínica. La inteligencia artificial, incluyendo ChatGPT4o, podría mejorar la accesibilidad y la precisión de las comparaciones indirectas emparejadas ajustadas, pero aún requiere una validación continua.*

Palabras clave: *Inteligencia artificial generativa. ChatGPT. CFVIII pegilados. Hemofilia A.*

Introduction

In Spain, three extended half-life factor VIII concentrates (FVIII-C) are currently available, where the technique used to prolong plasma half-life is pegylation. These pegylated FVIII-C (rurioctocog alfa pegol, damoctocog alfa pegol, and turoctocog alfa pegol) exhibit structural and pharmacokinetic characteristics that allow them to be categorized as extended half-life products[1]. However, this only translates into a marginal improvement in extending the dosing interval (Table 1) for most patients. Pharmacokinetic data, as well as efficacy results, are not necessarily comparable across different clinical trials conducted with these molecules due to methodological differences and the patient profiles studied. These products have demonstrated safety and efficacy for the treatment and prevention of bleeding in patients with hemophilia A in various settings, both in clinical trials and real-world scenarios. In the absence of head-to-head studies comparing different concentrates, adjusted indirect comparison methods have proven useful for aiding clinical decision-making in hemophilia A. However, their utility is tied to methodological rigor and maintaining an appropriate clinical context. Lack of consistency and contextual measures may limit the applicability of results, and these should never replace clinical judgment[2].

The objective of this study was to evaluate the potential use of basic artificial intelligence (AI), in this case ChatGPT4o (OpenAI®), as a tool to compare different pegylated FVIII-C, given the absence of direct comparative studies and the limitations of adjusted indirect comparisons.

Method

Data reported in the approved product summaries by the European Medicines Agency[3-5] were used as a reference for comparison. Statistical analyses proposed by ChatGPT4o were performed to compare the safety, efficacy and efficiency profile, considering an average patient weighing 70 kg. Based on the results, ChatGPT4o was asked to recommend the treatment with the best cost-efficiency ratio, assuming equal pricing (Table 1).

Results

First, based on the results in figure 1, ChatGPT4o performed a descriptive analysis and concluded that, to maximize efficacy and minimize dosing frequency, Esperoct® at a dose of 50 IU/kg every 4 days would be preferable in terms of bleeding control. If annual cost is a concern and slightly lower efficacy is acceptable, Jivi® weekly could be a viable option due to its lower IU/kg consumption. According to the differences observed in annual consumption and annualized bleeding rate (ABR), the least recommended regimen would be Esperoct® 75 IU/kg weekly, due to its high ABR (3.57). Although annual consumption is relatively low, its effectiveness in reducing bleeding is lower, which could imply insufficient control of bleeding episodes in patients (Fig. 1).

ChatGPT4o was, then, asked to perform a deeper statistical analysis and justify the selected techniques. It chose ANOVA and the Kruskal-Wallis test. The use of ANOVA was justified because it is particularly useful if the data meet assumptions of normality within each analysis group and homogeneity of variances across groups, being a robust parametric analysis for efficiently comparing multiple groups. The Kruskal-Wallis test was considered as a non-parametric alternative to ANOVA, ideal when data do not meet normality or homoscedasticity assumptions. The t-test was not considered because multiple products were being compared, nor was the chi-square test, as continuous rather than categorical data were being analyzed.

Regarding ABR, the ANOVA analysis showed a p value of 0.80 (> 0.05), indicating no statistically significant differences in mean ABR between the products and regimens analyzed. The Kruskal-Wallis test yielded a p value of 0.64, confirming that the observed differences in ABR between products and regimens are not statistically significant ($p > 0.05$).

For annual factor consumption, the ANOVA analysis showed a p value of 0.22, indicating no statistically significant differences in annual IU/kg consumption

Table 1. Pegylated factor VIII concentrates available in Spain

Drug (year of authorization)	Marketing authorization holder	Active ingredient	Origin/cell culture	Half-Life F8 (h)	Dosage, prophylaxis
Adynovi® (2018)	Baxalta Innovations GmbH	Rurioctocog alfa pegol	CHO	14.7	3 to 4 days
Jivi® (2019)	Bayer AG	Damoctocog alfa pegol	BHK	17	3 to 7 days
Esperoct® (2019)	NovoNordisk A/S	Turoctocog alfa pegol	CHO	14-20	4 to 7 days

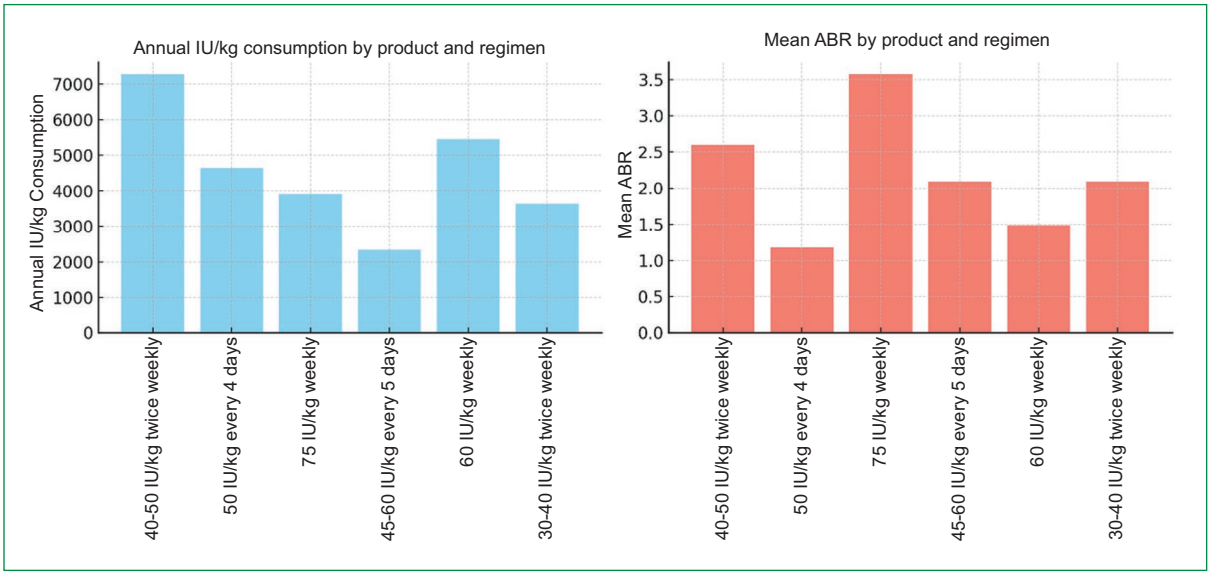

Figure 1. Graph of annual consumption and annualized bleeding rates by product and regimen.

between products and regimens. The Kruskal-Wallis test showed a p value of 0.30. Both analyses indicate no statistically significant differences in annual consumption between products and regimens ($p > 0.05$).

Regarding safety, Adynovi® generally has a slightly more favorable safety profile vs Jivi® and Esperoct®, particularly in terms of immune reactions and serious adverse events. Serious adverse reactions, such as anaphylaxis, are less frequent vs anti-PEG antibody-related complications observed with the other products.

When asked to perform a cost-efficiency analysis and recommend a product and regimen, assuming equal unit costs for all 3 options, ChatGPT4o concluded that the best option is Esperoct® every 5 days, followed by Jivi® every 7 days. If the goal is to maximize cost-efficiency under the same unit cost, Esperoct® at 50 IU/kg every 4 days emerges as the most cost-efficient option in terms of balancing low annual consumption (4641 IU/kg) and low ABR (1.18), followed by Jivi® at a weekly regimen of 60 IU/kg, with lower annual consumption (3276 IU/kg) than Esperoct® but a slightly higher ABR (1.49).

Analyzing whether there are statistically significant differences in efficiency, the Kruskal-Wallis test yielded a p value of 0.30 ($p > 0.05$) for annual factor consumption and 0.64 for ABR. This suggests that, in terms of efficiency, the observed differences between products and regimens are not significant enough to claim that one regimen or product is notably superior in efficiency.

Discussion

Currently, unlike AI, adjusted indirect comparison methods are well-validated statistical tools for comparing products in hemophilia A and have been used for various FVIII-C. For example, in 2019, Batt et al.[6] concluded that, when comparing damoctocog alfa pegol with other FVIII-C such as efmoroctocog alfa, rurioctocog alfa pegol, and

octocog alfa, the ABR was similar, but factor use was 20%-40% lower. However, this adjusted indirect comparison has limitations: undocumented baseline characteristics, absence of a common reference group, and differences in treatment exposure duration, among others. ChatGPT4o could mitigate some limitations of adjusted indirect comparisons, though it could not eliminate them entirely due to the intrinsic nature of the data and the limitations of indirect studies. For example, it could not fully compensate for the lack of a common reference group or population overlap limitations, as these are structural issues. On the other hand, the quality and accuracy of the training data used are always crucial. Similar limitations have been reported in other adjusted indirect comparisons[7,8], so while results are interesting, they must be interpreted cautiously and require additional confirmation for clinical application. ChatGPT4o demonstrates the ability to consolidate large amounts of information from different sources[9] and present it accessibly, but its use still requires necessary validation for these purposes. In our opinion, the comparative analysis performed between the pegylated products is quite accurate and logical, both in structure and reported results. The 3 compared FVIII-C have proven safe and effective fulfilling their intended purpose without issues. However, due to the appropriate balance between consumption, treatment burden, and efficacy, Esperoct® at a dose of 50 IU/kg twice weekly is likely the most suitable treatment option among the compared pegylated products.

Conclusions

ChatGPT4o and other AI platforms have the potential to improve the efficiency, accuracy, and accessibility of adjusted indirect comparisons in hemophilia A by simplifying the handling of complex data and interpretation of results. Their integration into the process can contribute to more robust comparisons and better communication of findings, benefiting researchers, clinicians, and patients alike. However, ChatGPT4o and other AI platforms require continuous validation processes to enable their implementation.

Funding

None.

Conflicts of interest

None.

Ethical considerations

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The recommendations of the SAGER guidelines have been followed according to the nature of the study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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REVIEW ARTICLE

Factor XI inhibitors: can the efficacy and safety of VKAs and DOACs be improved?

Inhibidores del factor XI: ¿se puede mejorar la eficacia y seguridad de AVK y ACOD?

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Abstract

Current available anticoagulants, represented by vitamin K antagonists (AVKs) and direct oral anticoagulants (ACODs), have demonstrated their efficacy in the prevention and treatment of venous and arterial thrombosis, but they are associated with an increase of bleeding complications. Inhibition of factor XI has emerged as a promising strategy to mitigate bleeding while preserving antithrombotic efficacy, because factor XI inhibition uncouples thrombosis from hemostasis. A variety of novel drugs, including antisense oligonucleotides, monoclonal antibodies and small molecules, have demonstrated both efficacy and safety in phase II trials, with phase III studies ongoing, which are covered in the current review.

Keywords: *Factor XI inhibitors. Venous thrombosis. Arterial thrombosis. Acute myocardial infarction. Cancer and thrombosis.*

Resumen

Los anticoagulantes orales de uso clínico, representados por los antivitamina K (AVK) y los anticoagulantes orales de acción directa (ACOD), han demostrado su eficacia en la prevención y tratamiento de numerosos problemas trombóticos arteriales y venosos, pero su empleo se asocia con un aumento de complicaciones hemorrágicas. La inhibición del factor XI emerge como una estrategia prometedora en el tratamiento de esos procesos, pero con una menor incidencia de hemorragias, por la menor contribución de este factor en la hemostasia en relación con su importante papel en la trombosis. Ello ha favorecido el desarrollo clínico de diversos grupos de inhibidores del factor XI, tales como oligonucléotidos antisentido, anticuerpos monoclonales y pequeñas moléculas. Estos agentes han demostrado marcada eficacia y seguridad en estudios en fase II, y se están completando estudios en fase III en la prevención y tratamiento de trombosis venosas y arteriales, motivo de la presente revisión.

Palabras clave: *Inhibidores factor XI. Trombosis venosa. Trombosis arterial. Infarto agudo de miocardio. Cáncer y trombosis.*

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Introduction

Arterial and venous thrombosis, responsible for clinical conditions such as acute myocardial infarction, ischemic stroke, and venous thromboembolism (VTE), is a significant cause of morbidity and mortality. Therefore, anticoagulant therapy, primarily based on the use of heparins, vitamin K antagonists (VKAs), or direct oral anticoagulants (DOACs), is highly effective in the prevention and treatment of thrombosis. However, these therapies are not without bleeding complications, some of which, such as intracranial hemorrhage, can be potentially fatal[1,2]. Heparin and VKAs act on various coagulation factors, while DOACs target specific factors, resulting in a lower but still clinically significant bleeding risk (Fig. 1)[1,2].

Factor XI, a precursor of the contact system in the coagulation cascade, plays a minor role in hemostasis but significantly contributes to the propagation of thrombosis[3]. Various experimental and clinical evidence supports this: individuals with congenital factor XI deficiency experience fewer bleeding complications and a reduced thrombotic risk, epidemiological studies indicate an elevated risk of venous thrombosis in individuals with high factor XI levels, and inhibition of this factor reduces thrombosis in animal models without increasing bleeding[4-7].

Factor XI is a serine protease primarily synthesized in the liver, which is converted into active factor XI (FXIa) by the action of factor XII or thrombin. During hemostasis, coagulation activation depends on the tissue factor (TF) pathway, which forms a complex with factor VII to generate thrombin and form fibrin, without the need for FXIa. However, during thrombosis, FXIa significantly contributes to thrombus growth[3,8,9].

In summary, FXIa plays an important role in pathological thrombosis, particularly during the amplification phase, promoting the generation of significant amounts of thrombin that contribute to intravascular thrombus growth. This paper reviews recent studies on the use of factor XI inhibitors in thrombotic pathologies and various clinical scenarios.

Pharmacological features of factor XI inhibitors

Several agents targeting FXI or FXIa have been developed, including antisense oligonucleotides, monoclonal antibodies, small molecule inhibitors, and aptamers[10-13]. Table 1 illustrates the pharmacological characteristics of the compounds with the most clinical development[14].

Antisense oligonucleotides

Composed of 12 to 30 base pairs, they specifically bind to mRNA, modulating the degradation of factor XI and inhibiting its synthesis in the liver. Their effect is slow and occurs several weeks after administration, with a half-life of 2 weeks, allowing for monthly administration. The preparations under clinical investigation are fesomersen and IONIS-FXIRx.

Monoclonal antibodies

They exert their neutralizing effect by blocking either the activation of factor XI or the activity of FXIa. The preparations under clinical investigation are osocimab, abelacimab, and sixomab, administered parenterally with a half-life of 30 up to 44 days. As they are not metabolized or excreted by the liver and kidneys, they are of particular interest in patients with renal insufficiency.

Small molecules

They block the active site of factor XI, show good oral bioavailability, and have a rapid onset of action. They undergo hepatic metabolism and renal excretion, with a half-life of 14 to 24 hours. The preparations under clinical investigation are asundexian and milvexian.

Aptamers

These are single-stranded oligonucleotides that directly inhibit factor XI or FXIa. They have a rapid onset and cessation of action, low immunogenicity, and no renal elimination. They have a short half-life and are administered subcutaneously or intravenously. The most developed preclinical preparation is the factor eleven inhibitor aptamer (FELIAP).

Clinical trials with factor XI inhibitors

Venous thromboembolism

The main studies in VTE have been conducted in patients undergoing major orthopedic surgery[15-18] (Table 2).

– Antisense oligonucleotides**:** the most important study used IONIS-FXIRX, initiated at different subcutaneous doses 36 days before surgery and continued until 3 days postoperatively. The rate of VTE, determined by bilateral venography, was 27% at 200 mg, 4% at 300 mg, and 20% with enoxaparin (comparator

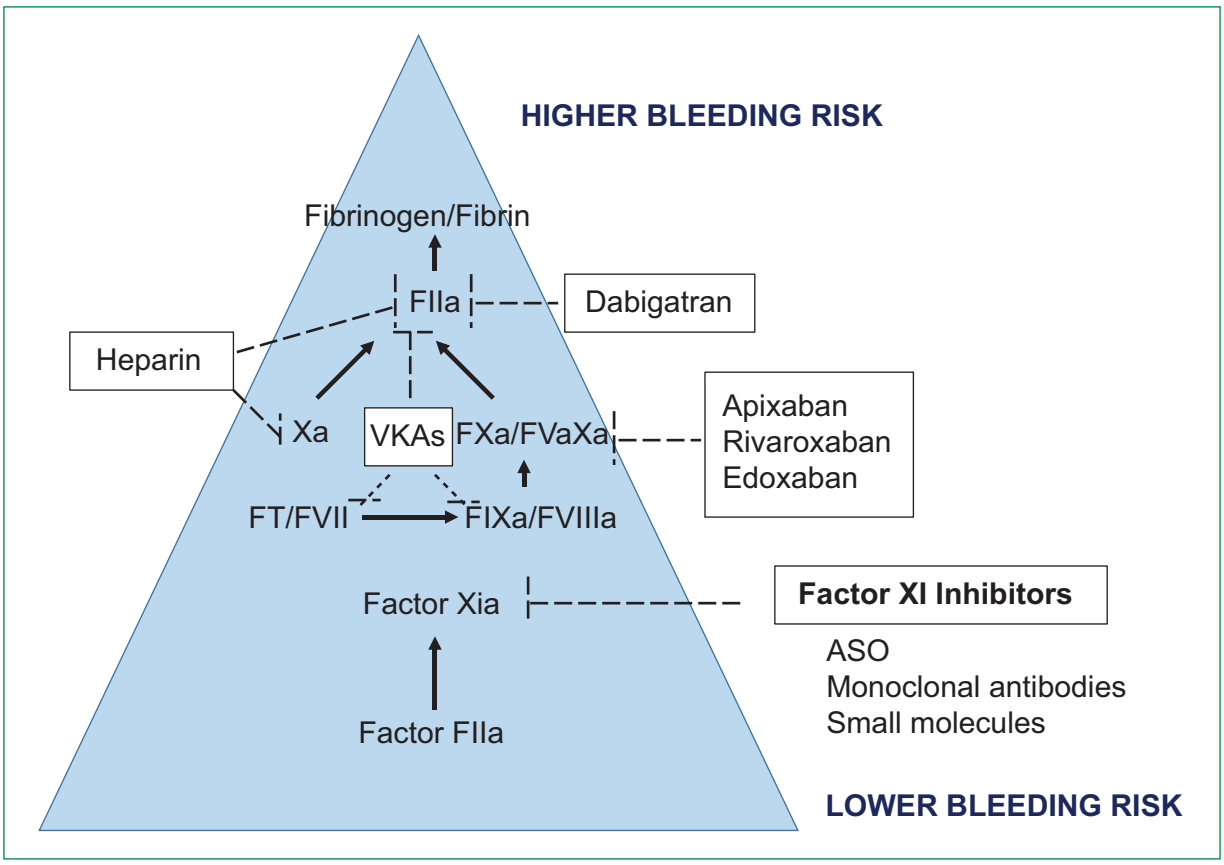

Figura 1. Threshold of bleeding complications associated with different anticoagulants.
ASO: antisense oligonucleotide; TF: tissue factor.

Table 1. Pharmacology of FXI inhibitors in clinical use (phase 2 and 3 studies)

Drug	ASO	Monoclonal antibodies	Small molecules
Agents	Fesomersen, IONIS/FXIRS	Abelacimab, Xisomab, Osocimab	Asundexian, milvexian
Mechanism	mRNA degradation	Direct FXI, FXIa, or FXIIa inhibition	Direct FXIa inhibition
Administration route	SC	IV or SC	Oral
Dosing	Weekly	Monthly	Daily
Onset of action	Weeks	Hours	Minutes/Hours
Half-life	2 weeks	30-44 days	14-24 hours
Drug interactions	None	None	Cytochrome P450 (milvexian)
Renal excretion	Minimal	No	No
Hepatic metabolism	Minimal	No	No

Ac.: antibodies; ASO: antisense oligonucleotide; IV: intravenous; SC: subcutaneous.

group). The rate of bleeding was 3% in the IONIS group vs. 8% with enoxaparin[15].

– Monoclonal antibodies: the FOXTROT study compared escalated doses of osocimab with enoxaparin and apixaban. Although high doses of osocimab were not inferior to enoxaparin in preventing VTE, none were superior to apixaban[16]. Bleeding complications were 5% with osocimab, 6% with enoxaparin, and 2% with

Table 2. Randomized trials for venous thromboembolism prevention in major orthopedic surgery

	FXI-ASO TKA[15]	FOXTROT[16]	ANT005[17]	AXIOMATIC-TKR[18]
Patients	300	813	412	1,242
Drug	IONIS-FXIRX	Osocimab	Abelacimab	Milvexian
Dosage	200 or 300 mg SC on days 36, 35, 33, 31, 28, 21, 14, 7 pre-op & 6 hrs, 3 days post-op	0.3 or 1.8 mg/kg pre-op	0.3, 0.6, 1.2, or 1.8 mg/kg IV post-op	30, 75, 150 mg IV 4-8 hrs post-op; 25, 50, 100, or 200 mg PO twice daily; 50 or 200 mg/day PO
Control	Enoxaparin 40 mg SC	Enoxaparin 40 mg SC vs. Apixaban 2.5 mg twice daily	Enoxaparin 40 mg SC	Enoxaparin 40 mg SC
Follow-up	8-12 days post-op	10-13 days post-op	8-12 days post-op	10-14 days post-op
Rate of thrombosis	27% (200 mg), 4% (300 mg), 30% (control)	29.9%, 0.3 mg pre-op 11.3%, 1.8 mg pre-op 23.7%, 0.3 mg post-op 15.7%, 0.6 mg post-op 16.5%, 1.2 mg post-op 17.9%, 1.8 mg post-op 26.3%, enoxaparin 14.5%, apixaban	VTE 13% (30 mg) 5% (75 mg) 4% (150 mg) 22% (enoxaparin)	VTE 21%, 25 mg twice daily 11%, 50 mg twice daily 9%, 100 mg twice daily 8%, 200 mg twice daily 25%, 25 mg/day 24%, 50 mg/day 7%, 200 mg/day 21%, enoxaparin
Rate of bleeding	3% (IONIS), 8% (enoxaparin)	MH/CRNMH: 4.7% (osocimab), 5.9% (enoxaparin), 2% (apixaban)	MH/CRNMH: 2%, 2%, and 0% (abelacimab 30, 75, 150 mg), 0% (enoxaparin)	4% (milvexian and enoxaparin)

MH: major hemorrhage; CRNMH: clinically relevant non-major hemorrhage; HR: hazard ratio; IV: intravenous; VTE: venous thromboembolism; PO: oral administration; SC: subcutaneous.

apixaban. Another small study used abelacimab, demonstrating superiority over enoxaparin[17].

– Small molecules: the AXIOMATIC-TKR study examined different doses of milvexian vs enoxaparin, observing a significant reduction in thrombotic events (12% vs. 30%), with a similar rate of bleeding complications[18].

One meta-analysis comparing factor XI inhibitors with low molecular weight heparin in VTE prevention, including 4 randomized clinical trials, found a reduction in thrombotic events (OR: 0.50; 95%CI, 0.36-0.69) and a significant reduction in bleeding complications (OR, 0.41; 95%CI, 0.22-0.75)[19].

Arterial thrombosis

The main studies in arterial thrombosis have focused on the prevention of ischemic stroke in patients with non-valvular atrial fibrillation (AF) (Table 3), non-cardioembolic stroke (Table 4), and acute myocardial infarction:

– Monoclonal antibodies: The phase II AZALEA-TIMI71 trial was terminated early after demonstrating a reduction in major and clinically relevant non-major bleeding with 2 monthly subcutaneous doses of abelacimab vs rivaroxaban in AF patients. A phase III study with a 150 mg dose is currently underway (American Heart Association communication 2023).
– Small molecules: The PACIFIC-AF trial compared 2 oral doses of asundexian with apixaban in AF patients, observing a significant reduction in bleeding complications (50% with the lower dose and 84% with the higher dose)[20]. The OCEANIC-AF phase III study compared asundexian 50 mg/day with apixaban and demonstrated the non-inferiority of asundexian for ischemic stroke prevention, with an incidence of 1.3% vs. 0.4% with apixaban and a lower rate of bleeding complications (0.2% vs. 0.7%)[21]. An ongoing study, LIBREXIA-AF, compares another small molecule, milvexian, with apixaban in stroke prevention in AF patients[22].

In the ischemic stroke setting, the PACIFIC-STROKE study used 3 different doses of asundexian or placebo administered 36 hours after stroke. The highest dose (50 mg) showed a non-statistically significant benefit, with no differences in bleeding complications[23].

Table 3. Phase II and III randomized clinical trials in atrial fibrillation

Variable	PACIFIC-AF[20]	OCEANIC-AF[21]
Patients	755	14,830
Drug	Asundexian	Asundexian
Dosage	20 mg or 50 mg/day PO	50 mg/day PO
Control	Apixaban 5 mg twice daily PO	Apixaban 5 mg twice daily PO
Follow-up	12 weeks	155 days
Thromboembolic rate	0.8% asundexian 20 mg 1.6% asundexian 50 mg 1.2% apixaban	1.3% asundexian 0.4% apixaban HR 3.79
Rate of bleeding (MH/CRNMH Ratios vs. Apixaban)	0.50 asundexian 20 mg 0.16 asundexian 50 mg 0.33 pooled asundexian	HM 0.2% asundexian 0.7% apixaban HR 0.32

MH: major hemorrhage; CRNMH: clinically relevant non-major hemorrhage; HR: hazard ratio; SC: subcutaneous administration; PO: oral administration.

Table 4. Phase II randomized clinical trials in non-cardioembolic stroke

Variable	PACIFIC-STROKE	AXIOMATIC-SSP
Patients	1,808	2,366
Drug	Asundexian	Milvexian
Dosage	10, 20, 50 mg/day PO	25 mg/day 25, 50, 100, 200 mg twice daily PO
Control	Placebo	Placebo
Follow-up	26 weeks	90 days
Rate of thrombosis	19% asundexian 10 mg 22% asundexian 20 mg 20% asundexian 50 mg 19% placebo	16.7% milvexian 25 mg vs. 16.8% placebo No dose-response relationship observed for milvexian
Rate of bleeding	MH/CRNMH 4% asundexian 10 mg 3% asundexian 20 mg 4% asundexian 50 mg	MH/CRNMH 1% milvexian 25 mg/day 1% milvexian 25 mg twice daily 2% milvexian 50 mg twice daily 2% milvexian 100 mg twice daily 1% milvexian 200 mg twice daily 1% placebo

MH: major hemorrhage; CRNMH: clinically relevant non-major hemorrhage; PO: oral administration.

A subsequent study showed that asundexian reduced the composite outcome of stroke and transient ischemic attack. The AXIOMATIC-SSP study evaluated 5 doses of milvexian vs placebo in patients with recent stroke who were also on dual antiplatelet therapy. While no differences were observed in the primary outcome of new stroke or infarction detected by brain MRI, a secondary analysis found lower rates of ischemic stroke with milvexian[24].

In acute myocardial infarction setting, the PACIFIC-AMI study investigated escalating doses of asundexian in patients undergoing coronary intervention, 80% of whom received dual antiplatelet therapy. At the 1-year follow-up, no differences were observed in the primary endpoint of major or clinically relevant non-major bleeding with asundexian vs. placebo[25]. Future studies will evaluate the effect of asundexian 50 mg/day in these patients.

Cancer and thrombosis

Two ongoing phase III studies, ASTER (NCT0517049), evaluating abelacimab with apixaban administered for 6 months, and MAGNOLIA (NCT05171075), evaluating abelacimab vs. dalteparin in cancer-related thrombosis, will determine if this strategy is beneficial vs other anticoagulant measures used in these patients.

Renal insufficiency and hemodialysis

Patients with renal disease on hemodialysis have a high risk of thromboembolic and bleeding complications, posing a significant challenge for anticoagulant use. The fact that the hemodialysis circuit stimulates coagulation activation via the contact system makes inhibitors of this phase particularly interesting in this clinical setting.

- Antisense oligonucleotides: different monthly doses of fesomersen were used in phase II in hemodialysis patients, with no significant increase in bleeding risk[26].
- Small molecules: the COVERT trial compared osocimab with placebo, observing no increase in bleeding complications but a reduction in the incidence of clots in the dialysis circuit[27].

Conclusions

The "ideal" anticoagulant for the prevention and treatment of thrombosis would be one with high efficacy and

no bleeding complications. From a hemostasis perspective, factor XI inhibition represents a promising target. Several agents, including antisense oligonucleotides, monoclonal antibodies, and small molecules, have shown efficacy and safety in phase II studies in patients with thrombosis. Ongoing phase III studies will need to demonstrate their superiority over conventional anticoagulants.

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Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality, informed consent, and ethical approval. The study does not involve personal patient data and does not require ethical approval. The SAGER guidelines do not apply.

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CASE REPORT

Hemophilic pseudotumor complicated by femur fracture: a case report

Pseudotumor hemofílico complicado con fractura de fémur: a propósito de un caso

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Introduction

Hemophilic pseudotumor is an encapsulated blood accumulation caused by repeated bleeding into soft tissues that did not receive appropriate treatment[1]. Its incidence rate in patients with hemophilia is approximately 1%-2%[2,3]. Due to its rarity, there are no standardized clinical practice guidelines for its treatment.

Available treatments include clotting factors, surgical resection, radiotherapy, and others such as endovascular embolization[4].

Below, we present a descriptive observational study in the form of a clinical case report.

Case report

This is the case of a 42-year-old male diagnosed with severe hemophilia A (basal factor VIII level of 0.48%) on tertiary prophylaxis with plasma-derived factor VIII at a dose of 20 IU/kg biweekly. The patient presents with hemophilic arthropathy and 2 long-standing pseudotumors: one in the upper third of his left leg—16 cm in diameter—and the other on the anterior aspect of his right thigh (25 cm in diameter).

He visited the emergency department of a tertiary referral center due to acute pain in his right thigh; upon standing, he perceived a cracking sound.

Physical examination revealed an increase in size and intense localized pain in the pseudotumor of the right thigh.

A plain radiograph of the lower limb showed a non-displaced linear fracture of the distal femur.

Computed tomography (CT) confirmed the presence of a 25 cm × 13 cm × 12 cm polylobulated mass of heterogeneous density, with calcifications and a complete linear fracture line. Conservative treatment with plasma-derived factor VIII was initiated, and a plaster cast was applied. The patient was admitted to the medical ward.

Hemostatic treatment plan with plasma-derived factor VIII: day 1: 50 IU/kg bolus; days 2-6: 25 IU/kg every 12 hours; days 7-10: 25 IU/kg every 24 hours.

On day 10, the patient was discharged due to good clinical progress, with a plaster cast and prophylactic treatment with factor VIII at 25 IU/kg 3 times weekly. Thromboprophylaxis with low-molecular-weight heparin at 1 mg/kg daily was also initiated upon admission.

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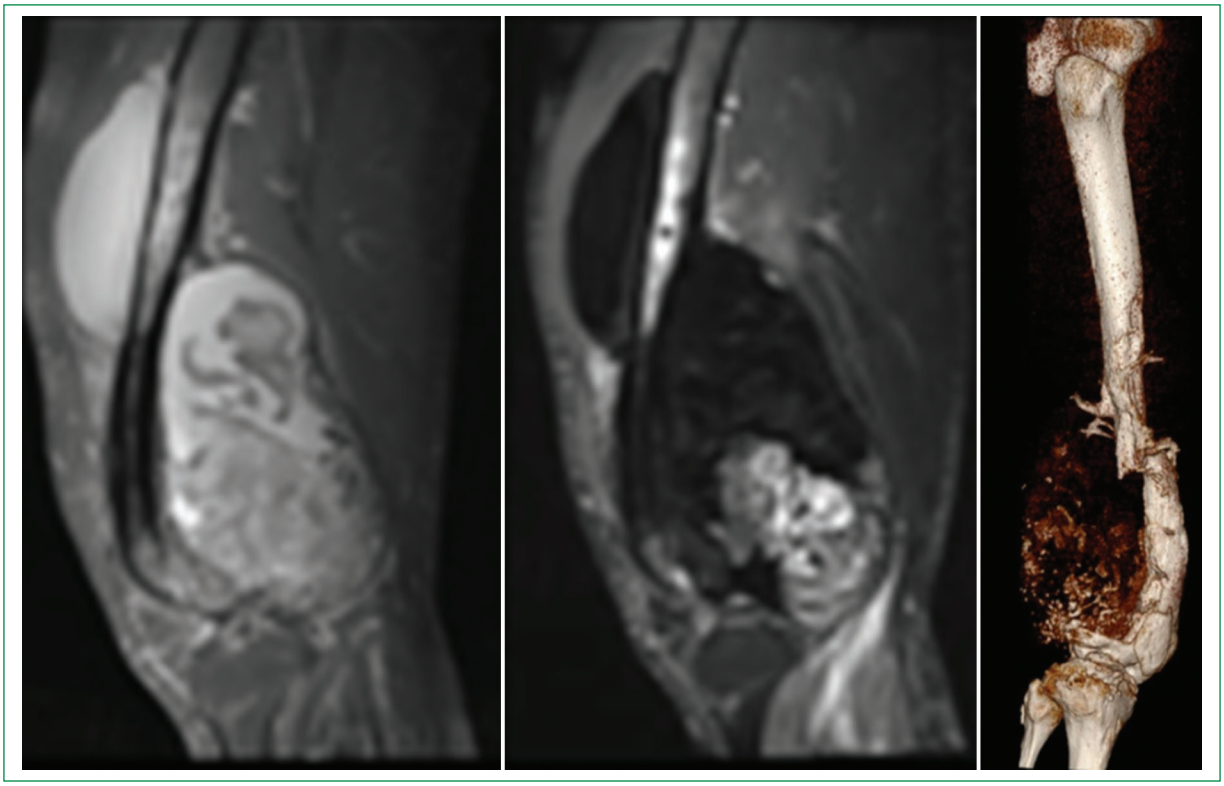

Figure 1. CT scan and 3D reconstruction showing a displaced and overriding fracture associated with a known pseudotumor.

One month later, a follow-up CT scan showed displacement of the fracture with overriding, as well as the persistence of the pseudotumor with the same size (Fig. 1). The patient was readmitted for surgical resolution of the displaced fracture and pseudotumor. The following hemostatic plan was implemented for surgery: immediate preoperative: 50 IU/kg bolus of factor VIII; days 2-6: 25 IU/kg every 8 hours; days 7-14: 25 IU/kg every 12 hours; days 15-17: 15 IU/kg every 12 hours; days 18-20: 20 IU/kg every 24 hours. Serial measurements of factor VIII activity levels were performed (Table 1).

Surgery was divided into 3 surgical acts: opening, lavage, and cavity filling. Under general anesthesia, a wide lateral approach to the thigh was performed, centered on the epicenter of the cavity, extending from the proximal to the distal femur, where a fistulization was present. Upon opening the cavity, the tumor contents drained spontaneously. The hemorrhagic material was removed in one piece, the fracture was corrected, and the cavity was filled with hydroxyapatite. The fracture was stabilized with a plate and screws, and the wound was closed with drainage and a compressive bandage (Fig. 2).

The patient experienced no postoperative complications. Due to good clinical progress, he was discharged after 21 days of hospitalization, with instructions for prophylactic factor VIII at 25 IU/kg 3 times weekly. Physical rehabilitation therapy was initiated, and at 12 months, the patient was able to walk at a normal pace and return to his daily activities (Fig. 3).

The pathology report described the presence of abundant partially organized fibrin mesh, red blood cells, and some amorphous calcifications in the absence of inflammatory infiltrates; all findings consistent with the diagnosis of hemophilic pseudotumor.

Discussion

Hemophilia is a congenital coagulopathy caused by X-linked recessive mutations in the genes encoding factor VIII (hemophilia A) or factor IX (hemophilia B)[5].

In 1918, Starker first described hemophilic pseudotumor in a 14-year-old adolescent with femoral involvement[4]. Hemophilic pseudotumor is a complication of hemophilia consisting of an encapsulated hematoma with progressive enlargement due to recurrent bleeding,

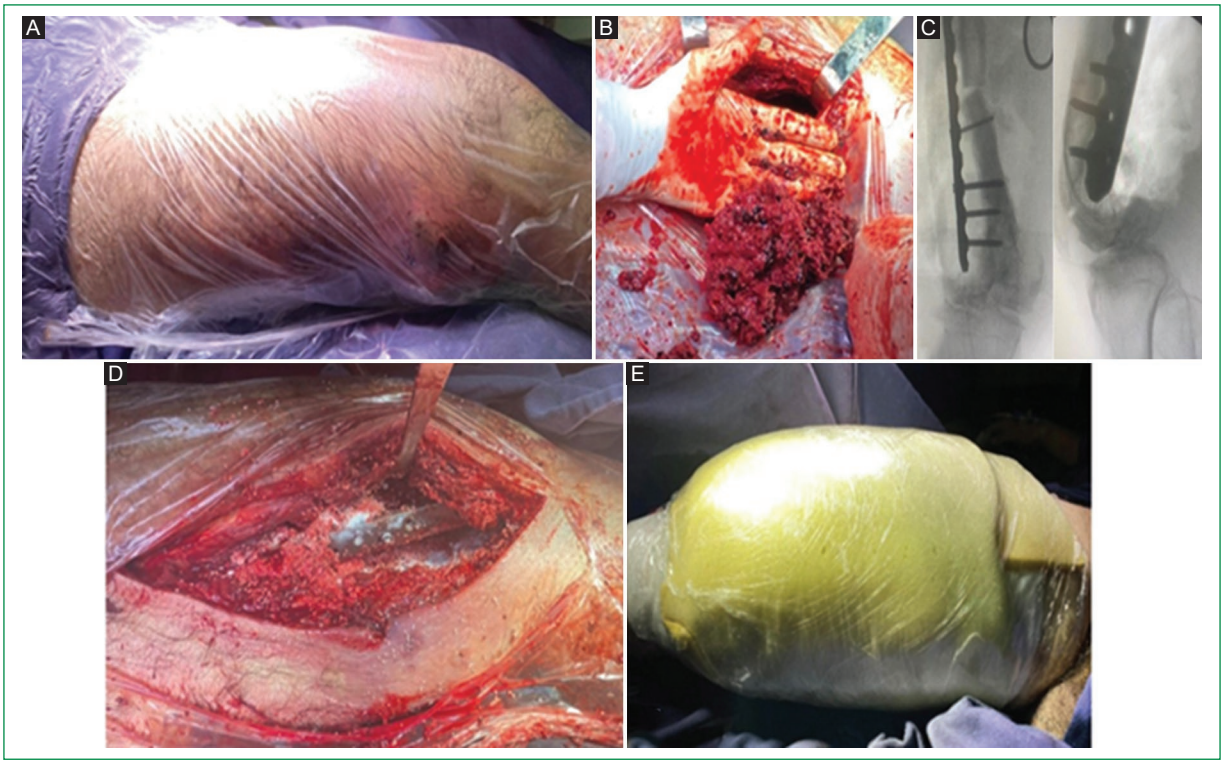

Figure 2. **A:** lateral approach centered on the tumor mass. **B:** evacuation of contents. **C:** revitalization of fracture focus and fixation with osteosynthesis. **D:** appearance of hydroxyapatite. **E:** compressive circumferential bandage with polyfoam and adherent fields.

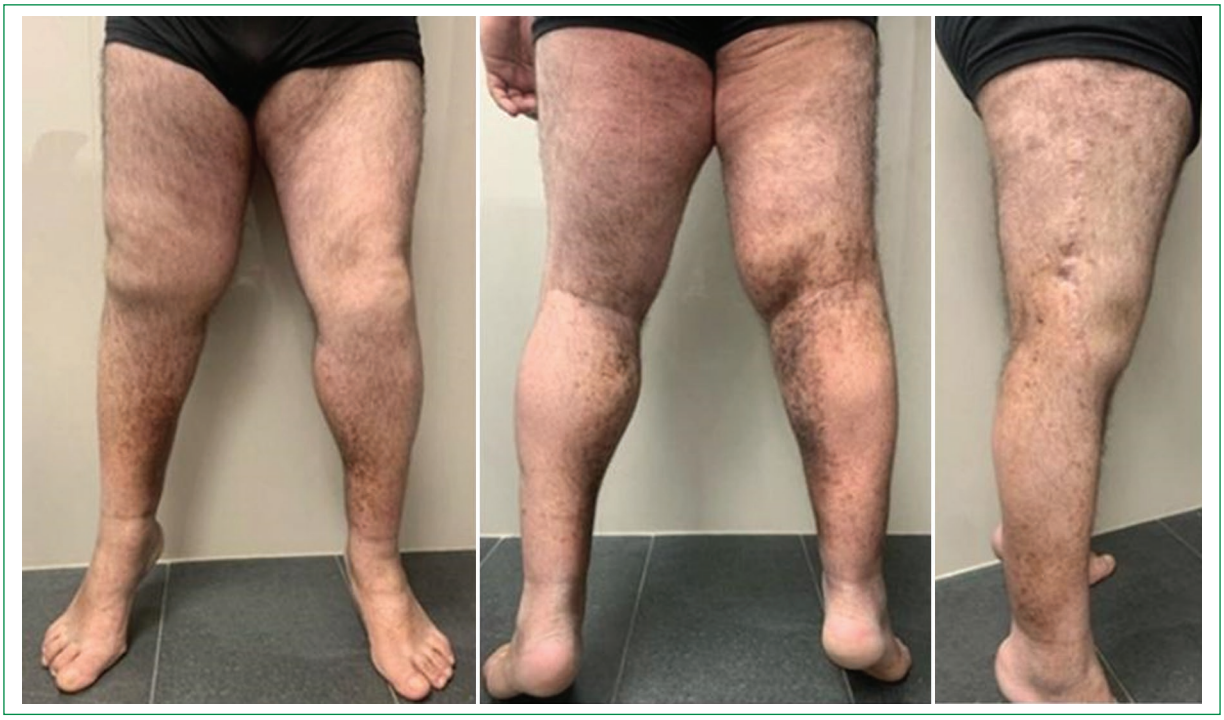

Figure 3. Patient standing 12 months postoperatively.

Table 1. Plasma factor VIII dosage and coagulation factor VIII activity percentage during and after surgery

Plasma factor VIII dose	Day	Factor VIII activity (%)
50 IU/kg	1	78%
25 IU/kg every 8 hours	2	72%
	3	77%
	4	139%
	5	-
	6	-
25 IU/kg every 12 hours	7	113%
	8	72%
	9	68%
	10	139%
	11	92%
	12	72%
	13	52%
	14	31%
	15	35%
15 IU/kg every 12 hours	16	45%
	17	-
20 IU/kg every 24 hours	18	32%
	20	50%

which can endanger limbs or life. Its pathogenesis is related to recurrent bleeding that did not receive adequate treatment[5].

Pseudotumors most frequently occur in relation to long bones[6], but small bones of the hands and feet can also be affected.

Clinically, they present as a firm, painless mass that increases in size and adheres to deep structures[1,7,8].

In terms of diagnosis, CT is more useful than plain radiography, as it allows for discrimination of size, relationships, and the presence of a fibrous capsule[5]. Magnetic resonance imaging (MRI) is equivalent, but its availability is a limiting factor[9,10].

Treatment of a pseudotumor depends on its location, size, growth, and involvement of adjacent structures. Options include replacement therapy with factor and monitoring, radiation, or surgical excision, with no standardized guidelines currently available.

Surgical excision may be necessary in cases of large pseudotumors and complex anatomical relationships, as in our patient. Surgery was planned using factor concentrate treatment and performed at a hemophilia-specialized center, with daily factor VIII dosing.

Evidence for surgical treatment of pseudotumor is based on case reports or case series. In a multicenter study by Magallón et al.[3], 8 out of 14 patients with pseudotumor surgery had good outcomes vs conservative treatment with factor, where only 2 out of 15 patients showed good progress.

In a retrospective study by Lin et al.[3] spanning 14 years (2006-2017) at the Hemophilia Center of Nanfang Hospital in China, 39 patients were diagnosed with hemophilic pseudotumor, and surgical treatment was decided for 34 of them, with good outcomes. In another retrospective study by Kamal et al.[8] over a 7-year period in an orthopedic and trauma department in Indonesia, 6 patients with hemophilia A and pseudotumor were described, concluding that surgery was the most effective treatment for these patients.

For major surgery in a patient with severe hemophilia A, the World Federation of Hemophilia guidelines recommend factor VIII levels of 80-100% preoperatively, 60-80% on days 1-3, 40-60% on days 4-6, and 30-50% on days 7-14. This same regimen was used by Lin et al.[3] in 34 pseudotumor surgeries.

As seen in table 1, adequate factor VIII levels were achieved for the planned surgery.

Conclusions

We report the case of a 42-year-old man with a hemophilic pseudotumor and a pathological fracture in the femoral diaphysis, treated with radical resection and orthopedic surgery. This case is the first documented in our country to associate a pathological fracture with the surgical treatment of a hemophilic pseudotumor, characterized by a highly favorable outcome.

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Conflicts of interest

None.

Ethical considerations

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The recommendations of the SAGER guidelines have been followed according to the nature of the study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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QUARTERLY IMAGE

Fulminant hyperfibrinolysis detected through thromboelastometry

Hiperfibrinólisis fulminante detectada mediante tromboelastometría

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Hyperfibrinolysis is a blood coagulation disorder in which fibrinolysis is excessively activated, potentially leading to massive hemorrhage. Thromboelastometry is a viscoelastic test that allows for the rapid evaluation of coagulation status at the point of care. This technique provides a visual representation with important information about coagulation activation, clot formation, and its stability[1,2].

The EX-test and the IN-test measure activation in the presence of tissue factor and contact activation, correlating with prothrombin time and activated partial thromboplastin time, respectively[3]. The FIB-test uses cytochalasin D, thus eliminating the contribution of platelets and represents the contribution of fibrinogen to the clot. These tests are typically performed on all patients, while the AP-test is reserved for cases of hyperfibrinolysis, as it uses aprotinin to inhibit fibrinolysis[1,2].

Figure 1. Representation of fulminant hyperfibrinolysis in ClotPro®. A(x): amplitude after (x) minutes; CFT: clot formation time; CT: coagulation time; MCF: maximum clot firmness; ML: maximum lysis.

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Figure 1 shows a case of fulminant hyperfibrinolysis in a 65-year-old patient who presented to the emergency department after a fall down the stairs. The EX-test, FIB-test, and IN-test show rapid and fulminant lysis of the fibrin clot before it fully forms, as reflected in the low clot amplitude after 5 minutes (A5). In contrast, the AP-test, which uses aprotinin (a potent direct antagonist of plasmin, the effector protease of fibrinolysis), shows the maximum clot firmness in the absence of hyperfibrinolysis (A5 is normal in this test) and confirms the utility of antifibrinolytic treatment.

In conclusion, thromboelastometry is crucial for the early detection of coagulation disorders, as delayed clinical intervention could result in significant bleeding and an increased risk of death for the patient.

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Conflicts of interest

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Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

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